DRUG INTERACTION MONITORING SERVICE IN INPATIENT PHARMACY DEPARTMENT AT BUMRUNGRAD HOSPITAL

AYURAPA PRIGSUWAN

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Ayurapa Prigsuwan
.....
Miss Ayurapa Prigsuwan
Candidate

.....
Assist. Prof. Preecha Montakantikul,
Pharm.D, B.C.P.S.
Major-Advisor

Suvatna Chulavatnatol
.....
Assoc. Prof. Suvatna Chulavatnatol,
Ph.D.
Co-Advisor

Jitra Anuras
.....
Prof. Jitra Anuras,
M.D., M.S.
F.A.C.P., F.A.A.A.A.I.
Co-Advisor

.....
Assoc. Prof. Rassmidara Hoonsawat,
Ph.D.
Dean
Faculty of Graduate Studies

.....
Assoc. Prof. Weena Jiratchariyakul,
Dr.rer.nat.
Chair
Master of Science in Pharmacy Programme
in Clinical Pharmacy
Faculty of Pharmacy

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on
April 19, 2004

Ayurapa Prigsuwan
Miss Ayurapa Prigsuwan
Candidate

Assist. Prof. Preecha Montakantikul, Pharm.D, B.C.P.S.
Chair

Suvatna Chulavatnatol
Assoc. Prof. Suvatna Chulavatnatol, Ph.D.
Member

Rapeepun Chalongsuk
Assoc. Prof. Rapeepun Chalongsuk, M.S., M.B.A., LL.B.
Member

Jitra Anuras
Prof. Jitra Anuras, M.D., M.S. F.A.C.P., F.A.A.A.A.I.
Member

Rassmidara Hoonsawat, Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

Weena Jiratchariyakul, Dr.rer.nat.
Acting Dean
Faculty of Pharmacy
Mahidol University

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Ayurapa Prigsuwan

DRUG INTERACTION MONITORING SERVICE IN INPATIENT PHARMACY DEPARTMENT AT BUMRUNGRAD HOSPITAL

AYURAPA PRIGSUWAN 4237171 PYCP/M

M.Sc. in Pharm. (CLINICAL PHARMACY)

THESIS ADVISORS: PREECHA MONTAKANTIKUL, Pharm.D, B.C.P.S., SUVATNA CHULAVATNATOL, Ph.D., JITRA ANURAS, M.D., M.S., F.A.C.P., F.A.A.A.A.I.

ABSTRACT

Providing drug interaction monitoring service is an important role of the pharmacist. The objectives of this study were to implement the service in which pharmacists detect and prevent drug interaction, to determine the physician's or nurse's acceptance of the pharmacist's intervention (directed to the prevention of adverse outcomes of drug interaction) and the results of the intervention in the patient care process, and to investigate both potential and actual drug interactions. In this study, a service was set up and implemented as the routine activity in an inpatient pharmacy department to monitor patients who were admitted in medical and surgical wards at Bumrungrad Hospital. Staff pharmacists used a non-computerized screening method consisting of a drug interaction card to check the various 35 alerting drug interactions of five alerting drugs. This was followed by a staff pharmacist or clinical pharmacist intervention. The results showed that, during the four months of the study, 81 drug interactions – 80 potential, one actual – were detected in 68 out of 4,624 patients. Of these 81, 50 (62%) were followed by intervention. Of these 50 interventions, 32% (16/50) were performed by staff pharmacists and 68% (34/50) were performed by a clinical pharmacist. The most common type of intervention performed by staff pharmacists was contacting nurses to change the time of drug administration between interacting drugs, whereas the most common type of intervention performed by the clinical pharmacist was recommending the physician to monitor laboratory tests or observe clinical signs and symptoms for adverse drug interactions. Physicians and nurses accepted 92% (44/48) of the interventions. Various forms of patient care regarding drug interaction were taken after the interventions. In conclusion, participation of pharmacists in the drug interaction monitoring service will assist in attaining the proper drug therapy for the patient.

KEY WORDS : DRUG INTERACTION / PHARMACY INTERVENTION / PHARMACEUTICAL SERVICE

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งานบริการการตรวจตราติดตามปฏิกิริยาระหว่างยา ในแผนกเภสัชกรรมผู้ป่วยใน โรงพยาบาลบำรุงราษฎร์ (DRUG INTERACTION MONITORING SERVICE IN INPATIENT PHARMACY DEPARTMENT AT BUMRUNGRAD HOSPITAL)

อายุรภา ปริกสุวรรณ 4237171 PYCP/M

ภ.ม. (เภสัชกรรมคลินิก)

คณะกรรมการควบคุมวิทยานิพนธ์: ปรีชา มนทกานติกุล, Pharm.D, B.C.P.S.,
สุวัฒนา จุฬาวัฒนทล Ph.D., จิตรา อนุราษฎร์, M.D., M.S., F.A.C.P., F.A.A.A.A.I.

บทคัดย่อ

การให้บริการตรวจตราติดตามปฏิกิริยาระหว่างยาเป็นบทบาทที่สำคัญของเภสัชกร การศึกษานี้มีวัตถุประสงค์เพื่อประเมินงานบริการการตรวจตราติดตามปฏิกิริยาระหว่างยาทั้งในแง่ของการตรวจหาและป้องกันปฏิกิริยาระหว่างยา ผลกระทบของการให้บริการต่อการยอมรับ และการดูแลผู้ป่วยของแพทย์และพยาบาล และศึกษาถึงปฏิกิริยาระหว่างยาทั้งที่อาจเป็นไปได้และที่เกิดขึ้นจริง งานบริการนี้ถูกจัดตั้งและดำเนินการโดยให้รวมเป็นเสมือนงานประจำของแผนกเภสัชกรรมผู้ป่วยใน เพื่อให้บริการแก่หอผู้ป่วยอายุรกรรมและศัลยกรรม โรงพยาบาลบำรุงราษฎร์ วิธีการตรวจหาเป็นแบบไม่ใช้คอมพิวเตอร์ โดยเภสัชกรงานบริการจะใช้บัตรบันทึกคู่ปฏิกิริยาระหว่างยา 35 คู่ ของยาเตือน 5 ตัว เพื่อตรวจหาปฏิกิริยาระหว่างยา และทำการป้องกันและแก้ไขโดยเภสัชกรงานบริการและเภสัชกรงานคลินิก ผลการศึกษาพบว่า ในช่วงเวลา 4 เดือนตรวจพบคู่ปฏิกิริยาระหว่างยา 81 คู่ ในผู้ป่วย 68 คนจาก 4,624 คน เป็นปฏิกิริยาระหว่างยาที่อาจเป็นไปได้ 80 คู่ และปฏิกิริยาระหว่างยาที่เกิดขึ้นจริง 1 คู่ เภสัชกรได้ทำการป้องกันและแก้ไข ร้อยละ 62 (50/81) ซึ่งร้อยละ 32 (16/50) ทำโดยเภสัชกรงานบริการ และ ร้อยละ 68 (34/50) ทำโดยเภสัชกรงานคลินิก เภสัชกรงานบริการจะแก้ไขโดยติดต่อกับพยาบาลเพื่อให้เปลี่ยนแปลงเวลาในการให้ยาสำหรับยาที่เกิดปฏิกิริยาต่อกัน ในขณะที่เภสัชกรงานคลินิกจะให้คำแนะนำแก่แพทย์เพื่อให้ตรวจตราติดตามผลทางห้องปฏิบัติการ อาการและอาการแสดงทางคลินิก แพทย์และพยาบาลยอมรับ ร้อยละ 92 (44/48) ภายหลังจากให้คำแนะนำพบกระบวนการดูแลผู้ป่วยในส่วนที่เกี่ยวข้องกับปฏิกิริยาระหว่างยาเกิดขึ้นหลายรูปแบบ โดยสรุปการมีส่วนร่วมของเภสัชกรในการบริการตรวจตราติดตามปฏิกิริยาระหว่างยาจะช่วยให้ได้รับความเหมาะสมของการใช้ยารักษาผู้ป่วย

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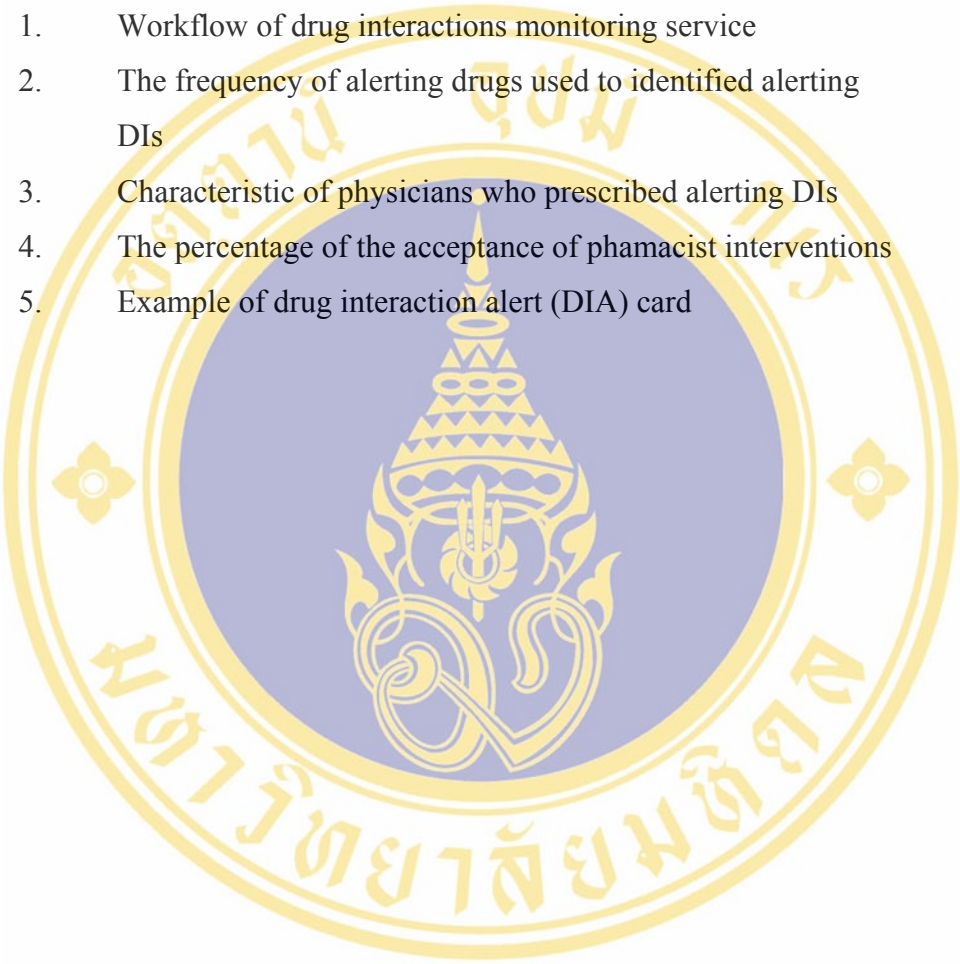

LIST OF ABBREVIATIONS

ACEI	angiotensin converting enzyme inhibitor
CC	chief complaint
CNS	central nervous system
CYP	cytochrome
DI(s)	drug interaction(s)
DIA card	drug interaction alert card
EPS	extrapyramidal side effects
GI	gastrointestinal
HIV	human immunodeficiency virus
HN	hospital number
hr(s)	hour(s)
INH	isoniazid
INR	international normalized ratio
IPD	inpatient department
MAOI(s)	monoamine oxidase inhibitor(s)
MAR	medication administration record
MAX	maximum
MIN	minimum
No.	number
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
OPD	outpatient department
PE	physical examination
PI	present illness
PT	prothrombin time
PTU	propylthiouracil
TIAs	transient ischemic attacks
VS	versus

CHAPTER I
INTRODUCTION

Drug interaction (DI) may be defined as the phenomenon that occurs when the effects or pharmacokinetics of one drug are altered by prior administration or coadministration of a second drug. (1)

Although there are many examples of desirable interactions such as cancer chemotherapy, antihypertensive regimens or antibiotic combinations (2), many interactions are the cause of adverse clinical outcome. Drug interaction may either diminish the effectiveness of pharmacological treatment or generate adverse reactions with minor to major severity. In previous study, Vagus et al (3) found that 20.2% of total adverse drug reactions were due to the joint action of various drugs and the number of adverse drug reactions rose significantly as the number of interaction increased.

Patients who have a number of chronic disorders, patients who take many medications or patients who have impair renal function are at increased risk for these problems. Special attention must be given to drugs that require blood level monitoring, because these agents have a narrow margin of safety. Such agents include theophylline, digoxin, anticonvulsants, and drugs with many potentially serious drug interactions such as warfarin and cyclosporin. In addition, DIs are likely occurred with enzyme inhibitors such as erythromycin and ciprofloxacin and enzyme inducers such as rifampin and Phenobarbital. (4)

The degree of interest generated by DIs has been increased progressively over the last few decades. A considerable number of articles have been published on this subject. To this growing theoretical interest, social and demographic changes were added since they have probably increased the clinical importance of such interactions. In the first place, the quantity of drugs in the market has markedly increased; furthermore, life expectancy has been increased in industrialized countries. These have, in turn, resulted in more frequent multipathology and polypharmacy (5) which increases the probability of DIs.

There were many studies reporting the incidence of potential DIs. It was ranging from 2.2 to 30% of hospitalized patients. (6) Steven and Balon (7) found that one in every 80 prescriptions was written for a drug which interacted with a previous prescribed drug and might have caused harm to a patient because of a major of drug interaction. When elimination of the drugs which weren't concurrently used, it was left only one potentially hazardous prescription in every 180.

In Thailand, there were several studies determining the incidence of potential DIs occurred in patients who were admitted in medical wards. Sripiroj (8), Jatupoomdecha (9) and Jongjarearnprasert (10) reported that the incidence of total DIs was 13.5%, 19.7% and 50.0% and the incidence of actual DIs was 2.1%, 1.9% and 0.9% respectively. Concerning actual DIs, the mortality rate accounted for 4.8%. (8) Although the variability in the reported incidence and clinical significance of DIs described in the literatures, the fact remains that certain drug combinations are indisputably hazardous. (11)

Strand et al (12) identified DIs as 1 out of 8 types of drug-related problems amenable to remedial intervention. Therefore, pharmacists must have an important duty and responsibility to prevent clinically important DIs or to minimize their effect if they occur. In addition, they must have an important role to identify, judge the clinical relevance and follow up a potentially serious adverse DIs in order to produce a positive outcome.

As the data of DIs has proliferated, it is difficult for pharmacists to recognize and identify all of potential DIs when initially reviewing all patient's medication orders. Weideman (13) found that the ability to identity potential DIs decreased as the number of drugs listed on the profile increased.

As stated previously, the effective DIs monitoring service had been developed and implemented in many hospitals. Previous study (14) surveyed the methods used by pharmacy department to manage DIs found that methods used to detect DIs can be classified into 2 types, one is detection by pharmacists or manual method such as through profile review of current medication order or through chart review including patient care round and the other one is by using a drug interaction computer program.

Several computerized drug interaction screening systems were developed and implemented in many pharmacy departments to help pharmacists detect possible DIs,

followed by their interventions to cope with these DIs. (15-17) However, in hospitals that have no computerized operation in pharmacy department or hospitals that computerized DIs screening program is incompatible with inhouse computer system, implementation of other effective DI monitoring services, identified DIs by manual method, had been reported to be successful. Garabedian et al (18) implemented a service to detect and prevent the occurrence of selected potentially serious drug-drug and drug-food interactions in their hospital in which pharmacy dispensing and profilling system is not computerized. When pharmacist identified an interaction which included in the DI monitoring service, pharmacist alerted physician or nurse by using a drug interaction alert card or by telephone. Impact of their service on patient care was assessed. They found that 34% and 82% of cards dispensed to nurses and physicians, respectively, resulted in some forms of action such as changing or discontinuing the dose of one or both drugs, measuring serum drug levels or changing medication administration time. Similarly, in the study of Cramer et al (19), pharmacists evaluated patient medication profile for selected 13 potential DIs and placed alert form on the front of patient's chart when alerting DIs were identified. Follow-up physician action was taken in 84% of identified cases. Both services had been well accepted by physicians, pharmacists and nurses due to many reasons. These were pharmacists appreciate with having opportunity to learn about potential interactions and ways to circumvent its occurrence while nurses and medical staffs thought that the service increased their awareness of potential drug-drug interactions.

Several studies in Thailand had identified the incidence of potential and actual DIs by clinical or ward pharmacist. (8-10) Clinical Pharmacist screened DIs manually through daily patient chart review. Intervention was communicated with physicians. One of these studies (9) preformed intervention which included providing an official lecture on DIs and providing a handout and a portable chart to all medical residence to compare the incidence of DIs before and after intervention. However, study designed to develop and implement the DIs monitoring service initiated from inpatient pharmacy department that staff and clinical pharmacists have an active participation to cope with the adverse DIs is shown to be lacking. Therefore, the present study was intended to indicate the role of pharmacists in detecting and preventing adverse DIs

and to determine the impact of pharmacists' interventions on physicians or nurses acceptance and patient care process.

Bumrungrad Hospital is a 525-bed private hospital. Inpatient pharmaceutical service has 24-hour pharmacist coverage. A total of approximately 2000 drugs are included in hospital formulary. There is computerized operation in pharmacy department but DIs screening program cannot be installed because it is incompatible with routine working computerized system. Survey study of DIs in inpatient at Bumrungrad Hospital found that the incidence of potential adverse DIs with significance rating 1 and 2 was 25.25%. (20) Drug interactions with significance rating 1 and 2 are DIs that have major to moderate severity and clinically well-documented. In this study, only DIs with significance rating 1 and 2 were selected to be monitored in the service by using alerting drugs as a guide for screening. Alerting drugs (i.e. theophylline, digoxin, phenytoin, warfarin and ciprofloxacin) were chosen from drugs which have narrow therapeutic index or involve in many potentially serious drug interactions or frequently reported of potential DIs in the previous survey study in Bumrungrad Hospital.

Objectives of the study

1. To implement the role of pharmacists in detecting and preventing adverse drug interactions as routine activities.
2. To determine the impact of pharmacists' interventions on physicians or nurses acceptance and patient care process regarding drug interactions.
3. To determine both actual and potential drug interactions.

Expected outcome and benefits

1. Establishment of drug interactions monitoring service in inpatient pharmacy department by incorporating the service into daily activities of staff pharmacists.
2. The service was expected to be an effective service for detecting and preventing adverse DIs in inpatient and implementation of this service was expected to increase awareness of pharmacists, physicians and nurses in an appropriate patient care process regarding potential DIs.

3. The service could serve as a role model in monitoring of drug interactions for other hospitals.

CHAPTER II
LITERATURE REVIEW

Drug interactions (DIs) are common cause of treatment failure and adverse reactions. (4) DIs represent one type of an adverse drug reaction and their clinical consequences are potentially preventable. (21) About 7% of hospitalizations are due to DIs. As number of medications a patient takes increases, the potential for DIs also increases. Other predictors for potential DIs include severity of diseases being treated, age of patient, and renal and hepatic dysfunction. Patients with HIV and those posttransplantations are taking a larger number of medications and are at higher risk for DIs.

As the development of new or more potent drugs continues, determining the interactive potential of an increasingly large number of possible drug combinations becomes more complex. (1) Unfortunately, it is not possible for the clinician to remember all of the necessary details for every DI. Nevertheless, knowledge of the interactive properties of drugs can enable one to predict many adverse DIs before they occur. (22)

I. Definition of DIs

A drug-drug interaction may be defined as the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or coadministration of a second drug. (1) The operational definition of DIs may also vary. Although there are many examples of desirable interactions among drugs including cancer chemotherapy, antihypertensive regimens, and antibiotic combinations. (2) This thesis will focus on drug-drug interactions, which lead to adverse clinical consequences in patients.

A DI pair typically consists of the object drug and precipitant drug. The activity of the "object drug" is altered and the drug causing this change is the "precipitant drug". (1)

II. Classification of DIs (1, 23)

DI is usually divided into three categories following the mechanisms commonly involved in DIs: pharmaceutic, pharmacodynamic and pharmacokinetic DIs.

A. Pharmaceutic DIs (23)

Pharmaceutic DIs are DIs which occur outside the body. It is often forgotten in the hurly-burly of clinical work that drugs may interact even before they are administered to the patient, whether orally or parenterally.

It is with parenteral mixtures that clinician has to be particularly careful, and guidance will usually be given by pharmacists. Additions of one drug to another in an intravenous infusion or syringe should always be avoided if possible. Problems particularly arise if other drugs are added to an infusion of heparin, penicillin, hydrocortisone, or theophylline.

The following drugs are physically incompatible with heparin: amikacin, amiodarone, diazepam, droperidol, erythromycin, gentamicin, kanamycin, morphine, pentazocine, pethidine, polymyxin, and promethazine; and if one of these drugs is added to a heparin infusion, a precipitate forms within 5-10 minutes.

Aminophylline is incompatible with chlorpromazine and other phenothiazines, such as promazine and prochlorperazine, dobutamine, pentazocine, pethidine, and some tetracycline salts. As stated earlier, good clinical practice dictates that no more than one drug should be placed in an infusion bottle or syringe. If it is vital to give two drugs by intravenous injection simultaneously, further advice should be sought. It may be appropriate, if venous access is difficult, to give one drug by injection into the side arm of a running infusion containing the second drug.

B. Pharmacodynamic DIs (1, 24-27)

Pharmacodynamic DIs are those in which one drug induces a change in a patient's response to a drug without altering the object drug's pharmacokinetics. That is, one may see a change in drug action without altered plasma concentration. Pharmacodynamic interactions are those where the effect of one drug are changed by the presence of another drug at its site of action. Sometimes the drugs directly compete for particular receptors (e.g., beta-2 agonists such as salbutamol and beta-antagonists such as propranolol) but often the reaction is more indirect and involves the interference with physiological mechanisms. (1)

1. Additive or synergistic interactions and combined toxicity

If two drugs which have the same pharmacological effect are given together, the effects can be additive. For example, alcohol depresses the central nervous system and, if taken in moderate amounts with normal therapeutic doses of any of a large number of drugs (e.g. hypnosedatives, tranquillizers, etc.), may cause excessive drowsiness.

Additive effects can occur with both the main effects of the drugs as well as their side-effects, thus an additive 'interaction' can occur with anticholinergics, antiparkinson drugs (main effect) or butyrophenones (side effect) which can result in serious anticholinergic toxicity. Sometimes the additive effects are solely toxic (e.g. additive ototoxicity, nephrotoxicity, bone marrow depression, QT interval prolongation). Examples of these reactions are listed in Table 1. It is common to use the terms 'additive', 'summation', 'synergy' or 'potentiation' to describe what happens if two or more drugs behave like this. These words have precise pharmacological definitions but they are often used rather loosely as synonyms because in practice in man it is often very difficult to know the extent of the increased activity, that is to say whether the effects are greater or smaller than the sum of the individual effects.

