Effect of Adsorbents on Drug Absorption I

Modification of Promazine Absorption by Activated Attapulgite and Activated Charcoal

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Effects on the rate and extent of absorption of promazine from the gastrointestinal tract produced by admixture with either activated attapulgite or activated charcoal were studied in humans using urinary excretion measurements. The initial rate of appearance of drug in the urine was slowed, but there was little decrease in total availability when promazine was administered in mixtures containing activated attapulgite. Activated charcoal decreased both the rate and extent of absorption. It is concluded that the forces through which the adsorption interaction is mediated are important to the effect obtained *in vivo* and that with further knowledge it may be possible to predict *in vivo* effects from the results of *in vitro* experiments.

IN VITRO experiments reported previously (1) show that certain materials used as pharmaceutic adjuncts and intestinal adsorbents can adsorb significant amounts of various phenothiazine derivatives. Calculations show that one-half of a 50-mg. dose of promazine could be adsorbed by 3.6 Gm. of kaolin, by 1.7 Gm. of talc, or by 0.55 Gm. of activated charcoal. Adsorption of medicinally active compounds by various types of adsorbents has been reported by other investigators (2–6). The literature on the subject is extensive, and a complete review is not possible within the scope of this paper. It is of particular interest that many adsorption studies report the interaction of tertiary amine-type compounds with a wide variety of adsorbents.

Since it is not uncommon that adsorbents are administered in combination with various drugs, it becomes a matter of practical importance to determine if adsorbents will interfere with absorption of drugs from the gastrointestinal tract. The ability of certain adsorbents to interfere with drug absorption is known through their use as antidotes for certain types of poisoning. Employment of adsorbents for *in vivo* inactivation of enteroviruses and bacterial toxins is reported (7, 8) and is the basis for numerous pharmaceutical products. Adsorption of certain drugs by ion exchange resins is utilized in design of some extended action dosage forms (9). Adsorption effects on drug absorption have been noted by Grote and Woods (10), Martin (8), and Oser *et al.* (11). Wagner (12) and Levy (13) have reviewed briefly the effects of various pharmaceutic adjuncts on drug absorption.

Most reports dealing with alteration of drug absorption by adsorbents have been concerned with toxicologic implications and fail to reveal the effects of adsorption on the concentration-time course of drugs within the human body. Little is understood about why adsorbent effects differ with both the nature of the drug and the adsorbent. The long-range goal of this research project is to establish a more complete understanding of the relationships which may exist between adsorption of a drug and its ability to be absorbed from the gastrointestinal tract. Of particular interest are the effects of adsorption on the rate and extent of drug absorption, the relationships which might exist between forces responsible for formation of the adsorbate and the effect on absorption, and whether it might be possible to predict an *in vivo* effect from a knowledge of *in vitro* adsorption characteristics.

This investigation and future reports will deal primarily with effects of adsorbents on the absorption of tertiary amines. These drugs are usually physiologically potent and are administered in small doses. Adsorption of even a few milligrams of such drugs may account for a significant fraction of the total dose, hence, adsorption effects might perhaps be of greatest signif icance with this class of compounds. The work reported here was undertaken to determine whether adsorption does significantly alter absorption characteristics of the drug chosen as a model tertiary amine and to evaluate the design of the *in vivo* testing procedure.

Promazine, 10-(dimethylaminopropyl)phenothiazine, was selected as the model tertiary amine because its adsorption characteristics are well known (1, 14), it is relatively nontoxic at the dosage level required to produce measurable levels of excretion, and it is reasonably well absorbed from the gastrointestinal tract of humans and laboratory animals (15, 16).

