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Reduction of Absorption of Paracetamol by Activated Charcoal and Cholestyramine: A Possible Therapeutic Measure

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Summary

The absorption of an oral 2-g dose of paracetamol was markedly reduced by the simultaneous oral administration of either activated charcoal or cholestyramine but was only slightly reduced when the adsorbents were given 60 minutes after the paracetamol. Since the absorption of a larger dose of the drug will probably be slow, the administration of adsorbents may be of value even when delayed several hours.

Introduction

A possible therapeutic measure to reduce liver damage after an overdose of paracetamol (Proudfoot and Wright, 1970; Clark *et al.*, 1973) would be the slowing of the absorption of the drug from the gastrointestinal tract. Oral administration of activated charcoal decreases the absorption of aspirin (Levy and Tsuchiya, 1972), while the anion-exchange resin cholestyramine also decreases the intestinal absorption of some drugs (Gallo *et al.*, 1965). Our *in vitro* experiments indicated that paracetamol was firmly bound by both of these adsorbents, and we therefore decided to investigate their efficacy in man in slowing the absorption of paracetamol from the gastrointestinal tract.

The presumptive absorption of a therapeutic dose of paracetamol in normal subjects was first studied by measuring plasma levels of the drug after an oral dose and then noting the effect on these of activated charcoal and cholestyramine given by mouth at two different times. We also measured the presumptive rate of absorption in patients who had previously taken an overdose of paracetamol to determine whether differences in absorption were responsible for the variable degrees of hepatic damage observed in these patients.

Methods

Normal subjects and patients were fasted overnight. Venous blood samples were taken 5, 10, 20, 40, 60, and 120 minutes after ingestion of 2 g paracetamol with 200 ml water. The plasma

concentration of paracetamol was determined as follows: 0.5 ml plasma was added to stoppered test-tubes containing 300 mg sodium chloride, 10 ml of diethyl ether (Analar) was added, and the tubes were shaken by hand for 30 seconds. After centrifugation at a maximum of 1,300 *g* for 10 minutes the upper phase was removed and the absorbance at 250 nm determined. Recovery of standard amounts of paracetamol from plasma by ether extraction was greater than 90%, and after calibration there was no significant difference between values obtained with five paired samples measured both by this spectroscopic method and by gas-liquid chromatography. The plasma paracetamol concentrations were plotted against time, and by using the trapezoidal rule the area under the curves was calculated as an estimate of the amount absorbed. Student's *t* test was used for assessment of statistical significance.

Results

The mean plasma absorption curve of paracetamol in 14 normal subjects is shown in fig. 1. The drug was rapidly absorbed, with peak plasma levels at 40 to 60 minutes. The concentrations at that time ranged from 18 to 87 $\mu\text{g/ml}$. The absorption of paracetamol was then restudied in these subjects under the same conditions but for the addition of activated charcoal or cholestyramine. Seven subjects ingested 10 g charcoal given as a suspension in methylcellulose (20 g/100 ml) immediately after the paracetamol. Mean plasma paracetamol levels were considerably lower (fig. 1), with a $63 \pm 7\%$ (mean $\pm$ S.E. of mean; range 32-87%) reduction in absorption measured as the

FIG. 1—Mean plasma levels of paracetamol—(a) in 14 normal subjects, (b) in 7 of these subjects after simultaneous administration of activated charcoal, and (c) in 4 of the subjects after administration of cholestyramine. Vertical bars show S.E. of mean.

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areas under the curves during the 120 minutes ($P < 0.01$). In the other seven subjects in whom the charcoal was not given until 60 minutes after the paracetamol the reduction in absorption over the following 80 minutes was only $23 \pm 8\%$ (range 0-44%) ($P > 0.05$).

Four subjects were given 12 g cholestyramine (Questran) suspended in 200 ml water immediately after the paracetamol. The mean plasma paracetamol levels were considerably lower (fig. 1) and the mean reduction in absorption was $62 \pm 14.5\%$ (range 30-98%) over 120 minutes; however, due to the large range of initial values this difference was not statistically significant. When the cholestyramine was given 60 minutes after ingestion of the drug there was only a $16 \pm 12\%$ (range 0-51%) mean reduction in absorption.

The mean plasma absorption curve of five patients who had taken an overdose of paracetamol during the preceding 18 months but who had shown no evidence of liver damage (Clark *et al.*, 1973) was compared with that of six patients in whom liver damage had developed after an overdose. There was no difference in the rates of absorption between these two groups or between either group and the 14 normal subjects (fig. 2).

FIG. 2—Mean plasma curves of paracetamol in 11 patients who had previously taken an overdose and in 14 normal subjects. Six patients had previously developed liver damage after an overdose and five had not.

Discussion

The absorption of paracetamol in the fasted normal subjects was rapid, presumably from the stomach and proximal small intestine (Weikel and Lish, 1959). This is in agreement with previous studies carried out in man (Carlo *et al.*, 1955; Gwilt *et al.*, 1963). There was no evidence from our study that absorption of paracetamol in patients who develop liver damage differs from normal.

The method for determining plasma paracetamol concentrations was developed for the rapid assessment of paracetamol levels in patients after deliberate overdose. Whereas it is not specific and may lack sensitivity, it compared favourably with the more specific but time-consuming method using gas-liquid chromatography (Prescott, 1971).

The simultaneous administration of activated charcoal or cholestyramine with the paracetamol markedly reduced its rate

of absorption. As has been shown for aspirin (Levy and Tsuchiya, 1972), the effect of absorption was much less when the adsorbent was given after an interval of 60 minutes. However, the large mass of paracetamol ingested in an overdose will probably be slowly solubilized and therefore absorption will be delayed. Thus in a patient in whom we measured serial plasma levels from one hour after an overdose the peak plasma level of paracetamol was not reached until three hours after ingestion, and absorption would continue after this. Most patients develop nausea after ingestion and some vomit, and this will alter intestinal motility and absorption (Rowland *et al.*, 1972). The presence of food in the stomach may also reduce absorption (Jaffe *et al.*, 1971; Heading *et al.*, 1972; McGilveray and Mattok, 1972), as may the use of antispasmodic drugs such as propantheline (Nimmo *et al.*, 1973) and lavage. It is likely, therefore, that administration of an adsorbent will frequently reduce absorption of paracetamol even if not given until several hours after an overdose. Reducing the total amount absorbed, or only slowing the rate of absorption of the overdose, could reduce liver damage if the hepatotoxicity of paracetamol depends on the temporary overloading of the normal hepatic mechanism for its conjugation and detoxification. It is also possible that once the liver has been damaged by paracetamol it is more susceptible to the effects of the drug absorbed subsequently.

We suggest that either cholestyramine or activated charcoal should be available in every casualty department (*British Medical Journal*, 1972) and that in cases of paracetamol overdose 50 g of adsorbent should be left in the stomach after it has been emptied by a wash-out. Perhaps propantheline should also be administered (Nimmo *et al.*, 1973). Such an approach adds no risk and might reduce the frequency and severity of hepatic damage.

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