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Research Article
Can Co-administration of Sulfadoxine-pyremathamine and Single-dose Activated Charcoal Reduce the Chances of Adverse Reactions in Cases of Inadvertent Repeat Dose?

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Abstract

Background: Adverse drug reactions from the use of sulfadoxine-pyremathamine (fansidar) as chemoprophylaxis and in uncomplicated malaria have been well reported. However, this occurrence differs from patient to patient and not always predictable with fatal consequences. These adverse events result from long duration of action and patients not observing the predefined interval and washout periods. The aim of this study was to assess the influence of a single dose activated charcoal on the body burden of sulfadoxine in male healthy volunteers. **Materials and Methods:** The study was crossover design carried out in 2 phases comprising of initial administration with sulfadoxine-pyremathamine alone. After 30 days washout, same subjects were given fansidar with a single dose activated charcoal. Urine samples were collected over 60 h period. Using Bratton-Marshall method modified by Almeida-Filho and Souza, amount of sulfadoxine was determined and body burden was calculated using Kinetica 5 software. **Results:** The study revealed reduced rates of excretion at 18 and 30 h for sulfadoxine alone and sulfadoxine plus activated charcoal respectively. The average amount in the urine was also reduced from 43-21% when activated charcoal was added and total body burden reduced as well. Also, activated charcoal did not influence kel, $t_{1/2}$ and t_{max} of sulfadoxine, but affected its C_{max} and $AUC_{(tot)}$ which were significantly reduced. **Conclusions:** Therefore, single dose activated charcoal effectively decreased the body burden by reducing the absorption of sulfadoxine. This suggests that timely use of activated charcoal will mitigate the effects of long acting sulfadoxine by reducing the body burden in cases of inadvertent overuse.

Key words: Sulfadoxine, activated charcoal, body burden, adverse reaction, fansidar

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Adverse drug reactions are reportedly more difficult to treat and take a longer time to resolve[1]. The predicted adverse reactions to sulfadoxine-pyrimathamine (fansidar) not withstanding, the emergence of chloroquine resistant *Plasmodium falciparum* paved the way for its use[2]. Also approval was given for its use in Intermittent Preventive Treatment in infants (IPTi) and Intermittent Preventive Treatment in pregnancy (IPTp) in people living in malarious regions[3-4]. This combination acts by reciprocal potentiation of its components achieved by sequential blockage of two enzymes involved in the biosynthesis of folinic acid in the parasite. It has the advantage of possessing long half-life, help to delay the emergence of resistance forms[5]. Hence, the use of sulfadoxine-pyremathamine in malaria epidemic has become wide spread across the continents[5-8]. Consequently, evidence has shown an increase in the adverse events from the overuse of sulfadoxine-pyremathamine in malaria patients for prophylaxis and treatment[9-10]. A recent study reported that about 20% cases of adverse reactions seen in the Nigerian children are from antimalarial[11]. These adverse reactions could be severe and include Stevens-Johnson Syndrome (SJS), erythema multiform, toxic epidermal necrolysis and fatalities[12-16]. Due to these inherent toxic effects, some countries are now recommending the use of sulfadoxine-pyremathamine for only travelers who are at the risk of being infected with chloroquine resistant strain. Some of the reasons for the observed adverse reactions might be people not adhering to predefined dosing interval and washout period due to nonprescription use. Self-medication with sulfadoxine-pyrimathamine is rampant and therefore its use has been reported to produce various predictable and unpredictable adverse reactions[1]. Studies also revealed that both children and adult are involved in these self-medication practices in other to mitigate the clinical effects of malaria[17-18]. This behaviour is largely predicated on malaria endemicity, inadequate healthcare facilities and poverty in most African and Asian countries[19-21]. In view of the fact that it has a prolonged duration of action, consequences of inadvertent overuse can be mitigated by either decreasing absorption or reducing its duration of action in the body[22]. Activated charcoal has the ability to adsorb drugs and other toxins and thereby prolonging the gastrointestinal emptying time. Previous study has shown that activated charcoal can adsorb up to 50% of sufadoxine *in vitro* and it is largely excreted unchanged in the urine[23]. The aim of this study was to assess the influence of a single dose activated charcoal on the overall sulfadoxine body burden with sulfadoxine-pyremathamine administration.

