Relationship between Effect of Activated Charcoal on Drug Absorption in Man and Its Drug Adsorption Characteristics *In Vitro*

TAMEHIRO TSUCHIYA and GERHARD LEVY▲

Abstract □ Parallel *in vivo* and *in vitro* determinations of the adsorption characteristics of activated charcoal were carried out with three drugs having a different pKa: aspirin, salicylamide, and phenylpropanolamine. *In vitro* adsorption isotherms at pH 1 and 8.2 and the effect of increasing pH on drug desorption characteristics suggested that, as these drugs pass from stomach to intestine, the *in vivo* adsorption of: (*a*) aspirin will be reversed significantly due to change in pH, (*b*) salicylamide will be decreased only slightly except for possible competitive effects of normal intestinal contents, and (*c*) phenylpropanolamine may be increased slightly unless intestinal content exerts a displacing effect. Absorption studies in human volunteers yielded results that are consistent with these predictions and that demonstrate the effect of dose and mode of charcoal administration on the efficacy of this adsorbent. These studies suggest that it may be possible to make reasonable predictions concerning the relative antidotal effectiveness of activated charcoal in man on the basis of appropriate *in vitro* adsorption studies.

Keyphrases □ Charcoal, activated—as *in vivo* absorption inhibitor of aspirin, salicylamide, and phenylpropanolamine, prediction from *in vitro* adsorption studies and physicochemical properties □ Bioavailability—relationship between *in vivo* activated charcoal absorption inhibition of drugs and *in vitro* adsorption and physicochemical properties □ Absorption inhibition—activated charcoal, *in vivo*, *in vitro* studies □ Adsorption, *in vitro*, activated charcoal—effect of pH □ Antidotes—adsorption, absorption characteristics of activated charcoal

The large number of acute accidental drug ingestions, particularly in children, has caused considerable interest to be focused on agents that can inhibit the absorption of ingested drugs, either by causing emesis and thereby removal of unabsorbed drug from the stomach or by adsorbing or sequestering drug in the GI tract so that the bound drug cannot be absorbed as such. Activated charcoal, by reason of its broad spectrum of *in vitro* adsorptive capability and its innocuousness, appears to be particularly promising as an antidote for the early treatment of acute accidental drug ingestions in the home and the clinic. There have been many investigations of the efficacy of activated charcoal in dogs and smaller animals (1), but very few studies have been done in man (2–6).

A comprehensive investigation in this laboratory demonstrated the efficacy of activated charcoal for the inhibition of aspirin absorption in man and elucidated the effect of dose, time of administration, food, charcoal-to-drug ratio, and site of release of aspirin on the inhibitory effect of the adsorbent (3). It is obviously impractical to carry out similar detailed studies with all drugs, and it is impossible for ethical reasons to do such experimental studies in man with pesticides, organic solvents such as kerosene, and certain other poisonous agents which may be ingested accidentally. The question arose, therefore, whether *in vitro* adsorption studies could yield information that would permit reasonable predictions concerning the likely antidotal effectiveness of activated charcoal under clinical conditions. This possibility has been explored by parallel *in vitro* adsorption experiments and absorption studies in man with three drugs representing, respectively, a weak acid (aspirin), a drug largely nonionized in the pH range of the GI tract (salicylamide), and a weak base (phenylpropanolamine). The results of this investigation demonstrate the efficacy of activated charcoal as an inhibitor of the absorption of all three drugs in man and suggest that the relative efficacy of the adsorbent can be predicted on the basis of *in vitro* studies and physical–chemical considerations.

