and is acceptable only because death is almost inevitable without operation.

Attempts to improve the operation and make it safer have led to several modifications. Thus, some surgeons have not removed the wall of the aneurysm and have used it to fold over the graft, which may be anastomosed by the inlay technique. Others have replaced the aneurysm by a straight tube graft when the aortic bifurcation is relatively healthy. Aortic aneurysms often splay the bifurcation, however, and are often associated with diseased or aneurysmal common iliac arteries. Orr and Davies² suggested that aneurysmal common iliac arteries with quite widely separated origins from the aorta are not necessarily an indication for a bifurcation graft, and they used straight grafts for aortic aneurysms in 90% of their more recent cases. This is a higher figure than that recorded by any other surgeons. Furthermore, they attributed a reduction in operative mortality from 64% to 38% to a change from bifurcation to straight grafts. Much more evidence will be required before these conclusions can be accepted.

Operative mortality depends on many variables, including the patient's age, the degree of shock, the presence of other disease, and accidents during the operation. My series, although consisting of only five patients, did not include a patient who would have been suitable for a straight graft. Chiariello *et al*¹² recorded a 79% survival in their large series of ruptured aneurysms, but they were able to use straight grafts in only 16% of cases. Aneurysm of the common iliac artery is not a benign disease. I found one fatal ruptured common iliac artery in the hospital series and Graham *et al*¹³ recorded five ruptured iliac aneurysms. Barker¹⁴ warned that dilatation of the common iliac artery may progress to late rupture below a straight graft. The choice of a straight graft should therefore depend on the finding of relatively normal iliac arteries. A bifurcation graft is safer when these vessels, or their origins from the aorta, are grossly abnormal.

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References

- ¹ Turk, K A D, *Proceedings of the Royal Society of Medicine*, 1965, **58**, 869.
- ² Orr, W M, and Davies, M, *British Journal of Surgery*, 1974, **61**, 847.
- ³ Creech, O, *Annals of Surgery*, 1966, **164**, 935.
- ⁴ Clifton, M A, *British Journal of Surgery*. In press.
- ⁵ Talbot, S, and Langman, M J S, *Postgraduate Medical Journal*, 1972, **48**, 414.
- ⁶ Pryor, J P, *British Medical Journal*, 1972, **3**, 735.
- ⁷ Cooley, D A, and DeBakey, M E, *Postgraduate Medicine*, 1954, **16**, 334.
- ⁸ Bahnson, H T, *Circulation*, 1954, **9**, 494.
- ⁹ Gerbode, F, *Surgery, Gynecology and Obstetrics*, 1954, **98**, 759.
- ¹⁰ Graham, A L, *et al*, *Archives of Surgery*, 1968, **97**, 1024.
- ¹¹ David, J P, Marks, C, and Bonneval, M, *Surgery, Gynecology and Obstetrics*, 1974, **138**, 591.
- ¹² Chiariello, L, *et al*, *American Journal of Surgery*, 1974, **128**, 735.
- ¹³ Graham, K J, Cole, D S, and Barratt-Boyes, B G, *Australian and New Zealand Journal of Surgery*, 1971, **41**, 113.
- ¹⁴ Barker, W F, *Peripheral Arterial Disease*, 2nd edn, p 412 and 430. Philadelphia, Saunders, 1975.
- ¹⁵ Mavor, G E, Davidson, L D, and Clark, C G, *British Journal of Surgery*, 1959, **47**, 292.
- ¹⁶ Savage, C R, and Harris, J D, *Lancet*, 1960, **2**, 466.
- ¹⁷ Martin, P, *Proceedings of the Royal Society of Medicine*, 1965, **58**, 867.
- ¹⁸ Calne, R Y, *Annals of the Royal College of Surgeons of England*, 1969, **44**, 18.
- ¹⁹ Tibbs, D J, *Lancet*, 1960, **2**, 1313.
- ²⁰ Kenyon, J R, *Annals of the Royal College of Surgeons of England*, 1963, **32**, 116.
- ²¹ Elliott, J, *Anaesthesia*, 1967, **22**, 406.
- ²² Moore, H D, *Lancet*, 1967, **2**, 184.
- ²³ Short, D W, and Mackey, W A, *Scottish Medical Journal*, 1968, **13**, 416.
- ²⁴ Slaney, G, *et al*, *British Medical Journal*, 1971, **2**, 524.
- ²⁵ Eastcott, H H G, *Arterial Surgery*, p 304. London, Pitman, 1973.

