

Incidence of sulphasalazine-induced male infertility

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SUMMARY Sperm analysis of 21 patients taking sulphasalazine for inflammatory bowel disease revealed that 86% had abnormal semen analysis and 72% had oligospermia.

Sulphasalazine was found empirically to be of value in the treatment of inflammatory bowel disease in the early 1940s.¹ It has become established both in the treatment of acute attacks of ulcerative colitis² and as a maintenance treatment to prevent relapse.³ Its use in the treatment of Crohn's disease is less well established, although recent reports demonstrate an advantage in its use in colonic Crohn's disease.⁴ Minor side-effects are relatively common and are dose-related.⁵ Serious side-effects are infrequent. In 1979, after nearly 40 years' use, there were reports from Toth⁶ and Levi⁷ of male infertility in association with sulphasalazine therapy. Both reported patients who had been referred to specialist infertility clinics and the authors made no attempt to survey the incidence of infertility in a population of males treated with sulphasalazine.

Methods

Male patients, between the ages of 20 and 55 years, taking sulphasalazine were selected from a gastroenterology clinic. The patients were interviewed as to the history of their inflammatory bowel disease together with details of their offspring and whether any infertility had been experienced. They were asked to produce two sperm samples at an interval of at least one week and the mean of the results for the two samples was calculated. The samples were produced by masturbation after a period of abstinence from sexual intercourse of at least 48 hours and placed and transported in universal plastic containers, at room temperature, to the cytology laboratory. The samples were immediately examined for volume, viscosity, and sperm density. Sperm

motility was assessed and graded from 0 to 4 as follows:

- Grade 0—No mobile sperm
- Grade 1—Sperm moving but no forward progression
- Grade 2—Slow forward progression
- Grade 3—Moderate forward progression
- Grade 4—Rapid forward progression

A stained film was prepared using the haematoxylin stain and this was examined for morphological abnormalities. The numbers of abnormal forms were counted and the percentage of normal sperm forms was calculated. The values compatible with fertility, used in the laboratory performing the semen analysis, were a sperm density greater than 40 million per ml and 60% of the sperm showing at least grade 3-4 motility at two hours after ejaculation.

Results

A total of 24 outpatients were interviewed. The average age was 32.8 years and age ranged from 18 to 53 years. Four patients had Crohn's disease and 20 patients had ulcerative colitis. All were clinically in remission, although two had had a relapse of their inflammatory bowel disease within the preceding six months. The average duration of the inflammatory bowel disease was 3.8 years with a range from two months to 10 years. Nineteen patients were on 2 g sulphasalazine a day and five were on 4 g. Five patients were also on steroids, two on ferrous sulphate, and one on azathioprine.

Twenty-two patients were married and they had fathered a total of 36 children, an average of 1.6 children per married man. However, only five of these children had been conceived while the father was taking sulphasalazine; one of

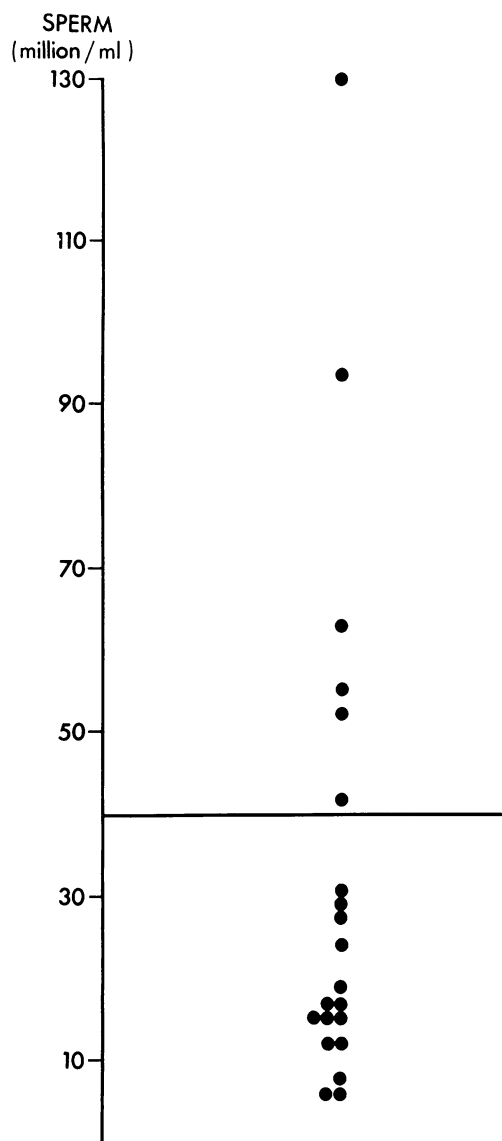


Fig. 1 Sperm density.

these babies was still-born. All 35 surviving babies were normal.

At the time of interview all the patients had normal haemoglobin, liver function tests, plasma proteins, and blood folates. On examination they all had normal male external genitalia and testes. None of the patients had had surgery for femoral or inguinal hernias.

