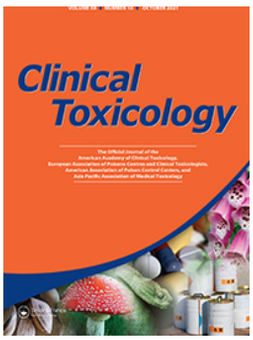

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# The Effect of Polyethylene Glycol on the Charcoal Adsorption of Chlorpromazine Studied by Ion Selective Electrode Potentiometry

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## ABSTRACT

*Background: This investigation was undertaken to study: a) the adsorption characteristics of chlorpromazine to activated charcoal and its formulations Carbomix® powder and Ultracarbon® tablets at gastric pH; b) the effect on chlorpromazine adsorption of polyethylene glycol and its combination with electrolyte lavage solution; c) the effect of the order of addition of polyethylene glycol-electrolyte lavage solution. Method: Ion selective electrode potentiometry, based on the selective, direct and continuous response of a chlorpromazine-ion selective electrode to the concentration of the free drug, was used. Successive additions of microvolumes of a chlorpromazine solution were made into a charcoal slurry in acidic medium of pH 1.2 with measurement of the chlorpromazine-ion selective electrode potential at equilibrium. Results: The maximum adsorption capacity values of activated charcoal, Carbomix and Ultracarbon, were 297, 563, and 382 mg/g respectively, while the affinity constant values were 40.2, 70.4, and 40.5 L/g, respectively. The adsorption of chlorpromazine to each of the Ultracarbon and Carbomix components was compared to the total adsorption of the formulations. The addition of polyethylene glycol-electrolyte lavage solution causes a slight desorption of chlorpromazine from activated charcoal at gastric pH, more pronounced when polyethylene glycol-electrolyte lavage solution follows the addition of activated charcoal, suggesting the possibility of a nonspecific binding of chlorpromazine to polyethylene glycol. The amount of chlorpromazine*

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*adsorbed to Carbomix and Ultracarbon was not significantly affected at gastric pH by the presence of polyethylene glycol or polyethylene glycol-electrolyte lavage solution added either concurrently or sequentially to these formulations.*

## INTRODUCTION

The oral administration of activated charcoal (AC) has long been a fundamental component of the treatment strategy and remains an integral part of therapy for most toxic ingestions.[1-6] Recently, whole bowel irrigation (WBI) with polyethylene glycol–electrolyte lavage solution (PEG-ELS) has been used as an adjunctive gastrointestinal decontamination procedure for ingestions of toxins not well adsorbed to AC (e.g. iron, lead, lithium) and for toxins with a delayed absorption phase, such as sustained release theophylline and enteric coated aspirin.[7-15] The procedure is simple, inexpensive, well tolerated in most patients and results in a rapid removal of gastrointestinal contents. While it has been suggested that a combined approach using AC and WBI could theoretically enhance the efficacy of both modalities,[3,13] this improvement remains largely speculative since data demonstrating its clinical advantage in routine overdose treatment are lacking.

Some recent *in vitro* studies concerning a possible interference of PEG-ELS with the adsorption of various drugs to AC at gastric and intestinal pH, as well as the initiation of WBI with PEG-ELS concurrent or subsequent to the administration of AC, revealed contradictory conclusions.[16-19]

This *in vitro* investigation was done to study: a) the adsorption parameters (maximum adsorptive capacity and affinity constant) of chlorpromazine (CHP) for various types of AC at gastric pH; b) the effect of PEG, as well as PEG-ELS, upon this adsorption at gastric pH; and c) whether the order of PEG-ELS addition would have an effect upon adsorption of CHP to AC.

CHP was used in this study as a model drug because intoxications by accidental overdoses or suicide attempts are common, giving rise to life threatening symptoms, although fatalities are relatively rare. Adult responses to CHP ingestion are highly variable, but significant central nervous system depression can be expected from doses exceeding 5 g.[20,21] The effect of WBI with PEG-ELS upon the adsorption of CHP to AC has not yet been studied.

