POLYMER COATING OF ACTIVATED CHARCOAL AND ITS EFFECTS ON BIOCOMPATIBILITY AND PARACETAMOL BINDING

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SUMMARY

1. The ability of activated charcoal, treated in differing ways with poly(hydroxyethylmethacrylate), to adsorb paracetamol was studied.

2. Activated charcoal was coated with 2, 4 or 10% by weight of poly(hydroxyethylmethacrylate). Neither the percentage by weight (2, 4 or 10%) coating of activated charcoal by the polymer nor the procedure used to apply the coat affected the total adsorption of paracetamol at equilibrium, but these factors did influence the speed of adsorption.

3. The impregnated charcoals, and those with the lowest percentage by weight coating (2%), removed paracetamol from a stirred solution most rapidly. These charcoals also removed the drug most efficiently during column perfusion.

4. Biocompatibility studied in vivo in the dog revealed a smaller fall in blood platelets with haemoperfusion through 4% encapsulated charcoal than with 4% impregnated charcoal.

5. Dye-adsorption studies indicated that impregnation produced less complete coating of the charcoal, and that the lower percentage by weight coatings were the least complete.

6. The most acceptable compromise for clinical use appeared to be the 4% encapsulated charcoal, as the removal of paracetamol was reasonably rapid and the fall in blood platelet levels was acceptable.

Key words: paracetamol, adsorption, charcoal.

Liver damage from an intentional overdose of paracetamol taken in a suicide attempt is an increasing problem in this country (Clark, Thompson, Borirakchanyavat, Widdop, Davidson, Goulding & Williams, 1973). If the drug could be removed from the blood during the first hours after an overdose, the risk of liver damage might be reduced. Activated charcoal binds...
paracetamol *in vitro* and studies *in vivo* with charcoal column haemoperfusion in the pig showed 90% extraction of paracetamol across the column, and during a 2 h perfusion nearly half the administered dose was adsorbed (Willson, Thompson, Winch & Williams, 1973). However, when this technique was used in the treatment of patients after an overdose, the mean percentage extraction of the drug was only 40% (B. G. Gazzard, R. A. Willson, M. J. Weston, R. P. H. Thompson & R. Williams, unpublished work). One possible reason for this reduced extraction may have been that, after the pig experiments, the thickness of the biocompatible polymer coating of the charcoal had been increased and the method of application changed.

In this paper we report investigations into the effects of the thickness and method of coating activated charcoal on the kinetics of paracetamol binding and the total adsorption of paracetamol. The completeness of the coating and the biocompatibility of the final product have also been investigated.

**METHODS**

The activated charcoal (Speakman coconut charcoal 610) was obtained from Sutcliffe-Speakman Ltd, Lancashire. It was coated by Smith and Nephew Research Department with 'polyhema', which is chemically poly(hydroxyethylmethacrylate), by two different techniques, one in which the charcoal is impregnated and the other in which it is encapsulated. The first method attempted to cover both the surface and the internal adsorptive area of the charcoal and the second provided a thin external coating only. A combination of the two techniques was used in the preparation of some batches. The percentage coating is expressed as the increase in weight of the charcoal after the coating procedure. The following coatings were investigated: 2% and 4% applied by impregnation or encapsulation, and 6% and 10% applied by the combined method. After coating, the charcoal was sieved to remove particles of less than 600 µm diameter and then cleansed by soaking in sodium chloride (0.154 mol/l) for 24 h. All experiments were carried out at 22°C and at pH 7.4.

**Dye-adsorption studies**

In order to investigate the completeness of the coating process we used the dye Lissamine Scarlet R100 (Imperial Chemical Industries Ltd), which is adsorbed by uncoated charcoal but does not penetrate or bind to 'polyhema'. Portions (250 mg) of the batches of coated charcoal were agitated for 48 h in aqueous solutions of the dye in concentrations 1–10 g/l. The amount of the dye adsorbed was estimated from the decrease in the spectrophotometrically determined (A max. 510 nm) concentrations of dye remaining in the supernatant after centrifugation. With increasing concentrations of dye in solution the amount adsorbed on to charcoal reaches a plateau (Fig. 1) when the dye monolayer is complete. Thus any lowering of this plateau of adsorption by coated charcoal is assumed to be due to areas of incomplete coating.

