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The effect of activated charcoal and hyoscine butylbromide alone and in combination on the absorption of mefenamic acid

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Mefenamic acid 500 mg orally was administered to nine healthy volunteers on four occasions 7 days apart. On two occasions allocated at random, activated charcoal (2.5 g of medicoal) was administered 1 h after the drug. Hyoscine butylbromide (20 mg intramuscularly) was given immediately after mefenamic acid on one of these occasions, and on one occasion after mefenamic acid without charcoal. Hyoscine significantly delayed the time to maximum mefenamic acid concentrations but did not affect the area under the plasma concentration-time curve. Charcoal reduced the area under the plasma concentration curve by 36% and charcoal and hyoscine reduced the area under the plasma concentration curve by 42% from their respective control values. We conclude that early charcoal administration in a ratio of 5 g to 1 g of drug effectively reduces the area under the plasma concentration-time curve after oral mefenamic acid administration. Early charcoal administration may be of value therefore in reducing the toxicity of mefenamic acid after deliberate or accidental overdosage.

Keywords mefenamic acid hyoscine activated charcoal

Introduction

Mefenamic acid (Ponstan) is a widely used non-steroidal anti-inflammatory agent. Because of its wide usage, it is being more frequently ingested in both accidental and deliberate overdose. It has been reported that convulsions can occur in 10–20% of patients who take this drug, particularly in those who ingest large amounts or who have high plasma concentrations of the agent (Balali-Mood *et al.*, 1981). The manufacturers of the compound recommend the use of activated charcoal to prevent the absorption after overdose but these recommendations are based solely on data in the rat (Glazko, 1966). We therefore felt it important to obtain the relevant information concerning the effect of charcoal on the absorption of this agent in man. Since this was difficult to perform in controlled conditions after overdose, it was assessed by a scaled down procedure in which conventional doses of mefenamic acid were combined with charcoal in corresponding amounts.

It has been suggested that gastric emptying is delayed in some patients after mefenamic acid overdose (Balali-Mood *et al.*, 1981) and in order to simulate the situation as closely as possible the anticholinergic agent hyoscine butylbromide (intramuscularly) was used.

Methods

Ten female subjects aged between 18 and 25 years were included into the study. The subjects were drug free and had normal clinical examination and normal haematology and biochemistry on screening. None had a history of previous allergic reaction to aspirin or any of the other non-steroidal anti-inflammatory drugs, asthma,

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inflammatory bowel disease or peptic ulceration. Each was enrolled into the study only after full written informed consent had been given and the study was passed by the local ethics committee.

Since it proved impossible to provide a matching placebo for charcoal, the study was not blind. The subjects received in random order 7 days apart hyoscine butylbromide 20 mg in 0.5 ml water intramuscularly at the same time as 500 mg mefenamic acid (Ponstan Forte) or normal saline 0.5 ml intramuscularly at the same time as 500 mg mefenamic acid each on two separate occasions at least 1 week apart with or without activated charcoal 2.5 g 1 h after the drug. Thus there were four separate study periods. Subjects took the drug in the fasting state. Venous blood (4 ml) was collected at 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480 min after drug ingestion. Blood was withdrawn into heparinised tubes and plasma centrifuged at 300 *g* for 10 min and separated within 2 h of withdrawal. The plasma was stored at −20°C and plasma mefenamic acid concentrations were measured by high performance liquid chromatography (Lin *et al.*, 1980). No untoward effects were noticed as a result of administration of the drug in any of the subjects although one subject was unable to complete the study because of a change in personal commitments.

The area under the plasma concentration-time curve was calculated using the trapezoidal method to the final time point with extrapolation subsequently using the calculated elimination rate constant for each individual. The elimination rate constant was calculated by least squares log linear regression analysis from the elimination phase of the curve and the half-life calculated directly from this result. In all cases $P < 0.05$ was taken as the minimum level of statistical significance.