The *in vitro* adsorption of several drugs onto AC has been studied with a variety of techniques[16-19,22-24] such as spectrophotometry, gas liquid chromatography and high performance liquid chromatography. These are tedious indirect techniques requiring filtration of the charcoal and determination of the free drug concentration in the resulting filtrate.

In this study the technique of ion selective electrode (ISE) potentiometry is used for the study of CHP adsorption onto AC using a chlorpromazine-ion selective electrode (CHP-ISE) constructed in our laboratory for the purposes of this study, following a modified procedure of a previously published work.[25] ISEs are electrochemical transducers that respond selectively, directly and continuously to the activity (or concentration at constant ionic strength) of the free ion of interest in solution. Due to their advantages (sufficient selectivity and sensitivity, wide analytical range of the analyte concentration, low cost, fast response, simplicity in assembly, capability of measuring in colored and cloudy sample solutions), they have found many applications, including binding studies of drugs with macromolecules (proteins, cyclodextrins)[26-30] and dissolution studies of solid drug formulations in which cloudy samples are gradually formed.[31,32] The CHP-ISE method was used in the present study to directly measure the concentration of the free CHP cation in the presence of AC and the adsorbed drug. A report in press describes the kinetic profile of CHP adsorption up to equilibrium (where the rate of adsorption equals the rate of desorption) as monitored by a CHP-ISE.[33]

## MATERIALS AND METHODS

### Reagents

CHP hydrochloride (Rhone Poulenc) was used without any further purification.

AC: Three types were used: a) AC (Merck, GR-Nr 2186) pure powder, produced for general laboratory purposes, dried in 10 g portions at 140°C

for one hour; b) Carbomix (Norit, Netherlands, Nr 1057), containing (w/w) 81.3% AC, 2.4% citric acid monohydrate, 8.1% acacia (gum arabic), and 8.1% glycerol; c) Ultracarbon 400 mg tablets (Merck), containing 250 mg of AC, 119 mg of bentonite and 31 mg of starch per tablet.

PEG average MW 3350, was obtained from Sigma; $Na_2SO_4$, concentrated hydrochloric acid, KCl, citric acid monohydrate from Merck; NaCl and starch from Fluka; $NaHCO_3$ from Ferak; and acacia and bentonite from local pharmaceutical industries. All chemical reagents were of analytic grade.

All solutions were prepared in an aqueous acidic medium (HCl solution pH 1.2) simulating gastric fluid. CHP 0.100 M stock solution and $4.00 \times 10^{-3}$ M working solution were prepared in the acidic medium pH 1.2 and stored in amber glass bottles. Polyethylene glycol working solutions in the concentration range 0.2 - 27.0 g/dL were prepared in the acidic medium pH 1.2. The PEG-electrolyte solution containing (g/dL) PEG 27.0, $Na_2SO_4$ 2.56, $NaHCO_3$ 0.76, NaCl 0.675, and KCl 0.31 was prepared by dissolving the appropriate amounts of reagents in the acidic medium pH 1.2.

## Electrode Construction

The CHP-ISE was of the polyvinyl chloride (PVC) membrane type[34] constructed as previously described[33] using the ion pair of CHP cation with tetraphenylborate anion in 2-nitrophenyloctylether as liquid ion exchanger. The ISE was stored in a 0.10 M CHP solution when not in use.

## Potentiometric Measurements

The system consists of an electrometer (Orion Ionanalyzer, model 801 pH/mV meter) with a readability of $\pm$ 0.1 mV, connected to a Radiometer Chart Recorder model 61. The emf values were measured against a Ag/AgCl reference electrode (Orion, single junction, model 90-01). All measurements were carried out in a 100 mL double-walled glass cell, thermostated at a temperature of 37 $\pm$ 0.5°C, with constant magnetic stirring of solutions.