**Equilibrium and kinetic studies of paracetamol adsorption**

As initial studies had shown that at equilibrium 100 mg of uncoated charcoal would adsorb between 0.03 and 0.2 mmol of paracetamol, 100 mg portions of different batches of coated charcoal were agitated for 48 h with 10 ml of a solution of paracetamol in human plasma or saline in concentrations of 3–30 mmol/l. The amount of paracetamol adsorbed was estimated from that remaining in the supernatant, paracetamol being measured by the method of Dordoni,
Willson, Thompson & Williams (1973). The adsorption of paracetamol to 600 μm beads of ‘polyhema’ was also studied by the same techniques. To investigate the kinetics of paracetamol uptake, a 500 mg quantity of the coated charcoal was agitated with 10 ml of paracetamol solution in saline or plasma (1-65 mmol/l) for periods of between 2 and 30 min. This lower concentration represents the plasma concentration of the drug frequently seen after an overdose.

![Graph](Image)

**FIG. 1.** Relationship between the concentration in solution at equilibrium of the dye Lissamine Scarlet and the amount of dye adsorbed to 250 mg aliquots of the various charcoals. ○, Uncoated; ▲, 2% encapsulated; ◻, 4% impregnated; ■, 4% encapsulated; ×, 10% combined method. The curve for 2% impregnated charcoal was almost identical with that for 2% encapsulated charcoal and has therefore not been shown.

**Extraction of paracetamol during column perfusion**

The glass columns (2 cm diameter x 15 cm long; Wright’s Scientific Ltd) contained 15 g of charcoal when lightly packed. Plasma solutions of paracetamol (0.3–2.6 mmol/l) were pumped through the columns at 25 ml/min with a Watson–Marlow roller pump. Simultaneous samples were obtained from the input and output tubing at intervals during perfusion, for estimation of paracetamol concentration.

**Biocompatibility studies**

Blood was obtained from patients with haemochromatosis during venesection therapy. It was heparinized (1 unit/ml) at the time of removal and was pumped within 2 h through the same columns at the same flow rates as were used in the previous experiments. Blood platelet
and white cell counts were measured from simultaneous samples taken from the input and output tubing.

The biocompatibility of two of the coated charcoals (4% impregnated and 4% encapsulated) were also assessed during the haemoperfusion of two healthy greyhound dogs (18 kg). Large columns (5 cm x 30 cm) containing 200 g of charcoal were used. The animals were heparinized with a loading dose of 2000 units followed by 1500 units hourly. A flow of 150 ml/min through the column was maintained for 4 h by a Watson–Marlow pump. Each of the two batches of charcoal was tested twice in both dogs and the removal of platelets was assessed from the input—output difference across the column at hourly intervals, and from the drop in arterial platelet count (expressed as a percentage of the initial count) during the period of perfusion.

RESULTS

The dye studies showed that adsorption occurred with the 2% and 4% impregnated as well as with the 2% encapsulated charcoals (Fig. 1), indicating that these charcoals had uncoated areas. There was less adsorption to the 4% encapsulated charcoal and very little to the charcoals coated by the combined technique, showing a more complete coating.

In the equilibrium studies it was shown that the final amount of paracetamol adsorbed was not affected by the percentage by weight coating or the technique of application (Fig. 2), and approximately 0.09 mmol of paracetamol was bound to 100 mg of coated charcoal. Identical results were obtained with plasma or saline solutions. It was also shown that paracetamol did

![Equilibrium concentration of paracetamol (mmol/l)](image)

**Fig. 2.** Equilibrium curves for the adsorption of paracetamol from plasma by 100 mg portions of the uncoated and coated charcoals. Each point represents the mean of two experiments. •, Uncoated; ▲, 2% encapsulated; ■, 4% encapsulated; □, 4% impregnated; ○, 6% combined method; ×, 10% combined method.
Paracetamol adsorption to coated charcoal

not adsorb to beads of 'polyhema'. In the kinetic studies an increase in the percentage by weight coating applied by either method slowed the rate of adsorption of paracetamol, and for the same percentage coating the drug was more rapidly removed by impregnated charcoal than that coated with the encapsulated technique (Fig. 3). However, for all charcoals the rate of removal of paracetamol was similar from plasma or saline.

Fig. 3. Rates of adsorption of paracetamol in plasma to 500 mg quantities of uncoated and coated charcoals. ●, Uncoated; ▼, 2% impregnated; ▲, 2% encapsulated; ○, 4% impregnated; ■, 4% encapsulated; □, 6% combined method; ×, 10% combined method.

