Investigation of Auranofin-induced diarrhoea

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SUMMARY Gastrointestinal function was assessed in six patients with rheumatoid arthritis who had developed diarrhoea on treatment with Auranofin. With the administration of Auranofin whole gut transit time decreased markedly (to 50% or less of control values) in five of six patients. The speed of passage of intestinal contents through the colon was certainly increased but attempts to assess transit through the upper gastrointestinal tract failed because the breath hydrogen method gave inconclusive results. There was no evidence of colitis and in all cases biopsy of the rectal mucosa appeared normal by light microscopy. In the five patients with rapid intestinal transit faecal weight increased more than two-fold (range +44 to +335%) although in only three cases were the changes sufficient to cause an increased frequency of bowel action. Overall the concentration of sodium in faecal water increased three-fold (mean values rose from 10.6 to 38.3 mmol/l). There were no significant changes in the concentrations of either potassium or chloride but bicarbonate was reduced. Faecal pH fell from a mean value of 7.5 (range 6.8-7.9) to a mean value of 6.4 (range 6.0-7.4). In the three patients who developed overt diarrhoea and in two others taking Auranofin the intestinal uptake of ^{51}Cr -EDTA was increased on average three-fold and there was a similar change in the ratio of the absorption of lactulose/mannitol. The mean clearance of alpha-1-antitrypsin from the circulation into the gastrointestinal tract was doubled. These data indicate an increase in intestinal permeability. In contrast the absorption of vitamin B₁₂ was unaffected and there was no significant change in the excretion of faecal fat although one patient developed mild steatorrhoea. Thus in a selected group of subjects with rheumatoid arthritis the administration of Auranofin caused diarrhoea in association with a reversible defect in intestinal permeability but without significant change in the absorption of nutrients.

Auranofin, an orally absorbed gold preparation, has been used in trials of treatment for rheumatoid arthritis over the past 10 years.¹ Abdominal pain and diarrhoea are common side effects which limit more widespread use of the drug. These symptoms occur most often during the first few weeks of treatment and usually disappear promptly if the drug is stopped. It is important, however, to determine the mechanism by which Auranofin causes diarrhoea especially in view of reports of enterocolitis induced by treatment with parenteral gold and one of a 69 years old woman given Auranofin.²

In a recent study of 25 patients taking Auranofin 11 had loose stools for a week or more during the course of treatment. The pathogenesis of the diarrhoea was not established. There was no evidence of malabsorption and because of the increased concentration of sodium in faecal water the authors of this report suggested that Auranofin may have a direct effect on the absorption of salt and water by the colon.³ In contrast the authors of a detailed study of a single patient who developed severe diarrhoea after being given gold thioglucose for two months concluded that the findings were consistent with a secretory diarrhoea.⁴

In this paper we report a clinical study of six patients with rheumatoid arthritis who developed diarrhoea as a result of taking Auranofin. The effect of the drug on bowel transit time, mucosal permea-

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bility, intestinal absorption and faecal fluid has been assessed.

Methods

PATIENTS

Six women with sero-positive, classical rheumatoid arthritis (ARA criteria) who had experienced loose stools or increased frequency of bowel action when taking Auranofin 6 mg/day were invited to partake in the study. They were drawn from two groups of patients entered to trials of Auranofin supervised by the Rheumatology Department, Addenbrooke's Hospital, Cambridge. The protocol for the present study was approved by the ethical committees of Addenbrooke's Hospital and of the MRC Dunn Nutrition Unit. The use of radioisotopic tracers was agreed with the Health Services Division of the DHSS. Patients were individually informed as to the nature and purpose of the study and their consent was freely obtained. None of the patients had evidence of haematological, renal, hepatic or cardiac disease, diabetes, inflammatory bowel disease, nor a clinically significant abnormality of haematology or biochemistry at the time of entry to the study. Care was taken to ensure that the patients studied had not a history of eczema or exfoliative dermatitis; nor hypersensitivity to heavy metals (other than Auranofin-induced diarrhoea).