## Calibration of the CHP-ISE

A series of successive aliquots of the 0.10 M CHP stock solution (5 $\mu$L - 1.67 mL) were added to 25 mL aqueous acidic medium pH 1.2 providing a concentration range of $2.0 \times 10^{-5}$ - $6.26 \times 10^{-3}$ M. The potential values $E_i$ (in mV) were plotted against the negative logarithm of the total molar CHP concentration for each addition ($-\log C_T$ or $pC_T$), according to the Nernst equation[35] and using a least squares fitting program:[36]

$$E_i = E_{cons} + S \times \log C_i \quad (1)$$

where $E_{cons}$ is a constant term and S the slope of the ISE, theoretically equal to -59.16 mV/pC at 25°C.

## Adsorption of CHP to Charcoal

A 25 mL aliquot of the aqueous acidic medium pH 1.2 was pipetted into the measurement cell and 0.5 g charcoal (2 tablets in the case of Ultracarbon) were dispersed in it; 2 mL of CHP stock solution were added and the electrode pair was immersed. After the potential was stabilized ($\pm$ 0.1 mV), 50 $\mu$L aliquots of CHP stock solution were added sequentially and the potential was recorded. The additions continued until the potential corresponding to the upper free CHP concentration limit of the calibration curve ($6.3 \times 10^{-3}$ M) was achieved. Experiments were run in triplicate for each type of charcoal.

The same adsorption procedure was used to examine the possible adsorption of CHP by the various components of Carbomix and Ultracarbon formulations. Synthetic mixtures similar to these two commercial formulations were then prepared from AC and the appropriate additives to elucidate the experimental adsorption observations with these two multicomponent formulations.

## Data Analysis

From the $E_i$ obtained after each addition in the adsorption experiment, the corresponding free molar CHP concentration ($C_f$) in the solution was estimated from the calibration curve. The molar concentration of CHP absorbed to AC ($C_{ad}$) for each addition was then calculated as $C_T - C_f$, where $C_T$ is the total molar CHP concentration.

The maximum adsorption capacity (MAC; N) or CHP g/charcoal g of the various charcoals, and the affinity constant (K) in L/g of the interaction between CHP and charcoal were calculated by linear least-squares fitting of the following expression of the Langmuir model:[37-39]

$$\frac{C_f \times m}{C_{ad} \times V} = \frac{1}{N \times K} + \frac{1}{N} \times C_f \quad (2)$$

where $C_f$ and $C_{ad}$ are the free and adsorbed CHP concentrations g/L in the solution after each

addition, N is the MAC in g/g, K is the affinity constant in L/g, m is the mass of charcoal used in the experiment in mg and V the total volume of the solution after each addition in mL.

### Adsorption in the Presence of PEG

To examine the effect of PEG on the adsorption of CHP to AC, experiments with the simultaneous addition of PEG and AC to a CHP solution were performed as follows (procedure B1). The pair of the electrodes was immersed in 25 mL of 4 x $10^{-3}$ M CHP solution in the measurement cell and the potential $E_1$ was measured and recorded after stabilization. A 4 mL slurry containing AC 0.5 g and PEG 0.5 - 27 g/dL in the acidic medium (PEG:AC w/w ratios 0.04:1 to 2.16:1, respectively) was injected into the measurement cell. The potential (E) vs time was recorded at a chart speed 1 cm/s until equilibrium was established (< 2 min). The series was completed with three more trials: a) a blank experiment (4 mL of the acidic medium); b) 4 mL of slurry containing only 0.5 g of AC (without PEG) for comparative purposes; c) slurry prepared by the dispersion of 0.5 g AC in 4 mL of PEG-electrolyte solution [(PEG-ELS):AC w/w ratio of 2.16:1], which corresponds to the usual therapy of intoxication.

