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Reversible male infertility induced by sulphasalazine

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Sulphasalazine (Azulfidine) was first introduced over 40 years ago as treatment for rheumatoid arthritis. The idea was to use two ‘wonder drugs’ as one compound, sulphapyridine and 5’-aminosalicylate. It was noticed that a patient who had coexisting ulcerative colitis had a marked improvement in his bowel symptoms when taking sulphasalazine (Swartz, 1942). Since then many controlled trials have confirmed this fortuitous observation and its efficiency as treatment of both the acute form of the disease and as long-term therapy to prevent relapses (Misewitz et al., 1965). It has also been shown to be effective treatment of Crohn’s disease particularly when it involves the large bowel (Summers et al., 1979).

Ulcerative colitis and Crohn’s disease have a peak age of onset in the late teens. The incidence of Crohn’s disease is rising and is estimated to be 8 per 100,000, with more than a two-fold increase in the last 20 years. The incidence of ulcerative colitis is static but is still more common than Crohn’s disease. Both diseases are commonest in North Eastern Europe and the USA. The sex ratio of male to female is roughly equal. The cause of both conditions is unknown, as is the exact relationship of one to another and it is possible that they are a spectrum of one disease (Kirsner and Shorter, 1982a, b).

SULPHASALAZINE METABOLISM

Sulphasalazine is a compound drug (Fig. 5.1) consisting of sulphapyridine linked by an azo bond to 5’-aminosalicylic acid. A small amount of the parent molecule is absorbed in the small intestine and the remainder is split

\[ \text{SULPHASALAZINE} \]

Fig. 5.1 Structure of sulphasalazine
MALE FERTILITY AND ITS REGULATION

by caecal bacteria to its component molecules. Eighty per cent of the sul-
phapyridine is absorbed and is either glucuronated or acetylated or both in
the liver and excreted by the kidneys. Circulating blood levels of sulpha-
pyridine can be used to monitor therapeutic levels. The rate of acetylation
is genetically determined. Slow acetylators are more prone to side-effects
and have high circulating levels of sulphapyridine (Das et al., 1973). The
5'-aminosalicylic acid is thought to be the therapeutically active part and to
exert its effect locally. There is, however, evidence that the parent molecule
is the active component. The exact way in which sulphasalazine exerts its
therapeutic effect is not known. However, it has anti-prostaglandin effects,
causes a decreased leukocyte chemotaxis, may alter immune function and
has antibacterial properties.

SIDE-EFFECTS OF SULPHASALAZINE

The side-effects of sulphasalazine can be divided into two groups. The
incidence of side-effects is estimated to occur in 30% of patients but are
relatively mild. The first group is dose related, acetylator phenotype depen-
dent and therefore predictable. These would include generalized side-effects
such as nausea, vomiting, malaise as well as haemolytic anaemia, reticulo-
cytosis and methaemoglobulinaemia. The second major group of side-
effects are hypersensitivity reactions that occur in an idiosyncratic manner,
skin rash, aplastic anaemia, hepatic and pulmonary dysfunction and auto-
immune haemolysis. These side-effects are not dose related and usually
occur soon after commencement of treatment. Some side-effects can be
overcome by a desensitization programme of slowly introducing the drug
(Taffet and Das, 1983). Reversible male infertility has only recently been
described as a side-effect of sulphasalazine and is dose related. It has been
estimated by Pharmacia that approximately 1.8–2.5 million people are tak-
ing sulphasalazine in the USA, a significant proportion of whom will be
males in the reproductive age.

REVERSIBLE MALE INFERTILITY INDUCED BY
SULPHASALAZINE

Male infertility due to sulphasalazine was first described by our group in
Great Britain (Levi et al., 1979) and simultaneously and independently by
Toth (1979) in the USA. Since then there have been numerous reports
confirming this observation from many different parts of the world (Birnie
et al., 1981; Freeman et al., 1982; Collen, 1980.). This side-effect is dose
related, appears to be due to the sulphapyridine moiety and is more pro-
nounced in slow acetylator phenotypes.

The effect is reversible in that sperm counts return to normal 3 months
after withdrawal of the drug (Toovey et al., 1981). Further evidence that
the antifertility effect is reversible in humans is that pregnancies occurred
following drug withdrawal. One resulted in early abortion but the rest were