EXPERIMENTAL

In vitro adsorption studies were carried out by dissolving aspirin (0.25%), salicylamide (0.16%), or phenylpropanolamine (0.25%) in aqueous solutions of various pH. These were prepared with 0.1 *N* HCl (pH 1), 0.18 *M* sodium bicarbonate (pH 8.2), 0.1 *M* sodium carbonate and HCl (pH 10), and 0.15 *M* disodium phosphate and NaOH (pH 12). Various amounts (0.1–1 g.) of activated charcoal USP XVII[1] were added to 50 ml. of drug solution and equilibrated at 37°. The suspensions were then filtered rapidly, and drug concentration in the filtrate was determined after suitable dilution by spectrophotometry at pH 1 and 275 nm. (aspirin) or 298.5 nm. (salicylamide) and by the method of Heimlich *et al.* (7) for phenylpropanolamine. Aspirin hydrolysis was negligible under the experimental conditions. The desorption rate of aspirin was determined by first equilibrating at 37° 20-ml. portions of 1.6% activated charcoal and 0.5% aspirin in 0.1 *N* HCl. Some of these were filtered and the amount of aspirin

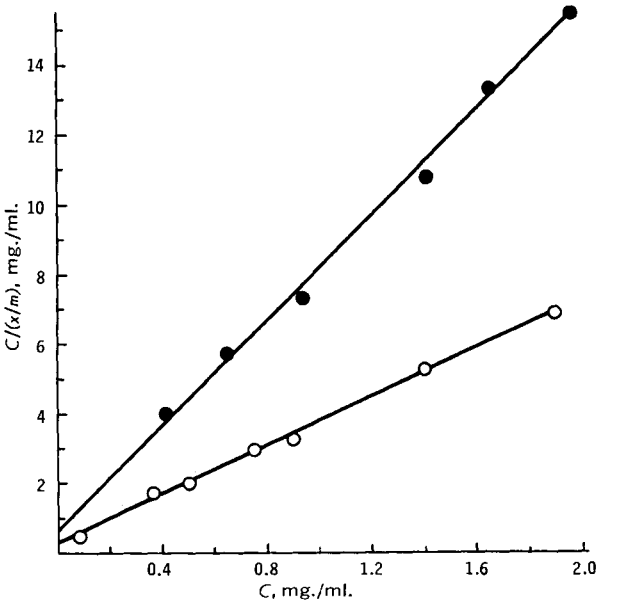

Figure 1—*Langmuir isotherm for adsorption of aspirin on activated charcoal at pH 1 (○) and pH 8.2 (●), 37°.*

[1] Norit, American Norit Co., Inc., Jacksonville, Fla.

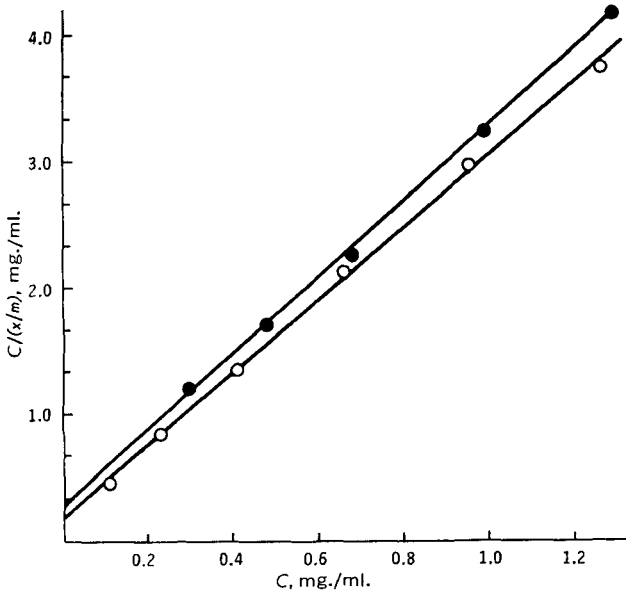

Figure 2—*Langmuir isotherm for adsorption of salicylamide on activated charcoal at pH 1* (○) *and pH 8.2* (●), *37°.*