The results of the column perfusion experiments closely paralleled those obtained in the kinetic studies (Fig. 4). Thus extraction of paracetamol with the impregnated charcoals was better than with the encapsulated varieties, and increasing the percentage by weight of both types of coating reduced the percentage extraction.

Both the blood platelet and white cell counts were diminished during perfusion in vitro across columns of various charcoal particles. With all the coated charcoals the reduction of platelet count expressed as a percentage of the initial count was less than with those uncoated (Table 1), but no consistent differences between the different percentages by weight and types of coatings were observed. During perfusion in vivo in dogs the drop in platelet count across
Fig. 4. Percentage extraction of paracetamol from plasma across columns containing 15 g of coated charcoal.

Table 1. Removal of platelets and white cells (expressed as a percentage of the initial count) during perfusion with fresh blood in vitro

Each value represents the mean of six separate measurements.

<table>
<thead>
<tr>
<th>Coating</th>
<th>Removal of formed elements (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Platelets</td>
</tr>
<tr>
<td>Uncoated</td>
<td>50</td>
</tr>
<tr>
<td>2% Impregnated</td>
<td>29</td>
</tr>
<tr>
<td>4% Impregnated</td>
<td>27</td>
</tr>
<tr>
<td>2% Encapsulated</td>
<td>44</td>
</tr>
<tr>
<td>4% Encapsulated</td>
<td>20</td>
</tr>
<tr>
<td>10% Combined</td>
<td>10</td>
</tr>
</tbody>
</table>
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the column of charcoal was small and variable. However, platelet counts measured in arterial blood from the animals did fall significantly during the period of perfusion. The mean platelet drop was 20% (range 10–30%) in the four perfusions with 4% encapsulated charcoal. By 24 h the count had returned to normal. With the 4% impregnated charcoal the fall was greater, mean 40% (range 20–60%), and the counts had not returned to normal within 24 h. No consistent changes in white cell count were observed.

DISCUSSION

Early use of haemoperfusion through uncoated charcoal particles in patients with barbiturate overdosage was accompanied by the loss of formed elements from the blood stream and also by the formation of charcoal emboli (Andrade, Kopp, van Wagenen, Chen & Kolff, 1972). The use of the polymer coating ‘polyhema’ has been shown to reduce the risk of both these complications (Andrade, van Wagenen, Chen, Ghavamian, Volder, Kirkham & Kolff, 1972). In this paper we have shown how the percentage by weight of coating and method of application of such a coating are important both in the biocompatibility of the particles and also in the speed of removal of substances from solution.

The total amount of paracetamol adsorbed by charcoal at equilibrium was unaffected by the type of polymer coating. However, adsorption took place more rapidly to charcoal with the lower percentage by weight coatings. This could be due in part to faster diffusion of paracetamol across the membrane, but we also showed in the dye studies that these coatings were incomplete, and adsorption of paracetamol to the ‘bare’ areas of charcoal may also account for the more rapid rates of removal. The more rapid removal of paracetamol by the impregnated charcoals is also accounted for by the incomplete coating achieved by this method of application.

In the treatment of patients, a compromise has to be reached between the rapid adsorption of toxic substances required and the prevention of too great a loss of the formed elements from the blood stream. The biocompatibility of the various charcoals is likely to be closely related to the completeness of the covering. The present studies in vivo showed clearly that perfusion through encapsulated charcoal was less injurious to platelets than perfusion through 4% impregnated charcoal. Adsorption of paracetamol was reasonably rapid, but the mean fall in platelet count in arterial blood over a 4 h perfusion was acceptable at only 20%. A fall in arterial platelet count during haemoperfusion is probably due not only to extraction by the column but also to sequestration of platelets within the body, as has been noted during heart–lung bypass procedures (de Leval, Hill, Mielke, Bramson, Smith & Gerbode, 1972). Indeed, in the dog haemoperfusion studies with the 4% encapsulated charcoal the greatest percentage loss of platelets occurred during the first hour, the platelet count returning towards normal at 4 h.

Although the present studies on adsorption and biocompatibility of charcoal have been in relation to the removal of paracetamol from the blood, the findings may have relevance to a considerably wider field of therapeutics. A number of groups are currently trying haemoperfusion through activated charcoal as a supplement to dialysis in the treatment of renal failure (Chang & Malave, 1970), and in the treatment of overdosage of other drugs including barbiturates and glutethimide (de Myttenaere, Maher & Schreiner, 1967).
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REFERENCES


