# Enhanced Pseudoephedrine Absorption by Concurrent Administration of Aluminum Hydroxide Gel in Humans

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**Abstract** □ Effects of the nonsystemic antacid aluminum hydroxide gel, the adsorbent kaolin, and the systemic antacid sodium bicarbonate were tested on the absorption of the basic drug pseudoephedrine hydrochloride, administered in tablet form to six young adult males. The absorption rate of pseudoephedrine, measured by its urinary excretion rate, was reliably increased by the aluminum hydroxide gel, probably because the antacid raised the GI pH, thereby increasing the amount of pseudoephedrine available in the nonionized form, which is more readily absorbable. On the other hand, the absorption rate of pseudoephedrine was decreased by kaolin, probably because adsorption competed with absorption. Sodium bicarbonate had no reliable effect, but pseudoephedrine absorption may have been underestimated because the pH was above 5.5 in most urine collections, thus possibly permitting tubular reabsorption of the pseudoephedrine. These drug interactions may provide helpful information for achieving more precise control of the effects of pseudoephedrine.

**Keyphrases** □ Pseudoephedrine absorption—effect of concurrent administration of antacids, man □ Antacids—effect on pseudoephedrine absorption, man □ Aluminum hydroxide gel—enhancement of pseudoephedrine absorption, man □ Absorption rates, pseudoephedrine—effect of concurrent antacid administration, man

Antacids, when administered concurrently with basic drugs, could increase their absorption by altering the pH of the GI milieu. The increased pH caused by antacids permits a greater fraction of the drug to exist in the nondissociated, more lipid-soluble form, which is the more readily absorbed species. According to the pH-partition hypothesis of Shore *et al.* (1), this would lead to more rapid and complete absorption of basic drugs when administered concurrently with antacids.

However, such enhanced absorption may not be realized if significant quantities of the drug were adsorbed onto the surface of the undissolved, dispersed, solid particles usually present in the GI tract subsequent to the administration of nonsystemic antacids. These nonsystemic antacids include calcium carbonate, magnesium hydroxide, magnesium oxide, and aluminum hydroxide. The insolubility of some of these, such as the aluminum hydroxide gel, is a desirable property of the antacid, because a fraction of the sedimented unreacted excess tends to remain in the stomach to yield a sustained effect (2).

The adsorption of promazine and other phenothiazine derivatives by dispersed solid particles was demonstrated *in vitro* and also *in vivo* when drug absorption in humans was significantly reduced (3–5). Forrest *et al.* (6) showed that the absorption of another phenothiazine, chlorpromazine, was significantly retarded when the antacid, aluminum hydroxide with magnesium hydroxide suspension[1], was regularly administered to human subjects concurrently with the chlorpromazine therapy. The objective of this study was to determine whether an altered absorption profile might also occur for a basic drug, pseudoephedrine hydrochloride, when administered concurrently with oral antacid therapy in humans.

[1] Aludrox, Wyeth Laboratories, Philadelphia, PA 19101

**Table I**—Mean Cumulative Amounts (Milligrams ± Standard Error), for Six Subjects, of Pseudoephedrine Hydrochloride Excreted for Each of Four Treatments

| Hours | Control (No Antacid) | Aluminum Hydroxide Gel | Kaolin | Sodium Bicarbonate |
|---|---|---|---|---|
| 0.75 | 0.4 ± 0.13 | 2.2 ± 0.44[a] | 0.2 ± 0.12 | 0.8 ± 0.30 |
| 1.50 | 4.3 ± 0.64 | 7.0 ± 0.45[b] | 2.4 ± 0.70[c] | 4.2 ± 0.74 |
| 2.25 | 9.4 ± 0.74 | 13.2 ± 1.35[a] | 6.1 ± 1.25[c] | 8.8 ± 1.47 |
| 3 | 13.2 ± 1.16 | 16.6 ± 1.89[a] | 11.0 ± 1.61 | 12.8 ± 1.81 |
| 4 | 18.5 ± 1.31 | 21.3 ± 1.53 | 16.3 ± 1.86 | 16.2 ± 2.16 |
| 6 | 25.8 ± 2.56 | 28.2 ± 3.14 | 24.2 ± 2.46 | 21.8 ± 1.70 |
| 8 | 34.7 ± 2.99 | 38.2 ± 4.64 | 31.2 ± 2.15 | 26.8 ± 1.34 |
| 12 | 45.1 ± 4.12 | 44.6 ± 4.99 | 39.0 ± 3.72 | 32.7 ± 2.07[c] |
| 24 | 57.6 ± 2.22 | 57.8 ± 1.18 | 52.2 ± 3.06[a] | 54.6 ± 1.77 |

[a] $p < 0.05$ for differences from control at same time. [b] $p < 0.01$ for differences from control at same time. [c] $p < 0.10$ for differences from control at same time.