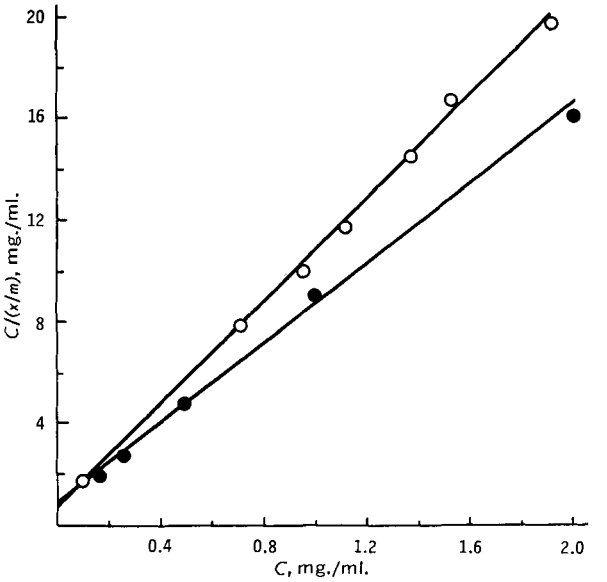

Figure 3—*Langmuir isotherm for adsorption of phenylpropanolamine on activated charcoal at pH 1* (○) *and pH 8.2* (●), *37°.*

was determined in the filtrate. To others, an equal volume of 0.4 *N* disodium phosphate or 0.4 *N* NaCl was added with continuous agitation, and filtrates were obtained at various times for subsequent assay.

The absorption studies were carried out with five healthy male volunteers, 22–31 years old. The volunteers were instructed not to take any drugs during the week before an experiment. One gram aspirin, 1 g. salicylamide, or 50 mg. phenylpropanolamine was administered in 200 ml. water in the morning on an empty stomach. In other experiments, various amounts of activated charcoal were dispersed in the drug solution and, in the case of phenylpropanolamine, were also given immediately following the drug solution. Urine was collected at intervals until no further excretion of drug occurred (48 hr.). No food was permitted for 4 hr. after drug administration. Total salicylate and salicylamide in the urine were determined after hydrolysis to salicylic acid, as previously described (8, 9). Phenylpropanolamine was determined by the method of Heimlich *et al.* (7).

RESULTS AND DISCUSSION

Langmuir isotherms for the adsorption of aspirin, salicylamide, and phenylpropanolamine on activated charcoal at pH 1 and 8.2 are shown in Figs. 1–3. The adsorption capacity of the charcoal for these three drugs, as represented by the reciprocal of the respective isotherm slopes, is listed in Table I. All three drugs are adsorbed significantly in the pH range of the GI tract. Adsorption is more extensive when the drugs are in nonionized form; the calculated adsorption capacity is similar for the three drugs when they are nonionized (about 2 mmoles/g. charcoal). These results suggest that as the drugs leave the acidic environment of the stomach and become exposed to the much higher pH of intestinal fluids, the adsorption of aspirin on activated charcoal is significantly reversed, that of salicylamide is decreased only slightly, and that of phenylpropanolamine may be slightly increased. The desorption of aspirin from activated charcoal due to increased pH is very rapid (Fig. 4).

In addition to these pH effects, it is necessary to take into consideration that certain components of GI fluids may displace adsorbed drugs from activated charcoal *in vivo* (3, 10, 11). These displacement effects could, in theory, superimpose sufficiently on the pH effects so that the latter may be of secondary importance. Studies in man were initiated, therefore, to determine the relationship of the *in vitro* data to the *in vivo* effects.

The absorption studies were designed to test the relative reversibility of drug adsorption in the GI tract and to determine the inhibitory effect of activated charcoal on drug absorption as a function of the dose of adsorbent. Aqueous solutions of each drug without activated charcoal were used as reference standards for the determination of relative bioavailability. In other tests, sufficient charcoal was added to the drug solutions to adsorb one-half of the dose at pH 1. The amount of charcoal required for this purpose was calculated from the adsorption isotherms and ranged from 0.5 to 1.9 g. In addition, the drugs were also administered with sufficient charcoal (5 or 10 g.) to adsorb more than 99% of the dose.