From the E - t curves, the final potential at equilibrium $E_{eq}$ was measured and the potential change $\Delta E = E_{eq} - E_1$ was calculated and corrected for the $\Delta E_{blank}$. The concentration of the adsorbed CHP at equilibrium was determined by the following equation, derived from the Nernst equations (1) corresponding to the potential readings prior to the addition ($E_1$) and after the completion of the process ($E_{eq}$):

$$C_{ad} = C_T (1 - 10^{-\Delta E/S}) \quad (3)$$

where: $C_T$ = 3.45 x $10^{-3}$ M and S is the experimental slope of the CHP-ISE calibration curve in the acidic medium estimated just before the experiments.

The effect of the addition of PEG on the adsorbed CHP on AC was also studied using the following procedure (B2). 0.5 g AC was added to 25 mL of a 4 x $10^{-3}$ M CHP solution; the slurry was stirred for 20 min in the measurement cell to establish equilibrium. The pair of electrodes was immersed in the cell and the potential was recorded and measured after stabilization. PEG solution 4 mL at concentrations 2 - 27 g/dL was then added, producing PEG:AC (w/w) ratios of 0.16:1 to 2.16:1. The potential was continuously recorded until equilibrium (< 2 min). The potential at this equilibrium was used to estimate the $C_f$ of CHP using the calibration curve of the ISE in the acidic medium. The $C_{ad}$ was then calculated from the total CHP concentration (3.45 x $10^{-3}$ M).

## RESULTS

### Electrode Characteristics

The CHP-ISE showed a slightly sub-Nernstian response in the linear concentration range (1.4 x $10^{-4}$ - 6.3 x $10^{-3}$ M) with a slope at 37°C varying from -54 to -56 mV/pC (r > 0.9998). The detection limit was found to be 2 x $10^{-5}$ M. The electrode membrane had an operative life of about one month before replacement. The electrode was free from serious drift and therefore adequate for reliable measurements in adsorption experiments. The potential of the CHP-ISE was practically stable in the pH range 1 - 4 (pKa of CHP 9.3 at 20°C).

Figure 1 shows calibration curves of the CHP-ISE in the acidic medium (a) and in the presence of 0.5 g AC (b). The decrease of the CHP free concentration in case (b) is very clear. The linear concentration range of the CHP-ISE response curve (E vs $pC_f$) is expanded from 1.4 x $10^{-4}$ to 3 x $10^{-5}$ M in the presence of AC (as well as by Carbomix and Ultracarbon). This expansion behavior has also been observed in the case of protein binding studies performed with direct potentiometry.[26]

### Adsorption of CHP to the Various Charcoals

Langmuir plots for AC, Ultracarbon and Carbomix are shown in Figure 2 with excellent correlation coefficients (0.9994 - 0.9999). This proves the validity of the model used and the ability of the ISE potentiometry to provide accurate adsorption data.

Adsorption experiments performed for each of the Carbomix and Ultracarbon additives showed no adsorbing properties, except for bentonite, which adsorbs CHP to some extent.

The adsorption parameters (N and K) for all charcoals are summarized in Table 1. The results revealed very good within and between run precision especially for the N parameter. Carbomix showed

