Adsorption of Imipramine onto Activated Charcoal and a Cation Exchange Resin in Macrogol-Electrolyte Solution

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Adsorption of imipramine onto activated charcoal and a cation exchange resin, sodium polystyrene sulfonate were evaluated in macrogol (polyethylene glycol) electrolyte solution (PEG-ELS) and JP XII second medium. The maximum adsorptive capacity of activated charcoal for imipramine was 610 mg and 372 mg per g of charcoal in PEG-ELS and JP XII second medium, respectively. On the other hand, the maximum adsorptive capacity of sodium polystyrene sulfonate for the drug was 272 mg and 667 mg per g of the resin in PEG-ELS and JP XII second medium, respectively. Adsorption of imipramine onto both adsorbents was greater when macrogol was omitted from PEG-ELS than in PEG-ELS itself. Adsorption of the drug onto activated charcoal was decreased when sodium sulfonate or sodium bicarbonate was omitted from PEG-ELS, whereas that onto sodium polystyrene sulfonate was decreased only when sodium bicarbonate was omitted from PEG-ELS.

Keywords imipramine; activated charcoal; cation exchange resin; sodium polystyrene sulfonate; macrogol electrolyte solution; adsorption; adsorptive capacity; salt

Introduction

In acute drug overdoses the drug should be removed as soon as possible before it is greatly absorbed by the gastrointestinal (g.i.) tract. Procedures such as gastric lavage or induction of emesis with syrup of ipecac are generally followed and then administration of adsorbents such as activated charcoal with cathartics or agents promoting intestinal motility is made as methods of g.i. decontamination. It is particularly important to use means that promote rapid removal in the case of drugs such as tricyclic antidepressants, anticholinergic drugs, antihistamines and opiates because an overdose of these drugs decreases bowel motility.[1] In overdoses of these drugs, it is thus difficult to discharge drug–charcoal complexes from the g.i. lumen since the complexes tend to remain in the lumen for a long time. Prolonged transit time may result in desorption of poisoned drugs from adsorbents.

Whole bowel irrigation with a macrogol (polyethylene glycol) electrolyte solution (PEG-ELS) has recently been used as a g.i. decontamination procedure in overdoses.[2-4] A whole bowel irrigation fluid is a routine preparation used prior to colonoscopy and large bowel surgery. This lavage solution was specifically developed to minimize absorption and/or secretion of fluids and electrolytes across the g.i. membrane. Its safety and efficacy have been demonstrated in clinical practice.[5,6] Administration of a large volume of PEG-ELS to the g.i. tract over several hours induces diarrhea and rapidly cleans the bowel. In drug overdoses, activated charcoal or ion exchange resin is frequently used in combination with the lavage solution. However, few studies have been made on whether adsorption of drugs was increased or decreased in the lavage solution such as PEG-ELS with rich macrogol and electrolytes.[7,8]

The present study was undertaken to elucidate how much the adsorptive capacity of activated charcoal and a cation exchange resin for imipramine were affected in PEG-ELS. A tricyclic antidepressant, imipramine was used as a common representative drug and this causes a reduction in peristalsis in acute drug poisoning.

Experimental

Materials Activated charcoal was a product of Inuhinode Seiyaku Co., Osaka and the particle size used in this study was less than 62 μm. A cation exchange resin was obtained as a commercial preparation (sodium polystyrene sulfonate, Kayexalate, Torii & Co., Tokyo). Imipramine hydrochloride was supplied by Ciba-Geigy (Japan) Co., Takarazuka, Japan. Two liters of PEG-ELS contains the following substances: 118 g macrogol 4000, 11.37 g sodium sulfate, 3.37 g sodium bicarbonate, 2.93 g sodium chloride, and 1.485 g potassium chloride. All other chemicals used in this study were of analytical grade.