The results of the studies with aspirin were reported previously (3) but are shown again in Table II to permit convenient comparison with the other data. The drug was recovered completely in the urine after administration of the solution without adsorbent. When the aspirin was given with enough charcoal (1.9 g.) to adsorb half the dose, almost 88% was absorbed. Administration of the drug in almost completely adsorbed form (with 10 g. charcoal) reduced absorption to 61%.

Activated charcoal was more effective in inhibiting the absorption of salicylamide (Table III). While *in vivo* desorption was still appreciable, the availability of a 1-g. dose was reduced to only 23% when given with 10 g. charcoal. The extent of desorption of salicylamide from charcoal in the GI tract was clearly less extensive than that of aspirin, consistent with the *in vitro* characteristics of these drugs.

Table I—Adsorption Capacity[a] of Activated Charcoal at Various pH's

Drug	pH 1.0	pH 8.2	pH 10	pH 12
Aspirin	283 (1.57)	133 (0.74)	—	—
Salicylamide	370 (2.70)	367 (2.68)	250 (1.82)	—
Phenylpropanolamine	95 (0.63)	128 (0.85)	—	303 (2.00)

[a] Milligrams (millimoles) per gram at 37°.

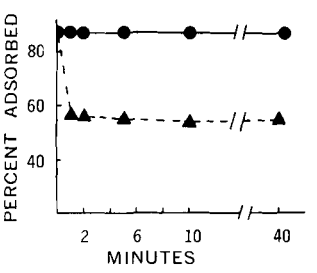

Figure 4—*Effect of twofold dilution of aspirin-activated charcoal suspension (pH 1) with 0.4* N *NaCl* (●, *final pH 1) and 0.4* N Na_2HPO_4 (▲, *final pH 7) on aspirin adsorption.*

Table II—Effect of Activated Charcoal on Aspirin Absorption

Subject	Activated Charcoal, g. 0	1.9	10
	Percent of Dose Recovered in Urine		
T.T.	96.9	84.6	63.0
B.K.	99.8	88.2	59.2
S.M.	101.6	87.8	61.9
W.H.	98.2	88.9	61.5
N.S.	101.8	—	57.6
Mean	99.7	87.4	60.6
R.A.[b]	100	87.7	60.8
Statistical significance[c]		$p < 0.01$	$p < 0.01$

[a] One gram aspirin in solution together with activated charcoal on an empty stomach. [b] Relative availability. [c] Paired *t* test.

The absorption data for phenylpropanolamine are summarized in Table IV. Only 0.5 g. activated charcoal was required to adsorb one-half of the 50-mg. dose. Little more than half the dose was absorbed after administration of the 50% adsorbate; an essentially 100% adsorbate (5 g. charcoal) released only 6.5% of the dose of phenylpropanolamine for absorption.

These results show that desorption of the drugs from activated charcoal in the GI tract definitely does take place—and to an extent that can be quantitatively significant. The results with phenylpropanolamine probably represent the net effect of further drug adsorption at the higher pH of intestinal fluids, desorption due to displacing effects of constituents of the GI fluids, and removal of drug from these fluids by absorption followed by dissociation of some adsorbed drug from charcoal. The GI residence time of the adsorbate and drug absorption or desorption rate (whichever is rate limiting) obviously influences the extent of desorption. In the case of the three drugs tested, it appears that the intrinsic adsorption characteristics, as reflected by their respective *in vitro* adsorption isotherms, are more important than possible differences in displacement effects. As already demonstrated by Andersen (12) in his pioneering studies, weak acids and bases are better adsorbed on charcoal when they are in nonionized form. On this basis, the bioavailability of drugs, given with enough activated charcoal so that a constant fraction of the dose is adsorbed at low pH, should increase with an increasing change in the extent of ionization from pH 1 or 2 to pH $\simeq$ 7. Such is the case with the three drugs studied in this investigation (Table V). The pronounced inhibitory effect of activated charcoal on promazine absorption, reported by Sorby (5), is also consistent with these findings. His observations concerning the importance of the desorption *rate* of drugs from an adsorbent must be taken into consideration when relating *in vitro* results to *in vivo* observations. While desorption of aspirin from charcoal was very rapid in the present study, Sorby (5) found that extensive dilution of a promazine–charcoal adsorbate did not cause desorption of the drug.