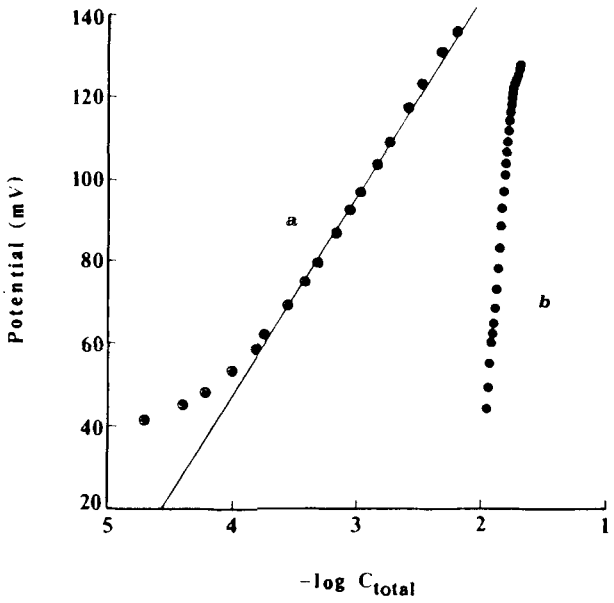


**Figure 1.** Response curves [potential E (mV) vs negative logarithm of total molar concentration ($pC_T$)] of the CHP-ISE in the acidic medium pH 1.2 (a) in the absence (calibration curve) and (b) in the presence of 0.5 g of AC. Potential readings of the adsorption curve (b) correspond to CHP free concentrations on the calibration curve (a).

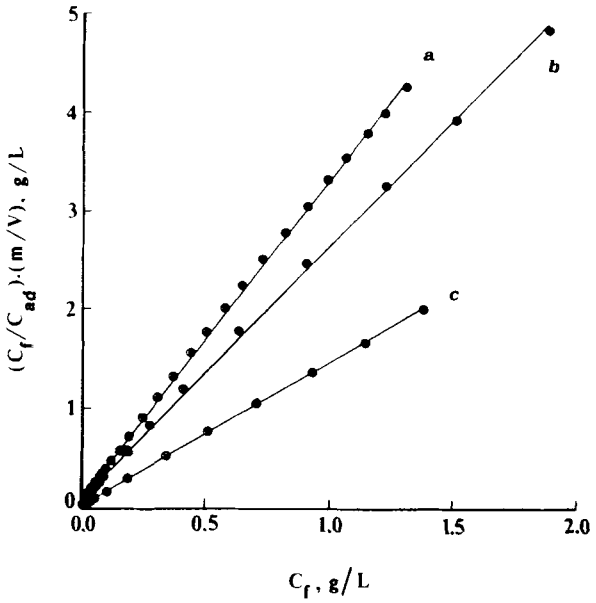


**Figure 2.** Langmuir plots (equation 2) of the adsorption of CHP to (a) AC, (b) Ultracarbon and (c) Carbomix at pH 1.2 and 37°C. The linearity substantiates the validity of the model used and the accuracy of ISE potentiometry.

the highest values for the N and K parameters and might be the most appropriate charcoal formulation for treatment of CHP poisoning.

## Adsorption of CHP on Mixtures of Charcoal with Bentonite and Starch

The contribution of the Ultracarbon additives (bentonite and starch) on the adsorption capacity of the formulation was examined using mixtures of AC with bentonite and/or starch with ratios similar to those encountered in the commercial formulation. The results obtained are listed in Table 2; the apparent values of the N and K parameters for each binary or tertiary mixture found are in accord with those predicted from the values of N and K of single components taking into account the % composition of the mixture. This observation verifies that the Langmuir isotherm model can also be used for mixtures of adsorbents showing additive and not competitive binding characteristics. The observed difference between the adsorption parameters of Ultracarbon (N = 382.4, K = 40.5, Table 1) and the synthetic mixture of its components (N = 282.4, K = 45.9, Table 2) can be attributed to the physical composition of the charcoal in the commercial formulations.

## Adsorption of CHP to AC in the Presence of PEG

The effect of PEG on the electrode response was first studied. Response curves (E vs $pC_T$) of the electrode obtained using PEG solutions in the range of 0.2 - 6.0 g/dL showed similar slopes with the calibration curve but a decrease in $E_{cons}$. This constant difference $\Delta E_{cons}$ was attributed to nonspecific binding of CHP to PEG, the extent of which was found to be dependent on the PEG concentration.