MODE OF STUDY

Clinical details of the six selected patients are given in Table 1. Three patients who had diarrhoea during

a previous trial of therapy with Auranofin (patients 1, 3, 4) were studied at a time when their bowel habit was normal. They were given Auranofin 3 mg bd and bowel function was studied during the second week of treatment. Three other patients who developed diarrhoea during a base trial of Auranofin (patients 2, 5, 6) were transferred to this study for tests of intestinal function. Treatment with Auranofin was then discontinued and the tests were repeated after bowel function had returned to normal. During each phase a stable state was established on minimal drug therapy before starting tests of intestinal function which took place over a period of five days. In particular treatment with non-steroidal anti-inflammatory drugs was discontinued over the test period because we and others have shown that they affect measurements of intestinal permeability. All tests were closely supervised by the principal investigator (RB) in a ward in which the nursing staff were familiar with the aims of the study.

MEASUREMENT OF INTESTINAL TRANSIT AND FAECAL ANALYSIS

On day 1 subjects ingested 40 radio-opaque markers and six encapsulated dialysis bags. They were maintained on their usual diets which contained 70–100 g fat and they collected each stool into a plastic bag. Stool weight, consistency, the presence or absence of mucus and the results of a 'Haemafec' test (Diamed Diagnostics) were recorded for each specimen. Faecal fluid was obtained from recovered dialysis sacs^{5,6} and stored at -20°C until analysis.

Table 1 Clinical details of the six women admitted to the study. Ritchie index is a measure of joint inflammation on a scale which goes from 0 to 80. Steinbrocker function is a measure of disease staging on a 4 point scale based on physical findings, functional status and radiological abnormalities

Patient	Age (yr)	Weight (kg)	Length of history (yr)	Ritchie index	Steinbrocker function	Drugs (other than Auranofin)	Period of treatment with Auranofin before study (weeks)	Order of study
1	48	74	23	12	II	Prednisolone 6 mg Azothiaprime 150 mg Naproxen 1 g* Trimipramine 75 mg Indomethacin SR* 200 mg Ferrous sulphate 300 mg Dextropropoxyphene 32.5 mg with paracetamol 325 mg Nitrazepam 10 mg Cimetidine 400 mg	41	Off/on AF
2	40	69	12	6	II	Indomethacin SR* 200 mg Ferrous sulphate 300 mg Dextropropoxyphene 32.5 mg with paracetamol 325 mg Nitrazepam 10 mg Cimetidine 400 mg	—	On/off AF
3	67	58	0.5	20	II	Indomethacin SR* 150 mg Cimetidine 400 mg	6	Off/on AF
4	45	59	5	12	II	Indomethacin SR* 150 mg Cimetidine 400 mg	5	Off/on AF
5	56	66	13	0	I	Nil	—	On/off AF
6	68	78	12	5	I	Fenbufen 600 mg*	—	On/off AF

* These drugs were discontinued during the course of the study.

Each stool was radiographed and the contained radio-opaque markers counted. Accumulated faeces for each patient were refrigerated until the end of the study. They were then homogenised and aliquots taken for the measurement of fat and alpha-1-antitrypsin.

ABSORPTION STUDIES AND TESTS OF INTESTINAL PERMEABILITY

On day 2 of each test period the absorption of vitamin B₁₂ with and without intrinsic factor was measured by a dual isotope technique. On day 4 intestinal permeability to ⁵¹Cr-EDTA (30 µCi; 90–120 µg Cr-EDTA, 270–720 µg Na-EDTA); ¹⁴C-mannitol (5 g; Sp act 0.1 µCi/g) and lactulose (10 ml Duphalac) was assessed. The probe molecules contained in 50 ml water were administered orally two hours before breakfast and urine was collected in two aliquots: 0–6 hours and 6–12 hours. Urine radioactivity was measured the following day and aliquots of urine stored at –20°C for analysis of lactulose (as a single batch of samples).

MEASUREMENT OF SMALL INTESTINAL TRANSIT

Breath hydrogen concentrations (end-expiratory samples) were measured using gas chromatography before and at 15 minute intervals after the ingestion of the poorly absorbed sugars. This provides a means of assessing the transit of fluid from mouth to proximal colon.^{7 8}

ASSESSMENT OF RECTAL MUCOSA

At the end of the Auranofin phase of the study sigmoidoscopy was undertaken on each subject and a biopsy of rectal mucosa taken for histology.

