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Effect of charcoal-drug ratio on antidotal efficacy of oral activated charcoal in man

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1 The effect of charcoal-drug ratio on the antidotal efficacy of oral activated charcoal was studied in six healthy volunteers in a randomized cross-over study and compared with the adsorption capacity of activated charcoal *in vitro*.

2 Aminosalicylic acid (PAS) 1 g and 5 g were ingested on an empty stomach in 30 ml of water. Immediately afterwards the subjects ingested 50 g of activated charcoal in 300 ml of water or 300 ml of water only. PAS 10 g and 20 g were only given with 50 g of activated charcoal administered immediately afterwards.

3 The plasma concentrations and the cumulative excretion of PAS into urine were measured for 48 h.

4 Increasing the dose of PAS from 1 g to 20 g reduced the antidotal efficacy of activated charcoal: at a charcoal-drug ratio of 50:1 under 5% of the dose was absorbed but at a ratio of 2.5:1 about 37%. These data correlated well to the saturation of adsorption capacity of charcoal *in vitro*.

5 To minimize the possibility of saturation of the adsorption capacity of charcoal in acute intoxications where the amount and type of drug taken is usually unknown, large doses (50–100 g) of activated charcoal should be used.

Keywords charcoal-drug ratio antidotal efficacy

Introduction

The optimal antidotal dosage of oral activated charcoal has been controversial since the beginning of its use as a clinical antidote. A few studies have tried to answer this question either in experimental animals or in man. However, for obvious reasons the human studies have been made using relatively small doses of charcoal and drugs (Levy & Tsuchiya, 1972; Chin *et al.*, 1973; Levy & Houston, 1976; Neuvonen & Olkkola, 1984). In order to study the effect of charcoal on the absorption of large amounts of drugs, fairly nontoxic aminosalicyclic acid (PAS) given as sodium aminosalicylate (sodium PAS) was employed as a test substance. The charcoal dose was held constant but that of PAS was increased stepwise from 1 g to 20 g. The adsorption of PAS to charcoal was determined *in vitro* in order to make comparisons *in vitro vs in vivo*.

Methods

Experiments in vivo

Six healthy female volunteers, aged 22 to 36 years, weighing 54 to 65 kg, participated in the study. The results of physical examination and routine laboratory tests before and after the study were normal. Written informed consent was obtained from each volunteer. The study protocol was accepted by the Local Ethics Committee. For the first 8 h after drug ingestion the volunteers were under direct medical supervision in an outpatient clinic.

A randomized cross-over study design with six phases was used at intervals of 2 weeks. Sodium PAS (NA-PAS, Ferrosan, Malmö, Sweden), dissolved in 30 ml of water and in amounts equivalent to 1 g or 5 g of PAS, was given at 08.00 h after an overnight fast and followed

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immediately by activated charcoal 50 g suspended in 300 ml of water or water without charcoal. Sodium PAS suspended in 30 ml of water and in amounts equivalent to 10 g or 20 g of PAS was given with 50 g of activated charcoal administered immediately afterwards. Activated charcoal (Carbomix, Medica Pharmaceutical Company Ltd, Helsinki, Finland) was a specially granulated form of Norit A, which rapidly forms a homogeneous suspension when shaken with water. No food was taken for 3 h from the beginning of the study.

Timed blood samples were taken into heparinized tubes at 0, 0.5, 1, 2, 3, 5, 8, 24 and 48 h after drug ingestion. Plasma was separated within 30 min. Urine was collected in fractions for 0–24 h and 24–48 h. All plasma and urine samples were stored at −20°C until analyzed within 1 week.

Determination of absorption

The effect of charcoal on the absorption of sodium PAS was characterized by the area under the plasma PAS concentration-time curve from 0 to 48 h ($AUC_{0-48\ h}$) which was calculated by the trapezoidal rule. In addition, peak plasma concentrations (C_{max}), peak times (t_{max}), and the cumulative excretion of PAS into urine over 0–48 h were calculated.

Experiments in vitro

The adsorption of PAS to activated charcoal was studied *in vitro* at pH 1.2 (0.1 M HCl) and pH 7.0 (0.05 M phosphate buffer) using charcoal-PAS ratios from 20:1 to 1:1. The incubations were performed at 37°C for 20 min as described earlier (Neuvonen *et al.*, 1984).

