Effect of Adsorbents on Drug Absorption: Importance of Preequilibrating Drug and Adsorbent

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Absorption of promazine from the human gastrointestinal tract is unaffected by small amounts of activated attapulgite and activated charcoal when drug and adsorbent are not equilibrated before administration of the test dose. These results are contrasted to previous experiments where the marked inhibition of absorption occurred with the same doses of drug and adsorbent in equilibrated systems.

PREVIOUS PUBLICATIONS (1, 2) have reported the effects of adsorbent materials on the absorption of promazine from the gastrointestinal tract of human subjects. Dosage forms which contained either activated attapulgite, 500 mg. or activated charcoal, 100 mg. equilibrated in an aqueous medium with 50 mg. promazine were studied (1). In such systems, both adsorbents interfered with absorption of promazine. Activated attapulgite slowed the initial rate of appearance of drug in the urine but there was no significant decrease in the total availability of promazine. Activated charcoal decreased both the rate and extent of absorption. The differences between the two adsorbents with respect to their effects on promazine absorption were related to similar differences in the way promazine was desorbed during *in vitro* experiments.

The effect on promazine absorption produced by a commercial antidiarrhea mixture containing activated attapulgite and pectin was studied (2) under conditions where the drug was not equilibrated with adsorbent prior to administering to the test subject. The experiment was designed to test whether previous observations (1) would be applicable under conditions more similar to clinical use. It was observed that the antidiarrhea mixture slowed the rate of absorption and also reduced the availability of promazine. In comparison to previous studies (1) the test subject was dosed with rather large quantities of adsorbent. Thus, the experiment did not specifically determine whether failure to equilibrate drug and adsorbent was important to effect on absorption. Research reported here was intended to determine whether preequilibration of drug and adsorbent is important to effects on drug absorption.

EXPERIMENTAL

Dosage Forms—Dosage forms consisted of promazine hydrochloride 50 mg. dissolved in 45 ml. distilled water. Suspensions were prepared to contain either 500 mg. activated attapulgite or 100 mg. activated charcoal in 50 ml. distilled water. If equilibrated, the activated attapulgite dosage form would contain 33.8 mg. promazine adsorbed. The activated charcoal would contain 23.5 mg. promazine adsorbed. These dosage forms were very nearly identical to those employed previously (1) except that the drug and adsorbent were not at equilibrium or, for that matter, even in contact with one another.

Adsorption Rate, In Vitro—A suspension of the adsorbent in distilled water as described under *Dosage Forms* was placed in a round-bottom flask. The flask was placed in a thermostat at 37.0° and fitted with a stirring apparatus. The rate of stirring was adjusted to 850 r.p.m. which was sufficient to maintain a homogeneous suspension of the adsorbent. The promazine solution described under *Dosage Forms* was then added and a timer started. Aliquots were removed from the flask at appropriate times and were immediately centrifuged. The concentration of promazine in the supernate was measured spectrophotometrically by a procedure described elsewhere (3). The total elapsed time between withdrawal of the aliquot and removal of supernate from the adsorbent was slightly less than 3 min.

In Vivo Tests—At the beginning of each experiment, the test subject first consumed the adsorbent suspension and immediately afterward, the solution of promazine. In all other respects the experimental method was identical to that reported previously (2). The results are summarized in Table I and in Fig. 1.

RESULTS AND DISCUSSION

Statistical comparisons of data in Table I were made by a t test for independent sample means. Two-tailed t values were used in assessing the significance of differences between means. In no case were the differences significant ($p > 0.10$) between mean values of promazine equivalents excreted at the various time intervals. Thus the results of *in vivo* tests show that within the experimental accuracy of the procedure neither adsorbent significantly affected promazine adsorption. This is in direct contrast to results obtained previously (1) where marked inhibition of absorption occurred with similar dosage forms when drug and adsorbent were preequilibrated before administration. Previous experiments with an antidiarrhea mixture (2) also showed an inhibition of promazine absorption.

Figure 2 shows results of *in vitro* studies assessing the rate of adsorption of promazine in a well-stirred system. It is noted that the majority of the interaction has taken place within the first 5 min.; however, some adsorption continues over a

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

Time After Administration of Test Dose, hr.	Mean Solution[b] Dosage Form	—Promazine Equivalents— Excreted Attapulgite[b] Dosage Form	Charcoal[b] Dosage Form
1	121 ± 78[c]	80 ± 23[c]	140 ± 152[c]
2	739 ± 265	773 ± 108	659 ± 164
3	1393 ± 303	1507 ± 279	1283 ± 269
4	1929 ± 411	2184 ± 451	1786 ± 539
5	2233 ± 429	2625 ± 567	2087 ± 547
6	2494 ± 480	2953 ± 416	2307 ± 543
8	2920 ± 496	3391 ± 851	2650 ± 518
10	3238 ± 452	3717 ± 958	2944 ● 554
12	3495 ± 434	3981 ± 1053	3147 ± 577
15	3801 ± 433	4319 ± 1152	3411 ± 636
18	4068 ± 448	4547 ± 1183	3617 ± 606
24	4429 ± 589	4895 ± 1213	3935 ± 503
30	4720 ± 747	4981 ± 1168	4114 ± 490
36	4906 ± 944	5091 ± 1084	4228 ± 528