## EXPERIMENTAL

Pseudoephedrine hydrochloride was administered in a dose of 60 mg. in the form of two 30-mg. tablets[2]. This dose was administered simultaneously with three different antacid or adsorbent treatments: (*a*) 30 ml. aluminum hydroxide gel[3]; (*b*) 5 g. sodium bicarbonate[4], administered as five 1-g. capsules; and (*c*) 30 ml. of a 30% kaolin[5] suspension (which also contained 0.2% benzoic acid, 0.1% sodium saccharin, 0.2% glycerin, and less than 0.1% peppermint oil).

The subjects were six normal males, all adults with a mean age of 23.2 years and a mean weight of 78 kg. Each subject received each of four treatments consisting of: (*a*) drug only, (*b*) drug and aluminum hydroxide gel, (*c*) drug and kaolin suspension, and (*d*) drug and sodium bicarbonate. A minimum of 1 week elapsed between treatments, and each subject was assigned a different treatment sequence to balance any possible sequential effects. Subjects received no other drugs, including vitamins, during this test period of several weeks. Water was allowed up to 1 hr. before the 8:00 a.m. treatment, but the subjects fasted from food and beverage from suppertime (6:00 p.m.) of the day preceding the test until noon of the next day, 4 hr. after the treatment, to minimize the effect of food on absorption.

After voiding completely, subjects took the prescribed treatment, with 180 ml. of water, at 8:00 a.m. Complete voids were then collected at 0.75, 1.50, 2.25, 3, 4, 6, 8, 12, and 24 hr. after the 8:00 a.m. treatment. Any voids occurring between these times were collected and pooled at the proper collection times. The subjects drank 180 ml. of water after each void from the 0.75- to the 4-hr. interval.

Maintaining an acidic urine was considered important to minimize possible reabsorption of pseudoephedrine in the kidney tubules and thus alter the observed urinary excretion pattern of pseudo-

[2] Sudafed tablets, Burroughs Wellcome Co., Research Triangle Park, NC 27709
[3] Amphojel, Wyeth Laboratories, Philadelphia, PA 19101
[4] USP grade, Mallinckrodt Chemical Works, St. Louis, MO 63160
[5] NF grade, Ruger Chemical Co., Inc., Hillside, NJ 07205

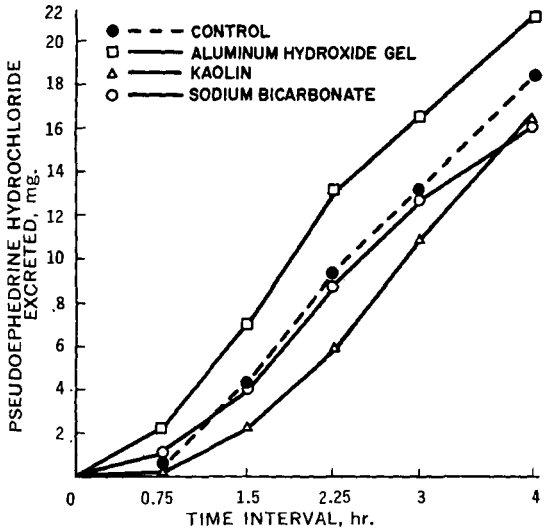


**Figure 1**—*Effect of the various treatments on the mean cumulative urinary excretion values of pseudoephedrine hydrochloride for six subjects during the first 4 hr. following its oral administration.*

ephedrine and its metabolites (7, 8). Pseudoephedrine excretion can be markedly decreased by high urine pH, especially above pH values of about 6.0 (9), and tubular reabsorption apparently can be avoided by maintaining urine pH at about 5.0–5.5, with no effect of urinary volume if the urine is acidic (7). Therefore, a 1-g. tablet of enteric-coated ammonium chloride[6], for the purpose of urine acidification, was administered five times: at 3:00 p.m., 6:00 p.m., 9:00 p.m., bedtime of the day preceding the test, and noon of the test day. Ammonium chloride was administered to all subjects in all studies.

The pseudoephedrine hydrochloride content of the urine was measured by a UV spectrophotometric assay, modified from the procedure of Heimlich *et al.* (10) for the phenethanolamine, phenylpropanolamine. The only modification of their procedure was a reduction of the agitation time of the samples from 10 to 5 min., which was found to yield identical results. Absorbance differences[7] were found to follow Beer's law in the concentration range studied.