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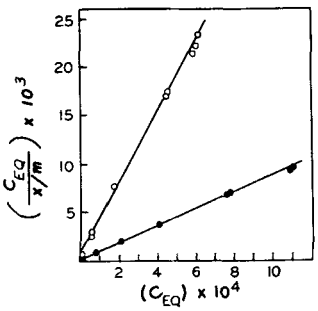

Fig. 1.—Langmuir isotherms for adsorption of promazine at 20.0°C. by activated attapulgite (○) and by activated charcoal (●). For activated attapulgite, $k_1 = 35.7 \times 10^3$, $k_2 = 2.77 \times 10^{-2}$; for activated charcoal, $k_1 = 3.51 \times 10^3$, $k_2 = 11.6 \times 10^{-2}$. C_{EQ} denotes molar concentration of promazine in solution at equilibrium, x/m, the millimoles of promazine adsorbed at equilibrium per 0.125 Gm. of activated attapulgite or per 0.100 Gm. of activated charcoal.

Activated attapulgite and activated charcoal[1] were selected as adsorbents for this study. Both exhibit an affinity for promazine; however, they are each representative of different classes of adsorbents and adsorption mechanisms.

EXPERIMENTAL

Determination of Adsorption Isotherms.—The adsorption of promazine by activated charcoal has been reported elsewhere (1, 14). Adsorption of promazine by activated attapulgite was determined at 20.0° by a method similar to that used previously. The results were plotted according to the Langmuir equation.

$$\frac{C_{EQ}}{x/m} = \frac{1}{K_1K_2} + \frac{1}{K_2} C_{EQ}$$

where C_{EQ} is the equilibrium concentration of promazine free in solution, x/m is the amount of promazine adsorbed by the amount of adsorbent used in the investigation, and K_1 and K_2 are constants with their usual meaning. The values of the Langmuir constants, K_1 and K_2, were obtained from the intercept and slope of a regression line calculated by the method of least squares from the experimental data. Results of these studies are presented in Fig. 1.

Preparation of Dosage Forms.—Preliminary experiments showed that a 50-mg. dose of promazine hydrochloride would insure measurable levels of excretion products in the urine for at least 24 hr. after administration. Dosage forms containing 50 mg. of promazine, adsorbent, and distilled water were prepared so that a significant fraction of the total drug content would be bound by the solid material. The amounts of adsorbent and water needed were calculated from the adsorption isotherms and were based on achieving saturation of the adsorbent surface with drug.

The ratio of adsorbent to total sample volume was such that the viscosity of the dosage forms did not appear to be significantly different from water.

Amounts of free and bound promazine existing at equilibrium were determined experimentally to check the accuracy of the calculated compositions (Table I). Calculated and actual compositions of the dosage form containing activated charcoal were found to differ markedly. Further investigation showed this difference to be caused by variation in adsorbent powers between two different commercial samples of activated charcoal. The dosage forms were prepared and used without further modification since it was not considered necessary to adjust them to concentrations predicted by theoretical calculations.

Dosage forms were prepared the day before administration to test subjects. After mixing, the preparations were placed in a container protected from light[2] and shaken for a period of time suitable to allow equilibration between the adsorbent and solution phase. The preparations were stored at room temperature until consumed by the test subject.

Conduction of In Vivo Tests.—*In vivo* testing was conducted according to a randomized blocks-type experiment design, using humans in apparent good health. The weight, age, and sex of each test subject is shown in Table II. Each subject received the three test preparations in a random order, and at least 1 week elapsed between administration of consecutive test doses to the same individual. Each subject received a sheet of written instructions with each test dose to insure that the same procedure of taking the test sample and collecting urine would be followed each time. Subjects were instructed to void all urine upon arising the morning of the test day and to consume immediately 4 oz. of water. One-half hour later, the subject voided his bladder, saving a portion of the urine for blank determination. The test preparation was consumed, and the bottle was rinsed with small portions of water to insure complete transfer of the test dose. The subject collected total urine samples over the time intervals shown in Table II. No further food or drink was consumed for at least 1 hr. Consumption of food and water was *ad libitum* for the remainder of the test period.

All samples were returned to the laboratory on the day the experiment ended and were analyzed immediately for their content of promazine and metabolites. The test subject was instructed to store the urine samples in the refrigerator protected from light during the course of the excretion experiment. This procedure was sufficient to maintain the stability of samples between time of collection and time of analysis.