Assay

The concentration of PAS in plasma and in the incubates was assayed for nonacetylated PAS and in urine for total PAS (nonacetylated + acetylated PAS + *p*-aminosalicyluric acid, PASU) using the Marshall colorimetric method as modified by Wan *et al.* (1974).

Statistical analysis

Friedman's two-way analysis of variance was employed for statistical analysis of the *in vivo* results. Duncan's multiple range test was applied to find the source of possible differences between various phases of the study (Duncan, 1955). Bartlett's test was used to judge its applicapability for the direct comparison of the data (Bartlett, 1937). In case of significant differences between variances, logarithmic transformation was used prior to Duncan's test.

Student's *t*-test for unpaired values was used for statistical analysis of the *in vitro* results.

Results

Experiments in vivo

When PAS was taken without charcoal, it was absorbed both rapidly and completely. t_{max} ranged from 0.5 h to 1 h and the 48 h cumulative excretion of total PAS from 96% to 101% of the dose (Figures 1, 2, 3 and 4; Table 1).

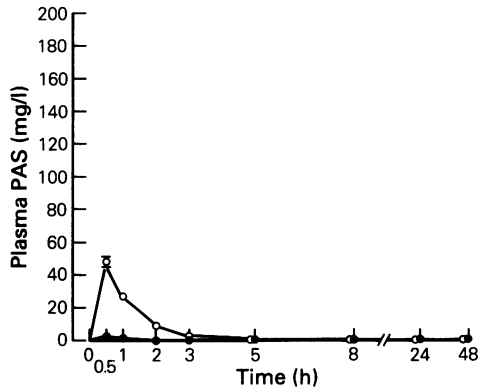

Figure 1 Effect of charcoal on the absorption of 1 g of PAS, reflected as the concentration of nonacetylated PAS in plasma. Mean ± s.e. mean in six healthy volunteers. ○ PAS 1 g, ● PAS 1 g + charcoal 50 g.

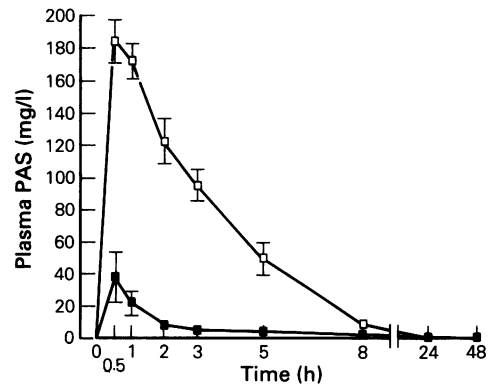

Figure 2 Effect of charcoal on the absorption of 5 g of PAS, reflected as the concentration of nonacetylated PAS in plasma. Mean ± s.e. mean in six healthy volunteers. □ PAS 5 g, ■ PAS 5 g + charcoal 50 g.

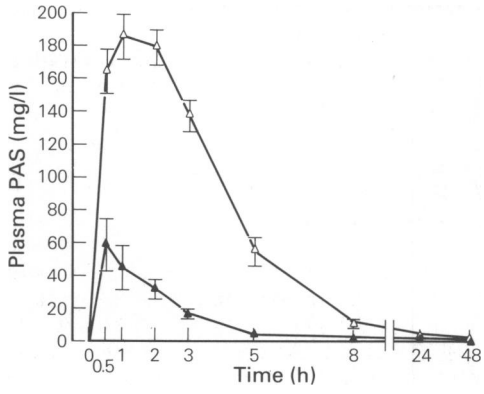

Figure 3 Effect of charcoal on the absorption of 10 g and 20 g of PAS, reflected as the concentration of nonacetylated PAS in plasma. Mean ± s.e. mean in six healthy volunteers. △ PAS 20 g + charcoal 50 g, ▲ PAS 10 g + charcoal 50 g.

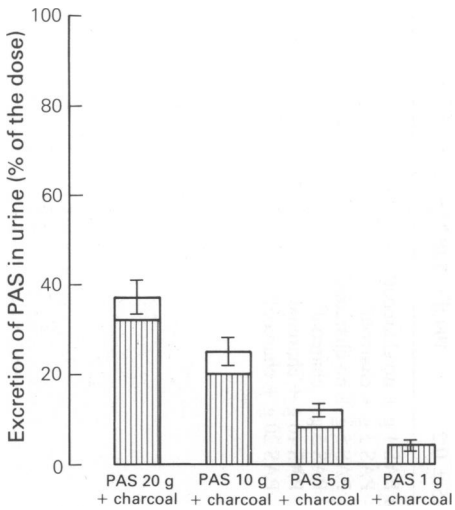

Figure 4 Effect of charcoal on the absorption of 1 g, 5 g, 10 g and 20 g of PAS, reflected as the cumulative excretion of total PAS (nonacetylated + acetylated PAS + *p*-aminosalicyluric acid, PASU) into urine over 0–48 h (■ 0–24 h, □ 24–48 h). Mean ± s.e. mean in six healthy volunteers.

