

Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution

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SUMMARY Seminal abnormalities are commonly found during sulphasalazine treatment. Although these changes appear reversible after drug withdrawal this may result in colitis relapse. Animal studies suggest that 5-aminosalicylic acid, the active component of sulphasalazine, does not impair fertility. Sixteen patients with quiescent ulcerative colitis were studied. Each patient produced three samples of semen at weekly intervals. Of the 48 samples analysed 39.6% showed oligospermia, 41.7% showed an increased number of abnormal forms and 91.7% showed impaired motility. Nine patients substituted enteric coated mesalazine (5-aminosalicylic acid) for sulphasalazine for a minimum period of three months. During this time one patient developed a salmonella associated colitis relapse; the others remained well. Improvement in sperm count ($p < 0.02$), motility ($p < 0.001$) and morphology ($p < 0.02$) occurred in all cases. To date, four successful pregnancies have resulted, three in couples complaining of long term infertility. Treatment with enteric-coated mesalazine allows the recovery of seminal abnormalities induced by sulphasalazine in patients with colitis.

Since its introduction in 1942 sulphasalazine (SASP) has proved useful in the management of ulcerative colitis. It is of some benefit in mild and moderately active colitis^{1,2} but its main value is its ability to reduce disease relapse rate^{3,4} and lifelong treatment is usually recommended.

Chemically, SASP is an unusual drug having two components: 5-aminosalicylic acid (5ASA) and sulphapyridine, linked by an azo bond. When taken by mouth most of the drug reaches the caecum intact where it is split by bacterial azoreductases into its component parts.⁵ Studies in active colitis have shown that 5ASA is the active therapeutic component⁶⁻⁸ and suggest that its action is mainly topical.⁹ When taken by mouth, however, 5ASA is rapidly absorbed in the small intestine¹⁰ and is unlikely to reach the colon in therapeutic concentrations. Azo

linkage to sulphapyridine prevents this absorption and allows delivery of 5ASA to its site of action.

Unfortunately many patients are denied the beneficial effects of SASP as unwanted effects are common. As most of these are attributed to the sulphapyridine component^{11,12} new drug formulations have been developed to deliver 5ASA to the colon without the need for this potentially toxic carrier.^{13,14} The evaluation of such compounds should involve not only an assessment of their clinical efficacy but also ensure their freedom from recognised SASP side effects.

Male infertility is one such side effect that has caused considerable concern in recent years. Although seminal parameters and fertility improve after drug withdrawal this leaves the patient at risk of colitis relapse. The aim of the present study was, therefore, to assess the effect of enteric coated mesalazine (5ASA) substitution of SASP treatment on seminal activity in patients with chronic ulcerative colitis.

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Received for publication 8 January 1987.

Methods

PATIENTS

Sixteen patients (aged 23–39 years) with chronic ulcerative colitis in well established clinical remission were studied. Each gave informed consent and the study protocol was approved by Salford Area Health Authority Ethical Committee. All had been taking sulphasalazine (Salazopyrin, Pharmacia) 2–3 g daily in divided doses for a minimum period of three months (mean 2.8 years). Patients with a history of colitis relapse or febrile illness in the three months preceding the study period and patients taking other drugs known to affect fertility were excluded.

Three samples of semen were produced at intervals of at least one week. Samples were obtained by masturbation after a minimum of 72 hours abstinence and were analysed within 60 minutes of emission. After liquefaction, ejaculate volume was noted and sperm density, motility and morphology were determined by standard methods¹⁵ (normal values: sperm density more than $40 \times 10^6/\text{ml}$, sperm morphology less than 30% abnormal forms and sperm motility more than 60% actively progressive forms within one hour from emission). During morphological assessment particular note was made of increased numbers of large headed sperm forms (normal range: less than 3%).¹⁶

After this initial assessment nine patients substituted enteric coated mesalazine (Asacol, Tillotts Laboratories) for sulphasalazine. Dose equivalence was based on a scale of 1 g sulphasalazine to 400 mg mesalazine. After a minimum period of three months a further three samples of semen were analysed.

STATISTICAL ANALYSIS

All results are expressed as mean \pm SD. Comparisons of semen volume, sperm mortality and sperm mor-

phology during the two treatment periods were analysed using paired *t* tests. Sperm counts, however, were not normally distributed and were therefore analysed using Wilcoxon's matched-pairs test.