Table 1. Additive, synergistic or summation interactions.

Drugs	Result of interaction
Anticholinergics + anticholinergics (anti-parkinsonian agents, hyoscine, orphenadrine, haloperidol, sedating antihistamines, tricyclic antidepressants, etc.)	Increased anticholinergic effects; heat stroke in hot and humid conditions; adynamic ileus; toxic psychoses
Antihypertensives + drugs causing hypotension (antianginals, vasodilators, phenothiazines)	Increased antihypertensive effects; orthostasis
CNS depressants + CNS depressants (alcohol, anti-emetics, sedating antihistamines, hypnosedatives, tranquilizers, etc.)	Impaired psychomotor skills, reduced alertness, drowsiness, stupor, respiratory depression, coma, death
QT prolonging drugs + other QT prolonging drugs (amiodarone, quinidine, lithium, terfenadine, cisapride, erythromycin, sparfloxacin, disopyramide, etc.)	Additive prolongation of QT interval, increased risk of torsade de pointes
Methotrexate + co-trimoxazole	Bone marrow megaloblastosis due to folic acid antagonism
Drugs with EPS + Drugs with EPS (cinnarizine, flunarizine, metoclopramide, haloperidol, fluphenazine, perphenazine, flupenthixol, etc.)	Akathisia, parkinsonism, acute dystonia
Drugs cause hypokalemia + drugs cause hypokalemia (thiazide and loop diuretics, mineralocorticoids, cathartics, sympathomimetics, amphotericin B, etc.)	Marked hypokalemia

Table 1. Additive, synergistic or summation interactions (Cont.).

Drugs	Result of interaction
Drugs cause hyperkalemia + drugs cause hyperkalemia (potassium-sparing diuretics, ACEI, NSAIDs, Cotrimoxazole, etc.)	Marked hyperkalemia

2. Antagonistic or opposing interactions

In contrast to additive interactions, there are some pairs of drugs with activities, which are opposed to one another. For example, the oral anticoagulants can prolong the blood clotting time by competitively inhibiting the effects of dietary vitamin K. If the intake of vitamin K is increased, the effects of the oral anticoagulant are opposed and the prothrombin time can return to normal, thereby canceling out the therapeutic benefits of anticoagulant treatment. Other examples of this type of interaction are listed in Table 2.

Table 2. Opposing or antagonistic interactions.

Drug affected	Interacting drug	Results of interaction
Anticoagulants	Vitamin K	Anticoagulant effects opposed
Carbenoxolone	Spironolactone	Ulcer-healing effects opposed
Hypoglycaemic agents	Glucocorticoids	Hypoglycaemic effects opposed
Hypnotic drugs	Caffeine	Hypnosis opposed
Levodopa	Antipsychotics (those with Parkinsonian side effects)	Antiparkinsonian effects opposed
Clonidine	Tricyclic antidepressants	Antihypertensive effects opposed

3. Interactions due to changes in drug transport mechanisms

A number of drugs whose actions occur at adrenergic neurones can be prevented from reaching those sites of action by the presence of other drugs. Thus the uptake of guanethidine and related drugs (guanoclor, bethanidine, debrisoquine, etc.) is blocked by chlorpromazine, haloperidol, thiothixene, a number of indirectly-acting sympathomimetic amines and the tricyclic antidepressants so that the antihypertensive effect is prevented. The tricyclic antidepressants also prevent the re-uptake of noradrenaline into peripheral adrenergic neurones so that its pressor effects are increased. The antihypertensive effects of clonidine are also prevented by the tricyclic antidepressants, one possible reason being that the uptake of clonidine within the CNS is blocked. Some of these interactions at adrenergic neurones are listed in Table 3.

Table 3. Interactions due to changes in drug transport mechanisms.

Drug affected	Interacting drugs	Results of interaction
Clonidine	Tricyclic antidepressants	Antihypertensive effects opposed, possibly due to interference in CNS with clonidine uptake
Noradrenaline (norepinephrine)	Tricyclic antidepressants	Pressor effects increased due to inhibition of noradrenaline uptake into adrenergic neurones

4. Interactions due to disturbances in fluid and electrolyte balance

An increase in the sensitivity of the myocardium to the digitalis glycosides, and resultant toxicity, can result from a fall in plasma potassium concentrations brought about by potassium-depleting diuretics such as furosemide. Plasma lithium levels can be increased if thiazide diuretics are used concomitantly because the clearance of lithium by the kidney is changed, probably as a result of the changes in

sodium excretion, which can accompany the use of these diuretics. Table 4 lists some examples.

Table 4. Interactions due to disturbances in fluid and electrolyte balance.

Drug affected	Interacting drugs	Results of interaction
Digitalis	Potassium-depleting diuretics	Digitalis toxicity related to changes in ionic balance at the myocardium
Lithium chloride	Thiazide and related diuretics	Increased serum lithium levels; intoxication possible
Guanethidine Chlorothiazide	Kebuzone Phenylbutazone	Antihypertensive effects opposed due to salt and water retention

C. Pharmacokinetic DIs

Pharmacokinetic DIs are those in which one drug alters the rate or extent of absorption, distribution, or elimination (metabolism or excretion) of another drug. This is most commonly measured by a change in one or more kinetic parameters, such as a maximum serum concentration, area under the concentration time curve, half-life, or total amount of drug excreted in urine. (1)

1. Altered absorption

Concerning absorption interactions, drugs can interact by altering the rate or extent of absorption of another medication. If the rate of absorption of the object drug is decreased, typically, the ultimate steady-state concentration of the object drug is not decreased. However, the slower rate of absorption may be clinically significant if the desired therapeutic effect of the medication is needed rapidly. For example, by slowing the rate of absorption of a medication used as a sleep aid, and analgesia the therapeutic effect may be delayed and the patient may not experience the desired therapeutic effects as usually encountered.

Second, if two medications interact and the extent of absorption of the object is decreased, the ultimate steady-state concentration of the object drug may be decreased. This decrease in steady-state concentration may in fact be clinically significant. This may lead to decreased therapeutic effects and the need for an upward titration of the dose of the object drug.

Absorption interactions typically occur in the small intestine. This makes logical sense because of the fact that the small intestine is the primary site from which orally administered medications are absorbed. The intestine is the primary site of absorption due to its very large absorptive area, increased permeability to drugs, and the large amount of blood flow through the intestinal capillaries, which allows for the absorbed drug to be transported to the systemic circulation. (28, 29)

a. Drug binding in the gastrointestinal tract (28)

Drug binding interactions are a common type of absorption interaction that pharmacists can help to prevent. Drugs that pharmacists should think about as potential interacting drugs are antacids, iron, cholestyramine, and colestipol. These agents possess a large surface area to bind drugs to themselves. This binding prevents the object drug from passing through the intestine and ultimately reaching the systemic circulation.

An example of this type of interaction occurs when cholestyramine is concomitantly administered with levothyroxine. Cholestyramine can potentially decrease the efficacy of levothyroxine and possibly induce hypothyroidism. The mechanism of this interaction is most likely due to the binding of levothyroxine in the GI tract by cholestyramine. Due to the enterohepatic recirculation of levothyroxine, cholestyramine has a longer duration of time to bind with levothyroxine. Therefore, the appropriate recommendation is to instruct patients to separate the administration of these medications by approximately 4 hours at a minimum. Some recommendations state that administration should be separated by up to 6 hours.

Cholestyramine, causes a reduction in the absorption and enterohepatic recycling of digoxin. To reduce this interaction, digoxin dose should be consistently given two hours before cholestyramine dose.

Another significant interaction occurs between multivalent cations and quinolone antibiotics. An 85% decrease in the absorption of ciprofloxacin occurs when this agent is taken five to ten minutes after a dose of an aluminum hydroxide/magnesium hydroxide antacid. (28) A common recommendation is to separate the administration of oral quinolones by at least two hours before or 6 hours after the administration of cations such as antacids, sucralfate, calcium, didanosine, iron and magnesium. (28,30)

Alendronate (Fosamax®), the new bisphosphonate for the treatment of osteoporosis, forms complexes with many drugs, thereby decreasing its already low absorption. According to the manufacturer, alendronate should be taken only with water, and it should be taken at least 30 minutes before food or other medications.

b. Alterations in GI motility (1, 28, 31)

The response to a medication can be altered because of a second medication changing the GI motility of the patient. As mentioned earlier, the small intestine is the primary site of absorption for orally administered medication. If the GI transit time is increased or decreased, the time available of absorption can be limited or maximized.

Medications such as anticholinergic agents and opiates can slow GI transit time. This slowing of transit time can allow for the object drug to be absorbed to a greater extent. This increased extent of absorption can lead to a clinically significant increase in pharmacologic effect.

Certain drugs can be expected to decrease GI transit time (i.e., metoclopramide, erythromycin, and laxatives). The decreased transit time may carry an object drug through the GI tract at a faster rate than is ordinarily encountered, and it may not allow an object drug to be absorbed to its fullest extent. This decreased extent of absorption may lead to a decrease in the object drug's pharmacologic effect. For example, digoxin plasma level may decrease by increasing GI motility by metoclopramide. In patient on maintenance digoxin therapy, receiving metoclopramide 10 mg three times daily for 10 days significantly reduces the mean serum digoxin concentration from 0.72 to 0.46 ng/mL after oral administration of slowly dissolving

digoxin tablets. Therefore, patient should be monitored for decreased therapeutic response to digoxin or for decrease digoxin serum levels. The dose of digoxin may need to be increased. (1, 31)

This type of interaction usually cannot be avoided by separating the medications by several hours. Typically, this type of interaction can be resolved by titrating the object drug to its appropriate therapeutic effect.

c. Alterations in GI pH (1, 28, 32, 33)

Many patients are currently receiving therapy with medications that alter the GI pH, therefore, it is prudent to be aware of the potential type of interaction this pH alteration can cause.

To understand the mechanism of the interactions we must understand that many of the currently available medications are weak acids or weak bases. The nonionized form of these medications can cross intestinal membranes and reach the systemic circulation. However, specifically speaking, drugs that are classified as weak acids are absorbed to a greater extent in an acid medium. Conversely, drugs that are classified as weak bases are better absorbed in a basic medium.

An example of a medication that can exhibit a GI pH alteration interaction is ketoconazole and itraconazole which the gastric dissolution and subsequent absorption are dependent on low gastric pH (pH<4). The bioavailability of these drugs are significantly reduced if a patient receives therapy with a medication that increases the pH of the stomach such as H_2 receptor antagonists, proton pump inhibitors, sucralfate and didanosine. The effect of the interaction could lead to a treatment failure. Therefore, co-administration of the interacting drugs should be avoided.

d. Alterations in intestinal flora (28, 34, 35)

Over the years, a number of case reports have appeared in the medical literature reporting contraceptive failure in patients receiving concurrent ampicillin or tetracycline with oral contraceptives. In addition, a variety of antibiotics have been reported to cause oral contraceptive failure. The suspected mechanism of interaction is that the antibiotic may suppress the intestinal flora that provide

hydrolytic enzymes essential for enterohepatic recirculation of necessary contraceptive hormone conjugates.

Another example is the interaction between the macrolides, mainly erythromycin and digoxin. Ten percent of the population converts up to 40% of an ingested digoxin dose to inactive digoxin reduction products (DRPs) in the gut by *Eubacterium lentum*, an anaerobic gram-positive rod which is a component of the normal flora. The proposed mechanism of the macrolide-induced digoxin toxicity suggests that erythromycin alters the gut flora by decreasing levels of *E. lentum*, thereby reducing the conversion of digoxin to DRPs and increasing the effective ingested digoxin dose.

e. Alterations in drug metabolism within the wall of the intestine (28)

A number of different types of metabolism are known to occur in the wall of the intestine. A partial list of the types of metabolism includes glucuronidation, sulfation, P-450 oxidation, and monoamine oxidation.

The simplest type of example to discuss concerning this type of interaction is the ingestion of a meal high in tyramine by a patient receiving a monoamine oxidase inhibitor. In this situation, the monoamine oxidation that is to occur in the wall of the intestine will be inhibited by the monoamine oxidase inhibitor. Therefore, the protective properties of monoamine oxidase in the intestine will be inhibited and the tyramine will reach the systemic circulation potentially leading to a hypertensive response.

2. Altered distribution (28, 36, 37)

Protein binding is a dynamic process in which there is an equilibrium between bound and unbound drug. The binding of drugs to proteins can be affected by the addition of other medications, specific diseases, and also the accumulation of endogenous substances. Drugs bound to serum proteins are physically inactive, with only the unbound drug being available to reach its site of action. The bound portion of the drug can be thought of as a reservoir to be released when needed. The primary serum protein related to drug binding is albumin.

Drugs may compete with each other for bindings sites on plasma protein or tissues. When this occurs, the unbound or free serum concentration of one or both drugs may increase; this may theoretically increase drug response. In practice, however, protein binding displacement interactions generally do not produce clinically important changes in drug response. Displacement interactions are usually not important unless the displaced drug is highly bound, has a limited distribution in the body, is slowly eliminated, and has a low therapeutic index. Even when a displaced drug possesses these properties, the enhanced pharmacologic effect only occurs transiently (i.e., for a few days) because more unbound drug is available for elimination by the liver and/or kidney. For this reason, protein binding displacement interactions may assume greater importance when the displacing drug (or some other drugs given concurrently) also reduces the elimination of the object drug. For example, the dramatic increase in hypoprothrombinemia seen when phenylbutazone is added to warfarin therapy results from the combined effects of displacement of warfarin from plasma protein binding sites as well as inhibition of hepatic warfarin metabolism.

3. Altered metabolism (23, 28, 38, 39)

Many of the clinically relevant DIs occur because of alterations in the rate of metabolism of the object drug. Metabolic processes convert the lipid-soluble drug to more water-soluble products that can be excreted in the urine or bile. There are two main types of drug metabolic process: phase I reactions involving oxidation, hydrolysis, or reduction; and phase II reactions, which are synthetic reactions involving conjugation of the drug (or its phase I product). The rate of drug metabolism varies widely between individuals and is determined by both genetic and environmental factors. There are many factors that can affect the rate of drug metabolism, and one of the most important is the concomitant administration of other drugs. The process of enzyme induction may increase the rate of drug metabolism. Whereas the rate of drug metabolism may be reduced by drugs that usually compete for the enzyme site although, rarely, the inhibiting drug may bind to the enzyme site and either inactivate or destroy it.

- CYP450 Isoenzymes: An overview

The cytochrome P-450 (CYP450) enzymes are the main enzymes responsible for phase I reactions. CYP450 enzymes are a group of heme-containing enzymes located on the membrane of the smooth endoplasmic reticulum of hepatocytes in the liver and in high concentrations on enterocytes of the small intestine. CYP450 enzymes are also located in small amounts in other tissues, specifically the kidney, lungs, and brain. The CYP450 name is derived from analysis of these enzymes on a spectrophotometer. The spectral absorbancy peak at or near 450 nm when carbon monoxide binds to the isoenzyme in its reduced state. The CYP450 system includes more than 30 isoenzymes. The isoenzymes are grouped into families and subfamilies according to their amino acid sequence. The current method of naming CYP450 enzymes involves the designation of the specific enzyme with the prefix "CYP", followed by an Arabic number indicating the P-450 family, followed by a capital letter denoting the subfamily, and then an Arabic numeral representing the individual enzyme. For example, the CYP3A4 isoenzyme by its designation indicates that it is a member of family "3", subfamily "A", and it is the fourth enzyme in subfamily "A". It is generally agreed that members of a CYP450 family have ≥40% amino acid sequence homology. Likewise, cytochrome enzymes within the same subfamily have >55% amino acid sequence homology. (23, 28)

Although more than 30 human CYP-450 isoenzymes have been identified to date, and 11 have been confirmed as potential sites of drug metabolism, the major ones responsible for drug metabolism are CYP3A4 CYP2D6 CYP1A2 CYP2E1 and CYP2C subfamily. (40, 41)

Knowledge of the substrates, inhibitors, and inducers of CYP450 enzymes is essential and can assist in the prediction and prevention of clinically significant drug interactions. The term 'substrate' is defined as a substance upon which an enzyme acts. The term 'inhibitor' denotes a drug known to interfere or compete with the enzyme, and 'inducer' describes as agent that accelerates the metabolism of a substrate. Many drugs use CYP450 enzymes as substrates for their metabolism. Drugs can inhibit or induce metabolism of other drugs, and they can also compete for metabolism for the available CYP450 isoenzymes. (40, 41) A list of

inducers, substrates, and inhibitors of the major CYP450 isoenzymes is included in Table 5-9.

Table 5. CYP3A4 isoenzyme : Substrates, inhibitors and inducers (40).

Substrates				
Alfentanil	Cyclobenzaprine	Ethosuximide	Miconazole	Rifampin
Alprazolam	(demethylation)	Etoposide	Midazolam	Ritonavir
Amitriptyline	Cyclophosphamide	Felodipine	Navelbine	Saquinavir
(minor)	Cyclosporin	Fentanyl	Nefazodone	Sertraline
Amlodipine	Dapsone	Fexofenadine	Nelfinavir	Tacrolimus
Astemizole	Dexamethasone	Ifosfamide	Nicardipine	Tamoxifen
Atorvastatin	Dextromethorphan	Imipramine	Nifedipine	Temazepam
Busulfan	Diazepam (minor)	Indinavir	Nimodipine	Terfenadine
Cannabinoids	Diltiazem	Isradipine	Nisoldipine	Testosterone
Carbamazepine	Disopyramide	Ketoconazole	Ondansetron	Triazolam
Cisapride	Donepezil	Lansoprazole(minor)	Paclitaxel	Verapamil
Clindamycin	Doxorubicin	Lidocaine	Pravastatin	Vinblastine
Clomipramine	Dronabinol	Losartan	Prednisone	Vincristine
Clonazepam	Erythromycin	Lovastatin	Quinidine	R-warfarin
Cocaine	Estrogens, oral contraceptives	Mibefradil	Quinine	Zileuton

Inhibitors				**Inducers**	
Amiodarone	Grapefruit juice	Metronidazole	Quinine	Carbamazepine	Rifabutin
Canabinoids	Indinavir	Mibefradil	Ritonavir	Dexamethasone	Rifampin
Clarithromycin	Itraconazole	Miconazole	Saquinavir	Ethosuximide	Troglitazone
Erythromycin	Ketoconazole	Nefazodone	Sertraline	Phenobarbital	
Fluconazole	Omeprazole	Nelfinavir	Troleandomycin	Phenytoin	
Fluoxetine	(slight)	Norfloxacin	Zafirlukast	Primidone	
Fluvoxamine					

Table 6. CYP2D6 isoenzyme : Substrates, inhibitors and inducers (40).

Substrates			
Amitriptyline (hydroxylation)	Dextromethorphan	Maprotiline	Perphenazine
	Donepezil	Meperidine	Propafenone
Bisoprolol	Doxepin	Methadone	Propranolol
Chlorpromazine	Flecainide	Methamphetamine	Risperidone
Clomipramine	Fenfluramine	Metoprolol	Thioridazine
Clozapine	Fluphenazine	Mexiletine	Timolol
Codeine	Fluoxetine	Morphine	Tramadol
Cyclobenzaprine (hydroxylation)	Haloperidol	Nortriptyline (hydroxylation)	Trazodone
	Hydrocodone		Venlafaxine
Desipramine	Imipramine (hydroxylation)	Oxycodone	
Dexfenfluramine		Paroxetine	
Inhibitors			**Inducers**
Amiodarone	Fluphenazine	Quinidine	Carbamazepine
Cimetidine	Haloperidol	Ritonavir	Phenobarbital
Clomipramine	Mibefradil	Sertraline	Phenytoin
Desipramine	Paroxetine	Thioridazine	Rifampin
Fluoxetine	Propafenone		Ritonavir

Table 7. CYP1A2 isoenzyme : Substrates, inhibitors and inducers (40).

Substrates	**Inducers**	**Inhibitors**
Amitriptyline (demethylation)	Phenobarbital	Cimetidine
Caffeine	Phenytoin	Ciprofloxacin
Clomipramine (demethylation)	Rifampin	Clarithromycin
	Ritonavir	Enoxacin
Clozapine	Smoking / PAH	Erythromycin
Cyclobenzaprine (demethylation)		Fluvoxamine (potent)
		Grapefruit juice
Desipramine (demethylation)		Isoniazid
Diazepam		Ketoconazole
Haloperidol		Levofloxacin
Imipramine (demethylation)		Norfloxacin
Tacrine		Omeprazole
Theophylline		Paroxetine
R-warfarin		
Zileuton		

Table 8. CYP2C isoenzyme : Substrates, inhibitors and inducers (40).

Substrates	Inducers	Inhibitors
Amitriptyline	Carbamazepine	Amiodarone (2C9)
Clomipramine	Phenobarbital	Chloramphenicol (2C9)
Diazeparm	Phenytoin	Cimetidine (2C9)
(demethylation 2C9)	Rifampin	Fluconazole
Imipramine		Fluoxetine
Losartan (2C9)		Fluvastatin
Omeprazole		Fluvoxamine (2C9, potent)
Phenytoin (2C9)		Isoniazid
S-warfarin (2C9)		Ketoconazole (weak)
Tolbutamide		Omeprazole (2C9, 2C19)
Topiramate (2C19)		Sertraline
		Topiramate (2C19
		Zafirlukast (2C9)

Some drugs may be metabolized by more than one CYP450 isoenzyme. For example, the pharmacologically active enantiomer S-warfarin is metabolized by CYP2C9 enzyme, whereas R-warfarin is metabolized by the CYP3A4 and CYP1A2 systems. Therefore, when one enzyme system is inhibited or induced by an interacting drug, a clinically significant interaction may or may not occur. Another example is tricyclic antidepressants, which are metabolized by CYP2D6, CYP1A2, and CYP3A4. Inhibition or genetic absence of one isoenzyme can lead to compensation through the secondary isoenzyme pathway. Similar to warfarin, metabolism can be preserved, and a clinically significant interaction may or may not occur. Additionally, a drug may inhibit or induce the activity of a specific isoenzyme even though it is not a substrate at that particular site. For example, guinidine is metabolized by the CYP3A4 enzyme, but it is a potent inhibitor of CYP2D6. (39,40)

a. Enzyme Induction (28, 39, 40, 42, 43)

The possible pharmacokinetic consequences of enzyme induction depend on the localization of the enzyme. They include decreased or absent bioavailability for orally administered drugs, increased hepatic clearance or accelerated formation of reactive metabolites, which is usually related to local toxicity.