When 50 g of activated charcoal was administered immediately after 1 g PAS, the total bioavailability was reduced by over 95%. Increasing the dose of the drug to 5 g reduced the efficacy of charcoal ($P < 0.05$) but the inhibition of absorption was, however, almost 90%.

As the dose of PAS was increased from 5 g to 20 g (decreasing the charcoal-drug ratio from 10:1 to 2.5:1), the efficacy of charcoal was further impaired: charcoal given after dosing subjects 10 g or 20 g PAS reduced the absorption of PAS by about 75% and 63%, respectively, based on the 48 h excretion in urine.

The amount of PAS excreted into urine was increased during 24–48 h when PAS was ingested with charcoal compared to when no adsorbent was administered.

Experiments in vitro

The fraction of unadsorbed PAS decreased from 55 ± 1% to 1.1 ± 0.1% as the charcoal-PAS ratio was increased from 1:1 to 20:1 at pH 1.2 (Figure 5). The unadsorbed fraction was significantly ($P < 0.001$) increased when the incubation was performed at pH 7.0. At a charcoal-PAS ratio of 20:1 the unadsorbed fraction at pH 7.0 was about 16%, i.e. 15-fold that at pH 1.2.

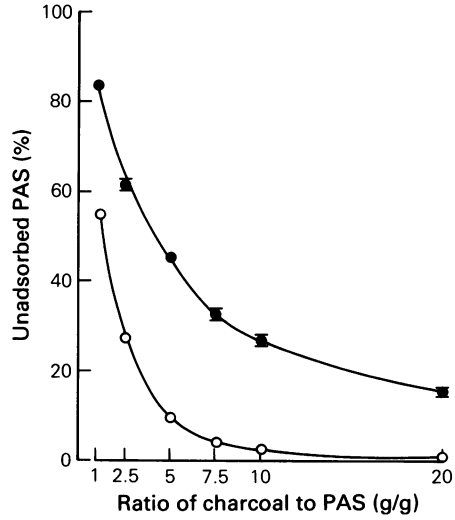

Figure 5 The percentage of unadsorbed PAS at pH 1.2 (○) and pH 7.0 (●) and at various charcoal-drug ratios. Mean ± s.e. mean in three experiments.

Discussion

Until recently the antidotal dosage of orally administered activated charcoal was based mainly on studies where the adsorption capacity of charcoal for various drugs had been determined *in vitro*. The direct application of these data to clinical toxicology is inappropriate and has led to the recommendation of extremely disparate amounts of the adsorbent during the past 10 years. The recommendations in the medical

Table 1 Effect of charcoal (50 g) on the absorption of different doses of PAS, measured as the peak time (t_{max}) and the peak plasma concentration (C_{max}) of nonacetylated PAS, the area under the plasma concentration-time curve ($AUC_{0-48\ h}$) and the 48 h cumulative excretion of total PAS (nonacetylated + acetylated PAS + *p*-aminosalicyluric acid, PASU) in urine. Charcoal was given immediately after PAS. Mean ± s.e. mean in six healthy volunteers

