

Adsorption Studies of Artesunate: Evaluation of Saline Cathartics as Additive in Management of Artesunate Poisoning

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The effect of saline cathartics magnesium sulphate, sodium sulphate, and sodium citrate on adsorptive capacity of activated charcoal (AC) was investigated *in vitro*. Solutions of artesunate alone and artesunate with 7.5 mg/ml cathartics solution were vortex mixed for 30 sec with different quantities of AC, incubated in water bath shaker for 30 min at 37°C and analysed for free artesunate spectrophotometrically at 328 nm. Addition of the cathartics caused a significant increase ($p < 0.05$) in the adsorption of artesunate to activated charcoal. The descending order of increased adsorption by the cathartics is magnesium sulphate, sodium citrate and sodium sulphate.

Key words — saline cathartic, artesunate, activated charcoal, adsorption

INTRODUCTION

Drug poisoning has been defined as a condition produced by any substance which when swallowed, inhaled, injected or absorbed percutaneously is capable of causing death, injury, toxic or untoward reactions.¹ Poisoning is a very common clinical problem and many drugs used in the treatment of a variety of diseases do not have specific antidote for

the management of accidental poisoning caused by the drugs. The major principles applied in the emergency treatment of accidental poisoning are dilution, emesis and adsorption.² In cases where no specific antidote exists prevention of further absorption using oral adsorbents may be of immense benefit in the management of drug over dose and or poisoning. Use of standard adsorbent, such as activated charcoal (AC) in the prevention of further absorption of drugs is recognized in clinical practice.

Artesunate, a succinic ester is a derivative of artemisinin a new antipyretic agent obtained from qinghaosu (OHS) by Chinese. Qinghaosu is an active substance extracted from the herb *Artemisia annua*,³ with a unique sesquiterpene lactone endoperoxide structure.

Artesunate is a water soluble semi-synthetic analogue of the Chinese medical herb Qinghaosu.⁴ Artesunate together with other derivatives of artemisinin are known for their potent antimalarial activity. In addition, anecdotal reports suggest that systemic artesunate has immunoregulatory effect.⁵ Topical artesunate has been shown to inhibit elicitation of contact hypersensitivity in guinea pigs. Although no serious side effect has been documented because artesunate seems to be well tolerated in humans.⁶ One may not totally rule out cases of overdose or accidental poisoning. It has been of immense value to administer saline cathartics; with adsorbent to prevent constipation or impaction.^{7–9} There are currently no documented information on antidotes for the management of artesunate poisoning hence in the present study, AC was evaluated as possible antidotes for the management of artesunate overdose and or poisoning.

This study was set to determine the adsorptive capacity of activated charcoal for artesunate and also to evaluate the effect of three cathartics solutions namely sodium sulphate, magnesium sulphate and sodium citrate on the adsorption of artesunate to AC.

MATERIALS AND METHODS

50–400 mg of activated charcoal (Ultra Carbon Merck) were placed in test tubes. Several solutions of artesunate (Gullin pharmaceutical works, Gunagxi, China) in 0.5, 1.0, 5.0 low therapeutic levels and 10.0 µg/ml simulated toxic concentrations were prepared in distilled water. Five milliliter of each solution was added to each adsorbent tube. The resulting artesunate–charcoal slurries were vortex

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mixed for 30 sec, incubated in water bath shaker for 30 min at 37°C and centrifuged at 3000 rpm for 5 min. The absorbance of the supernatant fluid (containing free drug) was then read using SP6-450 UV/VIS Pye Unicam spectrophotometer at the wavelength 328 nm.

In other experiments the effect of sodium citrate, sodium sulphate, magnesium sulphate on the adsorption of artesunate to AC were investigated. Five milliliter of solutions containing 7.5 mg $\text{Na}_2\text{SO}_4/\text{ml}$, 7.5 mg MgSO_4/ml or 7.5 mg sodium citrate/ml with 0.5, 1.0, 5.0 and 10.0 μg artesunate/ml were added to test tubes containing 50–400 mg AC. The tubes were vortex mixed, incubated, centrifuged and analysed similarly like above.