Adsorption Study *In vitro* adsorption studies were carried out by dissolving imipramine in PEG-ELS or JP XII second medium. The drug in various concentrations in both solutions (100 ml) was added to 10 mg of each adsorbent in a series of conical flasks and the suspensions were shaken at 37 °C. After equilibration, samples were filtered through 0.45 μm pore size membrane. Concentrations of imipramine in the filtrate were determined after suitable dilution by spectrophotometry at 250 nm. In addition, the adsorptive capacity of both adsorbents for imipramine (100 μg/ml) was estimated in 100 ml of JP XII second medium, PEG-ELS and solutions in which each constituent was omitted from a standard PEG-ELS formulation.

Estimation of Adsorption Parameters Adsorption parameters were estimated according to the following Langmuir equation:

$$M = abC_{eq}/(1 + bC_{eq})$$

where C_{eq} is the free drug concentration in solution at equilibrium, M is the amount of drug adsorbed by the quantity of charcoal used, a is the maximum amount adsorbed when the entire surface is covered by a monolayer and b is the equilibrium constant of the adsorption process.

Results

Figure 1 shows adsorption isotherms of imipramine onto activated charcoal and a sodium polystyrene sulfonate resin in PEG-ELS and JP XII second medium at 37 °C. Adsorptive capacity of both adsorbents for imipramine initially increased with increase in concentration of the drug, and then reached a constant value. Adsorption of imipramine onto activated charcoal in PEG-ELS was greater than that in JP XII second medium. However, adsorption of the drug onto a sodium polystyrene sulfonate resin in PEG-ELS was less than that in JP XII second medium. The maximum adsorptive capacity of both adsorbents was calculated by fitting the data to the linearized form of the Langmuir equation. The maximum adsorptive capacity (a) of activated charcoal for imipramine in PEG-ELS and JP XII second medium was 610 mg and 372 mg per g of charcoal, respectively, whereas that of a sodium polystyrene sulfonate resin for the drug in PEG-ELS

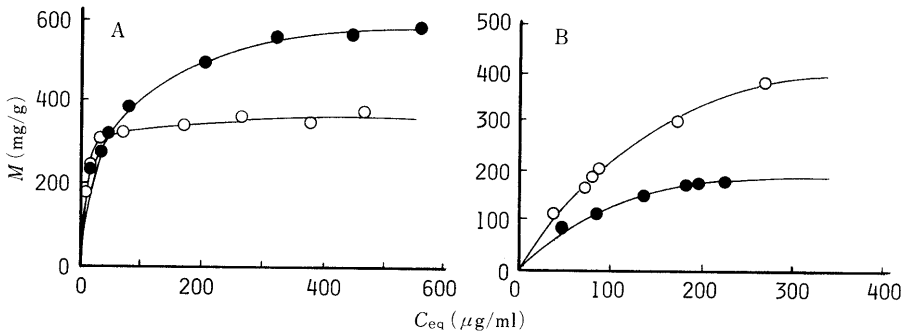

Fig. 1. Adsorption Isotherms of Imipramine onto Activated Charcoal and Sodium Polystyrene Sulfonate in PEG-ELS (●) and JP XII Second Medium (○) at 37 °C

A, activated charcoal; B, sodium polystyrene sulfonate.

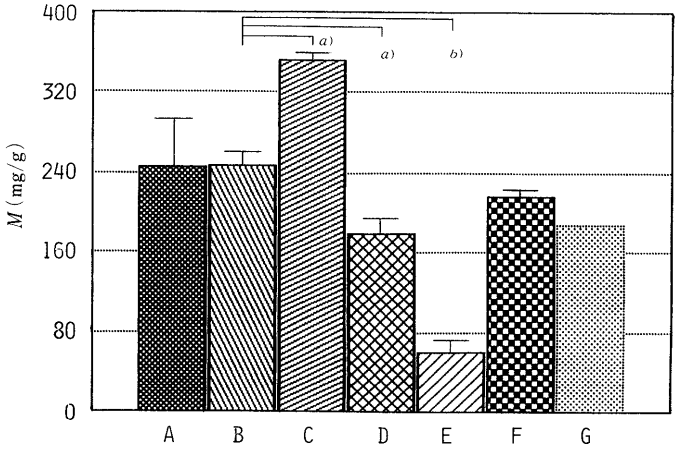

Fig. 2. Effect of Constituents Contained in PEG-ELS on Adsorptive Capacity of Activated Charcoal for Imipramine

Ten milligrams of charcoal was added to 100 ml of each solution containing 100 μg/ml of imipramine.