[a] A promazine equivalent is defined as representing the amount of promazine which, if carried through the assay procedure, would give an identical assay value as the urine sample in question. Units of promazine equivalents are micrograms. [b] Mean of five experiments. [c] Plus-minus values represent the 95% confidence intervals about means.

considerably longer period. In the gastrointestinal tract where stirring is obviously much slower, one might expect a slower rate of interaction between drug and adsorbent. Even though most of the drug appears to be rapidly adsorbed *in vitro*, it also appears that under *in vivo* conditions, this is not of significance. Several other factors may be important in this situation.

In previous experiments with an antidiarrhea mixture (2) involving nonequilibrated conditions, large amounts of adsorbent were employed. In addition, the subject was predosed with adsorbent over a 12-hr. period. Under such conditions one

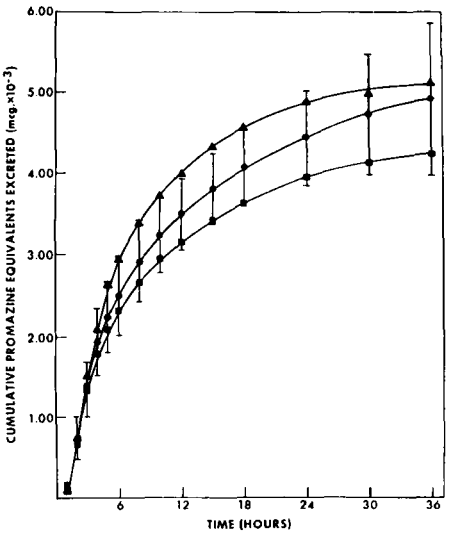

Fig. 1—Cumulative amounts of promazine equivalents excreted in the urine following administration of promazine hydrochloride (50 mg.) administered in simple aqueous solution. Key: ●, promazine administered alone; △, promazine administered immediately following 0.500 g. activated attapulgite in aqueous suspension; □, promazine administered immediately following 0.100 g. activated charcoal in aqueous suspension. Bars denote 95% confidence intervals about means of simple solution data.

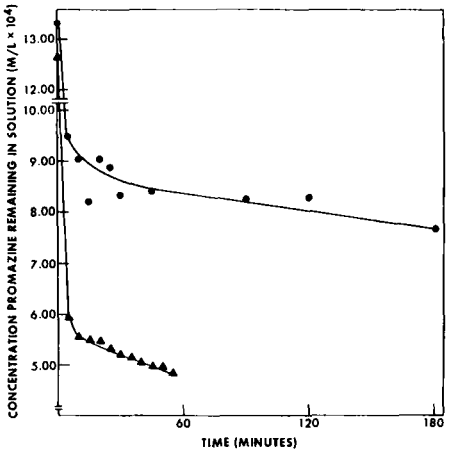

Fig. 2—Rate of adsorption of promazine by activated attapulgite and activated charcoal in a system stirred at 850 r.p.m. Theoretical concentration of promazine at time zero is 16.4 × 10^{-4} M. Key: ●, activated charcoal adsorbent; △, activated attapulgite adsorbent.

would expect adsorbent to be well distributed throughout the gastrointestinal tract. Mixing between drug and adsorbent would be facilitated by virtue of the probable widespread distribution of the relatively large amounts of adsorbent materials. In this experiment, however, a relatively small amount of adsorbent is employed. It is possible that mixing between drug and adsorbent in the gut is quite poor. Promazine appears to be quite rapidly absorbed, see data for drug in solution, and it is probable that significant amounts were absorbed before sufficient mixing could occur between drug and adsorbent. It may also be possible that the presence of high concentrations of hydrogen ion in the stomach retarded adsorption. Hydrogen ion was shown (3) to depress promazine adsorption by kaolin, talc, and activated charcoal.

CONCLUSIONS

It is concluded as a result of the experiments reported here that preequilibration between drug and adsorbent is an important factor with respect to the effect of an adsorbent on uptake of drug from the gastrointestinal tract. Maximal adsorbent effects should occur in the preequilibrated systems. In view of results obtained with the antidiarrhea mixture, it is suggested that the quantity of adsorbent administered may also be important. Predosing of adsorbent may also lead to greater effect on drug absorption in nonequilibrated systems.

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Keyphrases

Promazine absorption—adsorbent effect
Preequilibration—promazine, adsorbent
Absorption, effect—promazine-adsorbent preequilibration