Effect of Concomitant Administration of Magnesium Trisilicate on GI Absorption of Dexamethasone in Humans

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Abstract □ The oral absorption of dexamethasone in humans was compared to its absorption when coadministered with magnesium trisilicate. The bioavailability of dexamethasone was estimated by measuring the suppressive effect of the drug on the daily excretion of endogenous steroids. Administration of 1 mg of dexamethasone to six healthy male volunteers significantly decreased the urinary excretion of 11-hydroxycorticosteroids. However, the coadministration of magnesium trisilicate with dexamethasone decreased its absorption, as indicated by the increased urinary excretion of 11-hydroxycorticosteroids. The decrease in absorption was attributed to drug adsorption on the antacid surface. These results confirm previous *in vitro* findings.

Keyphrases □ Dexamethasone—absorption in humans, effect of concomitant administration of magnesium trisilicate □ Magnesium trisilicate—effect on dexamethasone absorption, concomitant administration in humans □ Absorption—dexamethasone in humans, effect of concomitant administration of magnesium trisilicate □ Glucocorticoids—dexamethasone, absorption in humans, effect of concomitant administration of magnesium trisilicate □ Antacids—magnesium trisilicate, effect on dexamethasone absorption, concomitant administration in humans

Corticosteroids, being ulcerogenic, are sometimes administered concomitantly with one or more commonly used antacids. Previous *in vitro* experiments (1) showed that a depletion in the concentration of several corticosteroids from their solution was observed in the presence of various antacids or adsorbents. Of the antacids tested, magnesium trisilicate exhibited the highest adsorptive capacity and a rather high affinity for the drugs. Eluting solutions of various pH values simulating the GI tract pH showed no significant release of the corticosteroids from the antacid surface.

Since no information is available on the effect of coadministration of antacids on corticosteroid bioavailability, the previously mentioned *in vitro* interactions were investigated *in vivo*.

BACKGROUND

Synthetic corticosteroid analogs produce a total or partial cessation of adrenal gland activity (2, 3). The decreased function of the gland can be tested by estimating the amount of endogenous corticosteroids secreted in the plasma or excreted in the urine. This principle was useful (2–6) in detecting the absorption of synthetic corticosteroids. Upon oral administration of triamcinolone to human subjects, the production of endogenous corticosteroids decreased, as indicated by their plasma cortisone and urinary 17-hydroxycorticosteroids content (2). On the other hand, urine volume increased. These changes were dose dependent.

The same principle was adopted (4–6) to test the percutaneous absorption of steroids from topically applied preparations. The determination of endogenously produced corticosteroids excreted in the urine can, therefore, be taken as an indication of the bioavailability of synthetic analogs.

The objective of the present work was to study the effect of coadministration of magnesium trisilicate on dexamethasone bioavailability in human subjects, as indicated by their natural corticosteroid daily excretion. Dexamethasone was selected because it was reported to be an effective and potent suppressor of adrenal gland activity (7). Moreover, it exhibited a rather strong interaction *in vitro* with magnesium trisilicate (1).

EXPERIMENTAL

Materials—Hydrocortisone acetate[1], 0.5-mg dexamethasone tablets[2], and magnesium trisilicate (BP) were used.

Methods—Six healthy male volunteers, capable of informed consent, participated in this crossover study. No hypoadrenal or abnormally hyperadrenal subjects were included. The subjects received no corticosteroid therapy within at least 4 weeks before the study and no other drugs during it.

None of the subjects was exposed to recognizable stressful procedures. Food and fluid intake were kept as uniform as possible. The 24-hr urinary excretion of endogenous corticosteroids was determined fluorometrically[3] according to Mattingly (8) subsequent to each of the following treatments: A, 24-hr urine collection with no drug administration; B, administration of 1 mg of dexamethasone with 100 ml of water; and C, concomitant administration of 1 mg of dexamethasone and 5 g of magnesium trisilicate with 100 ml of water.

At least 1 week elapsed between Treatments B and C for any subject. A treatment day began and ended at 11 pm. All administrations of the drug or the drug-antacid combination were at 11 pm (9). At that time, the subjects also emptied their urinary bladders and started to collect urine samples in dark-colored bottles, which were kept in a cool place until urine analysis.

The volume of the thoroughly mixed 24-hr urine of each subject was recorded. The normal daily excretion of endogenous corticosteroids in Subject SK was estimated twice at 1-week intervals. The response to a smaller dose of dexamethasone (0.5 mg) also was studied in the same subject. The steroid values reported are the averages of duplicate determinations.

RESULTS AND DISCUSSION

The daily excretion of endogenous corticosteroids, selected as a measure of the biological availability of dexamethasone in the absence and presence of magnesium trisilicate and referred to for convenience as 11-hydroxycorticosteroids, is shown in Table I. These 11-hydroxycorticosteroids are responsible for the particular reaction in the fluorescent test that is negative for synthetic analogs (8). The amount of free hydrocortisone in the urine, which changes rapidly with changes in adrenal activity, partly determines the magnitude of the 11-hydroxycorticosteroid excretion (8, 10). Therefore, 11-hydroxycorticosteroids are expressed in terms of hydrocortisone equivalents. Similarly to previous reports (8), a linear relationship (between 20 and 100 μg/100 ml) existed in the present study between the intensity of fluorescence and the concentration of hydrocortisone acetate standard.