MATERIALS AND METHODS

Materials: Sachets of fansidar containing 500 mg sulfadoxine and 25 mg pyrimathamine were purchased from Roche Pharmaceuticals Plc Lagos (Nigeria). Activated charcoal ultracarbon tablets, 250 mg each, a product of Merck Pharmaceutical was obtained from retail Pharmacy store in Lagos, Nigeria.

Enrollment of subjects: Seven healthy male subjects aged 18-24 years with an average weight of 68.5±4.58 volunteered to be part of this study. They were medically examined and confirmed to be healthy before they were allowed to participate in the study. Detailed medical examinations included all vital signs by physical examination like heart/respiratory rate, blood pressure, body temperature and reflexes. The medical examination was to ensure that subjects did not have hepatic, renal and GIT diseases through blood tests. All subjects who were allergic to sulphur containing compounds and have taken sulfadoxine-pyremathamine or any other medication for last two months were excluded from the study. In addition, subjects who had used alcohol for the past 48 h were not allowed to participate. The purpose of the study was explained in details to the subjects and a signed written informed consent was obtained from all participants. The Ethical Committee of the College of Medicine, the University of Lagos, Nigeria, approved this study. Experimental protocol was in line with WMA Helsinki declaration[24].

Sampling design: A crossover design was used as subjects selected served as their control. Prior to administration of sulfadoxine-pyrimathamine, subjects were asked to void urine before taken the medication after taken 400 mL of water. Last urine voided before administrations were used as blank samples. The study was conducted in two phases. In phase 1, subjects were given a single oral dose of sulfadoxine-pyrimathamine, containing 3 tablets, each with 500 mg sulfadoxine and 25 mg pyrimethamine after an overnight fast with 200 mL of water. Subsequently, subjects were allowed at least 200 mL of water hourly for next 6 h. They all observed 30 days washout period. In phase 2, subjects were again given another single dos of sulfadoxine-pyrimethamine, after 30 min 1 g activated charcoal was also given. In both phases, Urine samples were collected at intervals of 2, 4, 8, 12, 24, 36, 48 and 60 h. Subjects were instructed to completely empty their bladder during urine collection. Volume of voided urine was measured and 5 mL was taken out and stored at -20°C until analysis.

Analytical procedure: Only about 6-8% of sulfadoxine is metabolized therefore it remains largely unchanged and appears in the urine. The unchanged fraction of sulfadoxine in the urine samples was quantitatively determined. Method adopted for analysis of sulfadoxine was a modified method of Bratton-Marshall technique by Almeida-Filho and Souza[25]. The presence of sulfadoxine gives a persistent purple colour, with Bartton-Marshall reagent, which is then read at 540 nm absorbance using Pye unicam spectrophotometer. A standard curve of sulfadoxine was prepared from where its concentration in urine samples was determined.

Data analysis: Data presented represent Mean±SEM values and $p<0.05$ was regarded as statistically significant. Individual body burden parameter values were estimated using Kinetica 5 software version. The amount of sulfadoxine remaining in the body (µg) after 60 h was estimated by calculating the cumulative amount of sulfadoxine in the urine at that time and was fitted by regression analysis. Results obtained were subjected student t-test. The influence of activated charcoal on the amount of sulfadoxine administered was also analyzed and presented.

RESULTS

No adverse reactions were observed throughout the study and even after follow-up for 30 days after the last urine were collected. Figure 1 shows frequency of drug appearance in urine for both sulfadoxine alone and with the administration of activated charcoal. This appears to be slow mainly because of the behaviour of sulphonamides. The trend can be observed between 3 and 10 h post administration, showing 3000-3500 and 700-1300 µg/mL/h for sulfadoxine alone and sulfadoxine plus activated charcoal. In sulfadoxine alone group, the rate began to decrease from approximately 7000-4000 µg/mL/h after 18 h. Whereas, in the presence of activated charcoal reduced excretion rate started after 30 h (from 4500-1400 µg/mL/h). The study also, revealed individual variations as displayed by different rate characteristics in terms of amount found in the urine per unit time. This can be seen from the large value of SEM from±522±1800 for sulfadoxine and ±106±2000 for sulfadoxine and activated charcoal respectively as presented. The effect of activated charcoal can be clearly seen. The frequency appeared to be increasing initially in subjects who took sulfadoxine alone but eventually decreased as was shown by regression analysis with a slope of -24.84±30.50. For those who took sulfadoxine plus activated charcoal, the rate appeared faster but with a slope of -3.008±32.45, which was due to the fact that its absorption was reduced.