Enzyme induction interactions occur when an enzyme-inducing drug is administered and it gradually begins to stimulate the synthesis of additional CYP450 isoenzymes lead to an increase in metabolism of substrate drugs primarily metabolized by the induced isoenzyme. Enzyme induction can be detected within the first 2 days of drug administration; however it generally takes a week or more before maximal enzyme induction occurs. The onset of induction depends on the half-life of the inducing agent with longer half-life inducer having a slower onset of induction. For example, rifampin's short half-life results in enzyme induction (CYP3A4, 2C) apparent within 24 hours, whereas phenobarbital's longer half-life of 3–5 days requires approximately 1 week for induction (CYP3A4, CYP1A2, CYP2C) to become apparent. Both of these agents interact with warfarin metabolism. Whereas rifampin's effects occur within 4 days, phenobarbital's effects take 14 – 22 days to occur.

A complicating factor is that the time course of induction is also dependent on the time required for enzyme degradation and new enzyme production. In other words, the rate-limiting factor may be the half-life of CYP450 enzyme turnover, which ranges from 1 – 6 days. Since rifampin is eliminated more rapidly than the excess cytochrome enzymes, the rate-limiting factor in the duration of the interaction would be enzyme turnover. With phenobarbital, accumulation and elimination would be the rate-limiting factor in the onset and offset on induction.

In general, metabolites are less pharmacologically active than the parent drug and, therefore, enzyme induction results, in a reduction in pharmacological effect of object drug because of in creased drug metabolism. In contrast, if the drug is a pro-drug, metabolic activation by enzyme induction may be too rapid and resulting in serious high level of active drug, which can be toxic to the patients. However, good examples of clinical problems resulting from this phenomenon are not known yet. Induction may also increase the metabolism of the inducing agent. This phenomenon is called "autoinduction". The prototypical example an autoinducing compound is carbamazepine. (44)

Enzyme induction appears to be a dose-related process with larger doses of the inducer tending to produce a greater degree of enzyme induction. Also, enzyme induction can be influenced by age, with elderly patients not manifesting enzyme induction to the same degree as younger patients. Liver disease

may also influence enzyme induction, with cirrhosis or hepatitis patients being less susceptible to induction. Additionally, genetic differences in the activity of isoenzymes may explain some of the variation seen in drug interaction outcomes.

b. Enzyme Inhibition (28, 40, 45)

Enzyme inhibition interactions occur much more rapidly than induction interactions. Enzyme inhibition interactions are probably the most clinically significant type of CYP450 interactions. Inhibition of substrate metabolism tends to begin as soon as sufficient concentrations of the inhibitor are reached. Inhibition of metabolism of the substrate drug is usually maximal within the first 24 hours of administration of the inhibitor. The onset and offset of enzyme inhibition are dependent on the half-life and time to steady state of the inhibitor drug. For example, chloramphenicol (CYP2C9), acute ethanol ingestion and cimetidine (CYP1A2) inhibit drug metabolism within 24 hours of a single dose, but amiodarone (CYP2C9) inhibitory interactions may not surface for months because of its long half-life. Although the enzyme inhibition effect occurs rapidly, the time to maximum DI or the manifestation of adverse effects will require the substrate to accumulate to the new steady-state serum concentration or toxic level. For example, with the cimetidine-theophylline interaction, maximum increases in theophylline concentrations are not seen for approximately 2 days, since this time is required for theophylline to reach a new steady state. Another example is phenytoin. With its concentration-dependent half-life, steady-state changes in phenytoin serum concentration can take days to occur. Of interest, if the half-life of the inhibitor drug is shorter than that of the inhibited drug, less time is required to revert to a lower steady state concentration after the inhibitor is stopped than is required to increase to new steady-state concentration when the inhibitor is started. This is because the half-life of the affected drug is shorter after discontinuation of the inhibitor.

CYP450 enzymes can be inhibited competitively or noncompetitively. In competitive inhibition, the inhibitor acts as an alternate substrate for the isoenzyme. Competitive inhibition depends on the affinity of the substrate for the enzyme being inhibited, the concentration of substrate required for inhibition, and the half-life of the inhibitor drug. In the case of non-competitive inhibition, the

inhibitor inactivates the enzyme but substrate binding remains normal. The mechanism of inhibition may be an important consideration in determining the specificity of an inhibitor and the time course of interaction.

As with enzyme induction, enzyme inhibition also appears to be dose-related. Higher doses of inhibitor will result in greater inhibition, although some inhibitors may have maximal effect within their usual dosage range. Other factors that can alter enzyme inhibition are genetic polymorphism, age, concurrent therapy with an inducer or inhibitor and the presence of hepatic disease.

It appears that the elderly are at a greater risk from enzyme inhibition interactions. The increased risk is probably as a result of age-related decreases in drug clearance and the reduced ability of elderly patients to withstand the insult of the DI. Another contributing factor to the significant of enzyme inhibition is the hepatic extraction ratio of the affected drug. In general, systemic clearance of low-extraction ratio drugs is expected to be affected to a greater extent than that of high extraction ratio drugs. However, with high-extraction-ratio drugs with significant first pass metabolism, it is well known that significant changes in oral absorption can occur in the presence of inhibitory drugs. The example of low-extraction-ratio drugs are theophylline, phenytoin and warfarin whereas the example of high extraction ratio drugs with significant first pass metabolism is propranolol and lidocaine. (39)

This interaction, enzyme inhibition, usually produces an increase in serum drug concentration, resulting in a possible augmentation of both the pharmacologic and toxic effect of the object drug. Clinically significant interactions will be most frequent with those drugs that have a narrow therapeutic index and when the serum level is near the upper end of the therapeutic range. In contrast, if the drug is a pro-drug, metabolic activation by enzyme inhibition may be too slow and resulting in low level of active drug, which led to decrease of therapeutic efficacy. When an enzyme inducing drug is coadministered with an enzyme inhibitor, the effect of the inhibitor appears to predominate and effect of the inducer is attenuated.

There are many clinically important examples of enzyme inhibition DIs. Stereospecific DIs involving warfarin metabolism are most clinically significant when the greatest effect occurs with the more potent s (-) enantiomer. Erythromycin and other macrolide antibiotics can inhibit the metabolism of astemizole

and terfenadine, increasing the serum concentration of the antihistamines as well as the risk of life-threatening cardiotoxicity. Cisapride and other drugs known to be metabolized in the hepatocyte where cisapride is also metabolized, i.e.,the P4503A4 system such as ketoconazole and macrolide antibiotics can produce a prolonged QT interval associated serious cardiac arrhythmias of the ventricular type and fatalities. (46) Isoniazid inhibits the hepatic metabolism of phenytoin, producing an increase in serum phenytoin levels and a corresponding disease in the pharmacologic and toxic effects of the drug. Phenytoin toxicity appears to be most significant in patients who are slow acetylators of isoniazid.

4. Altered excretion (22, 24, 39)

Most renal excretion DIs involve reduced excretion of one drug by another, leading to increased plasma levels and possible toxicity. Although some mechanisms of drug-induced alteration in renal excretion have been elucidated, in many cases the precise mechanism is unknown. Some drugs are excreted by the kidneys by active tubular secretion. When a patient receives two drugs that are actively secreted by the same process, one or both drugs may interfere with the renal elimination of the other. Examples of drugs, which interact by this mechanism are amphotericin B, cephalosporins, methotrexate, NSAIDs, penicillins, probenecid, salicylates, and thiazides. Probenecid reduces the excretion of penicillin and other drugs by successfully competing for an excretory mechanism, thus, the “loser” (penicillin) is retained. But even the “winner” (probenecid) is also later retained because it is passively reabsorbed further along the kidney tubule.

Another mechanism by which drugs can alter renal excretion is through alteration of the urinary pH. For example, alkalinization of the urine reduces ionization of drugs that are weak bases. As a consequence, lipid solubility and reabsorption of drug from the renal tubule into the blood stream are increased as is the plasma drug concentration. Examples of weak bases that are affected by changes in urinary pH are quinidine, methadone, and many sympathomimetics (e.g., pseudoephedrine and amphetamines). The opposite is true for drugs that are weak acids (e.g., salicylates); urinary alkalinization enhances renal excretion and reduces

plasma levels. Fortunately, relatively few commonly used drugs undergo pH-dependent renal excretion, so this is not a common mechanism for adverse DIs.

Alteration in kidney blood flow is also one of many mechanisms involving renal excretion process. The flow of blood through the kidney is partially controlled by the production of renal vasodilatory prostaglandins. If the synthesis of these prostaglandins is inhibited by NSAIDs, the renal excretion of lithium is reduced and its serum levels rise as a result.

A number of drugs are excreted in the bile, either as unchanged or conjugated form to make them more water soluble. Some of the conjugates are metabolized to the parent compound by the gut flora which are then reabsorbed. This recycling process prolongs the stay of the drug within the body, but if activity of the gut flora is decimated by the presence of an antibiotic, the drug is not recycled and is lost more quickly. This may possibly explain the rare failure of the oral contraceptives which can be brought about by the concurrent use of penicillins or tetracyclines.

Finally, some drugs can produce nephrotoxicity, thus reducing the renal elimination of other drugs eliminated by glomerular filtration. For example, a patient on chronic digoxin therapy who develops aminoglycoside-induced renal failure is likely to develop marked increases in digoxin serum concentrations. Other drugs that often produce nephrotoxicity include amphotericin B and pentamidine.

III. Determining clinical significance of DIs (1, 22, 39, 45)

Many patients may receive potentially interacting drugs without evidence of an adverse effect. It has not been possible to distinguish clear-cut characteristics that determine who will or will not experience an adverse DI. The clinical manifestations of a DI are highly situational. There are many factors, which can affect the clinical outcome of DIs. Therefore, to monitor DI, pharmacist should assess these factors in individual patient. These factors include:

A. Order of administration

The patient is stabilized on the precipitant drug when the object drug is started. In this instance, no interaction may be observed unless the precipitant drug is discontinued. If a patient is receiving quinidine chronically and is then started on therapy with digoxin, digoxin is titrated in the presence of quinidine and appropriate digoxin level will be achieved even if the prescriber is unaware of the interaction. Of course, there is the danger that subtherapeutic digoxin will occur if quinidine is later discontinued. In contrast, if a patient is receiving the object drug chronically and is then started on therapy with precipitant drug, clinical manifestation of DI more often occurs than the prior instance because precipitant drug affects pharmacokinetic or pharmocodynamic of object drug.

B. Duration of therapy

In patient receiving digoxin who is then given quinidine, it takes approximately one week for serum digoxin concentration to reach a new steady state. If quinidine is discontinued after two days of treatment, digoxin serum concentration, although somewhat increased, may not reach the toxic range.

C. Adequate dose

Many DIs are dose-related. For example, the dose of quinidine is important in determining magnitude of the increased serum digoxin concentrations. Quinidine doses of ≤ 500 mg/day tend to produce relatively small increases in serum digoxin concentration. High-dose salicylates (e.g., aspirin > 3 g/day) antagonize the uricosuric action of probenecid, but occasional low doses do not. Common drugs with dose-related to affect the clinical manifestations of DIs are cimetidine, fluconazole, isoniazid, and verapamil.

D. Preexisting patient status

Preexisting patient status may determine the observability of a DI. Two important factors that may play a role in whether a patient develops evidence of an adverse experience because of a DI are the current serum level of the object drug and the individual's responsiveness to enzyme induction or inhibition. If the object's drug

blood level is in the upper therapeutic range, a moderate decrease in blood level in response to an enzyme inducer would probably result in a new level still within the therapeutic range. However, even a mild response to an enzyme inhibitor is likely to increase the drug level into the toxic range. This is complicated by the variation in individual responsiveness to an enzyme inducer or inhibitor.

E. Other drugs taken by the patient or multiple drugs

Example is in patient who is receiving chronic therapy with phenytoin and phenobarbital for seizures then quinidine is added to digoxin therapy. Since hepatic metabolism of quinidine is enhanced by enzyme induction, serum quinidine levels are often quite low in a patient receiving phenytoin and phenobarbital. Thus, the quinidine-induced increase in serum digoxin concentration is small. If the enzyme inducer is stopped in this situation, the rise in quinidine serum concentration may then result in considerable increase in serum digoxin concentration. This sequence of events has been observed clinically.

F. Variability in patient response

The factors listed below account for some of the variability.

1. Age: The very young and the elderly may be at increased risk for interactions. Studies indicate that ≥ 25% of all prescription drugs dispensed are prescribed to elderly patients; elderly patients also use over-the-counter medications extensively. Furthermore, elderly patients may have other chronic diseases or decreased organ function (e.g., renal, hepatic). However, regardless of age, monitor drug therapy more closely in any patient with decreased organ function should be performed.

2. Genetics: For example, the toxicity seen with the inhibitory effect of isoniazid on the metabolism of phenytoin appears to be most significant in slow acetylators of isoniazid.

3. Disease States: Disease states (e.g., impaired renal function, hepatic dysfunction, hypoalbuminemia) may influence the response to various drugs used concurrently.

4. Alcohol Consumption: Acute alcohol intolerance (disulfiram reaction) has occurred in patients consuming alcohol while taking other drugs, including cefamandole, cefoperazone, cefotetan, moxalactam, and metronidazole. Chronic alcoholism may cause changes that affect drug metabolism, primarily enzyme induction.

5. Smoking: Smoking increases the activity of drug-metabolizing enzymes in the liver. Smoking stimulates the metabolism of theophylline and mexiletine. Smokers may require larger doses of these drugs to maintain therapeutic serum levels.

6. Diet: Diet can affect drug absorption (e.g., milk and tetracycline), action (e.g., tyramine containing foods and MAOIs), and elimination (e.g., protein diet and urinary pH).

7. Environmental Factors: Environmental factors (e.g., some pesticides) may alter the effects of liver metabolizing enzymes.

IV. Clinical management of patient at risk (22)

Once a patient is assessed to be at risk for a DI, pharmacist must take the appropriate precautions to minimize the likelihood of an adverse consequence. The management may differ depending upon the type of DI, Table 9 shows the different types of DIs with their management.

Table 9. Management of different types of interactions.

Type of Interactions	Management	Example
A. Contraindicated combination	Avoid using the combination	MAOI + Fluoxetine (Never use together)
B. Interaction easily circumvented	Take necessary steps to circumvent interaction	Ciprofloxacin + sucralfate (Give ciprofloxacin 2 hr before sucralfate)
C. Alternative drug available with lower risk of interaction	It is generally preferable to use the alternate drug	Cimetidine + warfarin (Use H_2-receptor antagonist other than cimetidine)
D. Interactions that do not fall into categories A, B, or C	Assess risk to patient and take precautions to avoid adverse outcome	Antithypertensive + NSAID (monitor blood pressure; adjust doses as needed)

V. Method of detecting DIs

Detection of DI is an essential role of pharmacist. Many DI alerting systems have been developed in hospital setting and pharmacist can utilize these methods to screen DIs. These methods can be classified into 2 types, one is detection by manual or non-computerized method and the other is by computer software program. (14)

A. Non- computerized screening method

For non-computerized method (6), Block (47) proposed a checklist of factors that, when asked of the patient, would help the pharmacist estimate an individual patient's susceptibility to DIs. Whiting et al (48) developed a disc system for alerting prescribers and pharmacists, and Hanstan (49) developed a wall-chart system with a reprint library to help pharmacists screen for potential DIs. Other methods are daily review of patient medication profile to screen the selected DI pairs which are chosen to be monitored in DI monitoring service followed by pharmacist intervention, by using drug interaction alert (DIA) card, (18) and chart reviewing with information resource of DI during patient care round. (8-10)

For detecting DI, pharmacist needs a good reference book as a back up source of information. (50) Several references are recommended such as Drug Interaction Facts, Drug Interactions & Updates, Drug Facts and Comparisons, USP Drug Information volume I, Drug Information Handbook, AHFS Drug Information, and Evaluation of Drug Interactions. (51) The latter publication is prepared by the American Pharmaceutical Association in cooperation with the American Dental Association, American Medical Association, American Society of Hospital Pharmacists, Food and Drug Administration, and the National Library of Medicine. The book, therefore, represents the opinions of many health professionals. (50)

B. Computerized screening method

Detecting DI by using computer software program is another detecting method. (14) As the number of reported drug-drug incompatibilities rapidly increase, card files and chart systems become voluminous, and monographs require constant revision. The problem of assimilating and retrieving the newly available information

quite naturally lead to the use of the computer, a tool that is increasingly used for other functions in the hospital and in the pharmacy. (6)

From reviewing of the history of the development of DI screening program by Jankel (6), it was found that by late 1970s many commercial computer programs for screening DIs had been developed, and a 1982 article by Swanson et al (52) identified 22 out of the 30 currently available hospital pharmacy computer systems that offered DI screening as a standard option. Although several studies reported that these programs were able to detect potential DIs, only one study tried to determine whether detection and follow-up of potential DIs were improved by pharmacists' use of computer systems. In that study, Kirking et al (53) found that users of one of two computer systems detected and followed up on interactions more frequently and were more likely to report knowledge of DIs than nonusers. Frequencies of DIs and other related measures reported by user of the second system, however, were similar to those for pharmacists not using computers. The authors offered possible explanations for the differences observed in the two systems such as dissimilarities in the manner in which a pharmacist is informed of the DIs and referred to references, and the comprehensiveness of each program's knowledge base. They concluded that "general statements cannot be made about the effect of computer use on DI detection".

From the result of a survey evaluating the method that pharmacy department uses to manage DIs (14), it was found that using DI computer software programs may resulting in improved detection of DIs. However, over reliance on computer programs to identify interactions also is not advisable. Some programs designed to identify DIs list all possible interactions, forcing pharmacists to manually override alerts and increasing the chance that important interactions will be overlooked. In addition, these programs often are not frequently updated. Furthermore, although some programs rank possible interactions by severity, such rankings tend to be subjective. (54)

VI. Detection of DIs : A review of the study

There are many studies that had been performed to monitor DIs. These studies used various tools to detect DIs. These tools can be divided into two methods as described previously, non-computerized screening method and screening by computer software program. Several studies monitored DIs in various setting and reported incidence of DI whereas other studies implemented the DI monitoring service/program and determined its effectiveness by reporting the number of detected DIs, the interventions and the acceptance of physicians and nurses.

Table 10. Examples of DI studies.

Ref No.	Patients or setting (duration of study)	Methods for detecting DIs	Interventions	Results
8	990 patients who were admitted in female medical ward	Non-Computerized: clinical pharmacist daily reviewed patient's charts	-	The incidence of total DIs was 13.5%, possible DIs was 11.4% and actual DIs was 2.1%
10	450 petients who were admitted in medical wards (6 months)	Non-Computerized: clinical pharmacist daily reviewed patient's charts	-	The incidence of potential DIs was 50% and actual DIs was 0.9%
9	Patients who were admitted in medical ward, 528 patients in phase I and 497 patients in phase □ (3 months in each phase)	Non-computerized: clinical pharmacist daily reviewed patient's charts	- Providing an official lecture on DI, handout of lecture and portable chart to medical residents between phase I and phase II of study - Verbal intervention during phaseII period.	- The incidence of total, possible and actual DIs in phase I and phase II was 19.697, 17.803 and 1.894 VS 15.895, 15.090 and 0.805%, respectively. - The incidence of total and actual DIs were lower in phaseII.

Table 10. Examples of DI studies (Cont.).

Ref No.	Patients or setting (duration of study)	Methods for detecting DIs	Interventions	Results
18	IPD patients (6 months)	Non-computerized: pharmacists evaluated for selected potential DIs	Drug interaction alert (DIA) card to physicians or nurses	- 645 potential drug-drug and drug-food interactions were identified. - 328 of 645 DIA cards were reviewed for the effect of DIA cards: 34% cards dispensed to nurses and 82% cards dispensed to physician resulted in some forms of action.
19	IPD patients (13 months)	Non-computerized: pharmacists evaluated for 13 selected potential DIs	Informed physicians of potential DIs by placing alert forms on the front of patient's charts	- 477 possibles DIs were notified - 211 were review for follow up data. - Followed up physician action was taken in 84% of indentified cases.
55	1,004 IPD patients (43 days)	Computerized software program	-	The incidence of total potential DIs and actual DIs were 7.7% (77 of 1,004 patients) and 0.7% (7 of 1,004 patients), respectively.
17	IPD patients	Computerized software program	-	About 9% of DIs were detected per patient day or approximately 35 DIs detected per day. There were classified as follows, 29.8% major, 27.5% moderate and 42.6% minor.
56	100 patients received oral ciprofloxacin and cation at the same time (190 days)	Computerized program and identified by clinical pharmacist	Oral and written interventions to nurses	- 49 written and 51 oral interventions were performed to nurses - The interventions was accepted in 88% of cases, not accepted in 8 cases (5 written and 3 oral) and unknow in 4 cases

Table 10. Examples of DI studies (Cont.).

Ref No.	Patients or setting (duration of study)	Methods for detecting DIs	Interventions	Results
21	119 patients with four potential clinically significant DIs with coumarin derivatives	Computerized program and identified by pharmacist	In study group (60 patients), patient's profile with interacting drugs, DI information and questionnaire were informed to physicians. In control group (59 patients), no intervention was performed	- Over 75% of responding physicians would like to see the program expended to other clinically significant DIs. - Physicians informed with the information made a significantly greater number of drug therapy changes than those not informed
16	IPD patients (10 weeks)	Computerized software program	- Contacted with prescribers - Contacted with ward pharmacist, nurse and patient	- The prescribers were contacted on 8 occasions (2% of interactions and led to one drug change and one dose adjustment - One dose adjustment and seven patients were monitored carefully after the contact
57	IPD patients (1 year)	Computerized software program screening for DIs level 1 and 2	Pharmacists taken action such as by printing notice for physicians, straggering drug administration time and calling physicians to make therapy changes	- 9,526 resulted in an computer automatic screen notice - pharmacist documented making intervention 1,713 (18%) occasions - All level 1 interactions had appropriate action and documentation attached (16 times)

Table 10. Examples of DI studies (Cont.).

Ref No.	Patients or setting (duration of study)	Methods for detecting DIs	Interventions	Results
58	IPD patients (excluding the pedriatic unit) (100 days)	Computerized softwere program	Written DI reports and placed in the patient's chart to inform physician	- 1,219 potential DIs per 20,260 patient days - 116 of total detected DI were potentially clinical significant and physicians responded positively to 82% of the DI reports
15	927 IPD patients (3 months)	Computerized softwere program for screening 41 selected potential DIs	- Notified physicians immediately by telephone - Placed warning notice in the physician's mailboxes	- 1,004 potential DIs were detected - Changing in drug dosage were made in 44% of DIs, and in 75%, patients were monitored for the development of adverse clinical effects

VII. Some clinically significant DIs.

Pharmacists should have a mental list of several drugs which are involved in clinically significant DIs and pharmacists should look closely at when they receive an order to initiate or discontinue these drugs from their patients. Interactions frequently occur with drug with a narrow therapeutic index. Often, these are medications that require blood level monitoring, such as theophylline, digoxin and anticonvulsants. A few drugs are involved in so many potentially serious DIs. These include warfarin and cyclosporin. Cytochrome P450 enzyme inhibitors and inducers are often implicated in DIs. This topic summarizes potential clinically significant DIs involving the alert drugs (theophylline, digoxin, phenytoin, warfarin and ciprofloxacin) using in this study. These DIs are listed in table 11-15.