Each subject also was provided with a record card on which was entered the following information: name, date, dosage form tested, time of initial dose, and exact time at which each urine specimen was collected. A space was provided for listing any drugs taken during the time period, beginning 12 hr. before the test and continuing until collection of the final urine sample.

Analysis of Urine Samples.—Urine samples were analyzed by a procedure representing a modification of Eiduson's method (22). A column-type extrac-

[1] Activated attapulgite was supplied as Pharmasorb Regular by the Minerals and Chemicals Philipp Corp., and activated charcoal as Norit A by the American Norit Co.

[2] Many phenothiazine derivatives are subject to photochemical decomposition (17–21).

TABLE I.—CALCULATED AND OBSERVED COMPOSITION OF DOSAGE FORMS ADMINISTERED TO TEST SUBJECTS[a]

Adsorbent Content	Total Vol. of Prepn., ml.	Amt. of Promazine Free—Calcd., mg.	Amt. of Promazine Free—Observed, mg.	Amt. of Promazine Adsorbed Calcd., mg.	Amt. of Promazine Adsorbed Observed, mg.
Activated attapulgite, 500 mg.	45	14.4	11.5	35.6	38.5
Activated charcoal, 100 mg.	40	12.7	25.3	37.3	24.7
None[b]	45	50	50	0	0

[a] All dosage forms contained a total of 50 mg. of promazine. [b] Preparations containing promazine dissolved in simple aqueous solution were prepared for use as controls in assessing the effect of the adsorbents on absorption of promazine.

TABLE II.—CUMULATIVE PROMAZINE EQUIVALENTS PRESENT IN TOTAL URINE SAMPLES OF HUMANS AT THE END OF VARIOUS TIME INTERVALS FOLLOWING ADMINISTRATION OF TEST DOSAGE FORMS[a]

Subject and Dosage Form Tested	0.5 hr.	1 hr.	2 hr.	4 hr.	6 hr.	9 hr.	12 hr.	24 hr.
A (M, 79, 28)[b]								
Soln. (*1*)[c]	0	83	703	2293	3337	4230	4936	6826
Attapulgite (*3*)	41	91	750	1881	2631	4011	4630	5703
Charcoal (*2*)	14	52	170	550	970	1570	2064	2955
B (M, 70, 23)								
Soln. (*3*)	54	261	1233	2530	3148	3687	4152	5133
Attapulgite (*2*)	41	253	823	2117	2728	3423	4076	5260
Charcoal (*1*)	0	90	605	1580	1999	2423	2581	2891
C (M, 84, 23)								
Soln. (*1*)	0	269	1017	2151	2930	3697	4561	6446
Attapulgite (*2*)	21	94	536	1706	2437	3220	3670	4444
Charcoal (*3*)	4	94	470	1130	1510	1900	2150	2186
D (F, 56, 31)								
Soln. (*1*)	0	0	540	1614	2300	3050	3740	5199
Attapulgite (*2*)	0	0	473	1329	2313	3136	3551	5050
Charcoal (*3*)	0	21	654	1422	2300	3166	3723	4595
E (M, 82, 25)								
Soln. (*2*)	39	354	1604	3472	4540	6007	6866	7142
Attapulgite (*1*)	0	0	413	1441	2630	4311	5179	7157
Charcoal (*3*)	33	97	1246	2200	3146	4672	6206	6599
F (M, 64, 25)								
Soln. (*1*)	50	762	2944	5154	6294	7782	7997	8342
Attapulgite (*3*)	0	290	1440	3536	5016	6314	7268	10832
Charcoal (*2*)	11	349	1669	3133	3800	4504	5130	6212

[a] For a definition of the promazine equivalent, see under *Analysis of Urine Samples*. Units of promazine equivalents are micrograms. [b] In parentheses, letter refers to the subject's sex, the numbers to weight in kilograms and age in years, respectively. [c] Numbers in parentheses refer to the order in which the subject received the dosage forms.

tion procedure was used, however, and resulted in better recovery of material from the urine and increased the number of samples which could be handled at one time. Urine samples were diluted with 4 vol. of water before passing through the ion-exchange column. This decreased interference caused by the yellow-colored urine pigments and yet did not decrease the extraction of promazine and its metabolites. Color intensity of samples was measured at 515 mμ since spectra, determined with a Cary model 11S recording spectrophotometer, revealed 515 mμ to be the wavelength of maximum absorbance.