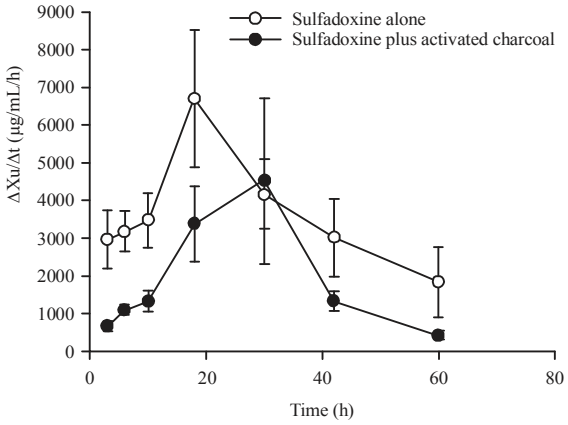

Fig. 1: Average rate of appearance of sulfadoxine before and after administration of activated charcoal in urine over a 60 h period

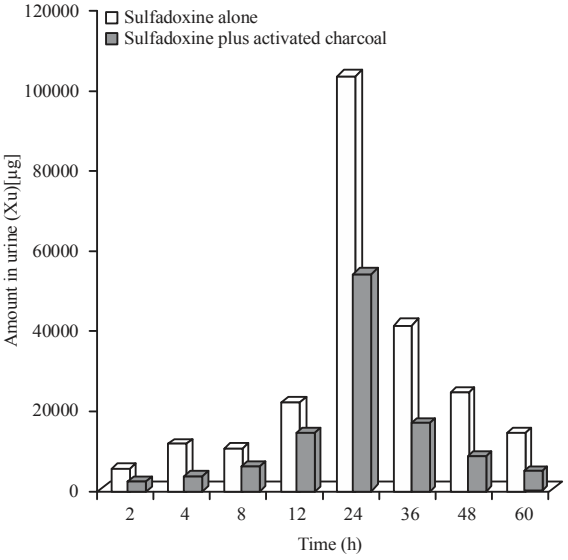

Fig. 2: Average amount of sulfadoxine found in the urine of subjects over 60 h period before and after activated charcoal administration

Average amount of sulfadoxine found in the urine over a period of 60 h is shown in Fig. 2. Interestingly, this study showed that the highest amount found in urine was at 24 h post administration for both groups (102,785.00 and 53,541.43 µg mL^{-1}, respectively). It appears that the higher the amount absorbed, the more it appears in the urine. Similar characteristics were exhibited by the two the group at 36 and 48 h, respectively in showing a decline in amount found in the urine, but the impact of activated charcoal produced a significantly different values ($p<0.05$).

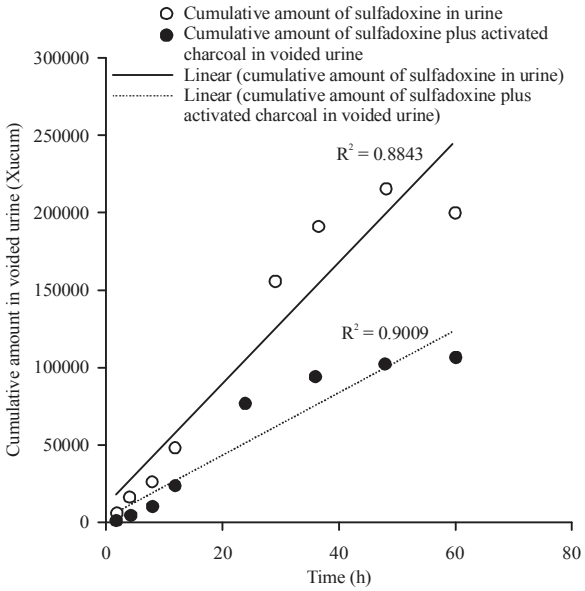

Fig. 3: Cumulative amount of sulfadoxine voided via urine over 60 h before and after activated charcoal administered

