Effect of Antacids on Activity of Oral Hypoglycemics

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Abstract □ The effect of some antacids on the dissolution and hypoglycemic activity of acetohexamide, tolazamide, and tolbutamide tablets was investigated, as was the adsorption of the three drugs onto the antacids. The dissolution rates of the three drugs in the presence of magnesium oxide, aluminum hydroxide, magnesium carbonate, and calcium carbonate increased (0.5–1 hr) and then plateaued or decreased (1–3 hr). Magnesium trisilicate directly suppressed the dissolution of the three drugs. The antacids reduced the hypoglycemic activity of tolbutamide in the following order: magnesium trisilicate > magnesium oxide > aluminum hydroxide > magnesium carbonate > calcium carbonate. The same order occurred for the first three antacids with acetohexamide and tolazamide. Decreased hypoglycemic activity of the drugs may have been due to their adsorption to the coadministered antacids.

Keyphrases □ Antacids—effect on oral hypoglycemics, dissolution, adsorption, hypoglycemic activity □ Hypoglycemics, oral—effect of antacids, dissolution, adsorption, hypoglycemic activity □ Dissolution—effect of antacids on oral hypoglycemics, adsorption, hypoglycemic activity □ Adsorption—effect of antacids on oral hypoglycemics, dissolution, hypoglycemic activity

The effect of antacids on the dissolution and bioavailability of drugs has been studied extensively (1–7). Drug–antacid interactions may be caused by several effects. Antacids can change the absorption rate by altering the ionization state of the drug molecule (1, 2), delaying stomach emptying (3), changing the fluid pH in the body (4), and adsorbing drugs (5–7). In addition to affecting bioavailability, a chemical or strong physical interaction between the antacid and drug can have important ramifications in therapy.

Since no information is available on the effect of coadministration of antacids on the bioavailability of oral hypoglycemics, the present study investigated the influence of commonly used antacids on the dissolution and hypoglycemic activity of acetohexamide, tolazamide, and tolbutamide. The adsorption of these drugs onto some antacids also was studied.

EXPERIMENTAL

Materials—Acetohexamide[1], tolazamide[2], and tolbutamide[3] tablets were used in the dissolution studies. Powdered acetohexamide[1], tolazamide[2], tolbutamide[3], magnesium trisilicate[4], magnesium carbonate[5], magnesium oxide[6], aluminum hydroxide[7], and calcium carbonate[7] were used as supplied in the adsorption and hypoglycemic activity studies.

Dissolution Testing—The dissolution rates of acetohexamide and tolbutamide tablets were tested according to USP XIX (6) using the USP rotating-basket dissolution apparatus[8]. Tolazamide tablets were tested similarly, but the absorbance[9] was measured at 262 nm. Tablets of the three drugs were tested for dissolution in their respective medium containing one antacid (1%).

Measurement of Blood Glucose in Rats—The effect of orally administered acetohexamide, tolazamide, and tolbutamide with and without antacids on blood glucose levels of adult male albino rats[10] was studied. Rats (180–250 g) were fasted 24 hr before the experiment but were allowed free access to water.

The effect of antacids on the hypoglycemic activity of tolbutamide was studied using six groups of 15 rats each. One group was given tolbutamide suspension (1%) in water containing 0.2% methylcellulose in a 200-mg/kg dose. Five other groups were given equivalent doses of tolbutamide but in the presence of 1% of the antacid.

Each group of animals was divided into five subgroups, each containing three rats. Each subgroup was kept in a separate cage and allowed free access to water. At 0.5, 1, 2, 3, 4, and 5 hr, the animals were sacrificed. A blood sample was taken from each rat and analyzed for blood glucose content (8). One group of animals was used as the control. The mean blood glucose levels of each subgroup were compared, and the differences were tested for significance by analysis of variance and a Student t test.

The effect of magnesium trisilicate, magnesium oxide, and aluminum hydroxide on the blood glucose level following administration of acetohexamide and tolazamide was tested in the same manner.

