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Antidotal Effect of Activated Charcoal and Selected Saline Cathartics on Simulated Bromazepam Intoxication

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Abstract:
Investigation of the effect of saline cathartics namely, magnesium sulphate, sodium sulphate, sodium citrate and sodium chloride on adsorptive capacity of activated charcoal (AC) in bromazepam poisoning was carried out in vitro. Solutions of bromazepam alone and bromazepam with 7.5mg/ml cathartics solution were vortex mixed for 30 seconds with two different doses of AC (100mg and 400mg), incubated in water bath shaker for 30 minutes at 37^{O}C and the clear supernatant obtained was analyzed for free bromazepamspectrophotometrically at 211nm. The addition of the cathartics resulted in a significant increase ($p<0.05$) in the adsorption of bromazepam to activated charcoal. The ascending order of increased adsorption by the cathartics is sodium citrate, sodium chloride, magnesium sulphate and sodium sulphate.

Keywords: *saline cathartics, bromazepam, activated charcoal, adsorption.*

1. Introduction

Poisons are substances that can cause disturbances to organisms usually by chemical reaction or other activity on the molecular scale. They are also substances which when ingested by inhalation or swallowed is capable of acting deleteriously on the body. According to Paracelsus, "All substances are poisons, there is none that is not a poison. The right dose differentiates a poison from a remedy" (Gallo, 2001). According to their mode of action, poisons may be classified as corrosive poisons, irritant poisons, neurotic poisons, cardiac poisons, as phylaxiants, miscellaneous (Chadha, 2003). The major principles applied in the emergency treatment of accidental poisoning are dilution, emesis and adsorption (Von-Ottingmen, 1983).

The most commonly ingested poisons are drugs, plants and contaminated food substances. This may occur either intentionally or unintentionally. The first goal of treatment of poisoning is to maintain the vital functions of organs if their impairment is imminent. The second goal is to keep the concentration of poison in the crucial tissues as low as possible by either preventing absorption or enhancing its elimination. The third goal is to combat the pharmacological and toxicological effect at the effector sites (Parker*et al*., 2008).

Activated charcoal has been used in the treatment of poisoning since 1830. Apart from having a direct intra-luminal binding, activated charcoal can also decrease the resorption of agents that undergo enterohepatic or enterogastric cycling (Neuvonen and Olkkola, 1988). It also has a "gastrointestinal dialysis" effect whereby the charcoal serves as a large "sink" with movement of toxin molecules across semi-permeable membranes from splanchnic circulation (Rowden *et al*, 1990). The use of multi-dose activated charcoal is now recommended for the clearance of drugs such as carbamazepine, digitoxin, glutethimide, nadolol, phenobarbital, phenylbutazone, theophylline and others (Campbell and Chyka, 1992). It has been of immense value to administer saline cathartics with adsorbents like activated charcoal so as to prevent constipation or impaction (Neuvonen*et al*., 1980; Pond *et al*., 1981 and Berg *et al*, 1982). Despite the advances in gastric decontamination and the development of new antidotes, the mainstay of treatment for the poisoning victim remains supportive care and frequent re-evaluation for a change in clinical status (Dasari *et al*, 2011).

Bromazepam, a benzodiazepine, commonly used as an antidepressant and antianxiety drug is highly subject to abuse by its users, hence leading to toxicity. Although Flumazenil is used as an antidote to benzodiazepines, it is contraindicated in numerous patients. Seizures may be precipitated and re-sedation may occur in patients who awakened following flumazenil administration. Seizures may increase morbidity and mortality of the overdose. Benefit: Risk ratio of administering flumazenil should be determined in each overdose patient. Indications for flumazenil are thus limited (Seger, 2004). This makes the use of activated charcoal to be important.
Most common symptoms of bromazepam overdose include CNS depression and intoxication with impaired imbalance, ataxia and slurred speech. Severe symptoms include respiratory depression, apnoea, cardiac arrest, pulmonary aspiration. Despite its relatively low theoretic half -life, bromazepam may induce a prolonged life-threatening coma, even in the absence of renal or hepatic failure (Lakhal *et al*., 2009).
This study was set to determine the adsorptive capacity of activated charcoal for bromazepam and also to evaluate the effect of four cathartic solutions namely sodium citrate, magnesium sulphate, sodium chloride and sodium sulphate on the adsorption of bromazepam to AC.

2. Materials and Methods

100 and 400 mg of activated charcoal powder (Kunimed Pharmachem Ltd., Nigeria) were separately placed in test tubes. Several solutions of bromazepam tablet in 2.0, 5.0 and 10.0µg/ml concentrations were prepared in methanol. Five milliliter of each solution was added to each adsorbent tube. The resulting bromazepam–charcoal slurries were vortex mixed for 30 secs, 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 SP3000 nanoOptima spectrophotometer at the wavelength 211 nm.
The effects of magnesium sulphate, sodium sulphate, sodium chloride and sodium citrate on the adsorption of bromazepam to AC were also investigated. Five milliliters of solutions containing 7.5 mg Na_2SO_4/ml, 7.5 mg $MgSO_4$/ml, 7.5mg Nacl/ml or 7.5 mg sodium citrate/ ml with 2.0, 5.0 and 10.0µg bromazepam/ml were added to test tubes containing 100 or 400 mg AC. The tubes were vortex mixed, incubated, centrifuged and analyzed similarly like above. The percentage of bromazepam adsorbed from the original solution was calculated from the percentage of drug remaining in the supernatant. Results were expressed as Mean □□standard error of mean (SEM) (n = 3) of absorbance from which % adsorptions were calculated and the significance of data was determined by Anova followed by Duncan *post hoc* test.