The assay method is relatively nonspecific since it is sensitive to all material bearing the intact phenothiazine ring (23) and detects both promazine and certain of its metabolites. In addition, the ion-exchange method of extraction does not remove all of the excretion products from the urine since it does not efficiently extract the various conjugated forms which may be present. Results of assays are therefore expressed in terms of promazine equivalents. A promazine equivalent is defined as representing the amount of promazine which, if carried through the assay procedure, would give a solution having the same color intensity at 515 mμ as the urine sample in question. A standard curve for known amounts of promazine in distilled water was prepared by following the assay procedure, and excretion products in urine samples were quantitated by comparing their per cent transmittance to the standard curve. A promazine equivalent representing the urine blank collected immediately prior to administration of the test dose was subtracted to obtain the actual amount of excretion product in each sample.

Determination of Desorption Characteristics.—Desorption of promazine from adsorbent surfaces was studied by two different methods.

Desorption Against High Dilution.—A 2-ml. aliquot of a test dosage form was added to a large quantity of distilled water contained in a flask thermostated at 25° and fitted with a stirring apparatus. Aliquots were removed from the rapidly stirred systems at various time intervals following initial mixing and, after centrifuging, the amount of promazine released to the solution was determined by a spectrophotometric procedure (1, 14). The

TABLE III.—DESORPTION OF PROMAZINE FROM ADSORBATES WHEN SUBJECTED TO HIGH DILUTION

Desorption from Activated Attapulgite		Desorption from Activated Charcoal	
Time after Initial Mixing,[a] min.	Cumulative % Desorbed	Time after Initial Mixing,[a] min.	Cumulative % Desorbed
3	31.4	4	0
5	34.2	8	0
7	34.2	12	0
9	35.9	17	5.0
68	31.8	22	0
		68	0

[a] The time after initial mixing was taken as the time elapsed from the moment of initial mixing to removal of the sample from the centrifuge tube. Total elapsed time for this procedure was approximately 3 min.

volume of water, sufficient to produce a seventyfold dilution of the activated attapulgite preparation and a 175-fold dilution of the sample containing activated charcoal, was chosen so that there would be sufficient free promazine in solution to attain the lower limit of sensitivity of the spectrophotometric assay, even if no drug was released from the adsorbate. Results are presented in Table III.

Elution Experiments.—Samples equivalent to the test dosage forms contained in tightly stoppered 50-ml. centrifuge tubes were placed in a rocker-type shaker immersed in a constant temperature bath at 25.0°. After equilibration, the samples were centrifuged, and the supernate was decanted carefully and set aside for assay. A 25-ml. portion of either distilled water or 0.01 *N* hydrochloric acid was added; after shaking for 2 hr., the tubes were removed and centrifuged. The clear supernate was again decanted, its volume measured, and the promazine content determined. A fresh 25-ml. portion of distilled water or 0.01 *N* hydrochloric acid was added to the contents remaining in the centrifuge tube, and the process was repeated. A total of 10 elutions was made on each sample. The amount of promazine released in each elution step was calculated. The results are summarized in Table IV.

Treatment of Excretion Data.—Methods used for treatment of urinary excretion data in Table II were similar to those utilized by others (23, 24).

The cumulative amount of drug excreted at the end of each time interval was calculated for each of the three dosage forms. The average urinary excretion rate[3] during each time period was calculated also for each dosage form. Curves showing mean cumulative excretion plotted as a function of time are shown in Fig. 2. Mean average urinary excretion rates plotted against time are shown in Fig. 3.