A, JP XII second medium; B, PEG-ELS; C, PEG-ELS without macrogol; D, PEG-ELS without Na_2SO_4; E, PEG-ELS without $NaHCO_3$; F, PEG-ELS without NaCl; G, PEG-ELS without KCl. *a*) $p<0.05$, *b*) $p<0.01$.

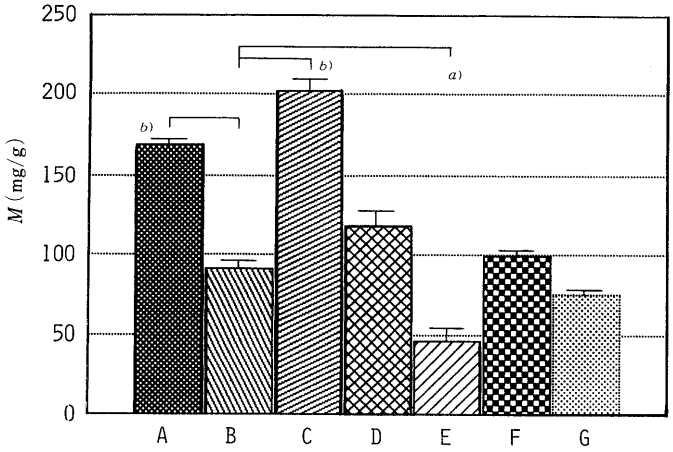

Fig. 3. Effect of Constituents Contained in PEG-ELS on Adsorptive Capacity of Sodium Polystyrene Sulfonate for Imipramine

Ten milligrams of charcoal was added to 100 ml of each solution containing 100 μg/ml of imipramine.

A, JP XII second medium; B, PEG-ELS; C, PEG-ELS without macrogol; D, PEG-ELS without Na_2SO_4; E, PEG-ELS without $NaHCO_3$; F, PEG-ELS without NaCl; G, PEG-ELS without KCl. *a*) $p<0.05$, *b*) $p<0.01$.

and JP XII second medium was 272 mg and 667 mg per g of the resin. In addition, the equilibrium constant (*b*) of activated charcoal for imipramine in PEG-ELS and JP XII second medium was 0.144 and 0.034, respectively, whereas that of a sodium polystyrene sulfonate resin for the drug was 0.008 and 0.005.

To explore the effect of constituents contained in PEG-ELS, adsorption of imipramine onto both adsorbents was investigated by eliminating each one from PEG-ELS. Figure 2 shows the changes of adsorptive capacity of activated charcoal for imipramine (100 μg/ml) in 100 ml of JP XII second medium, PEG-ELS and the solutions in which each constituent was elminated from PEG-ELS. As shown in Fig. 2, adsorption of imipramine onto activated charcoal was significantly increased in the absence of macrogol from PEG-ELS, while adsorption of the drug onto charcoal was decreased in the absence of sodium sulfate or sodium bicarbonate from PEG-ELS. Figure 3 also shows the changes in adsorptive capacity of a sodium polystyrene sulfonate resin for imipramine (100 μg/ml) in 100 ml of JP XII second medium, PEG-ELS and the solutions in which each constituent was eliminated from PEG-ELS. Adsorption of imipramine onto a sodium polystyrene sulfonate resin was more significantly increased in the absence of macrogol from PEG-ELS than in PEG-ELS itself. On the contrary, adsorption of the drug onto the resin was decreased in the absence of sodium bicarbonate from PEG-ELS.