Table 11. Clinically significant DIs with theophylline (1, 30, 37, 59, 60).

Precipitant drugs	Potential result	Implications for management
Cimetidine* Fluvoxamine	Significantly increased theophylline plasma concentrations with possible toxicity	Avoid these combinations, use ranitidine instead of cimetidine or an alternative antidepressant for fluvoxamine such as fluoxetine. If these agents must be given patient should be monitored for altered theophylline response and theophylline serum levels. The dose of theophylline may need to be adjusted.
Allopurinol Amiodarone Clarithromycin* Contraceptives, oral Diltiazem Disulfiram Erythromycin* Felodipine	Increased theophylline plasma concentrations. Toxicity may result if concentrations already in upper therapeutic range.	Avoid these combination, if possible. Otherwise, monitor plasma theophylline concentrations and reduce dose accordingly (about 25% reduction may be needed with erythromycin)

Table 11. Clinically significant DIs with theophylline (Cont.).

Precipitant drugs	Potential result	Implications for management
Fluoroquinolones (Ciprofloxacin*, enoxacin, norfloxacin, olfloxacin and pefloxacin) Interferon-α Isoniazid Pentoxifylline Propranolol* Tacrine Thiabendazole Ticlopidine Troleandomycin Verapamil Carbamazepine Isoproterenol Phenobarbital Phenytoin Rifampicin* (and other enzyme-inducing drugs including tobacco)	Decrease theophylline plasma concentrations	Larger than normal doses of theophylline may be needed. Monitor plasma theophylline concentrations and adjust does accordingly

* Alerting DIs included in DI monitoring service in this study. For more detail, see Appendix I.

Table 12. Clinically significant DIs with digoxin (1, 30, 37, 59, 62, 63).

Agents	Alteration / Management
• Aluminium hydroxide gel Aluminium hydroxide-magnesium hydroxide compounds, Activated charcoal, Cholestyramine, colestipo, Kaolin-pectin, dietary fiber Metoclopramide Neomycin, Sulfasalazine	Reduces gastrointestinal absorption, which may be prevented by administering digoxin 2 hr. before or 2 hr. after these agents. Digoxin plasma level may decrease by increasing gastrointestinal motility by metoclopramide, which may be prevented by monitoring therapeutic response to digoxin or digoxin serum levels. The dose of digoxin may need to be increased.
• Antibiotics (e.g.,erythromycin*, clarithromycin*,fluoroquinolones, tetracyclines; by inhibiting gut flora in select patients)	Increases absorption which may require a reduction in digoxin doses, necessitating attention to serum digoxin levels
• Verapamil*, diltiazem (moderate)	Reduction in renal excretion and non-renal clearance, increased inhibition of P-Glycoprotein digoxin transporter and a reduction in volume of distribution require reduced digoxin doses and closer attention to serum digoxin levels.
• Amiodarone* propafenone	Decreases renal and non-renal clearance of digoxin, increased inhibition of P-Glycoprotein digoxin transporter, may increase digoxin bioavailability and displace digoxin from tissue stores, requiring reduction of digoxin dose and close attention to serum digoxin levels.
• Quinidine	Reduces renal excretion, non-renal clearance, volume of distribution, tissue binding of digoxin and increases inhibition of P-Glycoprotein digoxin transporter cause a significant increase in serum digoxin levels; these effects necessitate routine monitoring of digoxin serum levels and 50% reduction in digoxin dose

Table 12. Clinically significant DIs with digoxin (Cont.).

Agents	Alteration / Management
• Spironolactone, triamterene	Reduction in renal tubular secretion of digoxin may require a reduction in digoxin doses and closer attention to serum digoxin levels
• Potassium-losing diuretics (thiazides, furosemide, etc.) Amphotericin B	Reduced potassium levels predispose patients to digoxin toxicity; serum digoxin levels and clinical effect must be closely monitored routinely
• Propylthiouracil*, methimazole*	Increase digoxin blood levels by reducing thyroid hormone. Hyperthyroid patients may require a reduce dose of digoxin if they become euthyroid.
•Cyclosporin Itraconazole Omeprazole	Increase plasma concentration of digoxin. Monitor plasma digoxin concentrations and adjust dose accordingly.

* Alerting DIs included in DI monitoring service in this study. For more detail, see Appendix I.

Table 13. Clinically significant DIs with phenytoin (1, 30, 41, 59, 64-66).

Agents	Potential Result	Implication for management
Dexamethasone* Methyprednisolone* Prednisolone*	Enhances steroid metabolism. Efficacy of steroid reduced with increased dose requirment	Increase corticosteroid dosage needed, particularly with the longer acting steroid (e.g. dexamethasone). A doubling of the usual steroid dosage may be necessary; careful follow up with further adjustments according to clinical response is essential.
Theophylline*	Decreases theophylline plasma concentrations	Larger than normal doses of theophylline may be needed in epileptics patients. Monitor plasma theophylline concentrations and adjust dose accordingly.
Trimethoprim*	Increase serum phenytoin concentration producing an increase in the pharmacologic and toxic effect of phenytoin in some patients	Monitor for phenytoin serum concentrations and observe the patient for phenytoin toxicity. Tailor the phenytoin dosage as needed

Table 13. Clinically signiticant DIs with phenytoin (Cont.).

Agents	Potential Result	Implication for management
Amiodarone*	Increased plasma phenytoin concentrations	Monitoring plasma phenytoin concentrations when amiodarone added to stable phenytoin regimen
Antacids Sucralfate	Significant reduction in plasma phenytoin concentrations in some patients	Space administration of phenytoin and either antacids or sucralfate as much as possible, and by at least 2 hours
Chloramphenical	Marked increase in plasma concentrations of phenytoin	Avoid use of chloramphenicol, or it essential, monitor plasma concentratiers of phenytoin and adjust dose accordingly
Cimetidine* Fluconazole* Erythromycin Clarithromycin	Marked increase in plasma phenytoin concentrations (Generally within 1 week)	Monitor plasma phenytoin concentrations and adjust dose accordingly; or substitute ranitidine, famotidine or nizatiding (no significant interaction reperted) for cimetidine; or Consider alternative of antiepileptic drugs.
Diazoxide (oral)	Mutual antagonism. Marked decrease in plasma concentration of phenytoin Hyperglycaemic effect of diazoxide antagonised	Avoid this combination
Dicoumarol	Marked increase in plasma concentration of phenytoin when dicoumarol added	Avoid this combination; subsitute warfarin
Disulfiram	Marked increase in plasma concentration of phenytoin in many patients	If possible, avoid this combination; or monitor plasma concentrations of phenytoin and reduce dose if necessary
Isoniazid*	Marked increase in plasma concentrations of phenytoin in some patients who are slow acetylators of isoniazid	Monitor plasma concentration of phenytoin when isoniazid added to stable phenytoin regimen, and reduce dose if necessary
Nutrient formulae (for nasogastric feeding)	Decreased plasma phenytoin concentrations by up to 75%	Monitor plasma phenytoin concentrations closely when commencing ceasing or changing nutrient formulae. Plasma phenytoin concentrations may be better maintained by giving a single daily dose during a period when enteral feeding is not taking place, such as at night

Table 13. Clinically signiticant DIs with phenytoin (Cont.).

Agents	Potential Result	Implication for management
Phenobarbital	Variable effect on plasma phenytoin concentrations also dependent on dosage; occasionally a marked increase may occur on adding phenobarbital or after its withdrawal (substrate competition for metabolism occurs immediately phenobarbital is started but a more slowly developing enzyme induction reverses this effect)	Monitor plasma concentrations of phenytoin whenever phenobarbital is added to a stable phenytoin regimen or if phenobarbital is withdrawn
Phenylbutazone	Maked increase in plasma concentrations of phenytoin in some patients	Avoid this combination. Substitute another NSAID such as ibuprofen indomethacin or naproxen
Rifampicin	Decreased plasma phenytoin concentrations	Monitor plasma phenytoin concentrations dosely when rifampicin is commenced or ceased in patients on a stable-phenytoin regimen
Sulphonarnides (sulfaphenazole sulfamethizole)	Marked increases in plasma concentrations of phenytoin in a few patients	Avoid this combination Substitute another antibacterial drug fexcept chloramphenicol)
Valproic acid	Marked but temporary increase in the free (unbound) plasma phenytoin concentration and in drug effects	Monitor plasma concentrations of phenytoin when valproic acid added to stable regimen. Free phenytoin concentration will initially be higher than expected for a given total plasma phenytoin concentration. Monitor for signs of phenytoin toxicity. An initial temporary reduction in phenytoin dosage may be necessary
Vigabatrin	Decreased plasma phenytoin concentration by 30% over 4 weeks	Monitor plasma phenytoin concentrations when commencing ceasing or altering dosage of vigabatrin. Note: Most clinically significant interactions with phenytoin become manifest within 1 to 6 weeks after addition of the other drug. Interactions with phenytoin may not

Table 13. Clinically signiticant DIs with phenytoin (Cont.).

Agents	Potential Result	Implication for management
		always be detrimental. Modest elevation of a low plasma concentration of phanytoin may actually improve seizure control. However, a marked increase in the plasma concentration increases the risk of ioxicity

* Alerting DIs included in DI monitoring service in this study. For more detail, see Appendix I.

Table 14. Clinically significicant DIs with warfarin (1, 59, 64, 67-69).

1. Drugs which increase anticoagulant action

Agents	Potential result	Implication for management
Allopurinol	Very variable increase in warfarin effect, ranging from nonsignificant to life-threatening increases in effect	Monitor INR closely after addition of allopurinol to a stable warfarin regimen
Amiodarone *	Marked potentiation of effect to warfarin	Avoid combination. Reduce dose of warfain. Monitor INR closely for several weeks after amiodarone started until control is re-established
Aspirin * NSAIDs	Increased risk of bleeding due to effect on platelet function and damaging action on gastric mucosa. No effect on degree of hypoprothrombinaemia with NSAIDs or at low doses of aspirin, although high dose of aspirin can produce hypoprothrombinaemia in their own right	Where possible, avoid this combination; substitute paracetamol. If aspirin or NSAIDs are essential, consider adding a cytoprotective agent such as misoprostol or cyclooxygenase-2 inhibitor, monitor INR and observe for the early signs and symptoms of bleeding especially from the GI tract
Azapropazone Oxyphenbutazone Phenylbutazone	Predictably and markedly potentiate effect of warfarin (by 50 to 70 %)	Avoid this combination. Substitute another NSAID, e.g. indomethacin, ibuprofen or naproxen (do not effect warfarin kinetics or anticoagulant control but may still increase risk of bleeding due to antiplatelet aggregating activity or risk of gastrointestinal bleeding)
Cephalosporins	Some cephalosporins (cefamandole, cefoperazone, cefotetan) markedly potentiate warfarin effect	Monitor INR closely where a cephalosporin is added to a stable warfarin regimen
Chloramphemicol Erythromycin Nalidixic acid	Potentiation of effect of warfarin	Monitor INR closely and adjust dosage of warfarin accordingly or select alternative antibiotic
Cimetidine *	Variable degrees of potentiation of warfarin effect, ranging from minimal to marked	Avoid this combination. Use ranitidine, famotidine or nizatidine instead
Ciprofloxacin Enoxacin Norfloxacin	Potentiation of effect of warfarin	Monitor INR closely and adjust dosage of warfarin accordingly or select alternative antibiotic
Clofibrate Gemfibrozil Lovastatin	Markedly potentiate effect of anticoagulant in many patients	Reduce dose of coumarin (e.g. by 25 or 30 % with warfarin) when clofibrate or lovastatin added. Monitor INR daily for a few days. Consider simvastatin as an alternative lipid-modifying agent (no reported interaction)
Cotrimoxazole* Sulfinpyrazone Other sulphonamides	Potentiation of effect of warfarin	Monitor INR closely and adjust dosage of warfarin accordingly or select alternative antibiotic

Table 14. Clinically significicant DIs with warfarin (Cont.).

Agents	Potential result	Implication for management
Dextroproproxyphene + paracetamol	Potentiation of effect of warfarin	Avoid this combination. Substitute paracetamol alone
Disulfiram	Potentiation of effect of warfarin	Monitor INR closely and adjust dosage of warfarin accordingly
Fluoxetine Fluvoxamine	Potentiation of effect of warfarin	Avoid this combination or monitor INR closely when adding these drugs to a stable warfarin regimen. Paroxetine appears to have less potential for interaction, although clinical experience is lacking.
Imidazole antifungals (ketoconazole*, fluconazole*, miconazole, itraconazole*)	Potentiation of effect of warfarin in some patients	Anticipate need to adjust dosage of warfarin if imidazole therapy is commenced, ceased or dosage is altered. Monitor INR closely.
Metronidazole*	Markedly potentiates effect of warfarin	Reduce dose of warfarin. Monitor INR for a few days or more, or substitute alternative antimicrobial agent
Omeprazole	Potentiation of effect of warfarin in some patients	Monitor INR closely after commencing, ceasing or changing doses of omeprazole
Propafenone	Potentiation effect of warfarin	Monitor INR when propafenone is commenced or ceased
Quinidine	Markedly potentiates effect of warfarin in some patients	Avoid this combination. Substitute procainamide or sotalol
Tamoxifen	Marked potentiation of warfarin effect in some patients	Monitor INR closely when tamoxifen is added to a stable warfarin regimen
Thyroid hormones*	Markedly potentiation effect of warfarin in virtually all patients	Reduce dose of coumarin (e.g. by one-third with warfarin) when thyroxine added. Monitor INR daily for a few days or more

2. Drugs which decrease anticoagulant action

Aminoglutethimide Mitotane	Marked decreases in effect of warfarin	Monitor INR closely and adjust dose of warfarin accordingly
Barbiturates Phenobarbital Primidone	Marked decrease in effect of coumarins (warfarin, dicoumarol, acenocoumarol) in many patients. Dose requirement may be increased many-fold (even up to 10x)	Avoid use of barbiturates as occasional hypnotics; substitute a benzodiazepine or consider use of behavioral or relaxation therapies. Barbiturates taken regularly as antiepileptics (i.e. in steady-state) do not affect anticoagulant control, unless the barbiturate is withdrawn or its dosage altered without modifying the dose of anticoagulant
Carbamazepine Dicloxacillin Nafcillin Sucralfate	Decrease in effect of warfarin	Monitor INR closely when these drugs are commenced, ceased or there is a change in dosage

Table 14. Clinically significicant DIs with warfarin (Cont.).

2. Drugs which decrease anticoagulant action (Cont.)

Agents	Potential result	Implication for management
Cholestyramine	Markedly reduces absorption of warfarin when given up to 3 hours after its administration	Give warfarin 2 or more hours before cholestyramine if possible, but monitor INR as an increase in dosage may still be required
Griseofulvin	Decrease in effect of warfarin in some patients	Monitor INR closely and adjust dose of anticoagulant carefully
Phenytoin	Changes in warfarin effect may be variable with an initial increase in effect followed by a decrease in effect from 7 to 10 days onwards	Monitor INR closely in the 4 weeks following addition of phenytoin to a stable warfarin regimen
Rifampicin	Marked decrease in effect of warfarin	Monitor INR and adjust dose of warfarin carefully, or avoid rifampicin in antituberculosis regimens (e.g. if compliance cannot be guaranteed). Note : Any adjustment of coumarin dosage should only be made on the basis of results derived from close observation of therapy and INR estimations over a period of time after the change

* Alerting DIs included in DI monitoring service in this study. For more detail, see Appendix I.

Table 15. Clinically significant DIs with quinolones (1, 41, 59, 70).

Drug name	Anticipated pharmacokinetic interaction	Anticipated pharmacodynamic interaction	Clinical management
Antacids* containing di- and trivalent cations	↓absorption of all quinolones		Separate doses by 2 hr, give quinlone first
Antiarrhythmics Class I,II,III		Theoretical potential for QTc prolongation	Uncertain significance. Use cautiously with quinolones that increase QTc interval
Caffeine	↑caffeine levels with certain quinnolones (enoxacin, ciprofloxacin, norfloxacin, trovafloxacin)		Unclear clinical significance
Cisapride		Theoretical potential for QTc prolongation and quinolones with similar effect	Unclear clinical significance; Use cautiously with quinolones that increase QTc interval
Cyclosporine	Case reports that CyA levels may ↑ with ciprofloxacin and norfloxacin	Possible ↑ nephrotoxicity effect	Unlikely to be clinically important
Didanosine standard tablet formulation	↓absorption of all quinolones		Separate doses by 2 hr, give quinolones first, or use enteric-coated didanosine
Iron* Calcium	↓absorption of all quinolones		Separate doses by 2 hr, give quinolone first
Macrolides (clarithromycin/ erythromycin)		Theoretical potential for QTc prolongation if used with quinolones with similar effects	Caution if used with quinolones that increase QTc interval
Multivitamins	Multivitamins with zinc cause a small ↓ absorption of all ciprofloxacin		Best to separate doses by 2 hr, give quinolone first
Sucralfate*	↓absorption of all quinolones		Avoid combination,or give quinolone 2 hr, before sucralfate
Theophylline*	↑Theophylline levels with certain quinolones (enoxacin, ciprofloxacin)		Ciprofloxacin is most likely to result in an interaction; most other quinolones safe such as olfloxacin, levofloxacin, sparfloxacin, gatifloxacin, trovafloxacin and moxifloxacin. The dosage of theophylline may need to be decreased in some individuals.
Tricyclic antidepressants		Theoretical potential for QTc prolongation	Caution if used with quinolones that increase QTc interval. Uncertain clinical significance.
Warfarin	Conflicting data		Monitor INR and PT when a quinolone is administered to patients receiving warfarin

CyA = cyclosporine; INR = International normalized ratio; PT = Prothrombin time; QTc = corrected QT interval; ↑ = increase; ↓ = decrease.

* Alerting DIs included in DI monitoring service in this study. For more detail, see Appendix I.

CHAPTER III
MATERIALS AND METHODS

Materials

1. Alerting drug interactions manual file for pharmacist (Appendix I)
2. Alerting drug interactions card (Appendix II)
3. Drug interaction record file (Appendix III)
4. Staff pharmacist's intervention form (Appendix IV)
5. Data collecting forms for patient's clinical data, alerting DI monitoring, pharmacist's intervention, physician or nurse acceptance and patient care process regarding DI after intervention (Appendix V)
6. Inpatient department (IPD) chart

Definition of terms

Drug interaction (1) defined as the phenomenon that occurred when the effects or pharmacokinetics of one drug were altered by prior administration or coadministration of a second drug. This study focused on drug-drug interactions which could develop adverse effect to patient.

Object drug (1) was the drug whose the activity was altered by the interaction.

Precipitant drug (1) was the drug that caused the altered activity of the object drug.

Potential drug interaction was drug interaction predicted from the pharmacological knowledge or pharmacokinetic basis which was documented in standard references.

Actual drug interaction was drug interaction actually occurred in patient, which was confirmed by any of the following; clinical signs and symptoms, laboratory investigation or physician's opinion. In cases of inconclusive evaluation, actual drug interactions would be confirmed by physician's opinion.

Staff pharmacists were pharmacists, working in inpatient pharmacy department, who had a responsibility to verify patient's medication profiles or check patient medication before dispensing.

Clinical pharmacist was a pharmacist who had a responsibility to prepare alerting drug interaction data, review patient charts of identified cases and determine the impact of this drug interaction monitoring service on the acceptance of physicians and nurses and patient care process. In this study clinical pharmacist was an investigator.

Alerting drugs were marked drugs that pharmacists had to recognize and used these drugs as a guide for screening of alerting drug interactions. In this study, alerting drugs were theophylline, digoxin, phenytoin, warfarin and ciprofloxacin. These drugs were selected based on any reason as follows;

1. Drugs which have narrow therapeutic index or involve in many potentially serious drug interactions.

2. Opportunity of drug interactions to occur in medical and surgical wards and rate of drug used in Bumrungrad Hospital during the study period.

3. Pharmacists' suggestion for drugs which involve in many serious drug interactions and are frequently dispensed in Bumrungrad Hospital.

4. Drug interactions reported in the previous survey study of potential drug interactions at Bumrungrad Hospital. (20)

Alerting drug interaction was drug-drug interaction between alerting drug and a second drug. In this study, thirty five alerting drug interactions were selected to be monitored in the drug interaction monitoring service.

Alerting drug interactions included in this service were selected based on at least one of the following specification:

1. Significance rating: especially significance rating 1 and 2. Based on the definition of Tatro (1), these ratings number are determined by the assessment of the severity and documentation of the interaction. In this study, significance rating 1 and 2 were defined as follows:

Significance rating	Severity	Documentation
1	Major	Established or probable
2	Moderate	Established or probable

Two degree of severity are defined as: (1)

- Major: The effects are potentially life-threatening or capable of causing permanent damage.
- Moderate: The effects may cause a deterioration in a patient's clinical status. Additional treatment, hospitalization, or an extended hospital stay may be necessary.

Two documentation levels were described as follows: (1)

- Established: Proven to occur in well-controlled studies.

An altered pharmacologic effect has been demonstrated in well-controlled human studies or

A pharmacokinetic interaction has been demonstrated in well-controlled human studies. An altered pharmacologic response is expected based on the magnitude of the kinetic effect; clinical observations support the occurrence of the interaction.

- Probable: Very likely but not proven clinically.

A pharmacokinetic interaction has been demonstrated in well-controlled studies. Based on the magnitude of the kinetic changes and the known plasma level-response relationship of the affected drug, an altered pharmacologic response will probably occur or

When controlled human experimentation is impractical, well-designed animal experiments confirm an interaction that is suggested by multiple case reports or uncontrolled studies.

2. Opportunity of drug interactions to occur in medical and surgical wards and rate of drug used in Bumrungrad Hospital during the study period.

3. Pharmacists' suggestion for drug interactions which are frequently detected in Bumrungrad Hospital.

4. Drug interactions reported in the previous survey study of potential drug interactions at Bumrungrad Hospital.

Mode of activity was the type of activity that staff pharmacist had to do when alerting drug interaction was identified. Mode of activity was classified into two types:

- Intervention by telephone: staff pharmacist intervened physician or nurse immediately by telephone and recorded necessary data in drug interaction record file

and staff pharmacist's intervention form when onset of the alerting drug interaction was rapid, with in 24 hours. (1)

- Record in file: staff pharmacist only recorded necessary data in the drug interaction record file when onset of the alerting drug interaction was delay, for a period of days or weeks. (1)

Methods

1. Study design

This study was designed as a prospective descriptive study.