The absorption data presented so far in this report are pertinent to a consideration of factors affecting the *in vivo* desorption of drugs administered as adsorbates. However, when adsorbents are used as antidotes to inhibit the GI absorption of drugs and other potentially poisonous agents, they are administered separately, as soon as possible after the drug or poison. We showed previously that activated charcoal, administered immediately after ingestion of aspirin, is just as effective as when given together with the drug (3). On the other hand, Sorby (6) found that charcoal, when given immediately after promazine, had no significant effect on promazine absorption. To extend these studies, we determined the effect of activated charcoal on the absorption of phenylpropanolamine when the adsorbent was administered separately, after ingestion of the drug. The results (Table VI) show that charcoal is an effective inhibitor of phenylpropanolamine absorption even if administered separately. However, it is more effective when given together with the drug.

The difference in the relative efficacy of activated charcoal when given together with the drug or separately, as noted with aspirin (where there was no difference), phenylpropanolamine (where there was some difference), and promazine (where the difference was very pronounced) may be due to the different amounts of charcoal used in each of these studies. Ten-gram doses were employed in the aspirin study, 0.5 and 2 g. in the phenylpropanolamine experiments, and only 0.1 g. in the promazine investigation. While these differences reflect the different doses of each drug and the relative adsorption efficacy of charcoal for these drugs, the competitive effect of GI contents is more pronounced with the smaller doses of

Table III—Effect of Activated Charcoal on Salicylamide Absorption[a]

Subject	Activated Charcoal, g. 0	1.5	10
	Percent of Dose Recovered in Urine		
T.T.	95.3	75.9	14.7
B.K.	88.9	74.1	24.8
V.B.	92.2	71.7	28.0
S.M.	93.4	65.6	18.0
Mean	92.5	71.8	21.4
R.A.[b]	100	77.6	23.1
Statistical significance[c]		$p < 0.01$	$p < 0.01$

[a] One gram salicylamide in solution together with activated charcoal on an empty stomach. [b] Relative availability. [c] Paired *t* test.

Table IV—Effect of Activated Charcoal on Phenylpropanolamine Absorption[a]

Subject	Activated Charcoal, g. 0	0.5	5
	Percent of Dose Recovered in Urine		
T.T.	75.4	31.9	3.1
B.K.	79.4	41.0	7.6
W.H.	85.2	43.9	4.6
M.S.	80.1	51.0	5.4
Mean	80.0	42.0	5.2
R.A.[b]	100	52.5	6.5
Statistical significance[c]		$p < 0.01$	$p < 0.01$

[a] Fifty milligrams phenylpropanolamine in solution together with activated charcoal on an empty stomach. [b] Relative availability. [c] Paired *t* test.

Table V—Relative Availability of Three Drugs when Administered as 50% Adsorbate on Activated Charcoal and Effect of pH on Their Ionization

Drug	pKa	Average Relative Availability[a]	Percent Ionized pH 1	pH 7	Difference
Aspirin	3.5	87.7	<1	100	+100
Salicylamide	8.2	77.6	0	6	+6
Phenylpropanolamine	9.0	52.5	100	99	−1

[a] From Tables II–IV.