Discussion

It is important to prevent absorption of toxic drugs in drug overdoses by adequate decontamination of the g.i. tract such as whole bowel irrigation. Our results showed that adsorption of imipramine onto activated charcoal was greater in PEG-ELS than that in JP XII second medium (Fig. 1). In general, adsorption of a drug onto activated charcoal is more extensive when the drug is in a unionized form than in an ionized form. Since imipramine is a basic compound with a pK_a value of 9.4, the drug is more unionized in PEG-ELS (pH 8.5) than in JP XII second medium (pH 6.8). Consequently, a possible explanation for the more extensive adsorption of imipramine onto activated charcoal in PEG-ELS than in JP XII second medium may be the higher pH value of PEG-ELS. Moreover, adsorption of imipramine in PEG-ELS was greater for activated charcoal than for a sodium polystyrene sulfonate resin (Fig. 1). These results suggest that use of activated charcoal combined with PEG-ELS would greatly contribute to decontamination of the g.i. tract in imipramine overdoses.

It was observed that absence of macrogol from PEG-ELS increased adsorption of imipramine onto activated charcoal and a sodium polystyrene sulfonate resin (Figs. 2 and 3). These results suggest that macrogol can interact with adsorbents or change the solvent property of the aqueous solution. Kirshenbaum *et al.*[4] reported that macrogol was adsorbed onto activated charcoal and that combining PEG-ELS with activated charcoal resulted in a decrease in adsorption of salicylic acid. Thus, one possible explanation for the increased adsorption of imipramine onto activated charcoal in the absence of macrogol from PEG-ELS is the competition of macrogol with imipramine for adsorbing sites. Sodium polystyrene sulfonate, on the other hand, is a cation exchange resin, and displaces sodium cation in the resin with protonated imipramine or the cations in the lavage solution. Since macrogol is a neutral substance, it does not appear to compete with imipramine for ion exchange sites of the resin.

Absence of sodium sulfate or sodium bicarbonate from PEG-ELS decreased adsorptive capacity of activated charcoal for imipramine (Fig. 2). This indicates that the adsorptive capacity of activated charcoal is affected by salts. There are several reports that adsorption of drugs onto adsorbents is affected in the presence of salts.[9-12] For example, Rademaker *et al.*[10] reported that sodium sulfate increased the adsorptive capacity of activated charcoal for antipyrine, phenobarbital and amitriptyline *in vitro*. Akintonwa and Orisakwe[12] also reported that saline cathartics, sodium sulfate and magnesium sulfate enhanced adsorption of sulfamethoxazole onto activated charcoal. The mechanism is most likely the salting-out of organic molecules from solution to adsorbent surfaces. These reports can support our results that the adsorptive capacity of activated charcoal for imipramine was increased in PEG-ELS with rich salts.

In addition to these salt effects, the pH effect must be taken into consideration. Adsorption onto activated charcoal is more extensive when the drug is in an unionized form. Since imipramine is a basic compound, the drug is more unionized in PEG-ELS (pH 8.5) than in JP XII second medium (pH 6.8). Consequently, adsorption of imipramine onto activated charcoal can be greater in PEG-ELS than in JP XII second medium. Moreover, the pH values of the solutions in which each constituent was omitted from PEG-ELS were almost consistent with the pH value of PEG-ELS, except for that (pH 5.9) of the solution in which sodium bicarbonate was omitted from PEG-ELS. Therefore, the reason why adsorption of imipramine was least in the absence of sodium bicarbonate in PEG-ELS may be due to the decrease in the unionized form due to a lower pH value than that of PEG-ELS.

Similar results were obtained for the adsorption onto a sodium polystyrene sulfonate resin. Adsorption on a cation exchange resin is generally affected by sodium cation and potassium cation in PEG-ELS. In fact, the absence of sodium sulfate which is contained in large amount in PEG-ELS, tended to enhance adsorption of imipramine onto a sodium polystyrene sulfonate resin (Fig. 3). However, in the absence of sodium bicarbonate from PEG-ELS, adsorption of imipramine onto the resin was least of all the solutions, even though imiramine is more ionized in the pH value (pH 5.9) of the solution. Further studies need to be performed to elucidate the mechanism.

In conclusion, oral activated charcoal would be useful in combination with whole bowel irrigation with PEG-ELS in imipramine overdoses since activated charcoal exerts an excellent adsorbability in PEG-ELS. However, sodium polystyrene sulfonate appears not to be effective in combination with PEG-ELS owing to the decrease in its adsorptive capacity in PEG-ELS.

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