ANALYSES AND CALCULATIONS

Mean whole gut transit time was estimated from the cumulative excretion of radio-opaque markers.⁹ Transit of the sugar solution through the small intestine was deemed to have occurred when breath hydrogen concentration rose 10 ppm above background.⁸

Faecal fat was measured by the classical method.¹⁰ Electrolyte concentrations (Na, K, Cl, HCO₃) in faecal fluid and stool pH were measured by standard laboratory techniques. The absorption of vitamin B₁₂ was estimated by the Dicopac method (Amersham International). ⁵¹Cr-EDTA in urine was estimated by measuring gamma emission and ¹⁴C mannitol by liquid scintillation counting. Lactulose was assayed by an enzymatic method.¹¹ The permeation across the intestine of each of the three probe molecules was recorded as the percentage of dose excreted in the urine.^{12 13} Protein loss into the intestine was measured by the alpha-1-antitrypsin

method.¹⁴ Biopsies of rectal mucosa were processed using routine histological techniques. The specimens were examined by a specialist in gastrointestinal pathology and by the principal investigator in this study (RB).

Results

CLINICAL OBSERVATIONS

Subjects remained reasonably well throughout the study except for patient 2. Initially, she was entered to a clinical trial of Auranofin at a dose of 6 mg/day. Treatment was stopped twice because of diarrhoea. The dose was then reduced to 3 mg/day. Four months after starting the treatment she developed oral ulceration which resolved after dental treatment. The patient agreed to enter the diarrhoea study and the dose of Auranofin was increased from 3 to 6 mg/day. Towards the end of the study oral ulceration recurred and this persisted until the drug was withdrawn.

During the course of the study most patients reported mild abdominal cramping after taking the morning dose of Auranofin. This led to an urge to defaecate after one to three hours. During the off Auranofin phase all patients had firm stools with a mean frequency of three to four bowel actions per five days. During the Auranofin phase of the study stool consistency changed for five out of the six patients but this led to an increased frequency of bowel action in only three subjects (with an increase in mean frequency from three to four to eight to 11 motions/five days). Stool weights were increased in five out of six patients during the test phase on Auranofin. For all six patients mean values were 155.8 g/day compared with 69.7 g/day off Auranofin (Table 2). Stools did not contain excess mucus but tests for occult blood were mildly positive on several occasions throughout the course of the study. There was no apparent change in blood loss as a result of giving Auranofin. The rectal mucosa was macroscopically normal in all subjects at the end of treatment with Auranofin.

FAECAL ANALYSIS

In patient 4 it was not possible to undertake a comparative study because the dialysis bags disintegrated during prolonged passage through the colon during the phase off Auranofin. In the other five patients there were significant changes in the composition of stool water. Mean values for faecal sodium increased from 10.6 (range 4–18) to 38.3 mmol/l (range 21–53) and faecal bicarbonate fell from 14.4 (range 8–18) to 8.7 mmol/l (range 6–14). There was no significant change in the concentrations of potassium or chloride ions (off Auranofin,

Table 2 Details of intestinal transit and bowel function in patients on and off treatment with Auranofin. Statistical analysis of data by signed rank sum test gave *p* values of 0.052 for transit time; 0.036 for stool weight

Patient	Frequency motion (per 5 days)		Whole gut transit time (h)		Small intestinal transit time (min)		Mean daily stool weight (g)	
	Off	On	Off	On	Off	On	Off	On
1	4	8	76	32	†	*	62	270
2	4	4	96	38	80	†	78	112
3	4	10	41	17	75	90	70	224
4	3	3	78	85	110	*	62	83
5	3	4	95	49	50	40	48	74
6	3	11	40	22	50	30‡	98	172
Mean values	3.5	6.7	71.0	40.5	...	...	69.7	155.8

* No rise in breath hydrogen.

† Persistently low concentration of hydrogen.

‡ Difficult to establish end-point (steady rise in hydrogen concentration from time 0).

K 27–107; C1 10–21 mmol/l; on Auranofin, K 41–99; C1 8–20 mmol/l). The changes in the concentration of electrolytes were associated with a decrease in pH of faecal water from a mean of 7.5 (range 6.8 to 7.9) to a mean of 6.4 (range 6.0 to 7.4).