	Nonacetylated PAS					
	t_{max} *(h)*	C_{max} *(mg l^{-1})*	*(% of the control)*	$AUC_{0-48\ h}$ *(mg l^{-1} h)*	*(% of the control)*	*Total PAS 48 h excretion (% of the dose)*
PAS 1 g + no charcoal (control)	0.5 ± 0.0	48.2 ± 2.9[b–c,f]	100.0	57.3 ± 1.0[b–c,d–f]	100.0	101.1 ± 2.2[b,d–f]
PAS 1 g + charcoal	—	1.0 ± 0.8[a,c–f]	2.1	0.7 ± 0.6[a,c–f]	1.2	4.2 ± 0.9[a,c–f]
PAS 5 g + no charcoal (control)	0.7 ± 0.1	193.5 ± 9.7[a–b,d–e]	100.0	690.6 ± 63.7[a–b,d–e]	100.0	96.0 ± 0.8[b,d–f]
PAS 5 g + charcoal	0.6 ± 0.1	38.5 ± 15.1[b–c,f]	19.9	86.6 ± 14.0[b–c,e–f]	12.5	11.8 ± 1.2[a–c,e–f]
PAS 10 g + charcoal	0.8 ± 0.3	63.4 ± 14.1[b–c,f]	—	202.7 ± 32.1[a–d,f]	—	25.2 ± 3.0[a–d,f]
PAS 20 g + charcoal	1.5 ± 0.2	199.8 ± 7.0[a–b,d–e]	—	949.9 ± 86.0[a–b,d–e]	—	37.0 ± 3.6[a–e]

a–f: significantly ($P < 0.05$) different from PAS 1 g + no charcoal[a]
PAS 1 g + charcoal[b]
PAS 5 g + no charcoal[c]
PAS 5 g + charcoal[d]
PAS 10 g + charcoal[e]
PAS 20 g + charcoal[f]

literature have varied from 1 g to 120 g (Swinyard, 1970; Hayden & Comstock, 1975; Klaassen, 1980; Neuvonen, 1982).

In vivo it has been demonstrated that an effective antidotal dose of activated charcoal is more than could be expected from binding studies *in vitro*. Also, at constant charcoal-drug ratio the effectiveness of charcoal increases with increasing dose (Levy & Tsuchiya, 1972; Chin *et al.*, 1973; Levy & Houston, 1976; Neuvonen *et al.*, 1984; Neuvonen & Olkkola, 1984). However, previous studies have used only small doses of drugs. In addition, the antidotal efficacy of activated charcoal has not been related to the charcoal-drug ratio as in the present study in which the charcoal dose has been constant while the dose of test drug has been varied, thus simulating more effectively a real intoxication.

Despite the minor importance of PAS in modern clinical toxicology it was chosen as the test drug in the present study because of its low toxicity in single doses. The dose of PAS could be changed from 1 g to 20 g (20-fold the lowest dose) with no analytical difficulties in detection of PAS reliably in plasma and urine even at the lowest dose level. The sodium salt of PAS was used in order to ensure rapid absorption and to reduce gastric irritation. No side effects, other than mild gastric irritation at high doses of PAS, occurred during the study. Likewise, charcoal was well tolerated. All subjects swallowed the charcoal suspension within 2–3 min on every occasion. Some of the subjects later complained of mild constipation which was treated with lactulose.

In vitro activated charcoal effectively bound PAS, but at charcoal-drug ratios less than 7.5:1, the unadsorbed fraction of PAS increased steeply, indicating saturation of the adsorptive capacity of charcoal. The effect of pH on the adsorption capacity was marked especially at high charcoal-drug ratios (at which the adsorptive capacity had not been exceeded). PAS was adsorbed better at acid pH than at neutral pH. This finding is in agreement with previous studies on the effects of pH on the adsorption of weak acids (Andersen, 1947; Neuvonen *et al.*, 1984). Drugs are best adsorbed by charcoal in their undissociated form. This fraction is dependent both on the pKa of the drug and on the pH of the medium, according to Henderson-Hasselbach equation.

As the proportion of PAS undergoing acetylation was beyond the scope of this study, only nonacetylated PAS in plasma was analyzed. The nonspecific colorimetric method used does not differentiate between unchanged PAS and the glycine conjugated, *p*-aminosalicyluric acid (PASU). However, on the basis of low concentrations of PASU found in plasma and the dose-independent formation of PASU, it is possible to analyze PAS in plasma by a nonspecific method which gives the same relative error of about 5% regardless of plasma concentration (Lauener *et al.*, 1957; Wan *et al.*, 1974).

Together acetylated PAS and PASU constitute more than 90% of the metabolites found in urine (Way *et al.*, 1948; Kawamata & Kashiwagi, 1955). The excretion of total PAS (nonacetylated + acetylated PAS + PASU) into urine was determined since it gave the best characterization of the amount of PAS absorbed. The absorption of the drug taken without charcoal was practically complete, the recovery of total PAS in urine varying between 96–101% of the oral dose. Therefore, the antidotal efficacy of activated charcoal was assessed by means of calculating the recovery in urine as a percentage of dose.