2. Study population

All patients who were admitted or referred to seven medical and surgical wards (7A, 8A, 8C, 8D, 11A, 11B and 11C) were recruited in the study.

The data from the previous retrospective survey study of potential drug interactions at medical and surgical wards of Bumrungrad Hospital were used to calculate sample size. From previous study, pharmacist retrospectively reviewed patient's medication profile to screen for the potential DI in patients who were admitted in 5 medical and surgical wards. The study found that the detection rate of DI with significance rating 1 and 2 was 25.25%. The number of sample population was then calculated by the following formula.

$$n = \frac{Z^2_{\alpha} pq}{d^2}$$

Z_{α} = Z-statistics for confidence which is 95% or $\alpha = 0.05$, thus the value of Z_{α} is equal to 1.96

p = The DI detection rate by pharmacist with significance rating 1 and 2 which was 25.25% or 0.25

q = (1-p) = 0.75

d = the maximum permissible error = 0.0125% (5%p)

$$n = \frac{(1.96)^2(0.25)(0.75)}{(0.0125)^2}$$

$$n = 4,609.92$$

$$n \approx 4,610 \text{ persons}$$

3. Period of study

Preparation period: March 2001 to June 2001 (16 weeks)

Implementation period: Started from 10 July 2001

4. Procedures

4.1 Preparation period

4.1.1 Characteristics and incidence of DIs in inpatients of medical and surgical wards were studies by retrospective chart review.

4.1.2 Drug dispensing system and pharmacists' activities in inpatient pharmacy department were observed.

4.1.3 Workflow or procedure of the DIs monitoring service was developed and the roles of pharmacists in monitoring of DIs were identified.

4.1.4 Developed materials used in the service such as an alerting drug interactions manual file for pharmacist, alerting drug interactions card and data collecting form.

4.1.4.1 Alerting drug interactions manual file for pharmacist was prepared. (Appendix I)

Process of preparation was described in the following flow chart.

Thirty five clinically significant alerting drug interactions were selected to be monitored in this service based on; drugs which have narrow therapeutic index or involve in many potentially serious DIs, severity and documentation of the interactions, opportunity to occur and rate of drug used, pharmacists' suggestion or DIs reported in the previous survey study of potential DIs at Bumrungrad Hospital.

↓

All of alerting DIs were collected in tabulated format. In this DI table, staff pharmacists could easily detect the two interacting agents either by generic or trade name and followed the mode of activity when alerting DI was identified.

↓

Clinical pharmacist prepared the important data of each alerting DIs (i.e.

the effect and mechanism of the interaction and a recommendation on how to monitor or circumvent the interaction). In addition, original and involving articles of each alerting DI were cited and filed by a reference number.

↓

The important data of each alerting DIs were summarized into another table grouped by alerting drugs. The reference number in each alerting DIs was linked to the reference number in the reference file in which original and involving articles were kept.

↓

The alerting DIs manual file was placed in the inpatient pharmacy department, in the area where staff pharmacists verified patient's medication profile and checked patient's medication before dispensing for quick referal.

4.1.4.2 Preparation of the alerting drug interactions card. (Appendix II)

This card was designed for staff pharmacist's convenience. It contained necessary information such as all of alerting DIs grouped by each alerting drugs, effect and significance rating of each alerting DIs, person to be alert and mode of activity. So, staff pharmacists could use it anywhere they verified patient's medication profile or checked patient's medication.

4.1.4.3 Preparation of the drug interaction record file.(Appendix III)

This file was prepared for recording necessary information such as patient's name, room number, detected alerting DI, detected date and time and staff pharmacist's name who identified the alerting DI. In addition, the staff pharmacist's intervention form (Appendix IV) was also kept in this file for recording the result of staff pharmacist's intervention.

4.1.4.4 Development of data collecting forms. (Appendix V)

4.1.5 Implementation of drug interaction monitoring service was informed to pharmacists, physicians, nurses and other related health professionals.

All staff pharmacists attended inservice meeting to learn about the procedures of the drug interaction monitoring service and review about the principle of drug interaction and all of alerting DIs monitored in this service. Detail of implementing drug interaction monitoring service was informed to involving committees, physician and nurse's meeting and publicized in the pharmacy newsletter.

4.2 Implementation period.

Procedures of implementation of DIs monitoring service were described as follows:

4.2.1 Staff pharmacist's role to implement DIs monitoring service.

4.2.1.1 Staff pharmacists identified alerting DIs by using the alerting DIs card while they were verifying patient's medication profile or checking patient's medication before dispensing as a routine job.

4.2.1.2 When the alerting DI was identified, staff pharmacist recorded patient's name, hospital number, room number, interacting drugs, date and time of detection and pharmacist's name in the DI record file to avoid duplications of efforts to intervention by other staff pharmacists. Then staff pharmacist performed the activity as guided in mode of activity.

4.2.1.3 In case of detected alerting DI with rapid onset, mode of activity was to alert physician or nurse immediately by telephone. Staff pharmacist recorded necessary data in the drug interaction record file then alerted and recommended the physician or nurse how to manage the interaction immediately. After that, staff pharmacist recorded an acceptance of intervention in staff pharmacist's intervention form (Appendix IV) which was placed in the drug interaction record file. In addition, if the recommendation was changing time of drug administration, the time in a medication administration record (MAR) would be corrected by staff pharmacist.

4.2.1.4 In case of detected alerting DI with delay onset, mode of activity was recorded in file. Staff pharmacists only recorded all of necessary data as describe previously in the drug interaction record file.

4.2.2 Clinical pharmacist's role to implement the DI monitoring service.

4.2.2.1 Clinical pharmacist collected data and number of alerting DIs identified by staff pharmacists from the drug interaction record file and staff pharmacist's intervention form everyday.

4.2.2.2 Clinical pharmacist recorded patient's data which were patient demographic, prescriber data and necessary clinical data including relevant medications, relevant clinical signs, symptoms and laboratory results regarding the alerting DIs in the patient profile record.

4.2.2.3 In case of mode of activity was intervention by telephone, clinical pharmacist recorded acceptance of intervention from staff pharmacist's intervention form. If the intervention was accepted, clinical pharmacist observed whether physician or nurse done as their acceptance. If the intervention was not accepted, clinical pharmacist reviewed and evaluated each patient's specific clinical data and contacted the physician or nurse to repeat the intervention. Then clinical pharmacist recorded acceptance of intervention and observed whether physician or nurse done as their acceptance again.

4.2.2.4 In case of mode of activity was recording necessary data in file. Clinical pharmacist reviewed and evaluated each patient's specific clinical data and contacted the physician or nurse for intervention. Then clinical pharmacist recorded acceptance of intervention and observed whether physician or nurse done as their acceptance.

4.2.2.5 Clinical pharmacist monitored relevant clinical data regarding the effect of alerting DI until patient would be discharged. The intervention would be performed again if necessary. Workflow of DI monitoring service was illustrated in Figure 1.

5. Data collection

The data during the study period was collected as follows :

5.1 Demographic and clinical data of patient with alerting DI were recorded in patient's profile record.

5.1.1 Demographic data: name, hospital number, age, gender, weight, height, admission date, discharge date and length of stay.

5.1.2 Diagnosis/impression on admission.

5.1.3 Relevant medication data including drug prior admission and drug allergy

5.1.4 Relevant clinical signs, symptoms or laboratory results regarding the alerting DIs.

5.1.5 Prescriber data : The number of physician treated for each patient and characteristic of physician who prescribed alerting DI, single or multiple prescriber(s).

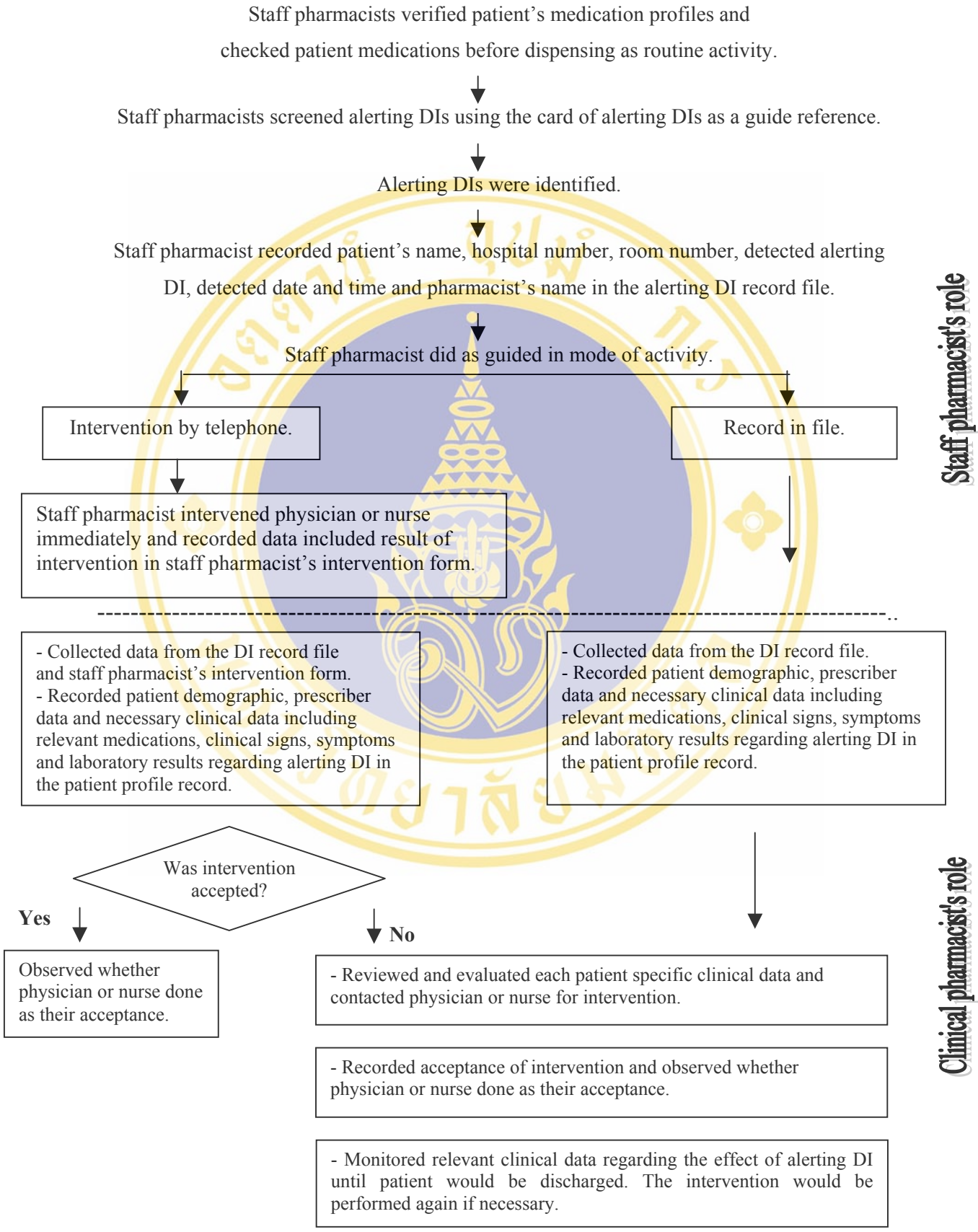

Figure 1. Workflow of drug interactions monitoring service.

5.2 Detection and intervention data of alerting DIs :

5.2.1 The number of detected DIs by staff pharmacists and clinical pharmacist in each day.

5.2.2 The number and category of staff pharmacist' interventions

Intervention by telephone, following data were collected from staff pharmacist's intervention form :

Name, hospital number, ward, detected DI, detection date and time, contacted person, recommendation and result of the intervention and detected pharmacist's name.

5.2.3 The number of clinical pharmacists' interventions.

5.3 Physician and nurse's acceptance to pharmacist's intervention :

5.3.1 The number and category of physician and nurse acceptance to staff pharmacist intervention.

5.3.2 The number and category of physician and nurse acceptance to clinical pharmacist's intervention.

5.4 Impact on patient care process data :

5.4.1 The number and type of action regarding DI after the interventions.

5.5 The number of actual and potential DIs

6. **Data presentation and analysis**

The data was analyzed by descriptive statistics and presented as follows :

6.1 Patient demographic data

6.2 DIs detection data :

6.2.1 The number and percentage of each detected alerting DIs.

6.2.2 The number and percentage of detected alerting DIs classified by alerting drugs.

6.2.3 The number and percentage of detected alerting DIs classified by significance rating, severity and mechanism.

6.3 Pharmacist's intervention data :

6.3.1 The number and percentage of staff pharmacists' interventions.

6.3.2 The number and percentage of clinical pharmacist's interventions.

6.4 Physician and nurse acceptance to pharmacists' interventions data :

6.4.1 The number and percentage of physician and nurse acceptance to pharmacist intervention.

6.5 Impact on patient care process data :

6.5.1 The number and percentage of type of action regarding DI after the interventions.

6.6 The magnitude of both actual and potential DIs

6.6.1 Incidence of actual and potential DIs

CHAPTER IV

RESULTS

The results of the study are presented in 4 main parts including demographic data, detection of alerting DIs both actual and potential DIs, pharmacist intervention and physician-nurse acceptance, and impact on patient care process regarding DIs.

Part I : Demographic data of patients

During 4 months of implementation period of DI monitoring service, 4,624 patients were admitted to 7 medical and surgical wards. All were monitored for DI. Sixty-eight patients who had the alerting DIs were identified by either clinical or staff pharmacists. Of these, 5 patients were admitted two times during the study period.

Of 68 cases, it was found that 61.76% (42 from 68 patients) were male and 38.23% (26 of 68 patients) were female (Table 16). The patients' ages ranged from 31 to 95 years with the mean$\pm$SD age of 65.29$\pm$15.16 years. The mean$\pm$SD length of hospital stay was 10.85$\pm$8.93 days with the minimum of 1 day and the maximum of 41 days. The average number (mean$\pm$SD) of active medical problems in these patients was 1.88$\pm$1.26 problems with the minimum of 1 problem and the maximum of 6 problems. Overall, 70 active medical problems diagnosed in all patients are showed in Table 17. The top three problems were cardiovascular (35.16%), neurologic (13.29%) and respiratory (10.94%) diseases, respectively. The average number (mean$\pm$SD) of medications prescribed while alerting DIs occurred was 9.23 $\pm$ 4.21 items with the minimum of 3 items and the maximum of 23 items. The average number of physicians treated for each patient was 3.12 persons (the minimum was 1 physicians while the maximum was 9 physicians).

Table 16. Demographic data of patients.

Characteristics	Number of patients (%)	Statistic value
Gender		
Male	42 (61.8)	
Female	26 (38.2)	
Total	68 (100)	
Age (years)		
≤ 59	22 (32.4)	Min 31 years
60-70	21 (30.9)	Max 95 years
71-80	12 (17.6)	Mean ± SD 65.29±15.16 years
81-90	12 (17.6)	Mode 68 years
≥ 91	1 (1.5)	
Total	68 (100)	
Length of hospital stay (days)		
≤ 5	22 (32.4)	Min 1 days
6-10	21 (30.9)	Max 41 days
11-15	5 (7.4)	Mean ± SD 10.85±8.93 days
16-20	9 (13.2)	Mode 4 days
≥ 21	11 (16.2)	
Total	68 (100)	
Number of active medical problems		
1	39 (47.6)	Min 1 problem
2	12 (14.6)	Max 6 problems
3	7 (8.5)	Mean ± SD 1.88±1.26 problems
4	7 (8.5)	Mode 1 problem
5	2 (2.4)	
6	1 (1.2)	
Total	68 (100)	
Number of medications prescribed while alerting DI occurred (items)		
2-4	8 (9.9)	Min 3 items
5-7	26 (32.1)	Max 23 items
8-10	19 (23.5)	Mean ± SD 9.23±4.21 items
11-13	18 (22.2)	Mode 6 items
14-16	6 (7.4)	
17-19	0 (0.0)	
≥ 20	4 (4.9)	
Total	81 (100)	
Number of physician per case (persons)		
1	7 (10.3)	Min 1 person
2-4	48 (70.6)	Max 9 persons
5-6	10 (14.7)	Mean ± SD 3.12 ± 1.64 persons
≥ 7	3 (4.4)	Mode 2 persons
Total	68 (100)	

Abbreviation : DI = Drug interaction, Min = Minimum, Max = Maximum

Table 17. Medical problems of patients upon admission.

Medical problems	Frequency (%)
Disorders of the cardiovascular system	45 (35.16)
Coronary artery disease	13
Atrial fibrillation	8
Congestive heart failure	6
Hypertension	6
Congestive heart failure with complication of pulmonary edema	3
Mitral regurgitation	2
Ischemic heart disease	2
Cardiomyopathy	1
Acute arterial occlusion	1
Mitral stenosis	1
Aortic regurgitation	1
Atrial flutter	1
Neurologic disorders	17 (13.29)
Head trauma	3
Brain metastasis	2
Old cerebrovascular accident	2
Subdural hematoma	1
Cerebral emboli	1
Malignant meningeal	1
Transient ischemic attacks (TIAs)	1
Cerebral infarction	1
Pontine hemorrhage	1
Cerebrovascular accident	1
Ischemic stroke	1
Subarachnoid hemorrhage	1
Spinal cord compression	1
Disorders of the respiratory system	14 (10.94)
Chronic obstructive pulmonary disease	4
Asthma	2
Bronchitis	2
Infectious bronchiectasis	2
Pleural effusion	2
Upper respiratory tract infection	1
Aspiration pneumonia	1

Table 17. Medical problem of patients upon admission (cont.).

Medical problems	Frequency (%)
Endocrinology and metabolism	12 (9.38)
Diabetes mellitus	7
Dyslipidemia	2
Hypothyroidism	1
Adrenal insufficiency	1
Hypoglycemia	1
Oncology and hematology	11 (8.60)
Prostate hyperplasia	2
Lung cancer	2
Anemia	2
Cancer of bladder	1
Cancer of left distal ureter	1
Mantle cell lymphoma	1
Venous thrombosis	1
Bone metastases	1
Disorders of the gastrointestinal system	10 (7.82)
Gastroenteritis	2
Enterocolitis	1
Chronic hepatitis B	1
Perianal abscess	1
Hemorrhoid	1
Enteritis	1
Gastrointestinal bleeding	1
Gastritis	1
Diarrhea	1
Disorder of the kidney and urinary tract	7 (5.47)
Urinary tract infection	2
Chronic renal failure	1
Pyelonephritis	1
Renal insufficiency	1
Hyperkalemia	1
Chronic renal failure with complication of pulmonary edema	1

Table 17. Medical problem of patients up on admission (cont.).

Medical problems	Frequency (%)
Infectious diseases	2 (1.57)
Toxoplasmosis	1
Septicemia	1
Disorders of immune system, connective tissue and joints	1 (0.79)
Rheumatoid arthritis	1
Miscellaneous	9 (7.04)
Bone fracture	3
Digoxin intoxication	1
Fever	1
Positional vertigo	1
Acute confusion state	1
Electrolyte imbalance	1
Cataract	1
Total	128 (100.00)

Part II : Detection of alerting DIs data

During 4 months of study, 4,624 patients admitted to medical and surgical wards were monitored for alerting DIs. Of these patients, there were 68 cases presented with alerting DIs (67 cases with potential DIs and 1 case with actual DI). Therefore, the incidence of total alerting DIs, potential DIs and actual DI in this study were 1.47% (68 out of 4,624 patients), 1.45% (67 out of 4,624 patients) and 0.02% (1 out of 4,624 patients), respectively. In these 68 cases, eighty-one events of alerting DIs were detected. Eighty events were potential DIs and 1 event was actual DI.

All of alerting DIs detected by pharmacists are shown in table 18.

Table 18. All of alerting DIs detected by pharmacists.

Alerting DIs	Frequency	Percent
Digoxin-Amiodarone	16	19.75
Ciprofloxacin-Ferrous fumarate	13	16.05
Warfarin-Aspirin*	9	11.11
Phenytoin-Dexamethasone	9	11.11
Theophylline-Ciprofloxacin	7	8.64
Warfarin-Amiodarone	5	6.17
Ciprofloxacin-Antacids, Aluminium hydroxide	4	4.94
Ciprofloxacin-Sucralfate	3	3.70
Digoxin-Verapamil	3	3.70
Phenytoin-Amiodarone	2	2.47
Ciprofloxacin-Ferrous sulfate	2	2.47
Theophylline-Cimetidine	1	1.23
Phenytoin-Prednisolone	1	1.23
Phenytoin-Trimethoprim	1	1.23
Warfarin-Co-trimoxazole	1	1.23
Warfarin-Levothyroxine	1	1.23
Warfarin-Metronidazole	1	1.23
Warfarin-Phenobarbital	1	1.23
Warfarin-Rifampin	1	1.23
Total	81	100.00

* 1 out of 81 was actual DI

There were 19 types of alerting DIs found in this study. Digoxin-amiodarone was the highest alerting DIs (19.75%) while ciprofloxacin-ferrous fumarate (16.05%) and phenytoin-dexamethasone and warfarin-aspirin (11.11%) were the second and third most frequently events, respectively.

When focused on the alerting drugs that staff pharmacists used to identified alerting DIs, it was found that ciprofloxacin had the highest events of all alerting drugs (27.16%). The other alerting drugs were digoxin (23.46%), warfarin (23.46%), phenytoin (16.05%) and theophylline (9.88%), (Figure 2).

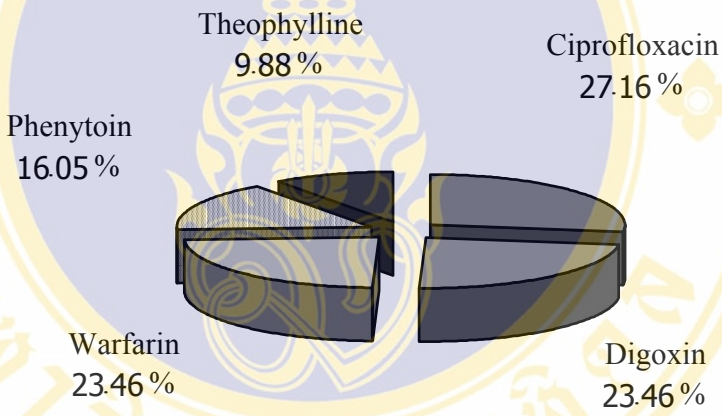

Figure 2 The frequency of alerting drugs used to identified alerting DIs.