The adsorption of CHP to AC in the presence of PEG was examined: a) by the simultaneous addition of PEG and AC to CHP solution (procedure B1), to mimic the situation of performing WBI with PEG concurrent with AC administration; and b) by the addition of AC to CHP solution and subsequent

*Table 1*

*Maximum Adsorption Capacity (N) and Affinity Constant (K) of Three Charcoals*

| | 1 | 2 | 3 | Mean ± SD* |
|---|---|---|---|---|
| AC | | | | |
| N ± SD† (mg/g) | 278.6 ± 0.8 | 305.7 ± 1.5 | 305.5 ± 2.3 | 297 ± 16 |
| K ± SD† (L/g) | 43.4 ± 4.9 | 37.6 ± 4.6 | 39.7 ± 9.4 | 40.2 ± 2.9 |
| r | 0.99994 | 0.9997 | 0.9996 | |
| Carbomix | | | | |
| N ± SD† (mg/g)‡ | 689.1 ± 2.5 | 699.2 ± 7.3 | 689.9 ± 3.0 | 693 ± 6 |
| K ± SD† (L/g) | 72.2 ± 6.5 | 70 ± 29 | 69 ± 13 | 70.4 ± 1.6 |
| r | 0.9999 | 0.9996 | 0.9999 | |
| Ultracarbon | | | | |
| N ± SD† (mg/g)§ | 383.3 ± 3.0 | 378.1 ± 2.7 | 385.7 ± 3.9 | 382.4 ± 3.9 |
| K ± SD† (L/g) | 35.6 ± 7.5 | 46 ± 11 | 40 ± 11 | 40.5 ± 5.2 |
| r | 0.9996 | 0.9997 | 0.9994 | |

*Between run standard deviation (n = 3); †Within run standard deviation (n = 13 - 27); ‡mg of CHP bound/g of charcoal; 1.23 g of Carbomix contain 1 g of charcoal; the calculated mean N is: 563.4 mg/g of Carbomix; §mg of CHP bound/g of Ultracarbon. All studies in triplicate.

*Table 2*

*Maximum Adsorption Capacity (N) and Affinity Constant (K) of Ultracarbon Components and Their Mixtures*

| | N ± SD (mg/g) | K ± SD (L/g) |
|---|---|---|
| AC | 297 ± 16 | 40.2 ± 2.9 |
| Bentonite | 314 ± 17 | 22.1 ± 6.8 |
| Starch | 0 | 0 |
| AC + Starch | 280 ± 11 | 63.4 ± 6.7 |
| AC + Bentonite | 313.6 ± 4.4 (302.2)* | 34.5 ± 10.8 (34.4)* |
| AC + Starch + Bentonite | 282.4 ± 2.4 (278.7)* | 45.9 ± 7.2 (46.2)* |

*Predicted values in parentheses assume additivity in adsorption using the single components parameter estimates and the percent composition of the mixture.

