The effect of charcoal on mefenamic acid elimination

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Mefenamic acid suppository 500 mg was administered by rectum to eight healthy adult volunteers followed by either activated charcoal 5 g orally at hourly intervals for 7 h or an equal volume of water on two separate occasions 7 days apart. Administration of charcoal did not significantly affect the pharmacokinetic variables of mefenamic acid. Thus the beneficial effects of charcoal in the treatment of mefenamic acid overdose are largely due to interference with absorption, rather than enhancement of elimination of the drug.

Keywords mefenamic acid activated charcoal

Introduction

The use of activated charcoal in the treatment of mefenamic acid overdose is recommended in the current data sheet for this product. Evidence of efficacy was, however, based on animal data only. We have recently shown that activated charcoal significantly reduces the absorption of a therapeutic dose (500 mg) of mefenamic acid in man when given in a ratio of 5:1 (ElBahie *et al.*, 1985). The effect was increased slightly on concomitant administration of hyoscine-*N*-butylbromide 20 mg i.m., to simulate delayed gastric emptying, a feature in overdose. There was also a non-significant trend towards a shorter half-life of the drug but the design of the study did not permit us to examine this properly.

Since an intravenous preparation of the drug is not available, we could not examine the effects of repeated oral charcoal doses on the systemic pharmacokinetics of mefenamic acid. A suppository form is available, however, which avoids the problem of direct contact with charcoal during absorption (company data on file).

Methods

Ten healthy adult volunteers (two male, eight female), aged 20–39 years, were recruited following a full examination including 12 lead ECG, routine haematological and biochemical screening and a screen for drugs of abuse. Volunteers gave written informed consent and the study was

approved by the Joint Ethics Committee, South Glamorgan Health Authority.

The study was of an open randomized cross-over design. Following an overnight fast, volunteers received on two separate occasions, 7 days apart, either mefenamic acid suppository 500 mg, rectally followed by activated charcoal 5 g in 100 ml of water, orally at hourly intervals for 7 h or mefenamic acid suppository 500 mg rectally and an equivalent volume of distilled water orally at hourly intervals for 7 h.

On each occasion blood samples (5 ml) were collected at 0, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 h after the administration of mefenamic acid.

Samples were collected in glass lithium heparinized tubes and centrifuged immediately at 3,000 g for 10 min. Plasma was removed and stored in plain glass tubes at -20°C until required for analysis.

Plasma mefenamic acid concentrations were measured by high performance liquid chromatography (Lin *et al.*, 1980), with flufenamic acid as the internal standard. The sensitivity of the assay was 0.1 mg l^{-1} and the within and between run precisions were 6.1 and 9.6 (% C.V.) respectively.

The area under the plasma concentration–time curve ($\text{AUC}_{0-8\text{ h}}$) was calculated using the trapezoidal method 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

($t_{1/2,z}$) calculated directly from this result. The maximum plasma concentration ($C_{p\max}$), and the time to reach maximum plasma concentration ($t_{\max}$) are reported as the actual observed values.

Results were analysed by paired Student's *t*-test. In all cases $P < 0.05$ was taken as the minimum level of significance.

Results

Individual and mean data ($\pm$ s.d.) for the pharmacokinetic variables are presented in Table 1. In five volunteers, plasma mefenamic acid profiles showed a late second peak plasma concentration. In these subjects it was not possible to calculate elimination half-life on one or both occasions. In another subject no mefenamic acid could be detected in the plasma after 1 h on both occasions indicating either poor absorption of the drug or an inability to retain the suppository. A further subject withdrew due to personal commitments. In both latter cases, results were excluded from the final analysis.

The pharmacokinetic variables $AUC_{(0-8\text{ h})}$, $C_{p\max}$, $t_{\max}$ and $t_{1/2,z}$ were not significantly different following administration of charcoal ($P < 0.05$ in all cases) (Table 1).

Discussion

In a previous study we have shown that activated charcoal significantly reduced the absorption of mefenamic acid (ElBahie *et al.*, 1985). Furthermore it was observed that in some volunteers there was evidence of a second peak plasma concentration which may indicate an enterohepatic or entero-enteral recirculation. Mefenamic acid glucuronide and other metabolites are avidly excreted in the bile in the Rhesus monkey (Glazko, 1966). We therefore considered that charcoal might enhance elimination of mefenamic acid in man, particularly if unchanged drug or glucuronide metabolite entered the bile. The results from this present study indicate that administration of activated charcoal does not significantly alter the elimination of mefenamic acid in man. A secondary peak concentration occurred in four of the subjects which prevented accurate measurement of the elimination half-life during the 8 h of the study. The secondary peak in plasma mefenamic acid concentration also occurred in two of the subjects during charcoal administration. The lack of reduction in the area under the curve after charcoal (indeed in six of the subjects it was actually greater after charcoal

Table 1 The effect of charcoal on the pharmacokinetics of mefenamic acid

Subject	No charcoal				Charcoal			
	$C_{p\max}$ (mg l^{-1})	$t_{\max}$ (h)	$AUC_{0-8\text{ h}}$ ($\text{mg l}^{-1}\text{ h}$)	$t_{1/2,z}$ (h)	$C_{p\max}$ (mg l^{-1})	$t_{\max}$ (h)	$AUC_{0-8\text{ h}}$ ($\text{mg l}^{-1}\text{ h}$)	$t_{1/2}$ (h)
1	1.2	3.0	6.4	3.6	1.1	2.0	3.7	2.9
2	2.1	3.0	9.7	5.9	2.8	5.0	12.7	6.3
3	2.5	4.0	11.6	1.2	1.3	2.0	3.9	2.3
4	1.7	3.0	9.0	—	1.5	3.0	9.2	—
5	1.5	2.0	7.1	—	2.0	5.0	11.9	6.0
6	1.4	8.0	7.8	—	1.8	8.0	9.9	6.1
7	1.2	7.0	4.7	—	1.2	4.0	6.7	—
8	1.5	1.0	8.3	2.8	2.1	4.0	10.0	4.7
Mean	1.6	3.9	8.1	3.4	1.7	4.1	8.5	4.7
$\pm$ s.d.	0.5	2.4	2.1	2.0	0.6	2.0	3.4	1.7
<i>n</i>	8	8	8	4	8	8	8	6

administration) makes it unlikely that there was a significantly enhanced systemic clearance of the drug.

In this study, it was possible to give large doses of charcoal after only a single therapeutic dose of mefenamic acid. Since the effect of charcoal is largely dependent upon the relative dose of charcoal the conditions of the experiment are probably optimal and it is unlikely that the effect of charcoal on mefenamic acid elimination in overdose will be greater than seen in this study.

It therefore appears that the beneficial effect of charcoal in mefenamic acid overdose is in preventing absorption and will be best achieved by early administration. Subsequent, repeated doses are unlikely to be of value in enhancing elimination of this agent in overdose.

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