In all, the percentage of the artesunate absorbed from the original solution was calculated from the percentage of drug remaining in the supernatant. The percentage of drug was plotted on the ordinate axis against the log quantity of adsorbents in mg on the abscissa. The remaining linear plot obtained by regression analysis of the best fitted points was analysed for the quantity of adsorbent which bound 50% of artesunate (B-50) as determined by the method of Tallarida and Murray, procedure 8.¹⁰⁾

Results were expressed as Mean \pm standard error of mean (SEM) ($n = 6$) and the significance of data was determined by Student *t*-test. Statistical analysis was performed with statistical package for social sciences (SPSS) version 8.0 software package.

RESULTS

Figures 1, 2 and 3 show the adsorption of artesunate alone to AC and the effect of Na_2SO_4 , MgSO_4 and sodium citrate on the adsorption of artesunate to AC, respectively. Artesunate adsorbed unto AC. This adsorption was found to be dependent on the amount of AC. Addition of cathartics produced significant ($p < 0.05$) increase in adsorption of artesunate to AC as follows: $\text{MgSO}_4 > \text{Sodium citrate} > \text{Na}_2\text{SO}_4$. The cathartics reduced the B-50 of artesunate at both the low therapeutic concentration and simulated toxic concentration (Fig. 4).

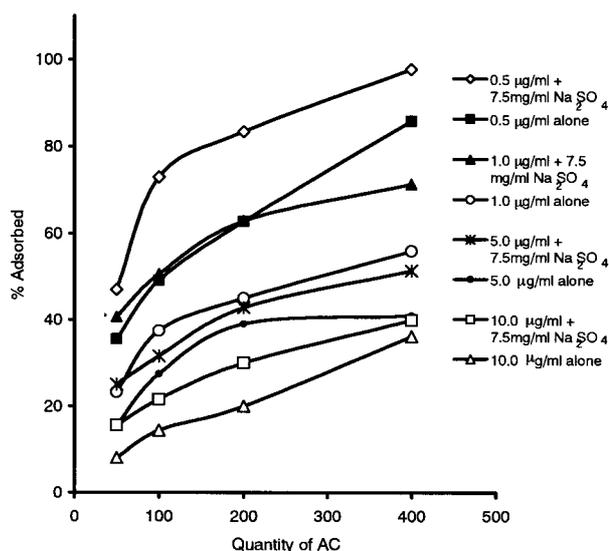


Fig. 1. Effect of Na_2SO_4 on Adsorption of Artesunate to AC

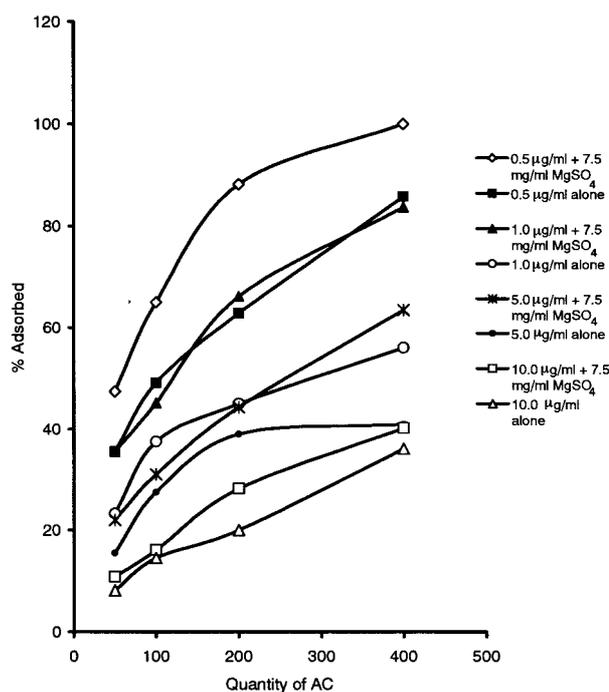


Fig. 2. Effect of MgSO_4 on Adsorption of Artesunate to AC

DISCUSSION

The objective of using adsorbents such as AC, kaolin, magnesium trisilicate or starch in the treatment of poison ingested is to cause binding of the poison by inhibiting its adsorption from the gastrointestinal tract thereby reducing mortality or fatality.¹¹⁾ AC, in particular is a potent adsorbent that rapidly inactivates many poisons if administered

