

Adsorption of Mexiletine onto Activated Charcoal in Macrogol-Electrolyte Solution

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Adsorption studies *in vitro* of mexiletine onto activated charcoal were performed in macrogol (polyethylene glycol)-electrolyte solution (PEG-ELS) and JP XII disintegration medium No. 2 (second medium). Mexiletine was adsorbed more extensively onto activated charcoal in PEG-ELS than that in JP XII second medium. The maximum adsorptive capacity of activated charcoal for the drug was 328 and 284 mg per gram of charcoal in PEG-ELS and JP XII second medium, respectively. In addition, the equilibrium constant of activated charcoal estimated according to the Langmuir equation was 0.079 and 0.034 l per gram of charcoal in PEG-ELS and JP XII second medium, respectively. Adsorption of mexiletine onto activated charcoal was decreased by omitting macrogol, sodium sulfate or sodium bicarbonate from a standard PEG-ELS formulation. Oral activated charcoal will be useful in combination with whole bowel irrigation with PEG-ELS in mexiletine overdose because of its excellent adsorbability in the solution.

Keywords mexiletine; activated charcoal; macrogol; polyethylene glycol; macrogol-electrolyte solution; adsorption

Introduction

Recently, whole bowel irrigation with a macrogol (polyethylene glycol)-electrolyte solution (PEG-ELS) has been used as a gastrointestinal (g.i.) decontamination procedure in overdoses.¹⁻³⁾ Administration of large volumes of PEG-ELS into the g.i. tract induces diarrhea which rapidly cleans the bowel. PEG-ELS was specifically developed to minimize absorption and/or secretion of fluid or electrolyte across the g.i. membrane, and its safety and efficacy have already been demonstrated in clinical practice.^{4,5)}

In drug overdoses, activated charcoal is frequently used in combination with the lavage solution in order to prevent the absorption of poisonous drugs from the g.i. tract. Several studies reported that saline cathartics such as sodium sulfate and magnesium sulfate changed the extent of adsorption of substances onto activated charcoal.⁶⁻⁸⁾ Thus, the adsorption of drugs onto activated charcoal may be influenced by constituents such as macrogol and electrolytes which are contained in PEG-ELS. However, there are only a few studies on the adsorption of poisonous drugs in PEG-ELS lavage solution.^{9,10)}

The present study was designed to determine how much the adsorptive capacity of activated charcoal for mexiletine was affected in PEG-ELS. An antiarrhythmic drug, mexiletine was used as a representative drug because intoxication by accidental overdoses of the antiarrhythmic drugs can give rise to life-threatening symptoms including loss of consciousness, cardiac arrhythmias and loss of spontaneous respiration.

Experimental

Materials Mexiletine hydrochloride and methylmexiletine were kindly supplied by Nippon Boehringer Ingelheim Co. (Hyogo, Japan). Activated charcoal was a product of Inuhinode Seiyaku Co., Osaka. The powder was passed through sieves (62 μ m) and was dried at 110 °C for several hours. PEG-ELS contained the following substances in 2 l: 118.0 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 Adsorption studies *in vitro* were carried out in mexiletine solutions in PEG-ELS and JP XII disintegration medium No. 2 (second medium). Ten mg of activated charcoal was added to the solutions (100 ml) containing appropriate concentrations of mexiletine in

a series of conical flasks, and the suspensions were shaken at 37 °C. After equilibration, a sample was filtered through a 0.45 μ m pore size membrane disk. After suitable dilution, concentrations of mexiletine in the filtrate were determined by spectrophotometry at 260 nm. In addition, the effects of constituents on the adsorptive capacity of activated charcoal for mexiletine hydrochloride (100 μ g/ml) were estimated in 100 ml of JP XII second medium, PEG-ELS and the 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, and 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.