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Further studies of sulphasalazine metabolism in the treatment of ulcerative colitis

G O COWAN, K M DAS, M A EASTWOOD

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Summary

Sixty-four outpatients with ulcerative colitis receiving maintenance treatment with sulphasalazine were studied to relate disease activity to serum concentrations of sulphapyridine. Of 43 patients in remission, 32 had serum sulphapyridine levels over 20 µg/ml. Ten of the 21 patients with active disease were for various reasons taking inadequate doses of sulphasalazine, as indicated

by low serum sulphapyridine levels, and of the remaining 11 patients, who had serum levels over 20 µg/ml, nine had faecal stasis proximal to active distal colitis and went into remission when treated with hydrophilic colloid or bran and an unchanged sulphasalazine dosage. This suggests that to be effective the metabolites of sulphasalazine must be delivered in the faeces to the lumen of the diseased distal segment of the colon.

High serum concentrations of sulphapyridine produce side effects; therefore slow acetylators of sulphapyridine need lower doses of sulphasalazine. Estimations of serum sulphapyridine concentrations, as well as identifying the patient's acetylation phenotype, can also be useful in assessing his compliance with treatment.

Introduction

The value of sulphasalazine (Salazopyrin) in treating ulcerative colitis is well-established.¹⁻⁴ Sulphasalazine consists of sulphapyridine linked by an azo bond to 5-aminosalicylic acid. A small

Wolfson Laboratories, Gastrointestinal Unit, Western General Hospital, Edinburgh EH4 2XU

G O COWAN, MB, MRCP, consultant physician. Lieutenant Colonel, RAMC

K M DAS, MD, PHD, research fellow (now assistant professor, Albert Einstein College of Medicine, Yeshiva University, New York)

M A EASTWOOD, MSC, FRCPD, consultant physician

proportion of sulphasalazine is absorbed from the small intestine, but most passes to the colon, where bacteria split the azo link.⁵⁻⁶ Sulphapyridine is mostly absorbed from the colon, and undergoes N-acetylation and ring-hydroxylation in the liver followed by conjugation with glucuronic acid. The serum concentration of sulphapyridine is partly dictated by the acetylator phenotype of the individual.⁷

The 5-aminosalicylic acid moiety is largely excreted in the faeces; the remainder, with most of the sulphapyridine, is excreted in the urine.⁸⁻⁹ Successful treatment of ulcerative colitis coincides with a serum sulphapyridine concentration greater than 20 $\mu\text{g/ml}$. The serum concentration of individual sulphapyridine metabolites is not important, only the total concentration, and the serum concentration of unmetabolised sulphasalazine does not correlate with therapeutic success.¹⁰

We describe here further studies of sulphasalazine metabolism in patients with active ulcerative colitis.

Patients and methods

Sixty-four patients (32 men, aged 16-76 (mean 43.9) years; 32 women, aged 19-69 (mean 42.3) years) who had been receiving maintenance treatment with oral sulphasalazine for chronic idiopathic ulcerative colitis were studied at their routine clinic attendances. They had had colitis for six weeks to 12 years.

The activity of their disease was determined according to their symptoms, the appearance of the rectal mucosa at sigmoidoscopy,¹¹ and, in most cases, the histological appearances of a rectal biopsy specimen. Remission was defined as the appearance of a normal rectal mucosa on sigmoidoscopy, with histological confirmation whenever possible. No distinction was made between mild and moderate disease activity. A form recording the personal details; the duration, extent, and activity of the disease; details of sulphasalazine dosage and probable compliance; and all other drugs concurrently used was completed, and a specimen of venous blood was obtained.

The blood was separated by centrifugation and the serum stored at -20°C . Each sample was analysed for sulphasalazine, sulphapyridine, and acetyl-sulphapyridine,^{12,13} using overnight incubation with β -glucuronidase to include sulphapyridine-glucuronide and acetyl-sulphapyridine-glucuronide in the estimations of sulphapyridine and acetyl-sulphapyridine, respectively. Acetylator phenotype was judged from the ratio of acetyl-sulphapyridine to total serum sulphapyridine. Assessment of the relation between serum sulphasalazine and total sulphapyridine metabolites provided an indication of the patients' compliance with their regular sulphasalazine treatment. The achievement of steady state levels of total sulphapyridine metabolites by regular dosage¹⁰ made it unnecessary to relate the timing of blood samples to the timing of oral sulphasalazine dosage.

Results

Forty-three patients were in remission, while 21 had mild or moderate disease activity. Twenty-nine patients were rapid acetylators of sulphapyridine, the normal population of the United Kingdom containing 55% of rapid acetylators. Fig 1 relates the disease state in rapid and slow acetylators to serum levels of total sulphapyridine metabolites. Fig 2 shows these levels in relation to sulphasalazine dosage. The 35 slow acetylators had a mean dose of sulphasalazine about 75% that of the rapid acetylators.