GUT TRANSIT TIME

Mean whole gut transit time decreased from a mean of 71.0 hours (off Auranofin) to 40.5 hours (on Auranofin) (Table 2). Much of the reduction must be due to more rapid transit through the colon. No firm conclusions can be drawn from the breath hydrogen data regarding transit through the small intestine. The more disabled subjects found it difficult to provide samples of end-expiratory air and in four of the 12 studies there was no apparent rise in breath hydrogen. Thus comparative data were obtained from only three subjects and the results were inconsistent.

INTESTINAL ABSORPTION

Overall the faecal excretion of fat was not significantly increased by the administration of Auranofin (off Auranofin mean value 10.5, range 6.7–13.0 mmol/day; on Auranofin mean value 13.8, range 6.6–27.0 mmol/day). Only one of 12 measurements exceeded the upper limit of normal fat excretion.

Vitamin B₁₂ absorption off Auranofin both without (mean 23.4%, range 15.7 to 29.0%) and with added intrinsic factor (mean 23.3, range 14.9 to 30.0%) was normal. It did not change on treatment with Auranofin (mean value of absorption B₁₂ alone 24.6%; with added IF 24.4%).

INTESTINAL 'PERMEABILITY'

The excretion of ⁵¹Cr-EDTA was increased three-fold by the administration of Auranofin from a mean value of 1.4% at 12 hours to a mean value of

4.3% (Fig. 1). There was similar increase in the excretion of lactulose over six hours (off Auranofin mean value 0.76%; on Auranofin mean value 1.26%) with no consistent change in the excretion of mannitol (a much smaller molecule which appears to be absorbed by a different route). The lactulose/mannitol ratio increased from a mean of 0.070 to 0.169 (Fig. 1). Protein loss from the circulation into the gastrointestinal tract increased two-fold during treatment with Auranofin. Clearance of circulating alpha-1-antitrypsin increased in all six individuals from a mean of 10.4 ml plasma/day (range 2.0–33.0) to a mean of 21.4 ml plasma/day (range 4.0–46.0) (Fig. 2).

Fig. 1 Intestinal permeability assessed by the excretion of ⁵¹Cr-EDTA and by the lactulose/mannitol ratio in patients on and off treatment with Auranofin. Using the signed rank sum test. *p* Values were 0.052 for ⁵¹Cr-EDTA and 0.036 for lactulose/mannitol.

Fig. 2 Protein loss assessed by clearance of α -1-antitrypsin in patients on and off treatment with Auranofin. p value = 0.036 (signed rank sum test).

HISTOLOGY OF THE RECTAL MUCOSA

In this group of patients sigmoidoscopic appearances were normal even during periods of diarrhoea. Histological examination of biopsies of the rectal mucosa showed no increase in inflammatory cells.

Discussion

For more than 50 years gold has been useful in the treatment of chronic polyarthritis especially in rheumatoid disease. The first available preparations could be given only parenterally (gold sodium thiomalate; aurothioglucose) and much of the gold injected was retained for long periods in body tissues – for example, 25% retention at 250 days.¹⁵ It is slowly excreted with more than twice as much appearing in urine than in faeces. Adverse reactions are common and include rashes, stomatitis, and

proteinuria. Occasionally the gastrointestinal tract is affected. Several cases of gold induced enterocolitis have been reported with some fatalities.¹⁶

In 1976 it was reported that Auranofin, an orally absorbed gold compound, was a well tolerated and effective anti-rheumatic drug.¹⁷ It has a complex structure – (2,3,4,6-tetra-O-acetyl-1-thio- β -D-glucopyranosato-S) (Tri-ethyl phosphine) gold – and of a dose of 6 mg only 25% is absorbed. A much lower percentage of gold is retained in the body than with the parenteral compounds. Up to 95% is excreted in faeces.¹⁵

Rash, stomatitis, and proteinuria occur infrequently during treatment with Auranofin. On the other hand nearly half of patients taking the drug complained of abdominal cramps and occasional diarrhoea.^{3, 18} In the Addenbrooke's series 30 of 44 patients developed diarrhoea. Ten patients refused to take the drug either because of the severity of the diarrhoea or because of associated abdominal colic (unpublished observations).