Based on the $AUC_{0-48\ h}$ and the recovery of PAS in urine, the inhibiting action of activated charcoal on the absorption of PAS was weakened as the dose of PAS increased. At a charcoal-drug ratio of 10:1 and in favourable *in vitro* conditions over 97% of PAS was adsorbed at gastric pH and about 73% at neutral pH. *In vivo* about 88% of PAS was adsorbed to activated charcoal at the same charcoal-drug ratio. There seems to be no discrepancy between these data since the charcoal-drug complex formed in the stomach undergoes a wide range of pH-changes when passing through the gastrointestinal canal. In addition, the adsorption process *in vivo* is exposed to other disturbing compounds in the incubation medium. At a charcoal-drug ratio of 2.5:1 about 73% and 38% were adsorbed *in vitro* at pH 1.2 and 7.0, respectively.

Because the adsorption of drugs to activated charcoal is a reversible process the desorption of acidic drugs from charcoal is possible during the passage of charcoal-drug complex from the stomach to less acidic areas of the intestine. In the present study the desorption of acidic PAS from charcoal was seen as a relatively high excretion of PAS into urine during the second day after ingestion of PAS and charcoal. For instance when 10 g of PAS was ingested with charcoal suspension given soon afterwards about 80% of the total excretion into urine took place during 0–24 h, and about 20% during 24–48 h. However, when 5 g of PAS was taken without charcoal nearly 99% of the excretion occurred within the first 24 h. The desorption increases the total amount of drug absorbed, but on the other hand, it does not invalidate the use of activated charcoal, since in acute intoxications the reduction of the peak plasma concentration of the drug may be as important as a reduction of its total absorption.

A rapidly absorbed (mean t_{max} 30–40 min without charcoal) solution or suspension of PAS was used since volunteers can hardly be claimed to ingest nearly 30 g sodium PAS followed by 50 g of activated charcoal unless easily swallowed formulations are given. Activated charcoal was taken immediately after PAS in order to diminish intra- and interindividual differences in drug absorption. Because of the differences in gastric emptying rates between the subjects the later administration of the adsorbent would have made any reliable studies of the effect of charcoal-drug ratio on the antidotal efficacy of charcoal impracticable. When charcoal was administered immediately after PAS practically all PAS was in the stomach at the moment of charcoal administration. Accordingly, charcoal-drug ratio at a given PAS dose was constant in all subjects. Thus the present results demonstrate the effect of charcoal-drug ratio on the absorption of that fraction of the test drug which is still in the stomach. As the delay before the administration of activated charcoal in acute intoxications is usually much longer than in the present experimental conditions the present results are not directly applicable to the typical clinical situation in respect of the percentage inhibition of absorption. However, these aspects are beyond the scope of this study.

The present results convincingly demonstrate the saturation of the adsorption capacity of activated charcoal both *in vitro* and *in vivo*. Because of no discrepancy *in vitro vs in vivo*, the potential antidotal efficacy of activated charcoal in real intoxication can be concluded by combining experimental *in vitro* and *in vivo* data also with drugs other than PAS. However, the relationship between studies performed in test tubes and the antidotal efficacy of charcoal in man has to be established by direct human studies of the drug in question. For instance *in vitro* structurally closely related aspirin is more effectively adsorbed to activated charcoal than PAS, but in man at charcoal-drug ratio of 50:1 the absorption of PAS is much better inhibited by the adsorbent than that of aspirin (Neuvonen *et al.*, 1984). In addition, PAS differs in many respects from most drugs since its adsorption to activated charcoal is relatively poor and the pharmaceutical formulation employed in the present study is absorbed extremely rapidly; furthermore, PAS is used in doses (average daily dosage 12 g in adults) which are seldom if ever needed with modern drugs. This implies that an acute intoxication of approximately 50 times the normal therapeutic dose with drugs with higher potency, and with better affinity to charcoal than PAS would not saturate the adsorptive capacity of activated charcoal as occurs with 20 g of PAS. Anyhow, despite its limitations, the selection of PAS as the test drug enabled the 20-fold increase in dose which has not been the case previously in experimental conditions. Accordingly, this made it possible to gain new information about the antidotal efficacy of activated charcoal.

In acute intoxications the amount and type of drug taken is usually unknown. The less charcoal given the more easily its adsorption capacity is saturated. Therefore, in the treatment of intoxications there should be no hesitation in administering adequately large doses (50–100 g) of activated charcoal.

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