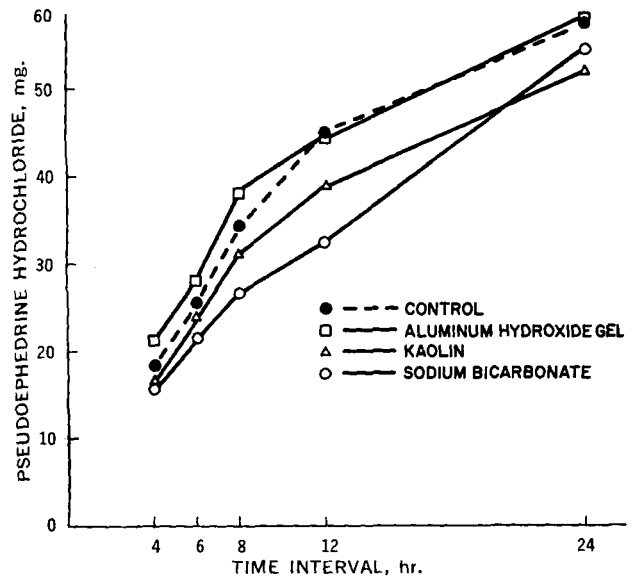


**Figure 2**—*Effect of the various treatments on the mean cumulative urinary excretion values of pseudoephedrine hydrochloride for six subjects during the 24-hr. period following its oral administration.*

[6] Eli Lilly & Co., Indianapolis, IN 46206
[7] Determined on a Beckman model DB-G spectrophotometer.

**Table II**—Urinary pH (Mean ± Standard Error) at Each Specified Time Interval for Six Subjects

| Hours | Control (No Antacid) | Aluminum Hydroxide Gel | Kaolin | Sodium Bicarbonate |
|---|---|---|---|---|
| 0.75 | 5.2 ± 0.14 | 5.2 ± 0.12 | 5.2 ± 0.08 | 5.4 ± 0.34 |
| 1.50 | 5.1 ± 0.13 | 5.4 ± 0.21 | 5.4 ± 0.14 | 6.4 ± 0.54[a] |
| 2.25 | 5.0 ± 0.13 | 5.3 ± 0.17 | 5.4 ± 0.19 | 6.3 ± 0.51[a] |
| 3 | 5.2 ± 0.21 | 5.2 ± 0.22 | 5.5 ± 0.19 | 6.3 ± 0.46[a] |
| 4 | 5.0 ± 0.14 | 5.2 ± 0.16 | 5.5 ± 0.25 | 5.8 ± 0.34[a] |
| 6 | 5.0 ± 0.07 | 5.1 ± 0.12 | 5.4 ± 0.20 | 5.7 ± 0.33[a] |
| 8 | 5.2 ± 0.11 | 5.2 ± 0.13 | 5.3 ± 0.16 | 5.7 ± 0.31 |
| 12 | 5.2 ± 0.12 | 5.2 ± 0.11 | 5.3 ± 0.11 | 5.5 ± 0.11 |
| 24 | 5.4 ± 0.21 | 5.3 ± 0.09 | 5.3 ± 0.08 | 5.4 ± 0.04 |

[a] $p < 0.10$ for difference from control at same time.

Urine pH and volume were determined at the time of sample collection.

The data were summarized in terms of average cumulative quantities of pseudoephedrine hydrochloride excreted (in milligrams) and average urinary pH levels at each of the nine time periods after each of the four treatments. Each average was accompanied by its standard error; but since each of the six subjects was tested with all treatments, the statistical test was by the method of paired observations (11), comparing each treatment with the control at each time interval. Therefore, statistical significance depended on the difference between pairs of treatments, calculated separately for each subject, rather than on the standard errors calculated separately for each time interval and treatment.

## RESULTS

Table I shows the average cumulative quantities of pseudoephedrine hydrochloride (milligrams ± standard error) excreted by the six subjects at each of the nine time periods after each of the four treatments. Statistically significant differences at the 5 or 1% level were found between the control (drug only) and the aluminum hydroxide gel treatments at each of the first four time periods (0.75 hr.: $t = 3.83$; 1.5 hr: $t = 6.30$; 2.25 hr.: $t = 3.38$; 3 hr.: $t = 2.79$, $df = 5$ in each test). Figure 1 portrays the results for the first 4 hr. In the first 0.75-hr. period, the excretion with the aluminum hydroxide gel treatment was 450% higher than the control. The sodium bicarbonate treatment also tended to be elevated at the 0.75-hr. interval, but the difference was not statistically significant. In contrast, the values for the kaolin treatment were lower than for the control, differing at the 10% level for the second and third time periods (1.5 hr.: $t = 2.08$; 2.25 hr.: $t = 2.09$; $df = 5$ in both tests) and at the 5% level for the final time period (24 hr.: $t = 2.64$, $df = 5$).