Adsorption Experiments—The drugs were dissolved in the fluid used for dissolution testing, and 50 ml of the solution containing 2.5–40 mg of the drug was placed in 100-ml glass-stoppered conical flasks containing the antacid (1%). The drug–antacid solution was equilibrated at 37 ± 0.1° and shaken mechanically for ~24 hr to reach equilibrium. After centrifugation, the drug concentration remaining in the supernate was determined spectrophotometrically at the respective wavelength used for dissolution testing against a blank. Three replicate runs were made, and the results were averaged.

Desorption—The desorption of adsorbed drugs was determined at 37 ± 0.5° in the fluid used for dissolution testing as described previously (6). Three experiments were performed in each case, and the average percent desorbed was calculated.

The least significant difference procedure was used to assess the difference between two means, and the completely randomized designs–analysis of variance technique was used to evaluate the level of significance between multiple determinations (9).

RESULTS AND DISCUSSION

Figure 1 shows the effect of the five antacids on the dissolution rates of acetohexamide, tolazamide, and tolbutamide tablets. With the exception of magnesium trisilicate, the antacids exhibited a minor increase in dissolution (0.5–1 hr) and then a plateau with a slight decrease toward the end. Magnesium trisilicate moderately decreased the dissolution rates of the three drugs. After 3 hr, the amounts of tolbutamide in solution were 82.5, 81, 66, 60, and 10% in the presence of calcium carbonate, magnesium carbonate, aluminum hydroxide, magnesium oxide, and magnesium trisilicate, respectively, as compared to 100% in the absence of these antacids. The amounts of acetohexamide, tolbutamide, and tolazamide in solution at 3 hr were 4.5, 40, and 30%, respectively, in the presence of magnesium trisilicate; at that time, complete dissolution of the three drugs was attained in the absence of antacids.

Figure 2 illustrates the effect of the tested antacids on the hypoglycemic activity of acetohexamide, tolazamide, and tolbutamide. The mean blood glucose concentration of 24-hr fasted rats was 73.25 ± 2.55 mg/100 ml and was significantly higher than all treated groups (Student t test, $p < 0.05$).

The reduction in blood glucose levels was lessened in the system containing the antacid (Fig. 2). At 2 hr, the mean blood glucose level of rats taking tolbutamide alone was 2.8 mg/100 ml; it increased to 18.3, 15.3,

[1] Dimelor tablets 1843 G-27023F, Eli Lilly and Co., Basingstoke, England.
[2] Tolinase tablets, The Upjohn Co., Kalamazoo, Mich.
[3] Rastinon tablets 586A474, Hoechst, Frankfurt, West Germany.
[4] BDH, Poole, England.
[5] Mayer & Baker, Dogenham, England.
[6] Hopkin & Williams, Essex, England.
[7] Riede De Haenog, Hanover, West Germany.
[8] Erweke-Heausenstamn Kr, Offenbach/Main, West Germany.
[9] Varian Techtron, UV-VIS, model 635.
[10] Sprague-Dawley, Agouzo Strain, Egypt.

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Table I—Blood Glucose Levels at 2 hr following a 200-mg/kg Single Oral Dose of Tolbutamide Aqueous Suspension Alone and Coadministered with Antacids

	Blood Glucose Level (n = 3), mg/100 ml					
	Tolbutamide	Tolbutamide plus Magnesium Carbonate	Tolbutamide plus Magnesium Oxide	Tolbutamide plus Magnesium Trisilicate	Tolbutamide plus Aluminum Hydroxide	Tolbutamide plus Calcium Carbonate
Mean	2.80	10.5	15.3	18.3	12.5	8.4
SD	1.54	4.32	0.85	3.27	2.72	2.59
CV, %	55.00	41.14	5.56	17.87	21.76	30.83

Analysis of Variance

Source of Variation	Degrees of Freedom	Sum of Squares	Mean of Squares	F^a Ratio
Among dosage forms	2	443.22	221.61	35.69
Error	15	93.16	6.21	
Total	17			

[a] Significance at the 5% level.

