SHORT REPORTS

Tea consumption: A cause of constipation?

Uncontrolled clinical observations in our outpatient clinic suggested that severe constipation in young adults was related to tea consumption of one to two litres daily. We have therefore carried out a study on healthy volunteers.

Subjects, methods, and results

Twelve healthy volunteers aged 23-30 years participated in the study, which comprised two test periods of seven days. Diet was unrestricted except for beverages, which in one test period were limited to two litres of tap water daily and in the other to two litres of tea (four bags of 2 g Assam/Ceylon Brook Bond tea per litre, steeped for five minutes). On day 5 of each test period the subjects ingested 20 radio-opaque plastic markers, and daily excretions of urine and faeces were collected on days 5, 6, and 7. On day 7 body weight was recorded and blood samples taken. Faeces were analysed for mass, total bile acid concentration,¹ and number of plastic markers excreted (to measure intestinal transit time²). Urine analysis included volume, specific gravity, and oxalate concentration. Each subject served as his own control, and the sequence of the test periods was randomised. The rank sum test was used for paired observations.

Significantly fewer plastic markers were excreted over 72 hours in the tea period than in the water period ($p < 0.05$), indicating significantly increased intestinal transit time (figure). The mean faecal bile acid output

Intestinal transit times expressed as percentages of plastic markers recovered in 72 hours. Difference between water and tea periods: $p < 0.05$.

decreased from 436 to 310 $\mu\text{mol}/24\text{ h}$ ($p < 0.05$) during the tea period, whereas faecal mass showed only a slight and non-significant reduction. Specific gravity of urine increased from 1014 to 1017 g/l ($p < 0.05$) in the tea period, and urine oxalate excretion rose from 0.36 to 0.41 mmol (3.2 to 3.7 mg)/24 h ($p < 0.10$); the urine volume showed only a slight non-significant increase. During the tea period the following mean plasma concentrations were increased ($p < 0.05$): albumin from 599 to 623 $\mu\text{mol}/\text{l}$ (4.13 to 4.30 g/100 ml); creatinine from 73 to 82 $\mu\text{mol}/\text{l}$ (826 to 927 $\mu\text{g}/100\text{ ml}$); urate from 0.27 to 0.29 mmol/l (4.5 to 4.8 mg/100 ml); sodium from 128 to 133 mmol (mEq)/l; potassium from 3.5 to 3.8 mmol (mEq)/l; and calcium from 1.97 to 2.11 mmol/l (7.8 to 8.4 mg/100 ml). No changes were seen in carbamide, haemoglobin, or phosphate values. There was no change in body weight.

Comment

The effect of tea was probably due to theophylline, which (presumably via the kidneys) causes extracellular dehydration, a secondary increase in intestinal fluid absorption, and hence constipation. This hypothesis agrees with the findings in a study of constipating cocoa products.³ The estimated daily intake of theophylline with tea in

our study was roughly 100 μmol ,⁴ sufficient to increase the renal glomerular filtration rate and decrease tubular reabsorption.⁵ The raised plasma concentrations of various components and the increased intestinal transit time during the tea period support the hypotheses of dehydration and constipation.

We suggest that the relation between fluid consumption and intestinal transit time should be considered in studies evaluating the influence of compounds—for example, dietary fibres and drugs—on intestinal function.

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Pseudomembranous colitis after treatment with metronidazole

Pseudomembranous colitis is a rare condition that may complicate the administration of certain antimicrobial agents. The most common of the many antibiotics that have been implicated are lincomycin and clindamycin. We report a case that followed a short course of intrarectal metronidazole used prophylactically in a patient undergoing emergency appendicectomy. To our knowledge there has been no recorded case of the condition in association with metronidazole alone. This has important implications as metronidazole has been suggested as a therapeutic agent to treat this condition.

Case report

A 13-year-old girl was admitted with a history of abdominal pain. Acute appendicitis was diagnosed and appendicectomy was performed. Histological examination showed early focal appendicitis. She was given prophylactic metronidazole rectally 1 g before operation and 500 mg three times daily for three days after operation. On the fifth day after operation she began to feel unwell, complaining of nausea and dizziness. She developed diarrhoea containing mucus and fresh blood. These symptoms persisted, and sigmoidoscopy two days later showed an inflamed rectal mucosa, biopsy specimens of which showed typical features of pseudomembranous colitis. Histological examination showed disrupted crypts, distended by mucus and polymorphs. There was also focal destruction of crypts with loss of the epithelial surface (figure). A mushroom-shaped pseudomembrane consisting of epithelial debris, mucus, polymorphs, and fibrin was adherent to the underlying mucosa and there was an abrupt change to the normal mucosa at the edge of the lesion.

A minor degree of clinical improvement followed, and repeat sigmoidoscopy on the ninth day after operation showed a yellow membrane partly adherent to the underlying mucosa at 15 cm. Repeat biopsy findings confirmed the previous findings. Specimens of faeces on days eight and 10 were culture-negative for campylobacter, shigella, salmonella, staphylococci,

Disrupted crypts distended by mucin and polymorphs and loss of the epithelial surface. Haematoxylin and eosin $\times 100$ (original magnification).

Clostridium perfringens, and *Cl. difficile*. Biopsy material from the second sigmoidoscopy was cultured on the medium described by George *et al.*¹ and yielded a growth of *Cl. cadaveria*. *Cl. difficile* was not isolated. Faecal specimens and biopsy material were examined by tissue culture assay for the presence of a cytotoxin that could be neutralised by *Cl. sordellii* antitoxin, but no toxin was shown. The strain of *Cl. cadaveria* isolated also failed to produce a cytopathic change. Despite these negative cultural and toxicological findings, we decided to treat the patient with vancomycin 500 mg four times daily for five days. At the end of this period her illness had completely resolved clinically, and appearances on sigmoidoscopy were normal.