On the cumulative amount of sulfadoxine in voided urine over 60 h (Fig. 3), after 24 h, 30.04% in sulfadoxine alone represented the cumulative amount of 150,195.3 µg in the urine, whereas, when activated charcoal was added, it came down to 15.4% representing 77172.6 µg. Total cumulative amount after 60 h was 43% of the dose administered as voided for sulfadoxine alone and in the presence of activated charcoal, it was only 21% of the same dose. Therefore, sulfadoxine plus activated charcoal predictably had less accumulated amount compared to sulfadoxine alone.

Figure 4 shows estimated amount of sufadoxine remaining in the body after 60 h. As expected, sulfadoxine plus activated charcoal had a lower concentration remaining in the body 3.62% as compared with 14.7% for sufadoxine alone), confirming the fact that not much was absorbed from the gut due to the presence of activated charcoal. Table 1 Illustrates the excretion characteristics of sulfadoxine in the absence and presence of activated charcoal. Values obtained from urine contents of sulfadoxine were subjected to analysis using the times of collection versus the amount from each collection, using Kinetica 5 software version for PK/PD data analysis. These were imputed as observational data into the work sheet of the software. However, despite the influence of activated charcoal on the absorption, accumulation and excretion of sulfadoxine, most of these values did not show any statistical significant difference with the exception of C_{max} with values of 11,649.79 and 5774.23 µg mL^{-1} for sufadoxine alone and sufadoxine plus activated charcoal, respectively. Also AUC (tot), showed values of 282521.2 and 83026.85 for sulfadoxine alone and sulfadoxine plus activated

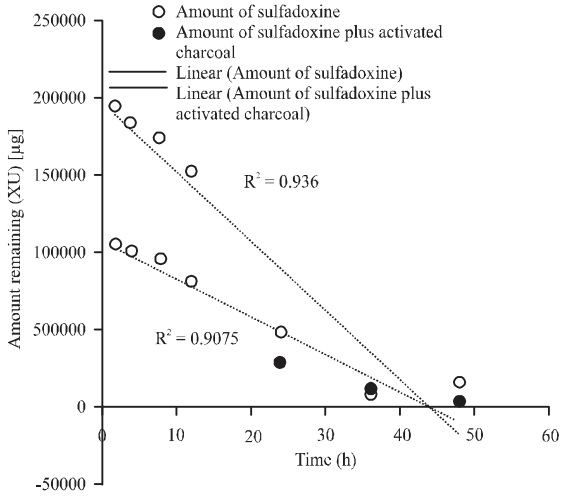

Fig. 4: Linear regression showing estimated amount of sulfadoxine remaining in the body after 60 h post administration in the absence and presence of activated charcoal

charcoal. This clearly demonstrates that the absorption was significantly reduced and consequently affected the body burden.

DISCUSSION

Adverse drug reaction is a well-known phenomenon in public health, pointedly the concerns of caregivers. It represents the two sides of a therapeutics coin in terms of efficacy and toxicity, in the bid to prescribe and use a drug

Table 1: Excretion characteristics of sulfadoxine in the absence and presence of activated charcoal in urine

Treatment	C_{max} (μg)	T_{max} (h)	AUC (tot)	Kel	$T_{1/2}$
Sulfadoxine	11649.79±5194.14	11.43±6.28	282521.2±90861.09	0.676±0.0356	13.85±6.79
Sulfadoxine plus activated charcoal	5774.23±5231.21	13.57±5.55	83026.85±61934.01	0.075±0.024	10.23±3.32