Auranofin is only slightly soluble in water and exerts no significant osmotic effect in the lumen of the intestine. It does not cause malabsorption as assessed by conventional tests. Our data supplement those from a previous study of three patients who were shown to absorb both fat and vitamin B₁₂ normally when taking Auranofin. Studies of the uptake of D-xylose and glucose also gave normal results.³ One cannot, however, exclude the possibility of a transient direct effect of Auranofin on transport systems across the surface membrane of the enterocyte. Experimentally Auranofin in a concentration of 100 μ g/ml (0.14 mmol/l) reduces the transport of glycine, galactose, Na⁺ and fluid across everted preparations of rat midintestine by 40–55%.¹⁹ It has been suggested that Auranofin causes these changes by a direct effect on sodium transport and that the transfer of monosaccharides and amino acids are reduced because they are sodium dependent. At present we have no data on the concentration of Auranofin in the human intestinal lumen following a therapeutic dose. It is reasonable to suppose that the drug would be diluted in at least 100 ml of gastrointestinal secretions and thus concentrations of 100 μ g/ml would be reached only transiently if at all.

Auranofin increases the rate of transit through the gastrointestinal tract as a whole. This may be due to a neurohormonal effect on gastrointestinal motility or to increased transit secondary to increased fluid in the lumen of the gut. As expected the more than two-fold increase in stool weight was associated with an increased sodium concentration in faecal water. This change occurs with most diarrhoeal illnesses irrespective of cause.⁶ The concentration of hyd-

rogen ion in faecal water also increased and there was a fall in the concentration of bicarbonate. The absence of change in the concentration of chloride suggests that Auranofin did not have a significant effect on the chloride-bicarbonate exchange mechanism. The fall in pH may occur as the result of accumulation of volatile fatty acids generated by bacteria principally from dietary residue.⁶ In this study it has also been shown that Auranofin increases intestinal permeability to ⁵¹Cr-EDTA and to lactulose and causes a small but consistent increase in the intestinal clearance of α -1-antitrypsin. These findings suggest that the drug exerts a direct effect on the absorptive membrane of the enterocyte *in vivo* similar to that described in rat intestine under experimental conditions.²⁰ *In vivo* perfusion of rat jejunum with a physiological solution containing electrolytes, glucose, mannitol, and taurocholate together with Auranofin (0.2 mmol/l) has been shown to induce electrolyte secretion, to inhibit the secretion of glucose and to allow an increase in the uptake of mannitol. A higher concentration of Auranofin (2 mmol/l) led to similar changes in intestinal function which were associated with histological evidence of mucosal injury (shedding of cells from the tips of villi). The authors of these observations conclude that Auranofin causes diarrhoea by inducing the secretion of intestinal fluid, in association with enhanced mucosal permeability. The changes are induced by Auranofin but not by myochrysine which suggests that the carrier molecule and not the gold is responsible for the change.

Thus there are unresolved differences between the two sets of investigations in experimental animals. One postulates a defect in absorption¹⁹ whereas the other indicates increased mucosal secretion²⁰ albeit in association with an impaired uptake of glucose. In both sets of experiments the concentration of Auranofin maintained in contact with the intestinal mucosa throughout the experiment would occur for only short periods under therapeutic conditions.

It is probable that the laxative-like effect of Auranofin on gastrointestinal function is pathophysiological rather than idiosyncratic. It occurs in a high percentage of subjects; it is closely related to the time of ingestion of the drug; it usually settles promptly after discontinuing medication and it may be relieved by reducing or dividing the dose. Some patients get mild abdominal cramp without diarrhoea and in others symptoms are transient.¹⁸ This was noted in patient 4 who had stopped taking Auranofin five weeks before the study because of diarrhoea. Her bowel habit remained normal when given Auranofin for a further two weeks even

though both intestinal permeability and the clearance of α -1-antitrypsin were increased.

It has been suggested that prostaglandins may be involved in the disturbance of bowel function caused by Auranofin.²¹ It is interesting to note that non-steroidal anti-inflammatory drugs (NSAID) which inhibit the synthesis of prostaglandins also increase intestinal permeability and occasionally have a laxative-like effect.^{22, 23} In this study patients were not allowed to take NSAID which might have supplemented or multiplied the effect of Auranofin. It is of course possible that the permeability effect and the development of diarrhoea are unrelated. Be that as it may we were unable to show inflammatory changes in the intestine as a result of Auranofin. It is probable that the single reported case of enterocolitis in a patient taking Auranofin is unrelated to the laxative effect of the drug.

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