Table VI—Influence of Mode of Administration of Activated Charcoal on Its Effect on Phenylpropanolamine Absorption[a]

Subject	Percent of Dose Recovered in Urine: 0.5 g. Charcoal Together	0.5 g. Charcoal Separate	2.0 g. Charcoal Together	2.0 g. Charcoal Separate
T.T.	31.9	74.8	6.3	16.3
B.K.	41.0	47.4	9.6	23.1
W.H.	43.9	51.8	6.3	22.9
M.S.	51.0	66.2	6.5	17.5
P.G.	—	—	8.4	25.8
Mean	42.0	60.1	7.4	21.1
R.A.[b]	52.5	75.0	9.5	27.0
Statistical significance[c]	N.S.		$p < 0.01$	

[a] Fifty milligrams phenylpropanolamine in solution, either together with or immediately followed by 0.5 or 2.0 g. activated charcoal. [b] Relative availability. [c] Paired *t* test.

charcoal (3). A rather small amount of charcoal also would be less likely to come into rapid and complete contact with drug in the GI fluids than would a larger amount of the adsorbent and a larger dose of drug. In a sense, this represents a mass law effect under dynamic conditions where competitive processes (mainly absorption) are operative.

Andersen (13) showed that the *in vivo* inhibitory effect of charcoal on drug absorption is quantitatively different in the rabbit and dog, possibly due to differences in rates of GI residence time. Similar quantitative differences are likely to exist between man and laboratory animals in general. It would seem, therefore, that *in vitro* adsorption studies, particularly when combined with desorption rate determinations using not only simple aqueous media but gastric and intestinal fluids, should be as useful in many instances as animal experiments for obtaining an estimate of the likely relative antidotal efficacy of activated charcoal for drugs and other potential poisons. Rigorously controlled studies *in man*, as described in the previous report in this series (3), are mandatory for a quantitative assessment of the antidotal efficacy of activated charcoal with respect to the many drugs for which it may be used.

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Relationship between Lipophilic Character and Anesthetic Activity

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Abstract □ The structure–activity relationships in the anesthetic action of a set of 26 aliphatic ethers were found to be parabolic functions of their octanol–water partition coefficients. The results obtained with the gaseous anesthetics were compared with correlations obtained for various hypnotics acting from solution. It was found that optimum lipophilic character (defined as log P_0 from the octanol–water system) is about 2.0 for general anesthetics, which is the same as that found for barbiturates, ureas, alcohols, *etc.*

Keyphrases □ Lipophilicity of aliphatic ethers—related to anesthetic activity, correlated with hypnotics in solution □ Anesthetic activity of aliphatic ethers—related to lipophilicity, correlated with hypnotics in solution □ Structure–activity relationships—lipophilicity and anesthetic activity, aliphatic ethers

The Meyer–Overton theory of the mode of action of anesthetics postulated a linear relationship between anesthetic potency and oil–water partition coefficients of the inert, nonspecific, general anesthetics as well as simple narcotics such as alcohols and esters (1). Despite the fact that linearity cannot hold indefinitely, relatively little thought was given until recently (2–5) to explaining the departures from linearity in such relationships. The efforts of Ferguson (6) stand out as an exception. The evidence is now quite clear that the linear relationship between biological response (usually defined as log $1/C$, where C is the molar concentration of applied drug) and lipophilic character (defined as log P) is not linear in the general sense, but is rather well approximated (7) by Eq. 1:

$$\log 1/C = -k_1 (\log P)^2 + k_2 \log P + k_3 \qquad \text{(Eq. 1)}$$

In Eq. 1, k_1–k_3 are parameters evaluated by the method of least squares using an IBM 360/40 computer. The apex of the parabola defined by Eq. 1 can be obtained by setting the derivative, $(d \log 1/C)/(d \log P)$, equal to zero and solving for log P. This constant of a given system has been termed log P_0. It represents the optimum lipophilic character for a set of congeners acting on a given system. It is a most useful reference point to determine early in any drug modification study, since it represents the maximum activity that can be obtained for a set of drugs simply by manipulation of the lipophilic quality.

In a study of the structure–activity relationships of 16 sets of hypnotics, eight of which were different sets of barbiturates and eight of which were other hypnotics, a mean log P_0 of 1.98 ± 0.35 was found (8). For these different sets of drugs acting on different kinds of animals, log P_0 was obtained from experiments in which the drugs were given by injection (mostly intraperi-