The urinary excretion of 11-hydroxycorticosteroids for the different subjects (Treatment A) ranged from 250 to 483 μg/24 hr with a mean value of 340 μg/24 hr (Table I). Variation between subjects in the amount of 11-hydroxycorticosteroids excreted, with a relatively high standard deviation, also was found by Mattingly (8). This result was attributed to the different physiological states of individuals. However, the values observed (Table I) fell within normal limits; consequently, the correlation between the urinary excretion of 11-hydroxycorticosteroid values and adrenal activity is acceptable (8). No significant week-to-week variation of 11-hydroxycorticosteroid excretion (360 and 340 μg/24 hr) was observed in Subject SK.

The effects of both 0.5 and 1 mg of dexamethasone administered at 11 pm [period coinciding with the least activity of the adrenal gland (9)] on the excretion of 11-hydroxycorticosteroids were tested in Subject SK. The level of 11-hydroxycorticosteroids in the urine decreased from 340

[1] El-Kahira Pharmaceutical and Chemical Co., Cairo, Egypt.
[2] Dexa-Scheroson, Schering A.G., Berlin, Germany.
[3] Hitachi Perkin-Elmer model 204 fluorescence spectrophotometer.

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Table I—Effect of the Coadministration of Magnesium Trisilicate on the Absorption of Dexamethasone as Determined by the Urinary Excretion of 11-Hydroxycorticosteroids

Subject	Age, years	Weight, kg	Treatment A Excretion, μg/24 hr[a]	Treatment A Urine Volume, ml/24 hr	Treatment B Excretion, μg/24 hr[a]	Treatment B Urine Volume, ml/24 hr	Treatment C Excretion, μg/24 hr[a]	Treatment C Urine Volume, ml/24 hr
SK	44	90	340	1410	37	1735	200	1510
HS	32	60	285	1390	80	1170	280	840
MB	35	60	250	1041	160	1265	220	1115
HB	36	80	380	1500	200	1100	286	780
EB	36	65	483	850	263	1550	480	1160
AH	52	70	300	990	50	1190	240	1050
Mean			340	1197	132	1335	284	1076
SD			83.4	269.1	90.6	250.8	101.5	261.1
Significance[b]					99.9%	N.S.	N.S.	N.S.
Significance[c]							99.5%	99.5%

[a] Concentration of 11-hydroxycorticosteroids in the urine in micrograms per 24 hr expressed in terms of hydrocortisone. [b] Paired *t*-test *versus* Treatment A. [c] Paired *t*-test *versus* Treatment B.

to 117 μg/24 hr with 0.5 mg and to 37 μg/24 hr with 1 mg of dexamethasone. Consequently, 1 mg of the drug was used in Treatment B.

The administration of 1 mg of dexamethasone to each subject (Treatment B) significantly decreased the 11-hydroxycorticosteroid content of the urine (Table I). The difference was statistically significant (>99.9% level). The average amount excreted in 24 hr was approximately 39% of the average amount excreted in the same time when no drug was administered. The administration of dexamethasone in a single oral dose at 11 pm was reported (9) to decrease the level of endogenous corticosteroids well below normal limits. This effect persisted for at least 24 hr, although the dexamethasone biological half-life in plasma is only 170–210 min (11). Normal levels are usually reached again after 24–48 hr (2, 9). In the present study, an increase of urine output in four of six subjects also was observed. However, such an increase was not statistically significant (six subjects).

The results of Treatment C (Table I) show that the coadministration of magnesium trisilicate with dexamethasone decreased the absorption of the latter as reflected by the amounts of 11-hydroxycorticosteroids excreted by the different individuals. The average quantity of 11-hydroxycorticosteroids excreted in the urine after Treatment C was 83.2% of that in Treatment A. On the other hand, the 11-hydroxycorticosteroid excretion in Treatment C was statistically significantly different (>99.5% level) from that in Treatment B. Moreover, urine volume in all subjects decreased in Treatment C compared to Treatment B.

The previous effects indicate a reduced bioavailability of dexamethasone in the presence of magnesium trisilicate, probably due to an adverse interaction in the GI tract leading to a decrease in the amount of the free drug available for absorption. Steroids have been reported to be absorbed by diffusion (12). The more lipoidal the compound, the greater will be its absorption rate. Similar to other steroids, dexamethasone is a nonionizing compound and, consequently, the alkalinity of magnesium trisilicate will not affect its absorption (12). For the same reason, the dissolution rate of the drug will not be influenced. Drug adsorption on the antacid surface seems the most probable cause of the reduced bioavailability (1).

From the present results, it can be concluded that a significant decrease in the bioavailability of dexamethasone results if the drug is coadministered with magnesium trisilicate. These *in vivo* results reflect previous *in vitro* findings.

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