Results

Of the 48 samples analysed during SASP treatment 39.6% showed oligospermia, 41.7% an increased number of abnormal forms and 91.7% impaired motility (Fig. 1). Only one of the 16 patients had normal values for sperm count, motility and morphology in all three samples. No significant correlation could be found between seminal impairment and SASP dose. Morphological assessment revealed an increased number of large headed 'megalo' forms in 29 of the 48 samples (Fig. 2).

Of the nine patients who substituted mesalazine for SASP eight remained well. One patient developed a relapse of his colitis associated with a salmonella infection but remained on mesalazine throughout and was studied three months after resolution of his symptoms.

Mesalazine substitution was associated with improvement in all seminal parameters. Mean sperm count rose from $50 \pm 66.7 \times 10^6/\text{ml}$ to $118 \pm 122 \times 10^6/\text{ml}$ ($p < 0.02$), sperm motility rose from $20 \pm 20.3\%$ to $52 \pm 17.1\%$ ($p < 0.001$) and the percentage of abnormal sperm forms fell from $32 \pm 17.6\%$ to $16 \pm 8.7\%$ ($p < 0.02$). Semen volume, however, showed no significant change ($p > 0.2$). Despite marked within subject variability, which is well recognised in normal fertile men,¹⁷ individual results show consistent improvement for each patient and also within each individual sample (Fig. 3). Megalo forms, however, found in excess in 67% of the samples during SASP treatment persisted in 46% of samples after three months mesalazine treatment.

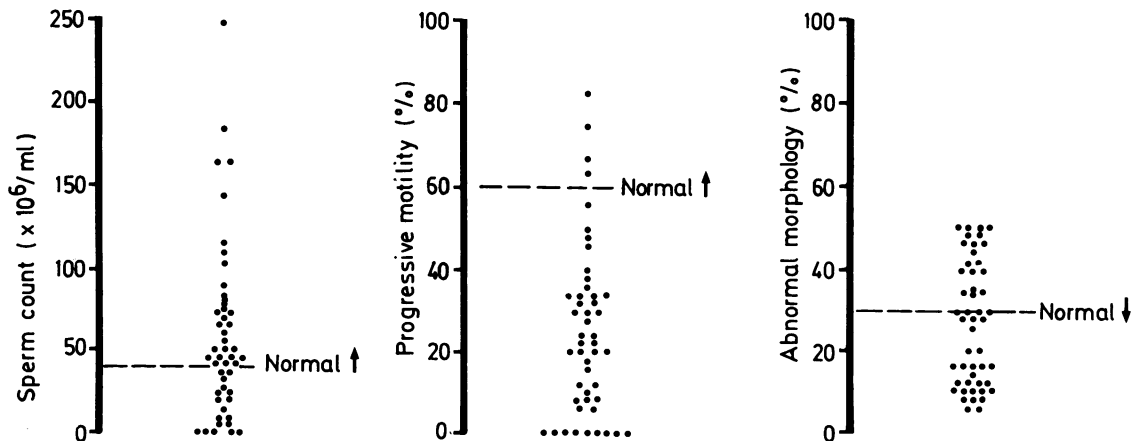


Fig. 1 Seminal activity during sulphasalazine treatment.