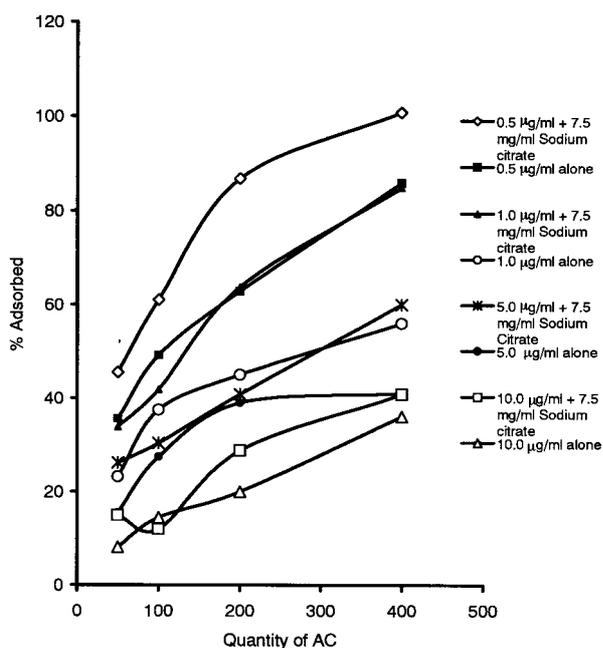


Fig. 3. Effect of Sodium Citrate on Adsorption of Artesunate to AC

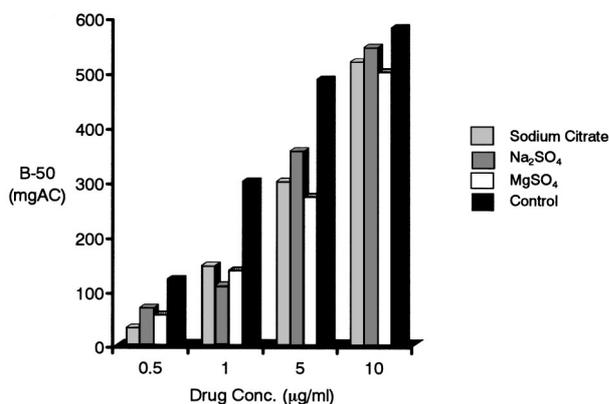


Fig. 4. B-50 Values of Different Concentrations of Artesunate

before much absorption has taken place. The rapid and marked effectiveness of activated charcoal *in vivo* emphasize the potential usefulness of this antidotes in the management of acute poisoning due to a rapidly absorbed chemical agent.¹¹ AC is well known in the management of poison,^{12,13} but the effect may be potentiated with the use of cathartics.

The quantity of AC needed to adsorb 50% of the AC (B-50) decreased in the presence of the cathartics. This agrees with the work of Czajka and Kanrod 1986¹⁴ which showed that pretreatment of AC with MgSO₄ increase the adsorptive capacity of aspirin to AC *in vitro*. Moris *et al.* (1987)¹⁵ reported that ingestion of MgSO₄ did not produce any sig-

nificant elevation of serum magnesium hence ruling out possible side effects or complication from the use of cathartics. The enhanced effect of sodium citrate on the adsorption capacity of AC to artesunate agrees with the work of Orisakwe and co workers where a significant increase was reported for the adsorption of doxycycline to AC in the presence of sodium citrate (unreported data).

In conclusion, this study shows that artesunate adsorbs to AC *in vitro*. Magnesium sulphate has the most significant increase in the adsorption of artesunate to AC evident by the lowering of B-50 values. Although *in vivo* study is required, this study indicates the beneficiary effect of magnesium sulphate in the management of artesunate poisoning using AC.

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