Table II—Blood Glucose Levels at 2 hr following a 200-mg/kg Single Oral Dose of Acetohexamide Suspension Alone and Coadministered with Antacids

	Blood Glucose Level (n = 3), mg/100 ml		
	Acetohexamide	Acetohexamide plus Magnesium Trisilicate	Acetohexamide plus Aluminum Hydroxide
Mean	22.5	45.50	37.50
SD	8.68	5.19	4.20
CV, %	38.58	11.14	11.20

Analysis of Variance

Source of Variation	Degrees of Freedom	Sum of Squares	Mean of Squares	F^a Ratio
Among dosage forms	2	818	409	10.24
Error	6	239.66	39.94	
Total	8	1057.66		

[a] Significance at the 5% level.

12.5, 10.5, and 8.4 mg/100 ml in the presence of magnesium trisilicate, magnesium oxide, aluminum hydroxide, magnesium carbonate, and calcium carbonate, respectively. Analysis of variance for the results in Table I showed a highly significant difference ($p < 0.05$) in the 2-hr mean blood glucose levels among the tested dosage forms. At 2 hr, there was a significant difference (least significant difference procedure, $p < 0.05$) between the mean blood glucose when tolbutamide was administered alone and when it was administered with each tested antacid. This result indicates that a decreased absorption of tolbutamide occurred in the presence of each tested antacid.

The antacids reduced the hypoglycemic activity of acetohexamide and tolazamide in the order magnesium trisilicate > aluminum hydroxide. At 2 hr, the respective mean blood glucose levels of rats taking acetohexamide alone was 22.5 mg/100 ml, which increased to 45.5 and 37.5 mg/100 ml in the presence of magnesium trisilicate and aluminum hydroxide, respectively. At 2 hr, the mean blood glucose level of rats taking tolazamide was 6.5 mg/100 ml, which increased to 18 and 13 mg/100 ml in the presence of magnesium trisilicate and aluminum hydroxide, respectively.

Analysis of variance for the data of the 2-hr mean blood glucose levels of rats administered acetohexamide alone and with the tested antacids

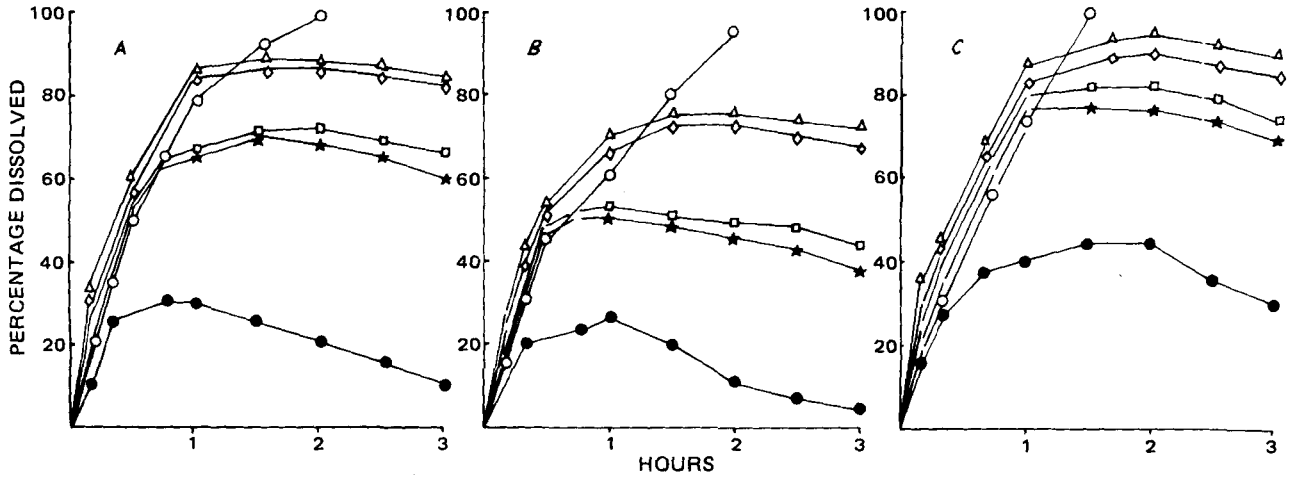

Figure 1—*Effect of certain antacids on the dissolution of acetohexamide (A), tolbutamide (B), and tolazamide (C). Key: ○, without antacid; and ●, ★, □, ◇, and △, in the presence of magnesium trisilicate, magnesium oxide, aluminum hydroxide, magnesium carbonate, and calcium carbonate, respectively.*