Four distinct groups were identified on the basis of their disease activity and whether they had serum total sulphapyridine concentrations above or below 20 $\mu\text{g/ml}$.

Group 1 comprised 32 patients in remission with sulphapyridine values of 20 $\mu\text{g/ml}$ or more. Their mean dose of sulphasalazine was 2.9 g/day, and none were receiving any other treatment. In four patients the whole colon was affected, in four the disease extended from the transverse colon, and in 24 the disease was confined to a distal proctocolitis. Colitis had generally lasted for three to seven years (total range 3 months to 20 years).

Group 2 comprised the remaining 11 patients in remission, who all had sulphapyridine values below 20 $\mu\text{g/ml}$. One patient had a concentration less than 5 $\mu\text{g/ml}$. The mean dose of sulphasalazine was 2.0 g/day, and seven remained in remission despite reduced doses of 1.0 to 2.0 g/day. The reductions in dose were necessitated by side effects on higher doses. Two had chronic disease in remission

FIG 1—Serum total sulphapyridine concentration related to disease state in rapid and slow acetylators.

FIG 2—Serum total sulphapyridine concentration related to sulphasalazine dose and disease state in rapid and slow acetylators.

for several months, felt well, and had stopped taking sulphasalazine, and one patient was also taking oral prednisolone. The whole colon was affected in one patient, the descending colon in two, and the distal sigmoid colon and rectum in eight. Again, the disease had generally lasted for three to seven years (total range 3 months to 11 years).

Group 3 comprised 11 patients with active disease and serum total sulphapyridine values of over 20 $\mu\text{g/ml}$. The mean dose of sulphasalazine was 3.0 g/day. All patients were also being treated with steroid enemas, two with additional prednisolone, one with intramuscular ACTH, and one with azathioprine. Two patients admitted to taking sulphasalazine irregularly because of nausea, but there was no evidence of irregular dosage in the remaining nine. These nine all had chronic distal colitis of moderate severity, which was confined throughout the illness to the rectum and sigmoid colon in five and extended temporarily as far as the splenic flexure of the colon in four. On further investigation all nine patients were shown to have faecal stasis proximal to the actively inflamed distal colon. In all nine cases remission of colitis was achieved within a few weeks of starting treatment with hydrophilic colloid or bran and without an increase in the dose of sulphasalazine.

Group 4 comprised 10 patients with active disease and sulphapyridine concentrations of under 20 $\mu\text{g/ml}$. Six had concentrations of under 5 $\mu\text{g/ml}$. The mean reported dose of sulphasalazine in the whole group was 2.7 g/day. Five of these patients (two men, three women)

were aged 16 to 21 (mean 21.6 years), had had colitis for several years, and took sulphasalazine very erratically. They included a 19-year-old woman who during subsequent inpatient treatment for relapsed colitis hoarded her tablets and then took them in one dose on days when she knew serum would be taken for analysis. On a reputedly regular dose of sulphasalazine 4 g/day she had high sulphasalazine concentrations (53.5–70.2 µg/ml) and low sulphapyridine concentrations (2.6–12.5 µg/ml). She presented many of the features of a disturbed psychopathic personality and later committed suicide. The other four young patients had disturbed personalities, which presented clinical and therapeutic difficulties.

Faecal stasis—As well as the nine patients in group 3, seven patients in group 1 and three in group 2 had faecal stasis. Faecal stasis was diagnosed, according to the criteria of Jalan *et al.*,¹¹ when constipation developed that required treatment with hydrophilic colloid. Evidence of the presence of hard faeces in the proximal colon was first obtained by clinical and radiological (plain abdominal films) examination. The overall incidence of faecal stasis in patients in remission was 23%, which compares with a 15.8% incidence in a previous series of 399 patients from this hospital. In this larger series faecal stasis was associated with left-sided colitis but not severity. The affected patients in group 1 included one with colitis of the whole colon, who also had diverticulitis, and six with proctocolitis, including one with diverticular disease. The three patients in group 2 with faecal stasis all had distal proctocolitis.

