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The effect of the non-steroidal anti-inflammatory drug choline magnesium trisalicylate on gastric mucosal cell exfoliation

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1 Gastric mucosal cell exfoliation was measured in 10 normal subjects taking choline magnesium trisalicylate (CMT), aspirin and placebo.

2 Both drugs resulted in significantly elevated rates of exfoliation although the serum salicylate levels achieved with aspirin were lower than those achieved by CMT.

3 Side-effects of tinnitus, nausea and increased faecal blood loss were more common while subjects were taking CMT.

Keywords choline magnesium trisalicylate gastric exfoliation

Introduction

Salicylate based preparations have remained the drugs of choice in the treatment of the arthritides. However, many studies have incriminated acetyl salicylic acid (ASA) in the promotion of gastrointestinal bleeding, mainly by its local action on gastric mucosa (British Medical Journal, 1981). The non-steroidal anti-inflammatory drug choline magnesium trisalicylate (CMT), Napp Laboratories Limited, has been introduced as an analgesic with anti-inflammatory properties suitable for use in the arthritides. It is said to be effective, well tolerated and to exhibit few gastrointestinal side-effects.

Cell loss from human gastric mucosa as measured by the estimation of deoxyribonucleic acid (DNA) in gastric washings has been shown to be reliable and reproducible (Croft *et al.*, 1966).

The aims of this study were to assess the effects of CMT on gastric cell exfoliation and to monitor its side-effects.

Methods

Gastric cell exfoliation was measured in 10 volunteers, nine female and one male (mean age 22 years). None of the subjects gave a history of gastrointestinal symptoms and during the active phases of the study were asked to refrain from the use of aspirin containing medications, alcohol and spicy foods. All subjects gave informed consent. Statistical analysis was performed using the paired *t*-test.

The study was designed as a four way randomised cross-over comparison. Gastric washings were performed on subjects while taking no drug (control), placebo, CMT 3×500 mg tablets twice daily and aspirin BP 3×300 mg tablets three times daily. Subjects took tablets for 7 days and each washing was performed 1–2 h following the ingestion of the last tablet. There was a rest period of 14 days before commencing the next phase of the study. The study design is outlined in Figure 1.

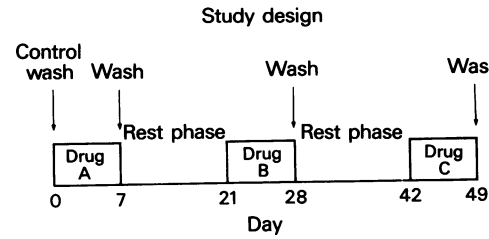

Figure 1 Study design showing 7 day treatment phases with 14 day rest phases.

The subjects fasted overnight and were intubated using a modified 18 French gauge Sherwood Salem Sump tube. In the left lateral position basal gastric secretions were aspirated. Saline (500 ml, 0.9% w/v) prewarmed to 37°C, was suspended 100 cm above the supine subject and infused into the stomach over 15 min. When completed the stomach contents were removed using minimal aspiration pressure and the first washing discarded.

Five subsequent washings with 500 ml saline were collected in ice-cooled flasks containing 25 ml ethylene diamine tetra acetic acid (EDTA) 0.2 M pH8, as an enzymostatic agent, the time of aspiration/infusion and volume recovered being noted. Each washing was transferred to polypropylene 1000 ml MSE centrifuge bottles and the DNA content of each washing was assayed according to the method described by Croft & Lubran (1965). The DNA content was expressed as μg/min DNA–P.

During the study routine haematological and biochemical indices were measured. A serum sample was taken at the time of each gastric washing (2–3 h after the ingestion of the last dose of drug), for the estimation of salicylate level. Serum salicylate was measured using the method described by Smith & Talbot (1950), and the results expressed as mg/100 ml. Subjects were also asked to test three consecutive stools for faecal occult blood (Haemoccult) during the treatment phases of the study.

Results

One female subject randomised to receive CMT in the first 7 day treatment phase developed nausea and vomiting and was withdrawn from the study.

The gastric cell exfoliation rate, expressed as μg/min DNA–P for each of the study phases is shown in Figure 2. The difference in cell exfoliation rate between control and placebo does not achieve statistical significance. Statistically significant differences exist between placebo and aspirin ($P<0.025$) and placebo and CMT ($P<0.025$). CMT exhibits higher gastric cell exfoliation rate than aspirin, but this does not achieve significance. The serum salicylate levels (mg/100 ml) are shown in Figure 3. In all subjects higher serum levels are achieved while taking CMT. These levels fall within the therapeutic range.

Side-effects are listed in Table 1. Of the 10 subjects, six experienced side-effects while taking CMT, one while taking aspirin and one while taking placebo. Four subjects had at least one positive faecal occult blood test on CMT, while one subject had positive tests during aspirin administration. Apart from a transient viral induced neutropenia in one subject, no significant changes were noted in the standard haematological and biochemical parameters.