When alerting DIs were grouped following the alerting drugs (Table 19), there were 22 events of alerting DIs affected the absorption of ciprofloxacin. Ferrous fumarate was the precipitant drug with the highest frequency for potential DIs (13 of 22 events). The other major precipitant drugs were antacids or aluminium hydroxide (4 of 22 events), sucralfate (3 of 22 events) and ferrous sulfate (2 of 22 events).

There were 19 events of alerting DIs involving with digoxin. Of these, the highest events was interaction with amiodarone (16 of 19 events) while verapamil contributed to 3 of 19 events.

Table 19. Alerting DIs classified by each alerting drug.

Alerting DIs	Frequency (%)
Ciprofloxacin	
Ciprofloxacin-Ferrous fumarate	13
Ciprofloxacin-Antacids, Aluminium hydroxide	4
Ciprofloxacin-Sucralfate	3
Ciprofloxacin-Ferrous sulfate	2
Total	22 (27.16%)
Digoxin	
Digoxin-Amiodarone	16
Digoxin-Verapamil	3
Total	19 (23.46%)
Warfarin	
Warfarin-Aspirin	9
Warfarin-Amiodarone	5
Warfarin-Co-trimoxazole	1
Warfarin-Levothyroxine	1
Warfarin-Metronidazole	1
Warfarin-Phenobarbital	1
Warfarin-Rifampin	1
Total	19 (23.46%)
Phenytoin	
Phenytoin-Dexamethasone	9
Phenytoin-Amiodarone	2
Phenytoin-Prednisolone	1
Phenytoin-Trimethoprim	1
Total	13 (16.05%)
Theophylline	
Theophylline-Ciprofloxacin	7
Theophylline-Cimetidine	1
Total	8 (9.88%)
Total alerting DIs	**81 (100.00%)**

Nineteen events from 7 precipitants drugs were found to possibly affect the action of warfarin. Among these precipitant drugs, aspirin had the highest frequency (9 of 19 events) of all events while amiodarone was the second precipitant drug with 5 of 19 events. The other precipitant drugs were co-trimoxazole, levothyroxine, metronidazole, phenobarbital and rifampin, each with 1 of 19 events of DIs.

As can be seen in Table 19, there were 13 events of alerting DIs involving with phenytoin. Dexamethasone was the object drug with highest events to interact with phenytoin (9 of 13 events) while prednisolone contributed only 1 of 13 events. Amiodarone and trimethoprim were the precipitants drugs interacted with phenytoin which accounted for 2 and 1 of 13 events, respectively.

The last alerting drug was theophylline. Eight events of DIs were found to possibly affect the action of theophylline. Among these precipitant drugs, ciprofloxacin caused highest events of all alerting DIs (7 of 8 events) while cimetidine contributed only 1 of 8 events.

All of alerting DIs could be classified by the significance rating of DIs as 45.68% (37 of 81 events) with significance 1 and 54.32% (44 of 81 events) with significance rating 2. When classified by severity of DIs, 45.68% (37 of 81 events) were major severity and 54.32% (44 of 81 events) were moderate severity. These DIs could be further divided into 12.35% (10 of 81 events) pharmacodynamic DIs and 87.65% (71 of 81 events) pharmacokinetic DIs. The details of these drug interactions are shown in Table 20.

Table 20. Drug interactions classified by mechanism, significance rating and severity.

Drug interactions	No. of events (%)	Significance rating	Severity
Pharmacodynamic DIs	10 (12.35)		
Warfarin-Aspirin	9	1	Major
Warfarin-Levothyroxin	1	1	Major
Pharmacokinetic DIs	71 (87.65)		
Digoxin-Amiodarone	16	1	Major
Digoxin-Verapamil	3	1	Major
Warfarin-Amiodarone	5	1	Major
Warfarin-Co-trimoxazole	1	1	Major
Warfarin-Metronidazole	1	1	Major
Warfarin-Phenobarbital	1	2	Moderate
Theophylline-Cimetidine	1	2	Moderate
Theophylline-Ciprofloxacin	7	2	Moderate
Phenytoin-Amiodarone	2	2	Moderate
Phenytoin-Dexamethasone	9	2	Moderate
Phenytoin-Prednisolone	1	2	Moderate
Phenytoin-Trimethoprim	1	2	Moderate
Warfarin-Rifampin	1	2	Moderate
Ciprofloxacin-Antacids	4	2	Moderate
Ciprofloxacin-Ferrous sulfate	2	2	Moderate
Ciprofloxacin-Ferrous fumarate	13	2	Moderate
Ciprofloxacin-Sucralfate	3	2	Moderate
Total	81 (100.00)		

Focusing on physicians who prescribed alerting DIs, it was found that 55.56% of alerting DIs (45 of 81 events) were prescribed by attending physician whereas consultant physician and multiple physicians, two physicians who prescribed two interacting drugs in one patient, were responsible in an equal number, 22.22% (18 of 81 events)(Figure 3).

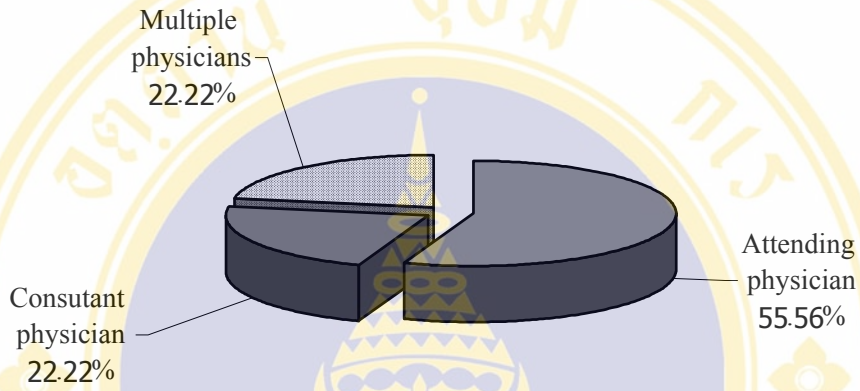

Figure 3. Characteristic of physicians who prescribed alerting DIs.

Part III: Pharmacist interventions and physicians' – nurses' acceptance

Of 81 events of alerting DIs, 50 (61.73%) interventions were performed (Table 21). Sixteen interventions (32.00%) were performed by staff pharmacists and 34 interventions (68.00%) were performed by clinical pharmacist. No intervention was performed in 31 events of identified DIs.

When focused on the number of identified DIs that staff pharmacist were found and had to perform the interventions. It was found that there were 21 events of alerting DIs. Thus, the intervention of staff pharmacist was accounted for 76.19% (16 of 21 events). Of these, 14 interventions were performed to nurse and 2 interventions were patient counseling (Table 21). All of these interventions were to separate the time of drug administration between ciprofloxacin and precipitant drugs such as antacids, iron salts and sucralfate which cause decreasing GI absorption of ciprofloxacin by formation of a complex.

However, there were 5 events of detected DIs that no intervention was performed by staff pharmacists. All of them were the DIs between ciprofloxacin and precipitant

drugs which decreased the absorption of ciprofloxacin. Two events were not intervened because staff pharmacists misunderstood that these interventions were performed by the clinical pharmacist. There were 3 events that interventions were not taken with unknown reasons. One event was detected during patient was discharged but no intervention was performed to involving persons. However, for other 2 events the interventions were performed by clinical pharmacist instead.

When focused on clinical pharmacist interventions (Table 21), it was found that 34 interventions were provided to nurses and physicians. Recommendations of changing time of drug administration between the interacting drugs were performed 3 times. Another two interventions were performed to nurse and physician by clinical pharmacist instead of staff pharmacists as mentioned previously. The other one intervention was performed to physician because the alerting DI was identified during clinical pharmacist reviewed patient's chart while staff pharmacists could not detect it.

Most of clinical pharmacist interventions (33 of 34 interventions) were provided to physicians. Recommending physician to monitor laboratory tests or observing clinical signs and symptoms which related to the effect of the interaction during cotherapy had the highest frequency of the interventions (28 of 34 interventions). The other interventions were decreasing dose of interacting drug and monitoring laboratory tests or observing clinical signs and symptoms when precipitant drug was discontinued. Each type of them was performed 2 times and 1 time, respectively.

The type and number of pharmacist interventions in each alerting DIs are shown in Table 22.

Table 21. The staff and clinical pharmacist interventions.

Interventions	No. of Interventions (events)	Percentage of intervention	No intervention (events)
By staff pharmacists			
• With nurse	14	28.00	
- Changing time of drug administration	14		
• Patient counseling	2	4.00	
No intervention	-	-	5*
Total	16	32.00	
By clinical pharmacist			
• With nurse	1	2.00	
- Changing time of drug administration	1		
• With physician	33	66.00	
- Changing time of drug administration	2		
- Monitoring relevant laboratory values or observing clinical signs and symptoms during cotherapy	28		
- Monitoring relevant laboratory values or observing clinical signs and symptoms when precipitant drug was discontinued	1		
- Decreased dose	2		
No intervention	-	-	28
Total	34	68.00	
Total interventions	50	100.00	
No intervention			31

* two out of 5 interventions were performed by the clinical pharmacist leaving the number of no intervention of 3

Table 22. The type and number of pharmacist interventions in each alerting DIs.

	Alerting drug interactions	Type of interventions				
		Decrease dose	Monitor lab/observe clinical during cotherapy	Monitor lab/observe clinical when precipitant drug was removed.	Change time of drug administration	Total
Staff pharmacist	Ciprofloxacin-Antacids, Aluminium Hydroxide				3	
	Ciprofloxacin-Ferrous sulfate				1	
	Ciprofloxacin-Ferrous fumarate				11	
	Ciprofloxacin-Sucralfate				1	
	Total				16	16
Clinical pharmacist	Theophylline-Cimetidine	1				
	Theophylline-Ciprofloxacin		6	1		
	Digoxin-Amiodarone		6			
	Digoxin-Verapamil		1			
	Phenytoin-Amiodarone		1			
	Phenytoin-Dexamethasone		3			
	Warfarin-Amiodarone		4			
	Warfarin-Aspirin	1	3			
	Warfarin-Co-trimoxazole		1			
	Warfarin-Levothyroxine		1			
	Warfarin-Metronidazole		1			
	Warfarin-Rifampin		1			
	Ciprofloxacin-Ferrous fumarate				1	
	Ciprofloxacin-Sucralfate				2	
	Total	2	28	1	3	34

There were 28 events that no interventions were performed by clinical pharmacist. This was because the same kind of problems were identified with the same physician. The effect and mechanism of such alerting DIs including recommendation on how to monitor or circumvent the interaction had been previously performed to that physician and he or she accepted with this interventions. However, patients were monitored until discharged and the interventions would be performed if necessary.

For some events of alerting DIs, the researcher could not perform interventions in time because of late detection, or patients were discharged the day after detection, or physicians stopped the object drugs from the patient's drug regimen shortly after the detection of the interactions, or patients had short duration of hospital stay or difficulty in physicians contact. The alerting DIs that no intervention was performed are shown in Table 23.

Table 23. The alerting DIs that no intervention was performed by clinical pharmacist.

Alerting DIs	Number (events)
Digoxin-Amiodarone	10
Phenytoin-Dexamethasone	6
Warfarin-Aspirin	5
Digoxin-Verapamil	2
Warfarin-Phenobarbital	1
Warfarin-Amiodarone	1
Phenytoin-Prednisolone	1
Phenytoin-Amiodarone	1
Phenytoin-Trimethoprim	1
Total	28

Of the 50 interventions, all of staff pharmacist interventions (16 interventions) were accepted as recommended. For clinical pharmacist interventions, most of them (30 of 34 interventions) were accepted as recommended while 3 interventions were accepted but in the different way from the recommendation. Of these, one intervention involved digoxin-amiodarone interaction. Alerting about the effect and mechanism of the interaction and suggestion to observe clinical signs and symptoms of digoxin toxicity and/or digoxin serum level were agreed but the physician decided to discontinue digoxin since it has a narrow therapeutic index and is difficult to control. Other 2 interventions involved ciprofloxacin-sucralfate interactions. Recommendation to separate the time of drug administration between the interacting drugs were consented but the physicians decided to discontinue one of these two drugs instead.

One unaccepted intervention was suggestion the physician to monitor INR and observe signs and symptoms of bleeding during the cotherapy between warfarin and thyroid hormone (Eltroxin®). The intervention was disagreed and implemented because the physician thought that the problem was not clinically significant.

In summary, of 48 pharmacist interventions performed to physicians and nurses 44 interventions (91.67%) were accepted as recommended. Three interventions (6.25%) were accepted but different process from recommendation was performed while only 1 intervention (2.08%) were unaccepted by the physician (Figure 4).

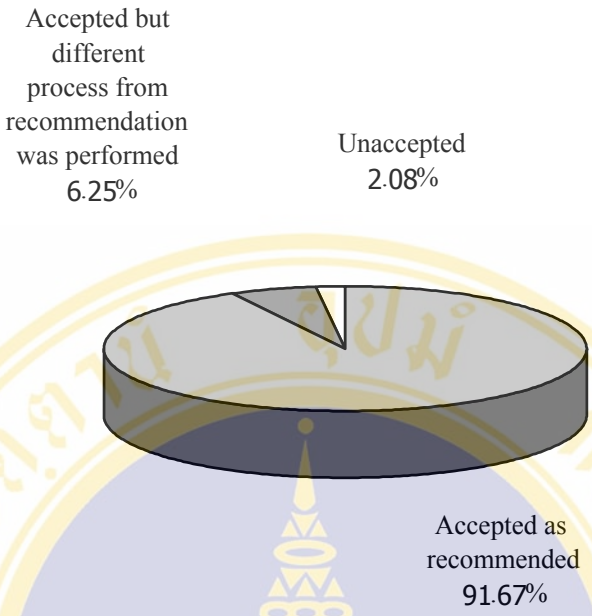

Figure 4.

Part IV: Patient care process regarding DIs after pharmacist interventions

After pharmacist interventions, the patient care process regarding DIs were monitored by clinical pharmacist. As can be seen in Table 24, observation of involving clinical signs and symptoms during cotherapy of the interacting drugs without any changing in therapy and changing time of drug administration were frequently performed, 38.00% and 26.00% respectively. The third rank of patient care process was monitoring the interaction by ordering laboratory test without changing therapy (12.00%). These processes were implemented conformed with the pharmacist interventions.

The other processes were observation of clinical sings and symptoms and discontinuation of drug (10.00%), and laboratory test order with dosage changed (4.00%). Four events (8.00%) could not be assessed because the interventions were patient discharge counseling or the patients were discharged shortly after interventions. In addition, one intervention which pharmacist recommended nurse to separate time of drug administration between the interacting drugs was not implemented after the pharmacist intervention was accepted.

Table 24. The patient care process regarding drug interaction after pharmacist interventions.

Patient care process after interventions	**Number of events (%)**
- Clinical signs and symptoms were observed, no change in therapy	19 (38.00)
- Time of drug administration was changed	13 (26.00)
- Laboratory test was ordered, no change in therapy	6 (12.00)
- Clinical signs and symptoms were observed, drug was discontinued	5 (10.00)
- Laboratory test was ordered, dosage was changed	2 (4.00)
- Could not assess	4 (8.00)
- Recommendation was not followed	1 (2.00)
Total	50 (100.00)

CHAPTER V
DISCUSSION

Drug interaction (DI) is a preventable cause of morbidity and mortality. (54) One of several sites that DI often occurs is the inpatient hospital setting especially medical ward because multipathology and polypharmacy always appear. Therefore, providing DI monitoring service to prevent patient from possible adverse outcome is an important role of pharmacist.

In the present study, to handle adverse DI, the DI monitoring service was implemented as routine activities in inpatient pharmacy department. The role of pharmacist in detecting and preventing DI was set up and the impact of the intervention on physician or nurse acceptance and patient care process regarding DI were assessed. Finally, incidence of both potential and actual DI were determined.

During 4 months of study, 68 patients with alerting DIs were detected by pharmacists from all 4,624 patients who were admitted in the study wards. Almost 70% of the detected patients were elderly with average 1-2 medical problem(s) but they received many medications mainly ranged from 5-13 items (average 9 items) while alerting drug was detected and had as many as 3 physicians per 1 patient. This finding supported that elderly patient was a group that had high risk of DI hence particularly susceptible by virtue of polypharmacy, comorbid illness, and treatment by multiple physicians. (5, 54) Therefore, monitoring of DI to prevent adverse outcome by pharmacist is likely to be useful for these patients.

Implementing the role of pharmacist in detecting and preventing adverse DIs as routine activities was one of the objectives. In this service, using 5 alerting drugs expanded to 35 types of selected alerting DIs was the method to screen DIs. By this non-computerized method, pharmacists could detect 81 alerting DIs which covered 19 types of selected alerting DIs. It was accounted for 54.28% of all alerting DI pairs (19/35 alerting DIs). This was hardly to determine the effectiveness of detection by this service because differences in prescribing patterns by physicians, diseases of

patients and pharmacist's awareness for detecting DI during the study period. However, when grouping all of detected alerting DIs by alerting drugs it was found that all alerting drugs were used to monitor DIs. Furthermore, most of full-time and part-time staff pharmacists in inpatient pharmacy department were able to detect DIs during routine work. This might reveal that this screening method is one of the good methods for pharmacist to detect DI. This study suggests that, for further study, the ability of the pharmacist's detection should be evaluated by comparing the number of alerting DIs detected by pharmacists with the real total number of alerting DI detected by set up computer program.

However, the non-computerized method must depend on the awareness and the responsibility of staff pharmacists. Therefore, in order to make more efficient DI detection, the present study suggests that there should be seminars on DI topic. The report of each pharmacist's detection should be publicized from time to time. The department manager should emphasize the importance of DI detection including create motivation and incentive among pharmacists by giving awards to those whose work is outstanding. Moreover, flagging the selected drug products (alerting drugs) with small pieces of colored paper may be helpful for the pharmacist to remind him or herself to check patient's medications for interacting drugs. (50)

The most common alerting DIs found in this study were the interactions between ciprofloxacin and multivalent cations such as ferrous salts, aluminium or magnesium-containing antacid and iron-containing drug, sucralfate. Co-administration of these drugs result in lower antibiotic serum concentration and may lead to therapeutic failure. The proposed mechanism is decreasing in quinolone absorption due to chelation between metal cations and the 3-carboxyl and 4-oxo-functional groups of quinolone molecule. (71, 72) The administration of ferrous sulfate, ferrous fumarate and ferrous gluconate reduce the absorption of ciprofloxacin by 40% to 65%. (30, 73) In addition, ciprofloxacin serum concentration is reduced 40% to 70% when antacid is used concomitantly. (30) Therefore, to avoid this potential interaction, oral ciprofloxacin should be taken at least 2 hours before any multivalent cations product or 6 hours after the antacid or sucralfate. (30, 71) This is an easily way for pharmacist to avoid these potential interactions by re-scheduling drug administration time or counseling their patients.

The other important DI with major severity commonly identified in this study was the interaction between digoxin and amiodarone. Amiodarone is most often used alone but also serves as a useful adjunct to digoxin in the treatment of various cardiac disorders when both inotropic and antiarrhythmic properties are required. (74,75) Amiodarone can cause accumulation of digoxin in serum and digoxin toxicity is occurred subsequently. (30) Several studies reported an approximate doubling of digoxin level. (1, 74, 76) Multiple mechanisms are probably involved. Amiodarone reduces the volume of distribution, the renal and non renal clearance of digoxin and also increases its bioavailability. Displacement of digoxin from tissue binding sites may also occur. (61, 62, 77) In addition, amiodarone-induced hypothyroidism also can reduce the clearance of digoxin. (78) Due to long half-life of amiodarone (50 days), the interaction with digoxin usually is noted after several days to weeks of concurrent therapy, especially if no loading dose of amiodarone is given, and the effects of the interaction may persist long after the drug is discontinued. (1, 30) In the present study, 16 events of the interactions were detected. Therefore, pharmacist should intervene physician to monitor digoxin serum levels when amiodorone is added to or deleted from therapy and be alert for signs and symptoms of digoxin toxicity. The recommended dose of digoxin will probably be reduced by approximately 25 to 50% if the drug is administered concurrently with amiodarone. (79, 80)

Concerning DIs with warfarin, the most common alerting DI detected in this study was warfarin-aspirin DI. Aspirin (even in small doses) increases the risk of bleeding in anticoagulated patients by inhibiting platelet function and possibly by producing gastric erosions. Larger aspirin doses (e.g., > 3g/day) may also enhance the hypoprothrombinemic response to warfarin. It is possible because salicylates displace oral anticoagulants from plasma protein-binding sites, but the significance of this mechanism is questionable. Low dose-aspirin 75 mg/day combined with low intensity warfarin (INR = 1.5) is associated with slightly greater minor and intermediate bleeding than giving low-dose aspirin or low-intensity warfarin alone. (1) In this study, all of detected patients received warfarin with low-dose aspirin for the treatment or preventing of several diseases involving blood coagulation disorder.

Aspirin should be combined with oral anticoagulant only when it is intentionally used for additive anticoagulant effects. Thus, if they must be used together, careful

monitoring of the prothrombin time (PT) or international normalized ratio (INR) and patient's signs of bleeding, especially from the gastrointertinal tract should be performed. (30, 80)

The second DI with warfarin commonly detected in the study was warfarin-amiodarone interaction. Hypoprothrombinemic effect of oral anticoagulant is augmented by concomitant amiodarone therapy. A decrease in warfarin metabolism by amiodarone is probably a mechanism. (80) Warfarin is usually administered as a racemic mixture and warfarin metabolism in humans is catalyzed by a variety of cytochrome P450. The S-warfarin, the more potent enantiomer, is metabolized primarily by CYP2C9 and the R-warfarin, the less potent enantiomer, is metabolized primarily by CYP1A2 and CYP3A4. (81) Amiodarone is a general inhibitor of the CYP450 catalized oxidation of both enantiomers of warfarin, but the metabolism of S-warfarin is more strongly inhibited than that of R-warfarin. (82) Prolongation of the prothrombin time and bleeding complication in some patients by this interaction is well documented, but the concomitant therapy is not contraindicated. The adverse interaction may by seen within 1-2 week(s) of concomitant use and may last up to 1-3 month(s) after amiodarone discontinuation. (83) In order to circumvent this interaction, a 25 to 50 % reduction in warfarin dose is typically required. Monitoring of prothrombin times or INR closely during the first 2 to 4 weeks of amiodarone therapy should be performed. These effects may persist for weeks to months after discontinuation of amiodarone, thus warfarin dose adjustment is necessarily continued. (1, 80)

Drug interactions between phenytoin and dexamethasone was also commonly identified in this study. Decreased steroid effects may occur within days of phenytoin initiation and persist for 3 weeks after discontinuation. Increased steroid metabolism via 6-beta-hydroxylation, because of enzyme induction by phenytoin is the proposed mechanism. (1) Chalk et al (84) reported that in neurological and neurosurgical patients who take dexamethasone with phenytoin had significant shorter dexamethasone mean terminal half-life, an approximately trebled mean plasma clearance, and a mean oral bioavailability of only 33%, compared with a mean of 84% oral bioavailability in those not receiving phenytoin. Hence, a ≥ 2 folds increase in the steroid dose may be needed to manage this interaction.