Discussion

These results agree closely with those of Das *et al.*,¹⁰ who found that 90% of outpatients whose ulcerative colitis was maintained in remission by sulphasalazine alone had serum total sulphapyridine concentrations of over 20 µg/ml. This concentration is achieved in rapid acetylators of sulphapyridine by doses of sulphasalazine of 3.0–4.0 g daily, whereas slow acetylators on this dose are likely to experience side effects because their serum sulphapyridine concentration will rise to over 50 µg/ml.¹² They should thus take only 2.5–3.0 g/day. Periodic estimations of serum total sulphapyridine concentrations are useful in determining the acetylator phenotype and in detecting non-compliance with treatment. While the serum concentration of sulphasalazine may fluctuate throughout the day, the serum sulphapyridine concentration changes only slowly. Therefore the time of taking blood is less important for estimating serum sulphapyridine concentrations.^{7, 10}

Active disease associated with low serum sulphapyridine concentrations despite apparently adequate sulphasalazine dosage should therefore suggest non-compliance by the patient, as 29% of those with active disease had very low (less than 5 µg/ml) serum total sulphapyridine concentrations. We assessed whether or not the patients were taking sulphasalazine regularly by comparing serum sulphasalazine and total sulphapyridine concentrations. No sulphasalazine and sulphapyridine in the serum suggests that no treatment is being taken. A high serum sulphasalazine concentration (say, over 50 µg/ml) and little (less than 5 µg/ml) or no sulphapyridine usually means that the drug was taken just before the clinic visit. Serum total sulphapyridine and sulphasalazine concentrations of over 5–10 µg/ml suggest a regular intake of sulphapyridine.

Most patients (82%) with active disease and serum total sulphapyridine concentrations over 20 µg/ml were classifiable as "constipated colitics," which suggests that adequate serum sulphapyridine concentrations alone do not ensure remission, notwithstanding absorption of sulphapyridine in normal amounts from the proximal colon. The fact that treatment with hydrophilic colloid or bran in such patients invariably induced remission, without the need for an increase in the dose of sulphasalazine, suggests that the metabolites of sulphasalazine must be delivered in the faeces to the lumen of the diseased distal segment of the colon to achieve therapeutic effect.

The stools of patients with untreated ulcerative colitis contain an excess of prostaglandins, which is reduced to normal by treatment with sulphasalazine. In vitro sulphasalazine and its 5-aminosalicylic acid moiety have antiprostaglandin effects similar to those of aspirin.¹⁶ Mennie *et al.*¹⁷ have shown the benefit of aspirin in prostaglandin-induced diarrhoea after abdominal radiotherapy. It therefore seems possible that the presence of the aspirin analogue 5-aminosalicylic acid in the lumen of the colon affected by ulcerative colitis is a major factor in producing the therapeutic benefit provided by sulphasalazine; 5-aminosalicylic acid is the moiety of the drug present in the highest concentration throughout the lumen of the colon. Sulphapyridine is a useful marker of drug dosage and compliance, but the pharmacological effect of this fraction in ulcerative colitis remains uncertain, although a high serum concentration of sulphapyridine is the main cause of the side effects of sulphasalazine.

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References

- 1 Truelove, S C, and Watkinson, G, *British Medical Journal*, 1962, **2**, 1708.
- 2 Baron, J H, *et al*, *Lancet*, 1962, **1**, 1094.
- 3 Dick, A P, *et al*, *Gut*, 1964, **5**, 437.
- 4 Misiewicz, J J, *et al*, *Lancet*, 1965, **1**, 185.
- 5 Peppercorn, M A, and Goldman, P, *Journal of Pharmacology and Experimental Therapeutics*, 1972, **181**, 555.
- 6 Peppercorn, M A, and Goldman, P, *Gastroenterology*, 1973, **64**, 240.
- 7 Schroder, H, and Campbell, D E S, *Clinical Pharmacology and Therapeutics*, 1972, **13**, 539.
- 8 Schroder, H, and Evans, D A P, *Gut*, 1973, **13**, 278.
- 9 Goldman, P, and Peppercorn, M A, *New England Journal of Medicine*, 1975, **293**, 20.
- 10 Das, K M, *et al*, *Gut*, 1973, **14**, 631.
- 11 Jalan, K N, *et al*, *Journal of the Royal College of Surgeons of Edinburgh*, 1971, **16**, 338.
- 12 Sandberg, M, and Hansson, K A, *Acta Pharmaceutica Suecica*, 1973, **10**, 107.
- 13 Hansson, K A, and Sandberg, M, *Acta Pharmaceutica Suecica*, 1973, **10**, 87.
- 14 Jalan, K N, *et al*, *Gut*, 1970, **11**, 688.
- 15 Das, K M, *et al*, *New England Journal of Medicine*, 1973, **289**, 491.
- 16 Gould, S R, and Lennard-Jones, J E, *Gut*, 1976, **17**, 828.
- 17 Mennie, A T, *et al*, *Lancet*, 1975, **2**, 942.

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