Statistical comparisons *versus* drug in solution were made for cumulative excretion following administration of dosage forms containing adsorbents. A one-tail *t* test for nonindependent sample means was used. Such data treatment procedures are recommended (25, 26) as being applicable to experiment designs of this type. Average excretion rates over the various time periods were compared in a similar fashion, using a two-tail *t* test for nonindependent sample means.

[3] Average excretion rate is calculated by dividing the total number of promazine equivalents excreted during the collection period by the number of hours encompassed by that time interval. These values were plotted (Fig. 3), against the midpoint time of the collection period.

Drug availability was calculated by dividing the 24-hr. cumulative excretion value for promazine taken with adsorbent by the corresponding value for drug in solution. Figure 2 reveals that excretion was not complete at the end of 24 hr. since none of the three curves have become parallel to the time axis at this point. Excretion was not followed beyond 24 hr., since the amount of assayable material had reached the lower accuracy limits of the analytical procedure. Others working at higher dose levels or with radioactive tracers have shown that excretion of various phenothiazine derivatives may continue at a low level for as long as several days following a single dose of drug (27–29). The 24-hr. values should be sufficiently accurate for purposes of comparing availability since Fig. 2 indicates little likelihood that the curves would cross each other or would diverge significantly after that time.

DISCUSSION

The fundamental principles underlying use of urinary excretion measurements to study dosage form effects have been presented adequately by Nelson *et al.* (24, 30) and by Campbell *et al.* (31).

In this experiment, the effect of the drug–adsorbent interaction on the urinary excretion of promazine will depend upon the fate of the complex within the gastrointestinal tract. Several consequences of adsorption are possible and would be discernible by urinary excretion measurements.

If bound drug remains adsorbed until the preparation reaches the general area of the absorption site, the concentration of drug presented to the absorbing surfaces will be considerably less compared to when the same amount of drug is administered in simple aqueous solution. A decreased driving force for absorption would occur, resulting in a slower rate of absorption and excretion. As the drug is absorbed, it is probable that the adsorbate will dissociate in an attempt to re-establish equilibrium with drug in its immediate environment. This would be facilitated by other substances existing within the gastrointestinal tract which might compete with promazine for adsorption sites. Thus, it is possible that adsorbed drug is also available for absorption; however, the rate at which it appears in solution at the absorption site is important. If the rate of dissociation is very fast, the concentration of drug free in solution at the absorption site will be maintained at some low level commensurate with the physical limitation of the drug–adsorbate equilibrium. In this case, adsorption rate would be slowed and in some cases might approach a nearly constant value. It is also possible that dissociation of the drug–adsorbent complex might become the rate controlling step in absorption, and again the absorption and excretion rate would be expected to change. In both of the preceding cases, a different apparent rate constant for absorption would be expected. If the rate of dissociation becomes sufficiently slow, decreased amounts of drug would be absorbed during the time the drug is within the area of the gastrointestinal tract favorable to absorption, and availability would be decreased. If virtually no drug is released, absorption and excretion kinetics would correspond to the situation where a smaller dose of drug in solution had been given. It must be remembered that all preparations contain free drug,

TABLE IV.—DESORPTION OF PROMAZINE FROM ADSORBATES BY REPEATED ELUTION AT 25°C.

Elutions, No.	Cumulative Amt. Desorbed from Attapulgite Adsorbates[a,b] — Water Solvent — mg.	% [c]	0.01 N HCl Solvent mg.	% [c]	Cumulative Amt. Desorbed from Charcoal Adsorbates[a,b] — Water Solvent — mg.	% [c]	0.01 N HCl Solvent mg.	% [c]
1	1.62	4.19	12.1	31.3	2.71	9.61	2.10	7.95
2	2.59	6.71	16.7	43.2	3.82	13.5	3.35	12.7
3	3.63	9.40	18.4	47.5	4.48	15.8	4.05	15.3
4	4.34	11.2	19.6	50.6	4.90	17.4	4.52	17.1
5	4.93	12.8	20.5	53.0	5.15	18.3	4.91	18.6
6	5.61	14.5	21.1	54.5	5.34	18.9	5.21	19.7
7	6.35	16.5	21.6	55.8	5.51	19.5	5.43	20.6
8	6.88	17.8	21.9	56.6	5.59	19.8	5.64	21.4
9	7.36	19.1	22.3	57.6	5.67	20.1	5.84	22.1
10	7.75	20.1	22.5	58.1	5.74	20.4	6.00	22 7