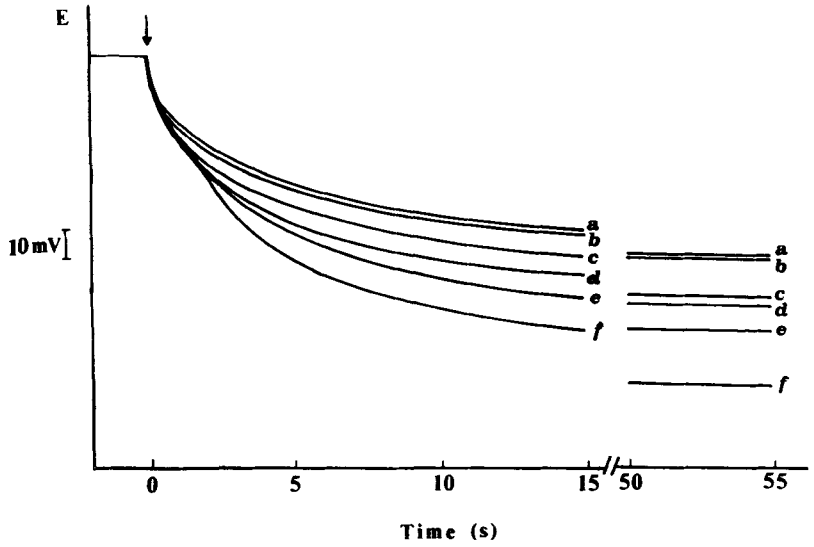


**Figure 3.** Plots of CHP-ISE potential vs time for the simultaneous addition of PEG and AC (0.500 g) to CHP solution (4 x $10^{-3}$ M) for various PEG:AC (w/w) ratios: a) 0.32:1; b) 0.16:1; c) 0.12:1; d) 0.08:1; e) 0.04:1; f) 0:1. The arrow indicates the time of the addition of the slurry (procedure B1). Adsorption of CHP decreases with PEG concentration.

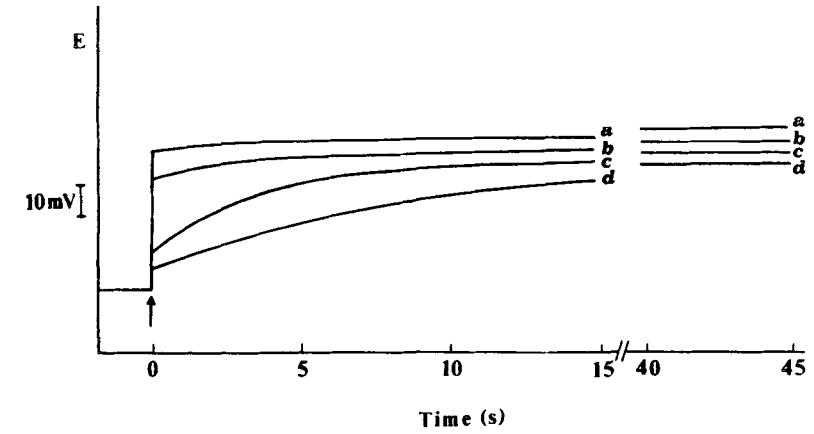


**Figure 4.** Plots of CHP-ISE potential vs time for the addition of AC (0.5 g) to CHP solution (4 x $10^{-3}$ M) and subsequent addition of PEG at various PEG:AC (w/w) ratios: a) 2.16:1; b) 1.08:1; c) 0.32:1; d)0.16:1. The initial horizontal line corresponds to the potential of the free CHP and the arrow indicates the time of the addition of the PEG solution (procedure B2) . The curves indicate that the subsequent addition of PEG causes a desorption of CHP from AC.

addition of PEG (procedure B2), to mimic the initial administration of AC followed by WBI with PEG-ELS solution.

In a typical overdose protocol, the patient would receive 60 g of AC in a slurry of 240 mL of water and 2 L of PEG-ELS within the first hour.[10,13] The composition of PEG-ELS is (in g/L): PEG (MW 3350) 60, NaCl 1.46, KCl 0.75, $NaHCO_3$ 1.68 and $Na_2SO_4$ 5.68.[19] According to this scheme, the proposed therapeutic PEG:AC w/w ratio is 2:1.

*Table 3*

*Effect of PEG on the Adsorption of CHP by AC at Equilibrium Following Two Different Modes of Addition*

| PEG (g/dL)‡ | PEG/AC (w/w) ratio§ | Percent CHP Adsorbed, $(C_{ad}/C_T) \times 100$ Simultaneous* Addition | AC First† |
|---|---|---|---|
| 0 | 0:1 | 99.1 | 99.1 |
| 0.50 | 0.04:1 | 97.7 | - |
| 1.00 | 0.08:1 | 97.1 | - |
| 1.50 | 0.12:1 | 96.5 | - |
| 2.00 | 0.16:1 | 93.7 | 90.6 |
| 4.00 | 0.32:1 | 93.4 | 89.0 |
| 13.5 | 1.08:1 | 93.4 | 86.9 |
| 27.0 | 2.16:1 | 93.4 | 82.6 |
| 27.0 ± E1 ‖ | 2.16:1 | 93.4 | 82.6 |

*Simultaneous addition of AC and PEG to CHP solution (procedure B1); †Addition of AC to CHP solution followed by addition of PEG (procedure B2); ‡Contained in 4 mL volume; §Constant AC amount of 0.500 g; ‖Electrolytes added to the PEG solution equivalent to PEG-ELS composition ($Na_2SO_4$ 2.56, $NaHCO_3$ 0.76, NaCl 0.675, KCl 0.31 g/dL).