Comment

Since the 1950s there have been many reports of an association between pseudomembranous colitis and antimicrobial treatment. Although lincomycin and clindamycin have been implicated often, many other antibiotic combinations have also been associated with the condition.² The circumstantial link between antimicrobial treatment and pseudomembranous colitis has been strengthened by the findings of Larson *et al.*,³ who reported that faeces from patients with pseudomembranous colitis contained a heat-labile cytotoxin, which could be neutralised by *Cl. sordellii* antitoxin. George *et al.*¹ implicated *Cl. difficile* in the production of the cytotoxin.

The main interest of the present case is that pseudomembranous colitis appeared in the absence of *Cl. difficile* and of demonstrable cytotoxin in a patient who had received metronidazole, to which *Cl. difficile* and other strict anaerobes are uniformly sensitive *in vitro*.

Pseudomembranous colitis has been reported in the absence of antibiotic treatment⁴ and, on occasions, after surgery. In this case it would be coincidental if pseudomembranous colitis occurred spontaneously, as the sequence of events would suggest a relation to either surgical intervention or metronidazole treatment. In addition, symptoms and signs occurred on the fifth day after operation, which was only two days after the final dose of metronidazole had been given. The fact that the patient remained fairly well despite the severity of the histological findings would indicate that only a small segment of bowel was affected, and this segment was situated some 15 cm from the anal margin as shown by sigmoidoscopy. The patient had received a total of 10 metronidazole suppositories and it would seem likely that this was the predisposing factor rather than surgical intervention for a totally different condition affecting another part of the bowel.

We conclude that *Cl. difficile* and its toxin may not be the sole cause of pseudomembranous colitis and that metronidazole as a single antimicrobial agent does not protect against the development of pseudomembranous colitis and may, in this case, have been instrumental in its development.

We thank Mr A J Mack for allowing us to report this case and Dr W McNaught for his helpful comments.

¹ George WL, Sutter VL, Citron D, Finegold SM. Selective and differential medium for isolation of *Clostridium difficile*. *J Clin Microbiol* 1979;91: 214-9.

² Keighley MRB, Arabi Y, Alexander-Williams J, Youngs D, Burdon SW. Comparisons between systemic and oral antimicrobial prophylaxis in colorectal surgery. *Lancet* 1979;i:894-7.

³ Larson HE, Price AB, Honour P, Borriello SP. *Clostridium difficile* with the aetiology of pseudomembranous colitis. *Lancet* 1978;i:1063-6.

⁴ Howard JM, Sullivan SN, Troster M. Spontaneous pseudomembranous colitis. *Br Med J* 1980;281:396.

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Mefenamic acid nephropathy: further evidence

A recent report¹ described six cases of non-oliguric renal failure that improved after withdrawal of mefenamic acid (Ponstan). All the patients were elderly, and several had pre-existing medical conditions; details of renal function before treatment were not available. We describe a previously fit woman who developed non-oliguric renal failure during treatment with mefenamic acid, with the added evidence of a second deterioration during inadvertent rechallenge.

Case report

A 55-year-old previously fit woman with an 18-month history of bilateral venous leg ulceration was admitted for consideration of skin grafting. She had no other medical history, and drug treatment before admission comprised only paracetamol for 10 months (dose less than 4 g/day) and bendrofluazide 5 mg daily for oedema. Examination showed only leg ulcers. Investigations showed haemoglobin 10.5 g/dl, white cell count $6.4 \times 10^9/l$ ($6400/mm^3$), urea 3.3 mmol/l (20 mg/100 ml), potassium 3.2 mmol (mEq)/l, and bicarbonate 29 mmol (mEq)/l. Urine analysis was negative for blood, cells, and protein. Liver function tests and blood glucose concentrations were normal. Mefenamic acid was prescribed to be given every four to six hours "when necessary" for pain, never exceeding 2 g a day. Other drugs were bendrofluazide 5 mg daily, ferrous gluconate, and potassium chloride. The figure shows her subsequent serum creatinine concentration and daily dose of mefenamic acid. After six weeks she developed diarrhoea, though

Serum creatinine concentration related to daily dosage of mefenamic acid. Normal range for creatinine concentration is indicated by horizontal lines.

Conversion: SI to traditional units—Creatinine: 100 $\mu\text{mol/l}$ $\approx$ 1.13 mg/100 ml.

the creatinine concentration was raised before this time. On day 49 the creatinine concentration was 460 $\mu\text{mol/l}$ (5.2 mg/100 ml) and urea 26.5 mmol/l (159 mg/100 ml). Mefenamic acid was accidentally stopped with immediate improvement in renal function.

Reintroduction of the drug after five days led to a second deterioration in renal function and recurrence of diarrhoea and vomiting. A presumptive diagnosis of mefenamic acid nephropathy was made two weeks later, when the creatinine concentration was 312 $\mu\text{mol/l}$ (3.5 mg/100 ml) and urea 21.0 mmol/l (126 mg/100 ml). Results of urine analysis and liver function tests remained normal, plasma bicarbonate concentration had fallen on each occasion to 12 mmol/l, and there was evidence of impaired concentrating ability. Intravenous urography yielded normal results. After mefenamic acid was withdrawn creatinine and urea concentrations fell gradually to 91 $\mu\text{mol/l}$ (1.03 mg/100 ml) and 5.2 mmol/l (31 mg/100 ml) respectively. Creatinine clearance improved from 28 to 66 ml/min, but concentrating ability remained impaired.