Figures 1 and 2 show that beginning at the 4-hr. period, the sodium bicarbonate treatment retarded cumulative excretion (12 hr.: $t = 2.07$, $df = 5$, $p < 0.10$). At the end of 24 hr., the percentage cumulative recovery of the 60 mg. pseudoephedrine ranged from 87% (kaolin) to 96% (aluminum hydroxide). The percentages were all close to complete recovery, with no statistically significant difference between any of the conditions.

Table II summarizes the urinary pH values (mean ± standard error) of the six subjects at each time period after each of the four treatments. No statistically reliable differences were found in urine pH values between the control and the aluminum hydroxide gel or kaolin treatments. Differences in urine pH values were found between the control and the sodium bicarbonate treatments, at the 10% level of statistical reliability, at the second through sixth time periods (1.5 hr.: $t = 2.28$; 2.25 hr.: $t = 2.56$; 3 hr.: $t = 2.26$; 4 hr.: $t = 2.45$; 6 hr.: $t = 2.37$, $df = 5$ in each test).

## DISCUSSION

This study has demonstrated, with aluminum hydroxide gel, the ability of an antacid to increase the GI absorption rate of a basic drug, which has been suggested as a potential drug interaction (12). The increased GI absorption rate of pseudoephedrine, indicated by the increased rate of urinary excretion, was probably due to the

increase in the pH of the GI juices caused by the antacid aluminum hydroxide gel. This would be expected to increase the fraction of pseudoephedrine present in the nondissociated (absorbable) form. When administered in a liquid dosage form, antacids initiate their action within about 5–15 min. (2) and, being viscous gel-type preparations, move slowly through the GI tract, thus maintaining their effect for a substantial time. The urinary excretion data suggest that the aluminum hydroxide gel enhanced absorption fairly rapidly, and this effect continued for 3 hr. throughout the first four collection periods (Table I).

The aluminum hydroxide with magnesium hydroxide suspension is an antacid similar in composition and properties to the aluminum hydroxide gel but containing in addition some magnesium hydroxide. Concurrent oral administration of this drug with phenothiazines, which like pseudoephedrine are basic drugs, has been observed to cause a decrease in phenothiazine excretion (6). With pseudoephedrine in the present experiment, the adsorption that apparently retarded absorption of the phenothiazines seems to have been negligible or overridden by the effect of increased gastric pH. Perhaps the well-known adsorptive characteristics of the phenothiazines (3–5) were of sufficient magnitude to overcome the effects of increased gastric pH, which could tend to increase the fraction of phenothiazine present in the absorbable form.

Adsorption probably accounts for the trend toward a decreased rate of excretion of pseudoephedrine, which was observed for subjects on the kaolin treatment. The results obtained for the first 3 hr., when compared with the excretion levels of pseudoephedrine produced by the other three treatments, indicate the more powerful adsorbent qualities of kaolin; the peak excretion rate occurred at the 3-hr. collection period with the kaolin treatment as compared with the 2.25-hr. collection period with the control (Table I).

Results with the sodium bicarbonate treatment give evidence for effects of its interference with urine pH. During the first collection period at 0.75 hr., when urine pH was below 5.5, sodium bicarbonate produced higher levels than the control or kaolin. As with aluminum hydroxide gel, this was probably due to the increase in gastric pH. The levels of pseudoephedrine might have been higher if the sodium bicarbonate had been administered in a solution dosage form because of the quicker onset of action than with capsules. By the time of the second collection (1.5 hr.), the systemic antacid sodium bicarbonate had been absorbed, raising the urine pH to a level where pseudoephedrine could be reabsorbed in the kidney tubules, thereby possibly decreasing the urinary excretion of pseudoephedrine and its metabolites. The elevated pH and retarded pseudoephedrine excretion persisted through the 12-hr. interval after treatment; at 24 hr. the pH had returned to normal, with enhanced pseudoephedrine excretion during the last 12 hr. Higher doses of ammonium chloride pretreatment might prevent this increase in urine pH, thereby enabling the use of the pseudoephedrine excretion level as a valid measure of the effect of sodium bicarbonate on the absorption rate.

The results of this study indicate that antacid substances, which are commonly coadministered with certain basic drugs like pseudoephedrine, may indeed affect the rate of GI absorption, apparently through pH alteration in GI fluids. The most clinically significant effect of this antacid–drug interaction is probably the more rapid onset of therapeutic activity.

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