Results

Hyoscine butylbromide administration significantly delayed the time to maximum concentration (from mean 140 ± 42 s.d. to 200 ± 72 min) ($P < 0.001$) but did not affect the area under the plasma concentration time curve (1954 ± 590 *vs* 1843 ± 715 mg^{-1} min control value) (Figure 1). Administration of charcoal resulted in a reduction in the area under the plasma concentration-time curve for mefenamic acid of 36% (from 1843 ± 715 to 1180 ± 551 mg l^{-1} min $P < 0.001$). Charcoal administered after hyoscine and mefenamic acid resulted in a reduction of the area under the curve of 42% (from 1954 ± 590 to 1137 ± 391 mg l^{-1} min $P < 0.001$ paired *t*-test). This percentage reduction was not significantly greater than that produced by charcoal alone, however.

Discussion

We conclude that charcoal administered 1 h after mefenamic acid resulted in a significant reduction in the area under the plasma concentration-time curve of 36%. We believe that early charcoal administration is likely to reduce the extent of mefenamic absorption in overdose although we believe that results seen here may underestimate the potential effect in overdose

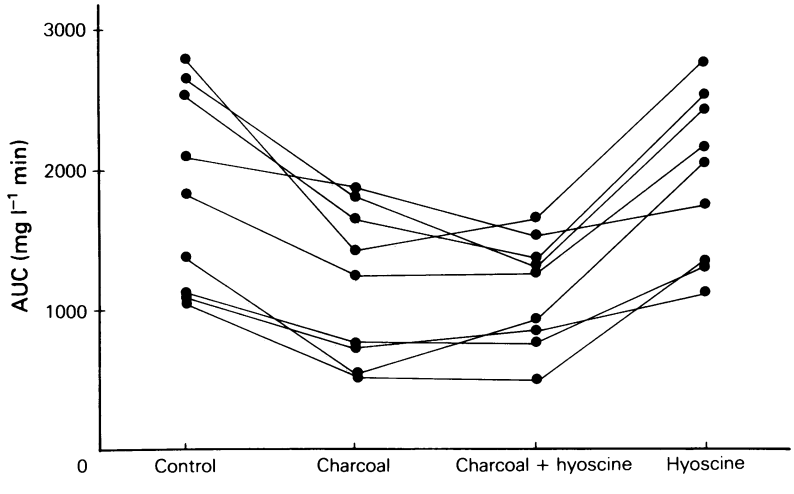

Figure 1 The areas under the plasma concentration-time curves for the subjects in each phase of the study.

for two reasons. Firstly, it has been shown that scaling down procedures underestimate the adsorption of drug to charcoal for both aspirin and paracetamol (Levy & Houston, 1976; Levy & Tsuchiya, 1972). This has been attributed to non-specific competition of gastric contents for adsorption on charcoal, the relative effect of which diminishes as the absolute dose of charcoal increases even though the ratio of drug to charcoal is kept constant. Secondly, although hyoscine butylbromide delayed the time to maximum concentration from 140 min to just over 3 h in our study, Balali-Mood and co-workers (1981) have shown that even greater delays in time to maximum concentration (up to 8 h) may occur in overdose with mefenamic acid. This may allow the charcoal to catch up with drug in overdose whereas in the experimental situation described, absorption of mefenamic acid was already considerable at the time that the charcoal was administered. We therefore concur with the manufacturer's recommendations to use charcoal at a ratio of at least 5 g to 1 g of drug in patients who have taken an overdose of mefenamic acid (preferably after induction of emesis or gastric lavage). The value of this agent is likely to be greatest early after overdose, however.

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References

Balali-Mood, M., Critchely, J. A. J. H., Proudfoot, A. T. & Prescott, L. F. (1981). Mefenamic acid overdosage. *Lancet*, **i**, 1354.

Glazko, A. J. (1966). Pharmacology of the fenamates. Experimental observations of flufenamic, mefenamic and meclofenamic acids III Metabolic disposition. *Ann. Phys. Med.*, Suppl: **23**.

Levy, G. & Houston, J. B. (1976). Effect of activated charcoal on acetaminophen absorption. *Paediatrics*, **58**, 432–436.

Levy, G. & Tsuchiya, T. (1972). Effect of activated charcoal on aspirin absorption in man. *Clin. Pharmac. Ther.*, **13**, 317–322.

Lin, C. K., Lees, C. S. & Perrin, J. H. (1980). Determination of two fenamates in plasma by high-performance liquid chromatography. *J. pharm. Sci.*, **69**, 95–98.

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