Measurement of Solubility An excess amount of mexiletine hydrochloride was introduced into 2 ml each of PEG-ELS, the solution omitting macrogol from PEG-ELS, or the solution omitting sodium sulfate from PEG-ELS. The suspensions were stirred for up to 10 h in a water bath at 37 °C. After equilibration, the saturated solutions were sampled by a 1 ml syringe and immediately passed through a 0.45 μ m membrane filter. The sample of saturated solutions was diluted to suitable volumes with the solutions, and its concentration was measured by spectrophotometry at 260 nm. Amounts of mexiletine are all shown as a hydrochloride salt.

Results

Adsorption of Mexiletine onto Activated Charcoal Figure 1 shows adsorption isotherms of mexiletine onto activated charcoal in PEG-ELS and JP XII second medium at 37 °C. It was observed that the adsorption of mexiletine onto activated charcoal increased as the concentration of the drug in both solutions was increased. Activated charcoal adsorbed mexiletine more extensively in PEG-ELS than in JP XII second medium. The maximum adsorptive capacity was calculated by fitting the data to the linearized form of the Langmuir equation. The maximum adsorptive capacity of activated charcoal for mexiletine was 328 and 284 mg per gram of charcoal in PEG-ELS and JP XII second medium, respectively. In addition, the equilibrium constant of activated charcoal for mexiletine was 0.079 and 0.034 l per gram of charcoal in PEG-ELS and JP-XII second medium, respectively.

Effect of Constituents in PEG-ELS on Adsorption To explore the influence of constituents in PEG-ELS on the adsorption of mexiletine, the adsorption onto activated

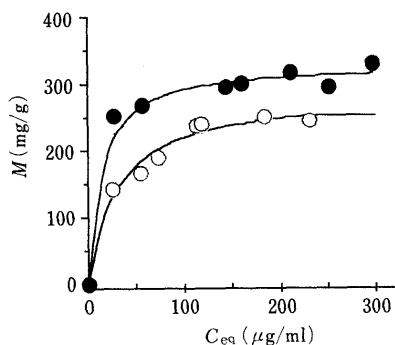


Fig. 1. Adsorption Isotherm of Mexiletine onto Activated Charcoal in PEG-ELS (●) and JP XII Second Medium (○) at 37°C
Lines are drawn by values calculated from the Langmuir equation.

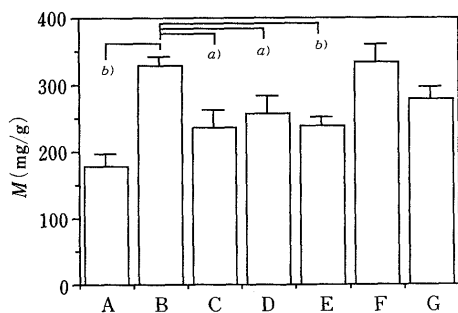


Fig. 2. Effect of Constituents Contained in PEG-ELS on Adsorptive Capacity of Activated Charcoal for Mexiletine at 37°C

Ten milligrams of charcoal were added to 100 ml of each solution containing 100 μg/ml of mexiletine. A: JP XII second medium, B: PEG-ELS, C: PEG-ELS without macrogol 4000, D: PEG-ELS without sodium sulfate, E: PEG-ELS without sodium bicarbonate, F: PEG-ELS without sodium chloride, G: PEG-ELS without potassium chloride. Each bar represents the mean ± SEM of 3 experiments. a) $p < 0.05$, b) $p < 0.01$.

charcoal was examined by omitting each constituent from a standard PEG-ELS formulation. Figure 2 shows the changes in adsorptive capacity of activated charcoal for mexiletine (100 μg/ml) in 100 ml each of JP XII second medium, PEG-ELS and the solutions in which each constituent was omitted from PEG-ELS. The adsorption of mexiletine onto activated charcoal decreased more significantly in the absence of either macrogol, sodium sulfate or sodium bicarbonate from PEG-ELS than it did in PEG-ELS itself. Thus, the solubility of mexiletine was examined in the respective solutions. The results were as follows: 635 mg/ml in PEG-ELS, 689 mg/ml in the solution omitting macrogol from PEG-ELS, and 700 mg/ml in the solution omitting sodium sulfate from PEG-ELS.