In this study, adsorption experiments of CHP to AC were performed under a variety of PEG:AC w/w ratios, including the therapeutically indicated one (2:1), as well as with PEG-ELS:AC w/w 2:1 ratio. In both procedures (B1 and B2), experiments without PEG served as controls.

Figures 3 and 4 show plots of potential E vs time for the simultaneous and sequential addition of AC and PEG to the CHP solution, respectively. From Figure 3, it becomes clear that $C_f$ increases (and $C_{ad}$ decreases) as PEG:AC increases from 0.04:1 to 0.32:1, above which a plateau is obtained. From Figure 4 it is concluded that a desorption of CHP from AC is caused by the subsequent addition of PEG. Table 3 lists the relative percent of CHP adsorbed in both cases. The percent of CHP adsorption decreases with increasing PEG. However for PEG-ELS:AC 2:1 w/w ratio, the simultaneous addition of PEG and AC caused a 6% decrease, while the subsequent addition reduced adsorption 16.5%.

Similar results were not observed in the presence of PEG and PEG-ELS with Carbomix and Ultracarbon. The $C_{ad}/C_T$ ratio decreased less than 1.5% on simultaneous or subsequent addition of PEG. This may be due to the presence of the additives contained in these formulations.

## CONCLUSIONS

In the present study, ISE potentiometry was useful for estimation of the adsorption parameters of AC for CHP. At gastric pH, Carbomix showed the highest maximum adsorption capacity and affinity constant for CHP. The acute fatal dose for CHP is variable.[21,40,41] Childhood deaths have been reported with oral CHP of 20 - 74 mg/kg.[21] Fatalities in infants have resulted from CHP ingestion of 350 mg.[21] Adult death has occurred after consumption of 2 g, although adult patients have survived 10 g and 17 g ingestions.[21,40] In CHP poisoning, emesis or lavage is indicated followed by administration of AC and a saline cathartic.[20]

The amount of CHP adsorbed to Carbomix and Ultracarbon was not significantly affected in gastric pH by the presence of PEG or PEG-ELS administered concurrently or sequentially. The addition of PEG-ELS resulted in slight desorption of CHP from AC at gastric pH; this was more pronounced when

PEG-ELS followed AC. A nonspecific binding of CHP to PEG can not be excluded. Similarly significant desorption of cocaine[16] and theophylline[17] from AC in the presence of PEG-ELS have been previously reported, with more extensive desorption on concurrent administration. *In vitro* investigation of the adsorption of both salicylate and PEG to AC and their interaction provides a possible mechanism.[19] In addition to demonstrating decreased adsorption of salicylate to AC in the presence of PEG, the authors found substantial adsorption of PEG onto AC. The decrease in adsorption of CHP to AC in the present study may represent competition between CHP and PEG for available AC adsorption sites as well as nonspecific binding of CHP to PEG.

Although the CHP-ISE method is reliable for the study of CHP adsorption onto AC at pH 1 - 4 or gastric pH, it is inappropriate for the study of adsorption at the higher pH of the intestine. In general, the adsorption of a drug onto AC is higher for unionized compounds.[4,16,38,42,43] Since CHP is a basic compound with a pKa value of 9.3, it is expected to be better adsorbed at the alkaline pH of intestines. Further studies at intestinal pH in the presence of PEG are required before extrapolation to any clinical recommendations. Similarly the results of this study may not apply to other toxic agents.

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