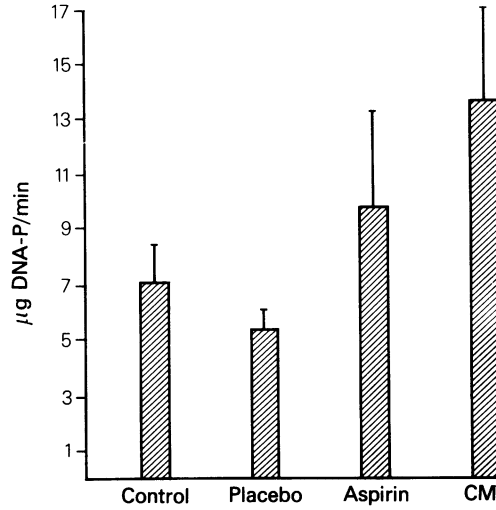

Figure 2 Gastric mucosal cell exfoliation rate (mean of four washes ± s.e. mean).

Discussion

Choline magnesium trisalicylate has been shown to be an effective drug in the treatment of rheumatoid and osteoarthritis (Giulian & Scharff, 1980; Goldenberg *et al.*, 1978). The recommended dose ranges from 2g daily in osteoarthritis to 3g daily in rheumatoid arthritis. It has been suggested that CMT therapy is associated with less gastrointestinal side-effects than conventional aspirin therapy (Cohen *et al.*, 1978). While it is an invasive investigative procedure, Croft's method of measuring gastric cell exfoliation rate by a saline perfusion technique was generally well tolerated by the subjects. In our hands it has provided reliable and reproducible results (Boyes 1974; Boyes *et al.*, 1971).

In this study of normal volunteers, the oral administration of 2.9g aspirin BP daily, resulted in higher gastric mucosal cell exfoliation than with placebo. Similar results were seen with 3g choline magnesium trisalicylate. However, the serum salicylate levels achieved by aspirin were considerably lower than those achieved by CMT. These findings may be explained partly by the greater availability of salicylate from CMT compared with aspirin BP (3g and 2.2g respect-

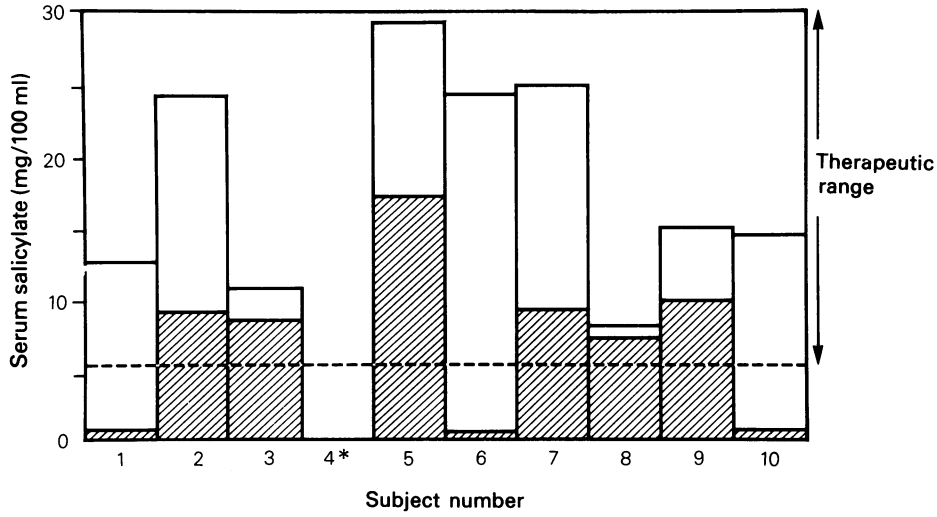

Figure 3 Serum salicylate level as measured 2–3 h after ingestion of last tablet (CMT 3g daily, aspirin 2.9 g daily). *Subject withdrawn from study.

Table 1 Side effects during treatment

	Placebo	*Aspirin*	*CMT*
Nausea	1	0	2*
Tinnitus	0	0	4
+ve FOB	0	1	4

* One subject withdrew because of severe nausea while taking CMT

ively), and partly by variations in the time of blood sampling after administration of the drugs.

Nevertheless gastric mucosal cell exfoliation was considerably increased at the same time as CMT achieved salicylate levels well within the therapeutic range for rheumatoid arthritis. Tinnitis and the gastrointestinal side-effects of nausea and blood loss as measured with the Haemoccult test occurred more frequently while subjects were taking CMT. Previous studies have suggested that these side-effects were rare while subjects were taking 2g CMT daily and uncommon while taking 3g daily (Cohen & Gerber, 1978; Cohen *et al.*, 1978).

These findings suggest that choline magnesium trisalicylate should be used with caution in patients with known gastrointestinal conditions and that side-effects should be closely monitored.

Further assessment of gastric mucosal cell exfoliation as a method of measuring the gastric irritation by other anti-inflammatory drugs may be of value.

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