[a] Values in table are average for two samples. [b] The dosage forms prepared for this experiment varied slightly in the relative amounts of free and adsorbed promazine. A total of 38.6 mg. was adsorbed initially by the attapulgite preparations eluted with water, 28.2 mg. by the activated charcoal preparations. For the activated attapulgite preparations eluted with 0.01 N HCl, 38.7 mg. was adsorbed initially, for activated charcoal 26.4 mg. [c] Based on the total amount adsorbed before elution.

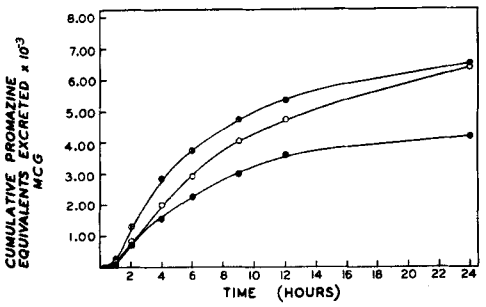

Fig. 2.—Cumulative amounts of promazine equivalents excreted in the urine following administration of various dosage forms to humans. Key: ⊙, promazine in simple aqueous solution; O, promazine plus activated attapulgite; ●, promazine plus activated charcoal.

and as a result, some absorption will always occur. The situation might also result where dissociation is virtually complete before reaching the absorption site. Presence of electrolyte and dilution by various fluids within the gastrointestinal tract would potentially hasten the latter situation. Absorption and excretion rates in this case would be identical to those for drug in solution.

Data presented in Figs. 2 and 3 show that both adsorbents modify excretion characteristics of the drug. From inspection of these curves and by considering data for *in vitro* desorption rates, it is possible to formulate explanations for the effects on absorption.

In spite of the delay in the excretion of drug administered with attapulgite,[4] it is apparent that virtually total release is obtained, manifested by the lack of a significant difference between attapulgite and drug in solution curves after 24 hr. Average excretion rates (Fig. 3) were slowed significantly by attapulgite ($p < 0.01$) until after the third hour. After the curves cross, the excretion rate following the attapulgite dosage form becomes faster, although virtually parallel to the solution curve. Of particular interest is the apparent delay in the time of peak excretion rate, denoting probably an alteration of the apparent rate constant for absorption.

[4] Except for the 1.5- and 24-hr. points, differences are significant at the $p = 0.10$ level. At 24 hr., $0.70 < p < 0.60$.

Although one can say that the absorption rate is altered, it is not possible to say, on the basis of excretion data, whether release from the adsorbent is the rate controlling step or whether absorption is slowed by virtue of reduced concentrations of drug free at the absorption site at any given time.

In vitro data in Table III show the rate of release of drug to be extremely rapid in a well-stirred system. Such a rapid rate, if it occurred *in vivo*, would not be expected to be so much slower than absorption rate that it could rate limit the over-all process. Data in Tables III and IV show that desorption is sensitive to concentration of drug in the external solution. Desorption occurs only to an extent sufficient to re-establish equilibrium with the external solution. Data in Table IV show that only a small amount of drug can desorb when the volume of solution is small. Thus attapulgite may act like a buffer to maintain a low concentration of drug in its environment. Dissociation of the adsorbate takes place rapidly, but only to an extent which replaces drug removed by absorption or transfer from the