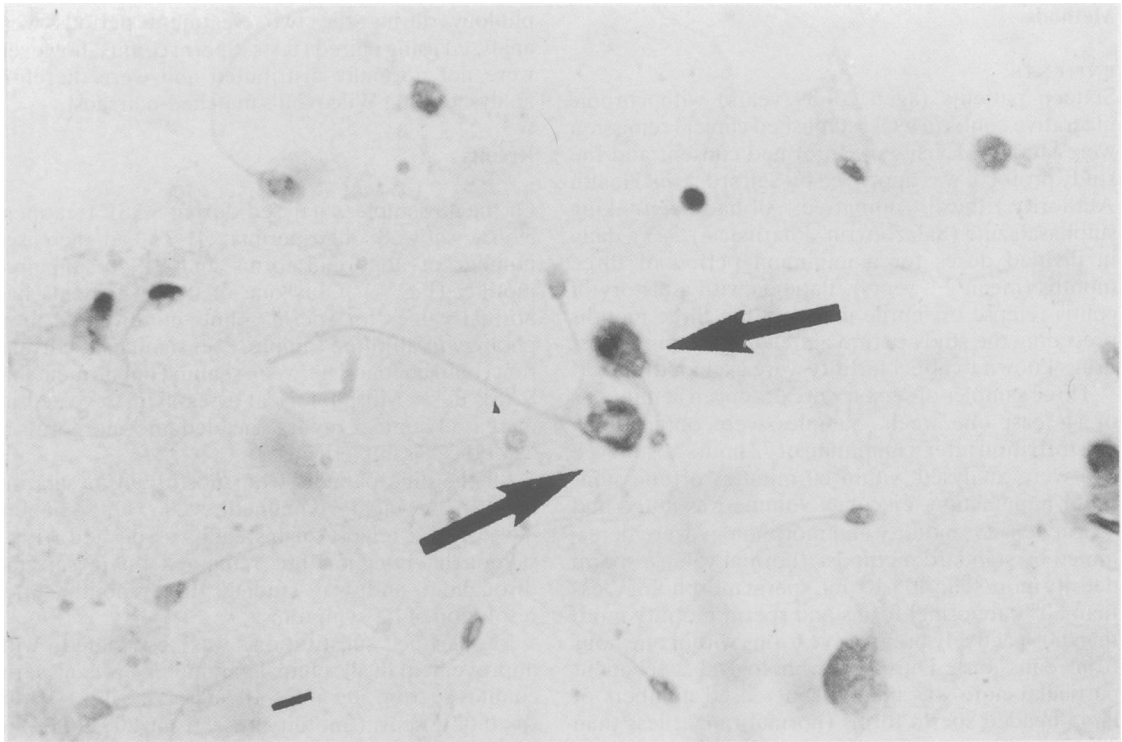


Fig. 2 Large headed 'megalo' sperm forms (arrows), excessive numbers often seen during sulphasalazine treatment.

In contrast with the changes seen in sperm count and morphology, where most values returned to the normal range, sperm motility showed suboptimal improvement. This prompted reassessment of two patients after 12 months of mesalazine treatment and in both further improvement occurred and megalo forms disappeared. Sperm motility, however, remained subnormal in one patient (Fig. 4).

Five pregnancies were conceived by four patients after a mean interval of 3.7 months on mesalazine treatment. Three of these pregnancies occurred in separate couples complaining of longterm infertility and in whom investigation of the wife had proved normal. One pregnancy conceived five weeks after substitution miscarried while the others have resulted in the delivery of four healthy offspring.

Discussion

Sulphasalazine associated male infertility was first reported independently by Levi *et al*¹⁸ and by Toth¹⁹ in 1979. Both described a small number of men complaining of infertility in whom seminal impairment improved on drug withdrawal and pregnancies

ensued. Others have confirmed these findings²⁰⁻²² and surveys show that the majority of men taking SASP have some degree of seminal impairment.^{23,24}

This impairment is characterised by oligospermia, poor sperm motility and an increased number of abnormal sperm forms either alone or in combination. A characteristic ballooned cell type, the megalo form, has also been described.¹⁹ In a study assessing sperm head size by image analysis Hudson *et al*²⁵ found that patients taking SASP had significantly larger sperm heads than non-colitic oligospermic men. After drug withdrawal, however, sperm head size increased further before becoming smaller and did not return to normal within the study period. Persistence of megalo forms after short term drug withdrawal has also been noted by others¹⁹ and in the present study 46% of samples contained megalo forms after three months mesalazine treatment. After 12 months mesalazine substitution excessive numbers of megalo forms were not present though the number of samples studied was small.

Nuclear chromatin abnormalities have also been observed in the sperm heads of patients with inflammatory bowel disease. Although it has been suggested that these abnormalities are characteristic of