Discussion

Our results show that the adsorption of mexiletine onto activated charcoal was greater in PEG-ELS than in JP XII second medium (Fig. 1). These results suggest that the use of activated charcoal combined with PEG-ELS would greatly contribute to the decontamination of the g.i. tract in the case of mexiletine overdose. It has been shown that the adsorption of a drug onto activated charcoal varies depending on factors such as ionization and the solubility of a drug and the temperature in a solution. In general, the adsorption of a drug onto activated charcoal is more extensive when the drug is in a unionized form than in an

ionized form. Since mexiletine is a basic compound with a pK_a value of 9.1, the drug is likely to be 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 mexiletine onto activated charcoal in PEG-ELS than in JP XII second medium could be the higher pH value of PEG-ELS than JP XII second medium (Fig. 1).

Kirshenbaum *et al.*¹⁰ reported that macrogol adsorbed onto activated charcoal caused a decrease in the adsorption of salicylic acid. Our previous report also showed that macrogol in PEG-ELS decreased the adsorptive capacity of activated charcoal for imipramine.¹¹ This interaction of macrogol with activated charcoal would therefore be expected to adversely affect the adsorptive capacity for mexiletine. However, contrary to our expectation, the presence of macrogol in PEG-ELS resulted in an increase in the extent of adsorption of mexiletine onto charcoal. That is, the adsorption of mexiletine onto activated charcoal in the solution omitting either macrogol, sodium sulfate or sodium bicarbonate from PEG-ELS was less than that in standard PEG-ELS (Fig. 2). These results suggest that the macrogol, sodium sulfate or sodium bicarbonate contained in PEG-ELS contributes to an excellent adsorption of mexiletine onto activated charcoal when PEG-ELS was used for whole bowel irrigation in mexiletine overdose.

One possible explanation for the decreased adsorption of mexiletine in the absence of macrogol from PEG-ELS may be due to a difference in the solubility of the drug between PEG-ELS and the solution omitting macrogol from PEG-ELS. In general, the extent of adsorption of a drug is inversely proportional to its solubility in the solvent from which adsorption occurs.¹² It has been shown that macrogol interacts with some compounds and results in affecting the dissolution rate or solubility.^{13,14} Thus, we examined the solubility of mexiletine in PEG-ELS, in the solution omitting macrogol from PEG-ELS, and in the solution omitting sodium sulfate from PEG-ELS. As a result, the solubility of mexiletine in PEG-ELS apparently decreased compared with that of the solution omitting either macrogol or sodium sulfate from PEG-ELS. These results suggest that macrogol or sodium sulfate in PEG-ELS may create suitable circumstances for adsorption of mexiletine onto activated charcoal, probably due to a decrease in the solubility of mexiletine.

In the present series of experiments, pH values of the solutions used were approximately 8.5 except for those of JP XII second medium (pH 6.8) and PEG-ELS free from sodium bicarbonate (pH 5.9). Therefore, the decreased adsorption of mexiletine onto activated charcoal in the solution free from sodium bicarbonate may be due to the relative decrease in the unionized form by its lower pH value as compared to the pH value of PEG-ELS.

Some studies have also shown that inorganic salts such as sodium sulfate and magnesium sulfate influence the adsorption of drugs onto activated charcoal.⁶⁻⁸ For example, Rademaker *et al.*⁶ reported that sodium sulfate increased the adsorptive capacity of activated charcoal for antipyrine, phenobarbital and amitriptyline *in vitro*. Akintonwa and Orisakwe⁸ also reported that saline cathartics such as sodium sulfate and magnesium sulfate enhanced the adsorption of sulfamethoxazole onto activated

charcoal, probably by altering the ionization species in the sulfamethoxazole. The mechanism has been proposed to be a strong salting-out effect of divalent anions. These reports can support our results that the adsorptive capacity of activated charcoal for mexiletine was increased in PEG-ELS rich in salts.

In conclusion, oral activated charcoal is expected to be useful in combination with whole bowel irrigation with PEG-ELS in mexiletine overdose because of its excellent adsorbability in the solution.

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