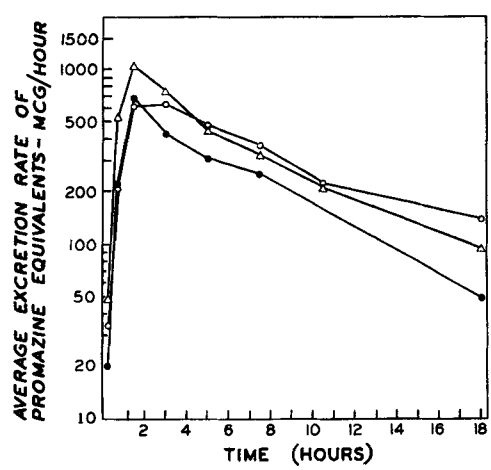

Fig. 3.—Average urinary excretion rate of promazine equivalents following administration of various dosage forms to humans. Key: △, promazine in simple aqueous solution; O, promazine plus activated attapulgite; ●, promazine plus activated charcoal.

immediate environment. Within the gastrointestinal tract, one might expect that the adsorbate would exist in near equilibrium with the solution around it, for removal of drug would be expected to be slow compared to the maximal rate at which the adsorbate can dissociate.

Thus, one might hypothesize that attapulgite alters absorption rate primarily by virtue of the fact that it probably limits the amount of drug available at the absorption site at any given time. This produces a nearly constant but slowly decreasing absorption rate for the period of time until release is complete.

Charcoal significantly decreased ($p < 0.025$) the amount of drug excreted at any given time. The reduction in total excretion during 24 hr. denotes a decreased availability of drug from this adsorbent. Curves in Fig. 3 show decreased excretion rates at all times; thus, charcoal differs from the effect of attapulgite. *In vitro* release studies (Tables III and IV) reveal that the promazine charcoal adsorbate has little tendency to dissociate, and it appears that only the drug initially free in the test dosage form is available for absorption. Excretion rate curves support this hypothesis. It is significant that the peak excretion rate occurs at the same time as for drug in solution, indicating little interference with the apparent rate constant for absorption. Also important is that the curve roughly parallels that for drug in solution after the time of maximum excretion rate. Thus, the charcoal curve is similar to what would be expected from a smaller dose of drug in solution. This would be the case if only that portion of the drug initially free was absorbed. It is also significant that availability, compared to drug in solution, is 0.65. The fraction of drug initially free in the dosage form was 0.50; however, if one considers Table IV to mean that approximately 6.0 mg. additional promazine may be desorbed, the fraction of the dose available for absorption would be 0.63, a figure very close to the availability calculated from *in vivo* data.

Differences between the effects of the two adsorbents on promazine absorption can be explained partially on the basis of the mechanisms by which they are thought to adsorb drug.

Adsorption of organic cations by clay-type materials takes place primarily by ion-exchange processes (32–34). Anionic sites on the clay usually are located on the surfaces or edges of the particles. These sites are readily accessible to the solution phase; as a result, adsorbed cations can be displaced readily by other cationic species competing for the adsorption sites or by other conditions which may upset the equilibrium situation. Attapulgite differs from this description because the exchange sites are thought to be located within large channels in the particles (32). As a result, release might be expected to be slow compared to when exchange sites are on particle surfaces. Desorption *in vitro* is very rapid, however (Table III), and bound material, even if located within channels, appears to be released readily. Increased desorption of promazine produced by raising the hydrogen-ion concentration (Table IV) is predictable on the basis of the ion exchange hypothesis and would obviously contribute to release of drug within the gastrointestinal tract. Even in the presence of increased hydrogen-ion concentrations, the amount of drug which can exist in equilibrium with the adsorbate is small, and the hypothesized mechanism for the action of attapulgite on promazine absorption would still be valid.

While many activated charcoals possess some ability to adsorb molecules by ion exchange, adsorption is thought to take place primarily as the result of other types of physical interactions (32, 33). Due to the porous nature of the charcoal particles, it is possible that some promazine is adsorbed within pores or fissures in the charcoal particles.[5] This fraction of adsorbed material would be in equilibrium with solution containing unbound drug also located within the pores. When the concentration in the phase external to the particle is reduced through absorption or dilution, drug within the pores would not sense such changes until mixing could occur or until a diffusional concentration gradient had been established between the external solution and the immediate environment of the bound material. Such changes would take place only slowly; hence, desorption from the charcoal would be expected to take place at a slower rate than from attapulgite.