The last common potential DI detected in this study was theophylline-ciprofloxacin interaction. Theophylline is predominantly eliminated as metabolites formed by hepatic cytochrome P450 enzymes. N-demethylation to 1-methylxanthine and 3-methyxanthine is mediated by CYP1A2 and hydroxylation to 1,3-dimethyluric acid is mediated by CYP3A3 and CYP2E1. (85, 86) Ciprofloxacin probably inhibits the N-demethylation (CYP1A2) of theophylline leading to an increase in serum concentration of theophylline and subsequently theophylline toxicity. In a number of case reports and clinical studies, ciprofloxacin can reduce theophylline clearance by 15 to over 50%. (1) Serum theophylline concentration appears to be increased over approximately 3 days after the antibiotic is started. Theophylline toxicity can occur and seizures have been reported with the combination, even when theophylline concentrations are within therapeutic range. (30) Therefore, in patient who receives theophylline, monitoring theophylline levels and observing for toxicity when ciprofloxacin is initiated or discontinued, and adjusting theophylline dosage as needed should be performed.

The important remark observed in this study was characteristics of the physician who prescribed the medications which caused the DI. It was found that majority of DIs were prescribed by single physicians either attending or consultant physicians (55.56% and 22.22% of all detected DIs). Despite, patients were commonly treated by more than one physician and received polypharmacy, DIs caused by multiple physicians presented only 22.22%. It is possible that individual physician might accidentally prescribe the interacting drugs or several alerting drug pairs are usually used concomitantly in clinical practice. Therefore, earlier informing the information of DI to the physician and monitoring of DI in the patient are beneficial role of pharmacist in this setting.

According to this study, both pharmacy staffs and clinical pharmacist had important role to prevent potentially adverse drug interaction. This study founded that staff pharmacists could perform the interventions to prevent DIs up to 16 out of 21 events of detected DIs. Most of the interventions were prevention of potential DIs among oral ciprofloxacin and various cation-containing drugs by providing the information about this DI to nurses and correcting administration time on the medication administration records. From this study, it is possible that other

interactions caused by chelation mechanism are potentially happened in this setting. To minimize these potential DIs, the pharmacists should directly take this responsibility. Thus, expanding this service to other chelation interactions with providing information about these DIs in the newsletter to nurses should be done connectedly.

There were only 5 DIs in which staff pharmacists did not perform the intervention due to unclearness about the study process, DI founded while patient was discharged and unawareness to perform the intervention by staff pharmacists. This study also suggested that it is necessary to expand the description of DI monitoring service to the staff pharmacists in the whole department. In case of DI founded when patient was about to go home, it is essential that staff pharmacist should notify clinical pharmacist who responses in discharge counseling. Furthermore, it is suggested that the department manager should focus on the importance of DI monitoring and the necessity of detecting DI to the pharmacist connectedly.

For clinical pharmacist, most of interventions (33 of 34 interventions) were provided to the physicians. Of these interventions, recommending the physician to monitor object drug serum level or laboratory tests and observe clinical signs and symptoms which relate to the effect of the interaction during cotherapy were chiefly performed. The reason was that most of alerting DIs in this service had the management option that interacting drugs could use together with drug monitoring. In addition, there were other reasons of this type of intervention such as in some patients, coadministration of interacting drugs was necessary and benefit outweigh risk such as digoxin-amiodarone and warfarin-amiodarone for the treatment of atrial fibrillation or warfarin-aspirin for the treatment of ischemic stroke. Furthermore, some patients were clinically stable with long period of cotherapy.

However, there were many DIs that no interventions were performed. The reasons of no intervention in this study were multifactorial, including physicians, short length of stay, limited time of clinical pharmacist and late detection of DIs. These problems might be circumvented by utilizing written intervention method such as using drug interaction alert (DIA) card or utilizing satellite pharmacist to closely contact the physicians and monitor the effect of DI on patient. In addition,

computerized-based DI detection will facilitate clinical pharmacist to early detect alerting DI.

Determining the impact of pharmacist's intervention on physician and nurse acceptance and patient care process regarding DI was the other objectives. About the consequence of pharmacist intervention, it was founded that both physicians and nurses accepted the recommendation during the intervention (91.67%). However, some physicians might not be totally agreed as recommended (6.25% of all interventions), but they still had a positive response, decided to prevent potential adverse DI by other alternative ways. For example, physicians decided to discontinue one of interacting drugs whereas clinical pharmacist recommended that both drugs could be used together with closely monitoring of patient or re-scheduling drug administration time. Discontinuation of drug could be performed if patient was unnecessarily to use such drug. However, if such drug still had the benefit to prevent or treat patient's disease, discontinuation of such drug might make patient lost an opportunity to use drug to control his or her disease. Therefore, pharmacist should be careful for this undesirable result. This suggests that for further study, monitoring of patient's outcome with pharmacist's intervention should be performed.

A lot of acceptance during pharmacist intervention was probably due to the way of pharmacist approach. In this study, pharmacist used verbal or face to face communication in which the purpose of monitoring DI was specified and DI data were provided with friendly to approach physicians and nurses. Many physicians were willing to discuss and agreed with this service. Some physicians stated that pharmacist monitoring DI was a good activity to help physician take care of patient. However, as described by Smith (50), because physician's prescribing is criticized by pharmacist, the qualification that pharmacist must own should be forethought and tact to approach the physician. The manner in which physician is advised by pharmacist will determine whether the advice is accepted. It is essential to realize that personalities are involved and a great deal depends upon previous experiences in providing information to the physicians and upon the rapport which has already been established. As a result, in order to get good acceptance from physician, pharmacist should consider these factors.

Patient care process regarding DI after intervention was also investigated. According to this study, physician and nurse tended to have the awareness in monitoring of DI. Several forms of action were taken to handle potential DI such as observing clinical signs and symptoms related to DI effect during cotherapy or discontinuing the interacting drug, changing time of drug administration between interacting drugs, ordering the laboratory test and/or changing drug dosage.

Changing time of drug administration was recommended to nurses for 15 interventions. Of these, 13 out of 15 interventions (86.67%) were accepted and implemented as recommended. This acceptance rate was similar to the result from the study of Briceland et al (56) which implemented avoidance program of oral ciprofloxacin-cation DI by using written or oral intervention to nurse. The study found that the intervention was accepted in 88% of cases and the program dramatically reduced the incidence of potential chelation interaction. According to well acceptance rate in our study, the effective intervention suggested by this setting when chelation DI was detected is to encourage pharmacist to intervene nurse and generate correct time in MAR.

Nevertheless, several results of patient care process after intervention was only the assumption that various forms of action taken by physician were the impact from the intervention of pharmacist. Because this information was received by the review of patient's chart after intervention. Hence, in order to get more accurate information, this study suggests that there should be checking boxes in DIA card for physician to chose how he or she will monitor or circumvent each DI (see Figure 5).

Determining both potential and actual DIs was also the objective. During study period, a total of 4,624 patients admitted to study wards were monitored for alerting DIs. Sixty-eight cases presented with alerting DIs (67 cases with potential DIs and 1 case with actual DI). Therefore, the incidence rate of total alerting DI, potential DI and actual DI were 1.47% (68/4,624), 1.45% (67/4,624) and 0.02% (1/4,624) respectively. These incidence rate was lower than the incidence rate reported in the previous study (8,9,10) in that incidence rate of total DI, possible DI and actual DI were ranged from 13.5 to 50%, 11.4 to 17.8% and 0.9 to 2.1% respectively. However, it was difficult to compare the incidence rate to other studies because of difference in methodologies and study designs such as method used for detecting DI, definition and

Date ……Time ……

DRUG INTERACTION ALERT

Attention doctor:

Your patient.…..……, is receiving both **Theophylline** and **Cimetidine.**

A potential interaction between these two drugs may result in increased theophylline levels (33 –50%) which toxicity may occur. Maximal changes usually occur within 72 hr. Probable mechanism is inhibition of the hepatic metabolism of theophylline.

♣ **Recommendation:**

If no previous interventions have been done, we recommend that if cimetidine is used with theophylline patient should be monitored for altered theophylline response and theophylline serum levels when cimetidine is used concurrently or discontinued. The dose of theophylline may need to be adjusted. Adding cimetidine may necessitate a 20% to 40% reduction in theophylline dose.

Or consider alternative : Ranitidine do not appear to affect theophylline disposition and thus would be preferable to cimetidine. Famotidine and Nizatidine are also unlikely to interact with theophylline.

Thank you.

For questions or further information contact clinical pharmacist-Inpatient Pharmacy Department at ext. 2115-6

Physician's acceptance checklist.

⏩ Accepted as recommended

□ *Use an alternative drug.* □ *Empiric adjust dose of theophylline.*

□ *Monitor for altered theophylline response or theophylline plasma levels when cimetidine is used concurrently; tailor theophylline doses as needed.*

□ *Monitor for altered theophylline response or theophylline plasma levels when cimetidine is discontinued; tailor theophylline doses as needed.*

⏩□ Accepted but difference (Please detail) ⏩□ Not accepted(Please detail) …..

……. ……..

…… ……..

……. …….

……. ……..

Figure 5. Example of drug interaction alert (DIA) card (adapted from reference 1, 18, 56).

the number of DI pairs used for screening DI, study population, etc. However, the low incidence rate reported in this study may be because the number of sample population for monitoring DIs was calculated from DI detection rate according to the result of preliminary study which all DIs with significance rating 1 and 2 were detected by pharmacist while in this study, only 35 alerting DI pairs were used for screening DIs. On the other hand, staff pharmacists detected DIs by using non-computerized method so it might cause underreported DI.

Of these 68 identified cases, eighty-one events of alerting DIs were detected. Eighty events were potential DIs and 1 event was actual DI. In this study, actual DI was confirmed by clinical signs and symptoms, laboratory investigations or physician's opinion. All suspected or inconclusive cases were discussed and confirmed by physician's opinion. The adverse effect occurred in actual case founded in the study was gastrointestinal bleeding with death. This was highly probable due to the concurrent use of oral warfarin and low-dose aspirin for preventing embolic formation after the events of right femoral arterial occlusion and ischemic stroke.

Although alerting DIs monitoring in this study were DIs with significance rating 1 and 2, not all potential DIs were turned to be actual DIs. Several reasons can affect this event. (28) Initially, object or precipitant drugs might be underdoses or initially administered in a lower than usual dose and slowly titrated to its full therapeutic effect such as the interactions between digoxin-amiodarone and theophylline-ciprofloxacin. Perhaps that initial lower dosage did not allow the interaction to manifest quickly or perhaps allowed object and precipitant drugs to equilibrate during the dosage titration. In addition, the manifestation of the interaction might take a long time to reach full effect, for example, DI between amiodarone and the object drugs such as digoxin and warfarin which the adverse interaction might be seen after several days to weeks of concurrent therapy. Therefore monitoring the interactions with a delayed onset for only during admission period, the adverse effect of the interactions might not be observed. Patient counseling and monitoring these interactions for adequate time by follow up patients in OPD setting should be performed. Finally, there are other predisposing factors that could affect the clinical manifestation of DI. These factors include sequence of interacting drugs administration, current serum level of object drug and the individual's responsiveness to enzyme inhibition or induction of patient,

aging, genetic factor, disease states, comorbid illness, changing in renal and hepatic functions, other concomitant drugs, etc. (1,22)

Although, only 1 patient developed clinical adverse effect but it was a serious life-threatening adverse outcome. Concerning other potential adverse DIs, they might also produce hazardous outcome to patient if there were some precipitating factors. Therefore, constant monitoring of DI is very essential and the pharmacist should take this valuable role to prevent patient from possible adverse outcome.

CHAPTER VI
CONCLUSION

Drug interaction (DI) monitoring service was implemented in inpatient pharmacy department to monitor patients admitted in medical and surgical wards. The role of pharmacists in detecting and preventing adverse DIs coupled with physician and nurse acceptance and patient care process after the interventions were prospectively determined in this study. Using non-computerized DI screening method, the pharmacists could detect 81 events of alerting DIs in 68 out of 4,624 patients. The incidence of total DIs, potential DIs and actual DIs were 1.47% (68/4,624), 1.45% (67/4,624) and 0.02% (1/4,624), respectively. The most common potential DIs founded in this study were oral ciprofloxacin-multivalent cation drugs, digoxin-amiodarone, warfarin-aspirin, warfarin-amiodarone, phenytoin-dexamethasone and theophylline-ciprofloxacin interactions. The pharmacists performed totally 50 interventions (61.73%) to resolve or prevent DIs-16 interventions (32%) by staff pharmacists and 34 interventions (68%) by clinical pharmacist. The most common interventions of staff pharmacists were avoiding oral ciprofloxacin-multivalent cation drugs by contact nurses and re-scheduling patients' drug administration time. The most common interventions of clinical pharmacist were recommending physicians to monitor laboratory tests or patient's signs and symptoms for clinical adverse effect during cotherapy. Of the 48 interventions performed to nurses and physicians, 44 interventions (91.67%) were accepted as recommended by pharmacists. After the interventions, various forms of patient care process regarding DIs were taken such as monitoring patients for clinical adverse DIs, changing time of drug administration, ordering of laboratory tests, discontinuing drug and changing drug dosage. According to the results, pharmacists had beneficial role in detecting and preventing adverse DI in their patients and this service was useful for monitoring DI in this setting. Concerning about multiple drugs use in a single patient coupled with the increasing use of new drugs, DI monitoring service should be performed continually to provide pharmaceutical care to patients.

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APPENDICES

APPENDIX I

Potential drug-drug interactions monitored by pharmacist			
Alerting drugs	**Interacting drugs**		**Mode of activity**
	BH name	**Generic name**	
Theodur Bronchil (Theophylline)	Cimidine, Tagamet	Cimetidine	Record in file
	Ciprobay, Cifloxin	Ciprofloxacin	"
	Klacid	Clarithromycin	"
	Erythrocin, Ilosone	Erythromycin	"
	Betalol, Inderal, Inderal-La	Propranolol	Telephone
	Rifamiso, Rifater, Rimactane, Rimactazid	Rifampin	Record in file
Lanoxin (Digoxin)	Cordarone	Amiodarone	Record in file
	Klacid	Clarithromycin	"
	Erythrocin, Ilosone	Erythromycin	"
	Tapazole	Methimazole	"
	PTU	Propylthiouracil	"
	Isoptin	Verapamil	"
Dilantin (Phenytoin)	Cordarone	Amiodarone	Record in file
	Cimidine, Tagamet	Cimetidine	"
	Decadron, Oradexon	Dexamethasone	"
	Diflucan, Flucozole	Fluconazole	"
	INH, Rifamiso, Rifater, Rimactazid	Isoniazid	"
	Depo-medrol, Depo-medrol with lidocaine, Solu-medrol	Methyprednisolone	"
	Di-Adreson F	Prednisolone	"
	Bronchil, Theodur	Theophylline	"
	Bactrim, Bactrim M, Co-Trimoxazole, Septrin	Trimethoprim	"
Orfarin (Warfarin)	Cordarone	Amiodarone	Record in file
	Aspent Gr.5, Aspent M, Aspirin,	Aspirin	"
	Cardiprin	Cimetidine	"
	Cimidine, Tagamet	Co-Trimoxazole	"
	Bactrim, Bactrim M, Co-Trimoxazole, Septrin	Fluconazole	"
	Diflucan, Flucozole	Itraconazole	"
	Sporal	Ketoconazole	"
	Fungazol, Nizoral	Levothyroxine	"
	Eltroxin	Metronidazole	"
	Flagyl	Phenobarbital	"
	Gardinal, Phenobarbitone, Phenobarb Elix.	Rifampin	"
	Rifamiso, Rifater, Rimactane, Rimactazid		
Ciprobay(Oral)* Cifloxin (Oral)* (Ciprofloxacin)	Actal, $Al(OH)_3$, Alumed, Dioval, Gacida, Gelusil, Veragel-DMS	Antacids, $Al(OH)_3$	Telephone*
	$FeSO_4$	Ferrous sulfate	Telephone*
	F.B.C, Feri-6	Ferrous fumarate	Telephone*
	Ulcefate, Ulsanic	Sucralfate	Telephone*

* = Intervention to nurse

Theophylline

Interacting drugs	Summary	Reference No.
Cimetidine	♦Increase theophylline levels (33 –50%) with toxicity may occur. Maximal changes usually occur within 72 hr. Probable mechanism is inhibition of the hepatic metabolism of theophylline. ♦Recommendation : If cimetidine is used with theophylline patient should be monitored for altered theophylline response and theophylline serum levels when cimetidine is used concurrently or discontinued. The dose of theophylline may need to be adjusted. Adding cimetidine may necessitate a 20% to 40% reduction in theophylline dose. : Consider alternative: Ranitidine does not appear to affect theophylline disposition and thus would be preferable to cimetidine. Famotidine and nizatidine are also unlikely to interact with theophylline.	1
Ciprofloxacin	♦Increase serum concentrations of theophylline and can induce theophylline toxicity. Ciprofloxacin reduced theophylline clearance by 15% to over 50%. The serum theophylline concentration appears to increase over approximately a 3–day period after the antibiotic is started. Probable mechanism is inhibition of the hepatic metabolism of theophylline. Quinolones reported to inhibit the metabolism of theophylline included norfloxacin and pefloxacin. ♦Recommendation : If these agents must be given, monitor theophylline levels and observe for toxicity. Adjust theophylline dosage as needed. : Consider alternatives: Olfloxacin, lomefloxacin, levofloxacin and sparfloxacin have been reported to produce no or minor changes in theophylline kinetics.	2
Clarithromycin Erythromycin	♦Increase theophylline serum concentrations and may produce toxicity. This interaction usually occurred only after several days of erythromycin therapy. The mechanism is inhibition of the metabolism of theophylline. Clarithromycin potentially could produce a similar interaction with theophylline. Roxithromycin produce small increase in serum theophylline concentrations. Azithromycin, data from double blind control trial found that no interaction with theophylline but there are some case reports involved this interaction. ♦Recommendation : Patient should be monitored theophylline plasma levels and observe for patient's response when starting or stopping erythromycin or clarithromycin. Tailor dosage of theophylline as needed. : Consider using a relevant anti-infective agent that is unlikely to interact.	3

Theophylline (Cont.)

Interacting drugs	Summary	Reference No.
Propranolol	♦Propranolol increases theophylline serum concentration in a dose-dependent manner. Theophylline and beta-blockers have antagonistic pharmacodynamic effects, thus reducing the effects of one or both drugs. Atenolol do not appears to alter theophylline pharmacokinetic but may interact pharmacodynamically. Others beta-blockers may produce similar pharmacodynamic antagonism. ♦Recommendation : If possible, beta-blockers should be avoided in patients receiving theophylline for bronchospastic pulmonary disease. If beta–blocker is required, cardioselective agent such as atenolol are preferable. Monitor patients for clinical changes such as a reduce in bronchodilator response.	4
Rifampin	♦Decrease plasma concentrations of theophylline; a reduction of theophylline efficacy may result. Probable mechanism is induction of the hepatic metabolism of theophylline by rifampin. ♦Recommendation : the addition or deletion of rifampin from a regimen that includes theophylline necessitate monitoring of theophylline serum levels and the patient's response; tailor theophylline dosage as needed. The theophylline dosage requirement may be higher in patient receiving rifampin.	5

Digoxin

Interacting drugs	Summary	Reference No.
Amiodarone	♦Serum digoxin level may be increased, resulting in an increase in the pharmacology and toxicity effect of digoxin. This drug interaction appears to be related to the dose of amiodarone. Due to the long half-life of amiodarone, the interaction with digoxin usually is noted after several days to weeks of concurrent therapy especially if no loading dose of amiodarone is given. Probable Mechanism is decreasing renal and nonrenal clearance of digoxin. ♦Recommendation **:** Patient should be monitored for signs and symptoms of digoxin toxicity, changes in digoxin serum levels and adjust the dose accordingly or consider empiric reduction of the digoxin dose during amiodarone therapy. Several weeks may be required before new steady-state digoxin concentration are achieved. In addition, patient should be monitored for converse effect when amiodarone is discontinued. Adjust digoxin dosage as needed.	6
Clarithromycin Erythromycin	♦The coadministration of macrolide antibiotics and digoxin may result in increased serum levels of digoxin in ≈ 10% of patients; toxicity may occur. Probable mechanism: in approximately 10% of patients, 30% - 40% of digoxin is metabolized to inactive digoxin reduction products by GI bacteria. Erythromycin or clarithromycin may reverse this tendency by altering GI flora, allowing for more active digoxin to be absorped. The steady state serum digoxin concentration approximately doubled. The effect of this interaction may occur for several weeks following erythromycin or clarithromycin administration. The effect of antibiotics on the bacterial flora that inactivate digoxin appears to persist for at least 9 weeks and may persist in some patients for several months. ♦Recommendation **:** Patient should be monitored for increased digoxin levels and symptoms of toxicity; reduce digoxin dosage as needed. **:** Consider using a relevant anti-infective agent that is unlikely to interact.	7
Methimazole Propylthiouracil	♦Serum levels of digoxin are increased in hypothyroidism or when hyperthyroid patients on a stable digoxin regimen are rendered euthyroid by methimazole or propylthiouracil. The therapeutic effect of digoxin may be increased: toxicity may occur. ♦Recommendation **:** Patient maintained in the euthyroid state by methimazole or propylthiouracil who are started on a digoxin require no special management. However, hyperthyroid patients may require a reduced dose of digoxin if they become euthyroid.	8

Digoxin (Cont.)