3. Results

Table 1 shows the adsorption of Bromazepam alone to AC. Tables 2, 3, 4 and 5show the effects of sodium chloride, magnesium sulphate, sodium sulphate and sodium citrate on the adsorption of bromazepam to AC, respectively.
Bromazepam adsorbed unto AC and this adsorption was found to be dependent on the amount of AC. The addition of the cathartics namely, sodium chloride, magnesium sulphate and sodium sulphate produced significant ($p < 0.05$) increase in adsorption of Bromazepam to AC while the cathartic, sodium citrate caused a decrease in the adsorption of bromazepam to AC.

Quantity of AC (mg)	**Absorbance**			**% Adsorption**		
	2µg/ml	5µg/ml	10µg/ml	2µg/ml	5µg/ml	10µg/ml
100	1.6090 ±0.00	1.3300 ±0.01	1.2535 ± 0.02	24.9	45.3	49.8
400	0.9107 ±0.03	1.0900 ±0.01	0.9793 ±0.00	57.5	55.2	63.7

Table 1: Adsorptive capacity of activated charcoal alone on bromazepam (control)
Results are expressed as Mean ± Standard error of mean (SEM) (n=3)

Quantity of AC (mg)	**Absorbance**			**% Adsorption**		
	2µg/ml	5µg/ml	10µg/ml	2µg/ml	5µg/ml	10µg/ml
100	0.6657 ±0.00	0.7350 ±0.02	0.7470 ± 0.01	68.9	66.0	70.0
400	0.8700 ±0.01	0.9663 ±0.00	0.9093 ±0.000	69.5	60.3	68.6

Table 2: Effect of sodium chloride on the adsorption of bromazepam to activated charcoal
Results are expressed as mean ± standard error of mean (SEM) (n=3)

Quantity of AC (mg)	Absorbance			% Adsorption		
	2µg/ml	5µg/ml	10µg/ml	2µg/ml	5µg/ml	10µg/ml
100	0.7717 ±0.02	0.6600 ±0.01	0.6350 ± 0.00	64.0	72.9	74.5
400	0.6837 ±0.00	0.7420 ±0.00	0.6240 ±0.01	68.1	69.5	75.0

Table 3: Effect of Magnesium sulphate on the adsorption of bromazepam to activated charcoal
Results are expressed as Mean ± Standard error of Mean (SEM) (n=3)

Quantity of AC (mg)	Absorbance			% Adsorption		
	2µg/ml	5µg/ml	10µg/ml	2µg/ml	5µg/ml	10µg/ml
100	0.7710 ±0.01	0.5860 ±0.01	0.6910 ± 0.00	73.4	75.0	72.3
400	0.6810 ±0.03	0.7485 ±0.01	0.6836 ±0.00	68.2	69.2	72.6

Table 4: Effect of sodium sulphate on the adsorption of bromazepam to activated charcoal
Results are expressed as Mean ± Standard error of Mean (SEM) (n=3)

Quantity of AC (mg)	Absorbance			% Adsorption		
	2µg/ml	5µg/ml	10µg/ml	2µg/ml	5µg/ml	10µg/ml
100	2.2920 ±0.01	2.2480 ±0.01	2.2340 ± 0.00	6.9	7.6	10.5
400	2.3537 ±0.02	2.2760 ±0.02	2.2840 ±0.00	9.7	6.4	8.5

Table 5: Effect of sodium citrate on the adsorption of bromazepam to activated charcoal
Results are expressed as mean ± standard error of mean (SEM) (n=3)

4. Discussion

The use of adsorbents such as AC, kaolin, magnesium trisilicate or starch in the treatment of ingested poison is to cause binding of the poison by inhibiting its adsorption from the gastrointestinal tract thereby reducing mortality or fatality (Orisakwe and Obi, 1993). Typical surface areas for ACs are about 800-1200 m2/g. Thus, a 50-g dose of activated has an adsorptive surface area equivalent to about seven football fields or 5183 m2 (Olson, 2010). AC has been used in the United States and elsewhere for the treatment of poisonings and overdoses especially in children.

AC is well known in the management of poison, (Orisakwe *et al.*, 1995; Urosevic *et al.*, 1999) but the effect may be potentiated with the use of cathartics (Orisakwe*et al.,* 2001a). The enhanced effect of sodium sulphate and magnesium sulphate on the adsorption capacity of AC to bromazepamagrees with the work of Orisakwe and others where a significant increase was reported for the adsorption of Artesunate to AC in the presence of sodium sulphate and magnesium sulphate (Orisakwe*et al*., 2001a). However, the decrease in the adsorptive capacity of AC to bromazepam by sodium citrate seen in this study, agrees with the findings of Orisakwe and his co-workers that citrate increased the binding of Rifampicin but decreased that of Doxycycline (Orisakwe et al., 2001b and Afonne et al., 2002).

In conclusion, this study demonstrates the *in vitro* adsorption of bromazepam to AC. Although *in vivo* study is required, this study shows the enhanced antidotal effect of AC when used together with sodium chloride, magnesium sulphate and sodium sulphatein the management of bromazepam poisoning.

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