Data in Table IV support this hypothesis because little promazine appears to be removable from the adsorbent. Inability of 0.01 *N* hydrochloric acid to significantly increase desorption from activated charcoal suggests that adsorption is not mediated to a large extent by ion exchange. Slow release rates evidenced *in vitro* are undoubtedly related to the decreased *in vivo* availability from charcoal. Some promazine is released (Table IV). However, it appears to be limited. No reason can be advanced to explain why no promazine was desorbed during the high dilution experiment.

CONCLUSIONS

One can conclude from data obtained for the cumulative excretion characteristics after administration of various dosage forms, from *in vitro* measurements of desorption rates, and from the calculated urinary excretion rates that the presence of adsorbents can interfere with absorption of promazine from the gastrointestinal tract. The degree of interference is dependent on the type of adsorbent agent and differs both qualitatively and quantitatively for the two adsorbents tested. Further work will be necessary before a complete understanding of the effect of adsorption on uptake of the drug is known. However, these results do indicate that the rate of release under certain *in vitro* conditions may be related at least qualitatively to the *in vivo* effect. Certain further modifications in the experiment design should enable one to develop better correlations between *in vitro* adsorption characteristics and absorption from the gastrointestinal tract.

The results also show that it is possible to use promazine as a model drug for study of the effects of adsorbents on absorption of tertiary amines. While the complex metabolic characteristics of this compound (16, 35, 36) make certain types of precise data treatment impossible, its conformity to various other ideal characteristics mentioned previously

[5] Some authors contend (32, 33) that pores within the average activated charcoal particles are too small to allow entrance of large molecules. The possibility of adsorption within pores cannot be ruled out entirely, since pore size is dependent upon the method of activation (33). Technical information brochures supplied by the American Norit Co. suggest that Norit A possesses some cavities or fissures which will admit the entrance of larger molecules.

make promazine a satisfactory model drug for this project. Since the major interest of the investigation is to study effects of adsorbents on absorption of tertiary amines, it is necessary to work with compounds which present experimental difficulties of this type.

Due to the complexity of the excretion products and the nonspecific nature of the assay procedure, several assumptions must be made in treating the data obtained during this experiment. It must be assumed that the fraction of total excretion products sensitive to the assay does not change significantly as a function of the amount of drug in the body. Thus, postabsorptive excretion curves from different doses of drug in solution are assumed to be parallel to each other over the time period studied. It is also necessary to assume that the apparent volume of distribution does not change and that the apparent rate constants for metabolism and excretion of the various metabolites also do not vary in magnitude or order as a function of dose. These same assumptions are made frequently in urinary excretion studies; however, the complex metabolism of phenothiazine derivatives makes it necessary to proceed with caution in this respect. Eiduson and Geller have shown (27) for thioridazine that there is a congruency between excretion as measured by a similar colorimetric method and by radioactive isotope procedures using radio-tagged thioridazine. The levels of thioridazine determined by the colorimetric procedure were low but accurately reflected the over-all characteristics of total drug excretion. Since in the present study comparisons are made relative to drug in solution, failure of the assay to measure the complete amount of material excreted at a given time is not of major importance. Similar assumptions must be made in accepting the results presented by others (23, 27, 37) who have investigated excretion of phenothiazine derivatives using a similar colorimetric procedure for assay of urine samples.

How well these results would describe the effects of adsorbents in general on the other amine drugs is unknown. It is probable that they would apply at least qualitatively to many other tertiary amines, especially to those of similar molecular weight, basicity, and adsorbability *in vitro*.

It should be pointed out that the results of this study apply to the situation in which the drug has been equilibrated with the adsorbent material prior to administration. Whether these results apply to nonequilibrated samples cannot be stated with certainty at this time.

The results of the experiment have achieved the original goals and have provided a sufficient survey of the subject. Further studies are in progress which should elucidate more facts pertaining to the effect of adsorbents on uptake of tertiary amines from the gastrointestinal tract.

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