Interacting drugs	Summary	Reference No.
Verapamil	♦Increase digoxin serum concentrations and digoxin toxicity may result. Verapamil increase serum digoxin concentrations by an average of ≈ 60%-75%. Probable Mechanism is inhibition of renal and/or extrarenal digoxin clearance. ♦Recommendation **:** If these two drug is used, patient should be monitored for digoxin plasma concentrations and observe for signs and symptoms of toxicity. Adjust the dose as needed. It may be necessary to decrease the digoxin dosage. **:**Consider alternative: Nifedipine, isradipine, nicardipine, felodipine and amlodipine do not appear to increase digoxin concentrations.	9

Phenytoin

Interacting drugs	Summary	Reference No.
Amiodarone	♦Increare serum phenytoin concentrations with symptoms of toxicity. In addition, phenytion may decrease amiodarone serum levels. Mechanism is probably decreased metabolism of phenytoin and increased metabolism of amiodarone. ♦Recommendation **:** Patients being treated with phenytoin should be monitored for phenytoin serum concentrations and observed for altering of phenytoin response when amiodarone is added to or removed from their drug regimen. In addition, patients taking amiodarone should be monitored for reduced antiarrhythmic efficacy, if phenytoin is added to their drug regimen. Be prepare to adjust the dose of either agent. Because effects may be delayed for several weeks, long-term monitoring is necessary.	10
Cimetidine	♦Increase serum phenytoin concentrations resulting in increased the pharmacological effects of phenytoin. Phenytoin intoxication was observed in some patients. Mechanism is inhibition of the hepatic metabolism of phenytoin by cimetidine. The increase in serum phenytoin level is dose dependent. When cimetidine is started in a patient maintained on phenytoin, serum phenytoin concentration usually to begin to increase after the first or two day(s) of cimetidine therapy. A new steady state of phenytoin may be achieved as soon as 4 to 5 days or as long as several weeks or more after starting cimetidine. Stopping cimetidine usually results in a return of serum phenytoin level to precimetidine levels within about 2 weeks. ♦Recommendation **:** Patient should be monitored serum phenytoin levels and observe for phenytoin toxicity when cimetidine is given concurrently. Adjust phenytoin dosage as needed. In a patient well stabilized on both drugs discontinuation of cimetidine may result in inadequate serum phenytoin concentrations. **:** Consider alternative: Ranitidine, famotidine and nizatidine would be preferable to cimetidine in most patients receiving cimetidine.	11
Dexamethasone Methylprednisolone Prednisolone	♦Decrease steroid effect within days of phenytoin initiations and persist for 3 weeks after discontinuation. Probable mechanism is increasing of steroid metabolism because of enzyme induction by phenytoin. ♦Recommendation **:** If unable to avoid this combination, patient should be monitored for a reduced of steroid efficacy in disease state. Adjust the dose of either agent as needed. A $\geq$ 2 – fold increase in the steroid dose may be needed.	12

Phenytoin (Cont.)

Interacting drugs	Summary	Reference No.
Fluconazole	♦Fluconazole may increase plasma phenytoin concentrations substantially, resulting in phenytoin toxicity in some patients. Probable mechanism is inhibition of the hepatic metabolism of phenytoin by fluconazole. Ketoconazole and itraconazole did not produce a significant change in phenytion pharmacokinetics. ♦Recommendation : Patient should be monitored for phenytoin serum concentrations and observed the patient for toxicity or a decrease in phenytoin activity if fluconazole is added to or discontinued from the treatment regimen. Adjust the phenytoin dosage as needed.	13
Isoniazid (INH)	♦Increase serum phenytoin levels, producing an increase in the pharmacologic and toxic effects of phenytoin. Patients who are slow metabolizers of isoniazid are at increased risk for the interaction. Probable mechanism is inhibition of the hepatic metabolism of phenytoin by isoniazid. ♦Recommendation : Patients receiving both isoniazid and phenytoin should be watched closely for signs and symptoms of phenytoin toxicity and serum phenytoin levels: the phenytoin dose should be decreased if necessary. If isoniazid is discontinued, monitor the patient for a decreased therapeutic response to phenytoin and increase the doses as needed.	14
Theophylline	♦Phenytoin reduce serum theophylline concentrations and may increase theophylline dosage requirements. Probable mechanism is enhancing the hepatic metabolism of theophylline by phenytoin. ♦Recommendation : Be alert for the need to increase the theophylline dose when phenytoin is started and decrease the dose when phenytoin is stopped. Patient on chronic phenytoin therapy may require larger than expected theophylline doses.	15
Trimethoprim	♦Increase serum phenytoin concentrations, producing an increase in the pharmacologic and toxic effect of phenytoin in some patients. Probable mechanism is inhibition of the hepatic metabolism of phenytoin by trimethoprim. Phenytoin half-life was similar prolonged by Co-Trimoxazole but sulfamethoxazole alone produce only a small increase in phenytion half-life. ♦Recommendation : Patient should be monitored for phenytoin serum concentrations and observed for phenytoin toxicity or a decrease in phenytoin activity if trimethoprim is added to or discontinued from the treatment regimen. Tailor the phenytoin dosage as needed.	16

Warfarin

Interacting drugs	Summary	Reference No.
Amiodarone	♦Hypoprothrombinemic effect of warfarin is augmented by concomitant amiodarone therapy; possible hemorrhage. The mechanism is nonstereoselective inhibition of warfarin metabolism. Amiodarone can increase the prothrombin time by 50% to 100% and can reduce warfarin clearance by 35%-65% probably in a concentration dependent manner. Following initiation of amiodarone therapy, the increase warfarin effect begins with in 1 week, stabilizes after a month and may continue for weeks to months after amiodarone is discontinued. ♦Recommendation **:** A decrease in the warfarin dose by 30%-50% may be necessary to maintain the prothrombin time with in the therapeutic range. Monitor hypoprothrombinemic response closely during the first 2 to 4 weeks of amiodarone therapy: adjust warfarin dose as needed. These effects may persist for weeks to months after discontinuation of amiodarone, necessitating continued warfarin dose adjustment.	17
Aspirin	♦Aspirin (even in small doses) increases the risk of bleeding in anticoagulated patients by inhibiting platelet function and possibly by producing gastric erosions. Larger aspirin dose (>3g/day) may also enhance the hypoprothrombinemic response to warfarin. Nonetheless, the benefit of low-dose aspirin plus warfarin appears to outweigh the increased risk of bleeding in selected patients. ♦Recommendation **:** Aspirin should be combined with warfarin only when used intentionally for additive anticoagulant effects. If both drugs is used, patients should be monitored for anticoagulant function and observed for the early signs and symptoms of bleeding especially from the GI tract. Adjust warfarin dose accordingly.	18
Cimetidine	♦Increase warfarin effects; possible hemorrhage. Probable mechanism is stereoselective inhibition of the hepatic metabolism of the less potent (R)–warfarin enantiomer. In patients receiving warfarin, the addition of cimetidine usually results in a gradual increase in hypoprothrombinemia over 1 to 2 weeks. It takes about 1 week for the prothrombin time to return to precimetidine levels when cimetidine is discontinued. ♦Recommendation **:** Avoid this combination if possible, use alternative H_2–antagonists such as ranitidine, famotidine and nizatidine instead of cimetidine. **:** If cimetidine is used, monitor for altered oral anticoagulant effect if cimetidine is initiated or discontinued. Adjust warfarin dosage as needed.	19

Warfarin (Cont.)

Interacting drugs	Summary	Reference No.
Co-Trimoxazole (Bactrim®)	♦The anticoagulant effect of warfarin may be enhanced, resulting in hemorrhage. The mechanism is unclear. However, co-Trimoxazole appears to inhibit hepatic metabolism of S-warfarin. ♦Recommendation **:** If possible, Co-Trimoxazole should not be used in patients anticoagulated with warfarin. A non–interacting antibiotic or heparin anticoagulation could be considered. **:** If the combination is used, monitor the patient carefully for an increased hypoprothrombinemic response and risk of bleeding during cotherapy and decrease effects upon discontinuation of Co-Trimoxazole. Adjust warfarin dosage as needed.	20
Fluconazole **Itraconazole** Ketoconazole	♦Azole antifungal agents such as ketoconazole, itraconazole and fluconazole also have been reported to increase the hypoprothrombinemic response to warfarin. Mechanism is probably inhibition of hepatic metabolism of warfarin. ♦Recommendation **:** If the combination is used, monitor the patient carefully for altered anticoagulant effect during cotherapy and decreased effect upon discontinuation of azole antifungal agent. Adjust warfarin dosage as needed.	21
Levothyroxine (Eltroxin®)	♦ The anticoagulant action of warfarin is amplified the anticoagulant action of warfarin during concurrent administration of thyroid hormones. Probable mechanism is a more rapid disappearance of vitamin K-dependent clotting factors as a result of thyroid hormone administration. ♦Recommendation **:** Closely observe for clinical signs of bleeding and monitor coagulation indices. Warfarin doses may need to be decreased during administration of thyroid hormone. Conversely, warfarin doses may need to be increased if concurrent thyroid hormone administration is discontinued	22
Metronidazole	♦Increase the hypoprothrombinemic response to warfarin and bleeding has occurred in some patients receiving both drugs. Mechanism is inhibition of the more active S-isomer of warfarin by metronidazole. ♦Recommendation **:** Concomitant use of metronidazole and warfarin should be avoided if possible. If these drugs must be given, patient should be monitored for an increased anticoagulant effect when metronidazole is begun and converse effect when metronidazole is discontinued. Adjust warfarin dosage as needed.	23

Warfarin (Cont.)

Interacting drugs	Summary	Reference No.
Phenobarbital	♦Reduce the effects of warfarin. Probable mechanism is increased hepatic metabolism of warfarin by phenobarbital. A patient on an oral anticoagulant who starts taking barbiturate may become underanticoagulated. A patient on both barbiturate and oral anticoagulant therapy who stops taking the barbiturate runs the risk of hemorrhage if his or her anticoagulant dosage is not readjusted. A decrease in anticoagulant response usually develops gradually after a barbiturate is initiated, with maximal effects occurring at about 2 weeks. The time course following discontinuation of the barbiturate is similar; the results of enzyme induction usually begin to diminish within a week, with little induction remaining by 2 to 3 weeks. ♦Recommendation **:** Patients receiving phenobarbital will need modification in their warfarin doses. Monitor warfarin action and tailor dosage as needed. Termination of phenobarbital therapy will result in decreased warfarin requirements. Monitor patients for several weeks. **:** Consider using an alternative: If phenobarbital is being used as a sedative/hypnotic, alternative sedetive/hynotic drugs unlikely to interact with warfarin included diazepam, flurazepam, chlordiazepoxide or diphenhydramine should be considered.	24
Rifampin	♦Reduce the hypoprothrombinemic effect of warfarin to a clinically significant extent in most patients by increased hepatic enzyme metabolism of warfarin. Dose adjustment of ≥ 50 % may be required in some patients. Rifampin–induced inhibition of warfarin hypoprothrombinemia is maximal 5 to 10 days after starting rifampin; it probably dissipates over a similar time period when rifampin is discontinued. ♦Recommendation **:** When rifampin are administered concomitantly with warfarin, patients should be monitored for anticoagulant response. Increased dosage of warfarin will likely be required. In addition, monitor coagulation parameters closely when rifampin are discontinued to avoid excessive hypoprothrombinemia and bleeding.	25

Ciprofloxacin (Oral)

Interacting drugs	Summary	Reference No.
Antacids: $Al(OH)_3$, $Al(OH)_3$-$Mg(OH)_2$	♦Aluminum hydroxide or Aluminum-Magnesium hydroxide containing antacid could substantially decrease the absorption of oral ciprofloxacin; potentially decrease ciprofloxacin effectiveness. ♦Recommendation **:** This interaction can be minimized by giving the oral ciprofloxacin at least 2 hours before or 6 hours after the antacid.	26
$FeSO_4$ Ferrous fumarate (F.B.C)® (Ferli-6)®	♦Iron salts including Ferrous sulfate, Ferrous fumarate and Ferrous gluconate could decrease GI absorption of ciprofloxacin by 40% to 50% by formation of an iron-ciprofloxacin complex; potentially lowers ciprofloxacin serum concentration and may lead to therapeutic failure. ♦Recommendation **:** This interaction can be minimized by giving ciprofloxacin at least 2 hours before any oral iron product.	27
Sucralfate (Ulsanic®)	♦The administration of sucralfate markedly reduces ciprofloxacin serum concentrations (up to 85%); loss of antibiotic effect may occur. This effect may be due to complexation between ciprofloxacin and aluminum contained in sucralfate which inhibits the absorption of ciprofloxacin. Sucralfate could produce a similar interaction with norfloxacin, olfloxacin, lomefloxacin and sparfloxacin. ♦Recommendation **:** This interaction can be minimized by given oral ciprofloxacin several hours before or > 6 hours after sucralfate.	28

APPENDIX II

Alerting Drug Interactions with Theophylline , Digoxin , Phenytoin , Warfarin , Oral ciprofloxacin

Theodur®, Bronchil® (Theophylline)

BH name		Generic name
Cimidine , Tagamet	↑	Cimetidine
Ciprobay , Cifloxin	↑	Ciprofloxacin
Erythrocin , Ilosone	↑	Erythromycin
Betalol , Inderal , Inderal – La	↑	Propranolol
Rifamiso , Rifater , Rimactane , Rimactazid	↓	Rifampin

Lanoxin® (Digoxin)

BH name		Generic name
Cordarone	↑	Amiodarone
Klacid	↑	Clarithromycin
Erythrocin, Ilosone	↑	Erythromycin
Tapazole	↑	Methimazole
PTU	↑	Propylthiouracil
Isoptin	↑	Verapamil

Ciprobay®, Cifloxin® (Oral) * (Ciprofloxacin)

BH name*		Generic name*
Actal, $Al(OH)_3$, Alumed , Dioval , Gacida , Gelusil , Veragel – DMS	↓	Antacid , $Al(OH)_3$
$Feso_4$	↓	Ferrous sulfate
F.B.C , Feri – 6	↓	Ferrous fumarate
Ulcefate , Ulsanic	↓	Sucralfate

Key

- " * " = Intervene a nurse by telephone
- " Red letter " = Intervention by telephone
- " Black letter " = Recording in a drug interaction record file
- " Bold letter " = Significance rating 1
- " Roman letter " = Significance rating 2
- " ↑ " = Increase alerting drug serum level
- " ↓ " = Decrease alerting drug serum level
- " – " = Pharmacologic antagonism
- " + " = Additive / Synergistic effect
- " ↓ " = The effects of interacting drug are decreased by alerting drug

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APPENDIX II

Alerting Drug Interactions with
Theophylline , Digoxin , Phenytoin , Warfarin , Oral ciprofloxacin

Orfarin® (Warfarin)			Dilantin® (Phenytoin)		
Cordarone	↑	Amiodarone	Cordarone	↑	Amiodarone
Aspent Gr.5, Aspent M, Aspirin, Cardiprin	+	Aspirin	Cimedine, Tagamet	↑	Cimetidine
			Decadron, Oradexon	↓	Dexamethasone
Cimidine, Tagamet	↑	Cimetidine	Diflucan, Flucozole	↑	Fluconazole
Bactrim, Bactrim M, Co – Trimoxazole, Septrin	↑	Co-Trimoxazole	INH, Rifamiso, Rifater, Rimactazid	↑	Isoniazid
			Depo-medrol, Depo-medrol with lidocaine, Solu-medrol	↓	Methyprednisolone
Diflucan, Flucozole	↑	Fluconazole			
Sporal	↑	Itraconazole	Di-Adreson F	↓	Prednisolone
Fungazol, Nizoral	↑	Ketoconazole	Bronchil, Theodur	↓	Theophylline
Eltroxin	+	Levothyroxine	Bactrim, Bactrim M, Co-Trimoxazole, Septrin	↑	Trimethoprim
Flagyl	↑	Metronidazole			
Gardinal , Phenobarbitone, Phenobarb Elix.	↓	Phenobarbital			
Rifamiso, Rifater, Rimactane, Rimactazid	↓	Rifampin			

Key

" * "	= Intervene a nurse by telephone	" ↑ "	= Increase alerting drug serum level
" Red letter "	= Intervention by telephone	" ↓ "	= Decrease alerting drug serum level
" Black letter "	= Recording in a drug interaction record file	" – "	= Pharmacologic antagonism
" Bold letter "	= Significance rating 1	" + "	= Additive / Synergistic effect
" Roman letter "	= Significance rating 2	" ↓ "	=The effects of interacting drug are decreased by alerting drug

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Appendix III

Status	Patient's name	HN	Room No.	Drug Interaction		Detected date-time	Detected pharmacist
				Alerting drug	Interacting drug		

APPENDIX IV

Staff pharmacist intervention form

Date of detection_____Time_____

Patient name_____HN_____Room_____

Detected drug interaction_____VS_____

Contact to ☐ Physician ☐ Nurse

Intervention _____

Result of intervention
☐ Accepted
☐ Not accepted
☐ Unknown

Pharmacist _____

APPENDIX V
Data collecting form

1. Patient profile	
Patient name _____ HN _____Room No. ____ Age _____ Gender □1Male □2Female Height _____ Weight _____ Admission date _____ Discharge date _____ Duration of hospital stay _____ Ward □ 1 7A □ 2 8A □ 3 8C □ 4 8D □ 5 11A □ 6 11B □ 7 11C Attending physician _____ Consultant physician _____ _____ _____ No. of physician/case _____ CC:_____ _____ PI:_____ _____ _____ Past medical history: _____ _____ _____ _____ Allergy:_____ Social history:_____ PE:_____ _____ _____ Impression on admission/diagnosis: _____ _____ Drug prior admission: _____ _____ _____ _____ _____ _____ _____	1. HN_____ 2. ___years 3. □1 □2 4. _____ days 5. □1 □2 □3 □4 □5 □6 □7 6. 7. _____ 8.

2. Medication profile			
Drug and dosage	Date/Time (start)	Date/Time (Stop)	Physician

3. Laboratory tests

1. Biochemistry										
Glucose	70-109 mg/dl									
BUN	10-20 mg/dl									
Cr	0.5-1.5 mg/dl									
Uric acid	2-8 mg/dl									
Na^+	135-145 mEq/l									
K^+	3.5-5.5 mEq/l									
Cl^-	95-105 mEq/l									
CO_2	22-32 mEq/l									
T.billi	0.2-1.3 mg/dl									
D.billi	0-0.4 mg/dl									
A.P.	20-110 U/l									
AST	5-40 U/l									
ALT	5-40 U/l									
Albumin	3.8-5 gm/dl									
Trig	0-150 mg/dl									
Chol	0-200 mg/dl									
Gamma GT	5-45 U/l									
Other										

2.Hematology								
Hct % (M 40-54, F 37-47)								
Hb (14-18 gm/dl)								
WBC (5-10x10^3/µl)								
N (55-75%)								
L (20-35%)								
E (1-5%)								
PLT (150-450x10^3/µl)								

3. UA								
Color/Transparency								
Specific gravity								
PH								
WBC/RBC								
Cast								
Epithelial cell								
Nitrite								

4. Vital sign									
Time									
Temp									
RR									
PR									
BP									
Input									
Output									

5. Bacteriology	Result	Sensitivity

6. Others	Investigate	Details

Date	Progress	Physician

4. Monitoring of drug interaction

Relevant drug regimen	Date														

Relevant drug regimen	Date														

* = Date of intervention.
** = Date that physician or nurse do as their acceptance.

Patient outcome

DI assessment □1.Actual DI □2.Potential DI Discharged status □1.Recovered □2.Improved □3.Not Improved □4.Dead	9. □1 □2 10. □1 □2 □3 □4

5. Alerting drug interaction data

Date of detection _____ Time _____	11. Date _____
Detected drug interaction _____ VS _____	12. □1 - □35
Significant rating □1 □2	13. □ 1 □2
Severity □ 1.Major □ 2.Moderate	14. □1 □2
Mechanism of DI □ 1.Pharmacodynamic □ 2.Pharmacokinetic	15. □ 1 □2
Detected by □ 1.Staff pharmacist □ 2.Clinical pharmacist	16. □ 1 □2
Detected pharmacist _____	17.
Person to be contacted □ 1.Physician □ 2.Nurse	18. □1 □2
DI occurring before admission □ 1.Yes □ 2.No	19. □1 □2
No. of patient drug items while potential DI were prescribed____	20. _____
Drug interaction prescriber □ 1.Attending physician □ 2.Consultant physician □ 3.Multiple prescriber	21. □1 □2 □3

6. Intervention, acceptance and impact on patient care process regarding DI.	
Assessment _____ _____ _____ _____ _____ _____ _____	
Intervention date _____ Intervention to _____ Intervention _____ _____ _____ _____ _____ _____ _____	22.
Intervention taken □ 1.Yes □ 2.No _____ Intervention by □ 1.Staff pharmacist □ 2.Clinical pharmacist □ 3.Staff&Clinical pharmacist Mode of intervention □ 1.Telephone □ 2.Face-to-face	23. □1 □2 24. □1 □2 □3 25. □1 □2
Type of intervention □ 1.Suggest alternative drug □ 2.Increase dose □ 3.Decrese dose □ 4.Discontinue drug □ 5.Monitor laboratory test/serum level of _____or observe clinical signs & symptoms during cotherapy. □ 6.Monitor laboratory test/serum level of _____ or observe clinical signs & symptoms when precipitant drug is discontinued. □ 7.Change time of drug administration. Result of acceptance □ 1.As recommended □ 2.Difference from recommended _____ □ 3.Can not assess □ 4.Not accept Reason for not accept □ 1.Patient can be stable on this interaction for long Time. □ 2.The problem is not clinically significant. □ 3.Other _____	26. □1 □2 □3 □4 □5 □6 □7 27. □1 □2 □3 □4 28. □1 □2 □3

Action taken regarding DI after intervention □ 1.Laboratory tests ordered, drug discontinued. □ 2.Laboratory tests ordered, empiric adjusted dose. □ 3.Laboratory tests ordered, no changed in therapy. □ 4.Laboratory tests ordered, dosage changed. □ 5.Laboratory tests ordered, changed drug. □ 6.Observed clinical signs and symptoms, drug discontinued. □ 7.Observed clinical signs and symptoms, empiric adjusted dose. □ 8.Observed clinical signs and symptoms, no changed in therapy. . □ 9.Observed clinical signs and symptoms, dosage changed. □ 10.Observed clinical signs and symptoms, changed drug. □ 11.Changed time of drug administration. □ 12.Other _____	29. □1 □2 □3 □4 □5 □6 □7 □8 □9 □10 □11 □12
Time to action after acceptance □ 1.Immediately □ 2.Next physician's round □ 3.Within 24 hrs. □ 4.After 24hrs. □ 5.Can not assess □ 6.Not do as acceptance Reason for not do as acceptance _____ _____ _____	30. □1 □2 □3 □4 □5 □6 31.

BIOGRAPHY

NAME Miss Ayurapa Prigsuwan

DATE OF BIRTH 31 August 1972

PLACE OF BIRTH Bangkok, Thailand

INSTITUTIONS ATTENDED Silpakorn University, 1995:
Bachelor of Science in Pharmacy
Mahidol University, 2004:
Master of Science in Pharmacy
(Clinical Pharmacy)

POSITION&OFFICE Department of Pharmacy
Nakornnayok Hospital
Nakornnayok Thailand
Position : Pharmacist
Tel. 037311151
E-mail: ayurapa@yahoo.com

HOME ADDRESS 93/210 Moo 5, T. Anusawaree
A. Bangkhen, Bangkok 10220
Tel. 025222420