Twenty-one patients were able to produce two sperm samples and the average time for production to examination in the laboratory was 57 minutes. Fifteen out of 21 patients had sperm

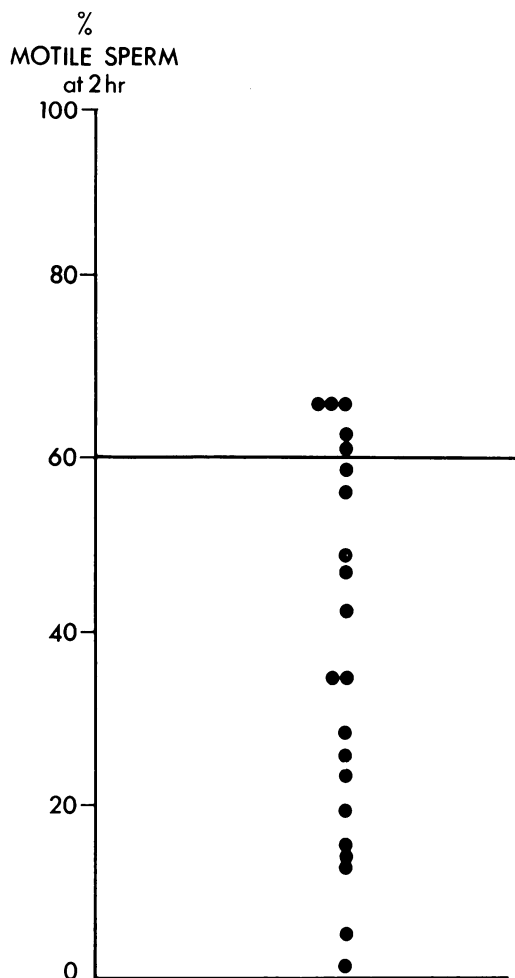


Fig. 2 Percentage of sperm motile at one hour.

counts of less than 40 million per ml, and of these 11 had a sperm count of less than 20 million per ml (Fig. 1). Sixteen patients had less than 60% of the sperm motile at one hour and six out of 21 (Fig. 2) had less than 60% of normal sperm forms in the average count (Fig. 3). It was impossible to reliably identify specific morphological abnormalities in the specimens. Only three patients had normal semen analysis.

Sulphasalazine was discontinued in one patient who wanted to increase his family and this was followed by a return to normal of semen analysis (Fig. 4) within two months.

Conclusion

In a group of 21 patients with inflammatory bowel disease who were taking sulphasalazine 18

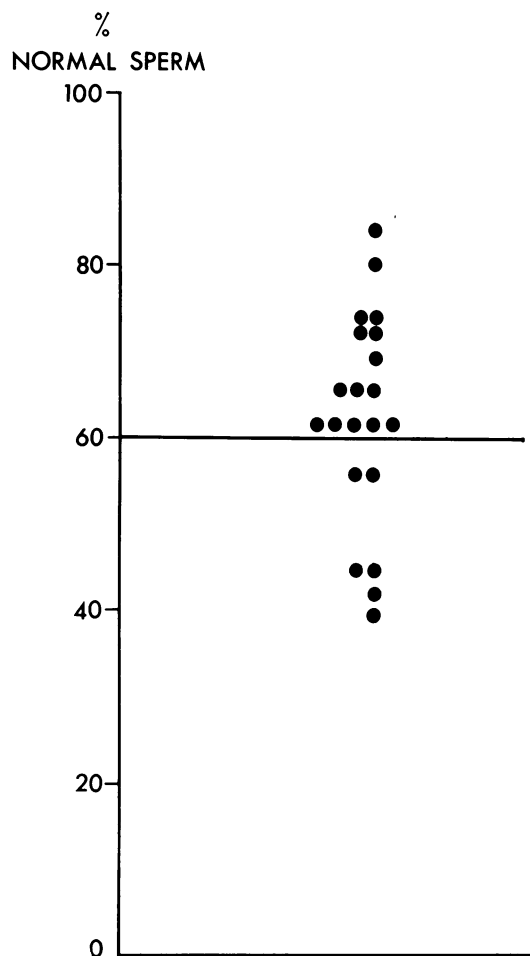


Fig. 3 Percentage of normal sperm.

(86%) had abnormal semen analysis and 15 (72%) had oligospermia. The lack of uniformity of effect on semen may represent a genetic predisposition to sensitivity to sulphasalazine but is more likely to reflect the variation of blood levels which have been demonstrated in the population of patients taking this drug.⁸

It has been demonstrated that sulphapyridine levels in the blood correlate closely with therapeutic efficacy and with many of the common side-effects.⁵ It is hoped later to correlate seminal analysis with serum sulphapyridine levels.

The mechanism by which sulphasalazine exerts its effect on semen quality remains to be explained. Sulphasalazine is split in the colon to sulphapyridine and 5 amino-salicylic acid. There are no reported cases of infertility in association with sulphonamides, although these are not

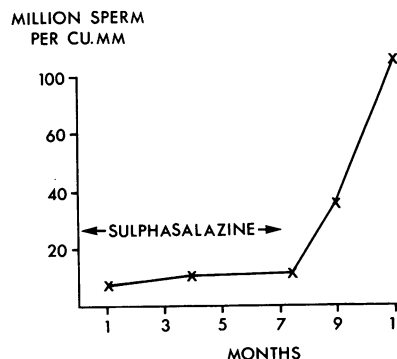


Fig. 4 Rise in sperm count after discontinuation of sulphasalazine.

usually prescribed in prolonged courses. Five amino-salicylic acid has an action as a prostaglandin synthetase inhibitor and it has been speculated⁴ that this may be the cause of the infertility associated with sulphasalazine therapy.

We conclude that impaired semen quality is a common and reversible feature of sulphasalazine therapy. In our experience most of our patients had completed their families before contracting inflammatory bowel disease. However, three patients had previously sought advice regarding infertility and had been told that they were infertile. It is important to screen all men on sulphasalazine who wish to have more children for these abnormalities, and if they are having difficulty in fathering a family they should have the sulphasalazine withdrawn under close medical supervision. If a relapse occurred an alternative remedy would have to be used.

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