ANTIFERTILITY EFFECT OF SULFASALAZINE AND ITS METABOLITES
IN THE MALE RATS

BY

ANANT SRIKHAO

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ANANT SRIKHAO

Department of Physiology, Faculty of Science, Mahidol University,
Rama VI Road, Bangkok 10400

ABSTRACT

Antifertility activities of sulfasalazine and its metabolites were tested in the male rats, mice and hamsters. These drugs were given either via an oral or subcutaneous route daily for a period of 5-6 weeks. The percentage fertility of the male animals was determined by counting the number of implantations and corpora lutea in the cohabited females before, during and after drug treatments.

Male rats were more susceptible to the effect of sulfasalazine than both mice and hamsters. Sulfasalazine caused a dose-related reduction in fertility of the male rats by 1 to 5 weeks after forced feeding. Complete recovery occurred within 3 weeks after drug withdrawal. Sulfasalazine had no effect on libido since numbers of the male successfully mated during treatment were not significantly different from the controls. Sulfasalazine (400 mg/kg) and sulfapyridine (250 mg/kg), but not 5-aminosalicylic acid (150 mg/kg), produced a marked decrease in fertility by 4 weeks after subcutaneous injections. Only sulfapyridine, not sulfasalazine, was detected in the serum of the male rats when either sulfasalazine or sulfapyridine was subcutaneously injected
suggesting that sulfasalazine was broken down by intestinal microflora to form sulfa-pyridine possibly via the enterohepatic circulation. Thus, an equivalent dose on molar basis of sulfasalazine and sulfa-pyridine caused an equal reduction in per cent fertility at Week 5 after subcutaneous injections. Complete infertility was observed at high dose (500 mg/kg) of sulfa-pyridine. Blood testos-terone and weights of the testes, epididymides and other accessory sex organs, i.e., seminal vesicles, prostate glands and coagulating glands, all were in normal range after sulfasalazine and sulfa-pyridine administrations. In addition, histological pictures of the testes and all regions of the epididymis of the treated rats appeared to be normal. Spermatogenesis measured in terms of daily sperm produc- tion was also not altered by sulfa-pyridine at various doses (125, 250 and 500 mg/kg). When compared to the controls, sperm count, sperm density, spermatocrit and motility of spermatozoa taken from the cauda epididymidis of sulfasalazine or sulfa-pyridine treated rats were all significantly decreased whereas the sperm counts in the caput and the corpus were unchanged. Morphology of spermatozoa of Geimsa's stained smear from the cauda epididymidis appeared normal in sulfa-pyridine receiving groups. Subcutaneous injection of sul- fa-pyridine (500 mg/kg) for five weeks induced an enhancement of translocation along the epididymal length of $^3$H-thymidine labelled spermatozoa without altering the luminal diameter or the tubular epithelial thickness. This finding could account for the reduction in sperm count, sperm density, spermatocrit and possibly motility of spermatozoa in the cauda epididymidis of the treated rats.
Body weights of the sulfasalazine treated male rats, mice and hamsters, showed a steady increase to an equal extent to that of control and the animals appeared otherwise healthy throughout treatment periods. Furthermore, weights of the vital organs, i.e., liver, heart, lung, spleen and kidney in sulfapyridine (500 mg/kg) treated groups were normal, except that of the kidney which was slightly but significantly decreased. However, the histological structures of all these organs were normal. It is concluded that the rat is the appropriate animal model for further studies since it is most sensitive to sulfasalazine and its response resemble those reported in man. The active moiety of sulfasalazine is, in fact, sulfapyridine or its metabolic intermediates which somehow interfere with normal maturation of the epididymal spermatozoa possibly by accelerating sperm transit time and thus brings about a reduction in sperm motility, sperm density and sperm count in the ejaculate.