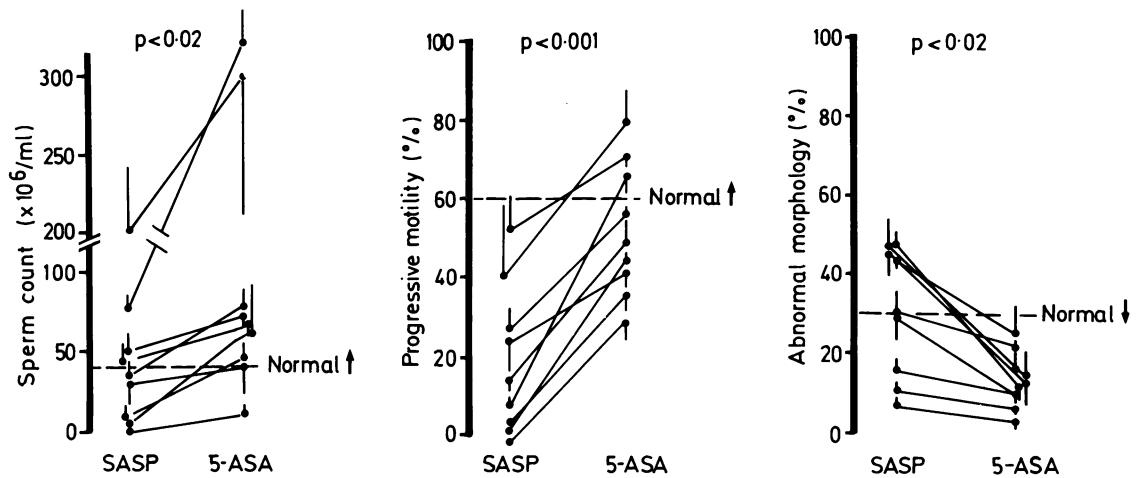


Fig. 3 Influence of mesalazine substitution on seminal activity. Mean \pm SD of three samples during each treatment period ($n=9$).

inflammatory bowel disease their relationship to SASP treatment has been questioned.²⁶

In the present study motility was the seminal characteristic most frequently affected by SASP treatment. It was, therefore disappointing to find only partial recovery of motility during mesalazine treatment, especially as other indices improved so dramatically. The published data, however, suggest that this may occur after SASP withdrawal alone²⁷ and a mesalazine effect thus seems unlikely.

The mechanisms by which SASP induces seminal abnormalities remains obscure.²⁸ The prolonged recovery period after drug withdrawal suggests an

effect early in spermatogenesis, which in man takes 74 ± 4 days,²⁹ and direct drug toxicity at this stage seems likely. Animal studies suggest the sulphapyridine component of SASP is responsible while 5ASA does not appear to affect fertility.²⁸

Studies of human seminal parameters with alternative salicylate formulations have been limited. Three cases of SASP associated infertility successfully treated with Balsalazide have been reported.³⁰ Chemically, this compound comprises 5ASA linked by an azo bond to an inert, non-absorbed carrier, 4 amino- β -benzoylalanine. Although pharmacokinetic studies have shown it is metabolised in a similar manner to SASP³¹ studies of its clinical efficacy are awaited.

In addition to the present study two cases of SASP infertility treated with enteric coated mesalazine (Asacol) have been reported.^{32,33} This formulation aims to deliver 5ASA to the colon by means of its coating, Eudragit S, an acrylic resin that disintegrates releasing 5ASA only above pH 7, the prevailing pH of the terminal ileum and colon.^{34,35} Clinically, it may be useful for patients intolerant of SASP³⁶ and preliminary studies suggest it may be as effective as SASP in the maintenance treatment of ulcerative colitis.³⁷ The present studies show that it allows the recovery of seminal abnormalities commonly seen in patients taking maintenance SASP treatment for chronic ulcerative colitis.

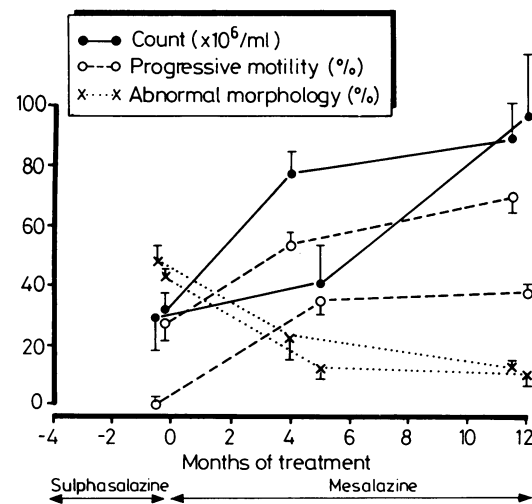


Fig. 4 Results of prolonged mesalazine substitution in two patients. Mean \pm SD of three samples.

The authors gratefully acknowledge the advice of Dr M Haeney, Department of Immunology, Hope Hospital, Ms J Rostron for preparation of the manuscript, and the participation of their patients. Preliminary reports of this study were presented at

the BSG Meeting, September 1986 (*Gut* 1986; **27**: A1272) and at the World Congress of Gastroenterology, September 1986 (*Dig Dis Sci* 1986; **31S**: 3195).

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