that is effective and safe in one breath[26]. Adverse drug reactions due to sulfadoxine-pyremathamine are well documented and occur mainly in outpatient settings[1,13,27]. Patients who use the medication as a weekly prophylaxis has been reported to be mostly affected and classified as serious risks in 1 out of 5000 users[7,12]. In WHO[28] recommended sulfadoxine-pyremathamine as emergency self-medication, if treatment is not immediately available. Although, sulfadoxine-pyremathamine is also recommended for IPTp and IPTi in malaria endemic regions[29], the doses are administered at predefined intervals with beneficial effects[7]. Sulfadoxine after oral administration becomes bound to plasma protein and thereby exhibits long duration of action in the body[30]. Frequent use or nonadherence to predefined washout period could foreshadow danger. Appearance of rash reported in literature amongst children who received recommended doses is still a pointer that there is a potential danger. This study did not observe any adverse effects in any of the subjects who volunteered. Wide individual variations were observed among the subjects who participated in the study in terms of sulfadoxine kinetic characteristics as reported by other studies[31-32]. Differences could be in protein binding characteristics and urinary pH, which is known, can affect sulfadoxine renal clearance according to WHO report[33]. However, in a similar study conducted in China also using male volunteers, 15.2% adverse events due to the drug were recorded[5]. These were mainly in form of rash, thrombocytopenia, leukopenia and folliculitis depicting the inherent danger. A recent study revealed pretreatment levels of sulfadoxine in 13 patients, indicating its long stay in the body and an attempt to administer another dose could potentially put the patients at risk of unprecedented adverse reaction[34]. From this study, decreased rate of sulfadoxine excretion was observed. Reduced rate of excretion indicates that the drug is having a prolonged stay in the body and will need a longer washout period in other to reduce the body burden. Use of sulfadoxine-pyremathamine in the presence of renal impairment and hepatic disease further makes the drug to accumulate[33,35]. In healthy individuals, the excretion of sulfadoxine is slow with long half-life of >200 h[5]. An immediate use of another dose will increase the body load of the drug and the potential for toxicity will also be greatly enhanced. On the other hand, activated charcoal tablets are frequently used by locals in the treatment of diarrhea. Its use appears to be relatively safe, but in cases where it is dissolved and given in slurry form, cases of regurgitation have been reported[36]. Some of the side effects associated with this event include bronchiolitis obliterans or adult respiratory syndrome. Administration of 1 g kg^{-1} to patients was shown to cause nausea and vomiting[37-38]. While, Dorrington *et al.*[39] reported that these side effects occur infrequently, position paper by American Academy of Clinical Toxicology/European Association of Poisons Centres and Clinical Toxicologists suggested that activated charcoal should be administered to patients with intact protected airway[40].

The predictable decrease in the amount of sulfadoxine found in subject's urine with co-administration of activated charcoal was evidently due to decreased absorption. At 24 h, 20% of the initial dose was detected with sulfadoxine alone, whereas, only 1.1% of the total dose was found when activated charcoal was added. This is another pointer that it has slow exit characteristics and it can accumulate under certain prescribed conditions. The total cumulative amount of sulfadoxine found in the urine after 60 h for subjects who took it alone was 43% of administered dose. While subjects who were given sulfadoxine and plus activated charcoal had 21% total cumulative amount in the urine. The study also estimated the amount of sulfadoxine remaining in the body as the body burden over time, was less for sufadoxine plus activated charcoal than for sulfadoxine alone. This demonstrated that with activated charcoal, the body burden will be less and washout period will be reduced. The concern for adverse drug reaction to sulfadoxine/pyrimetamine is that it occurs mostly in outpatients and recognition of what has happened might be too late.

CONCLUSION

The use and overuse of sulfadoxine/pyrimethamine is evident as it is available and cheap. Therefore, repeated prophylactic use might likely increase the body burden and easily lead to toxicity. Activated charcoal is expected to decrease the body burden by reducing absorption, particularly in a case of inadvertent overuse. This study has demonstrated that it can be a form or part of treatment strategy in preventing accumulation of sulfadoxine. Timely administration will prevent hospitalization and reduce fatality.

One of the limitations of this study is in not using different doses of activated charcoal for comparism. In addition, activated charcoal was given at 30 min post administration of

sulfadoxine/pyrimethamine only. Suggestion is hereby given for further study, to try different doses and at different time's interval like 60, 120 and 240 min, respectively post administration of the test drug with a larger cohort.

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