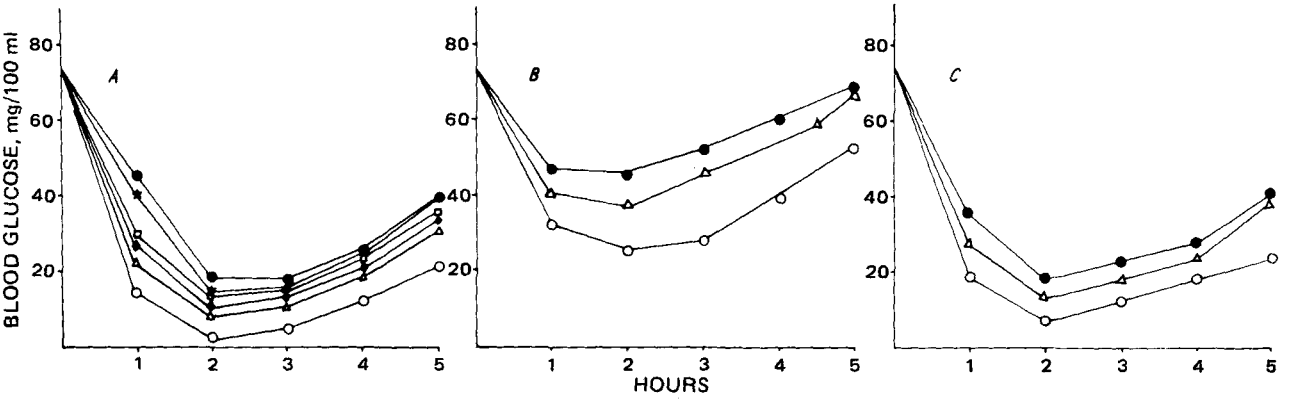

Figure 2—*Effect of certain antacids on the hypoglycemic activity of tolbutamide (A), acetohexamide (B), and tolazamide (C). Key: see Fig. 1.*

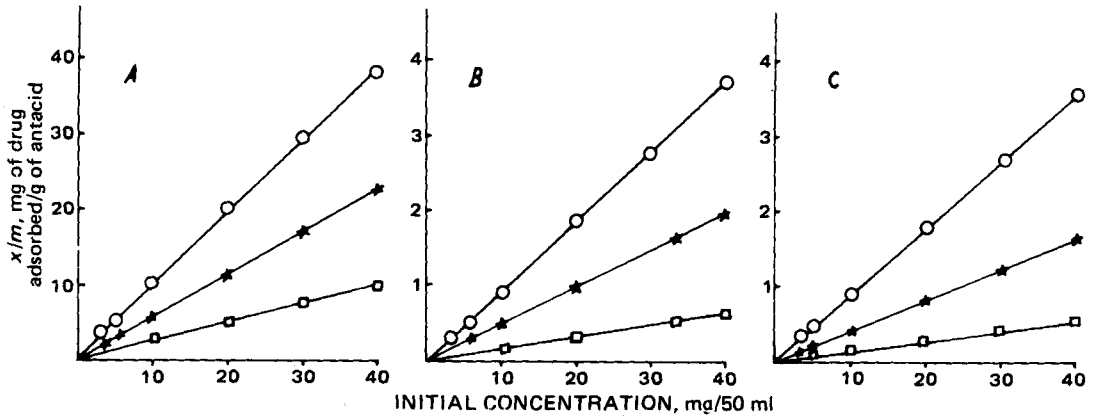

Figure 3—*Adsorption of acetohexamide (A), tolbutamide (B), and tolazamide (C) on certain antacids (1% w/v). Key:* ○, *magnesium trisilicate;* ★, *magnesium oxide; and* □, *aluminum hydroxide.*

Table III—Blood Glucose Levels at 2 hr following a 200-mg/kg Single Oral Dose of Tolazamide Aqueous Suspension Alone and Coadministered with Antacids

	Blood Glucose Level (n = 3), mg/100 ml		
	Tolazamide	Tolazamide plus Magnesium Trisilicate	Tolazamide plus Aluminum Hydroxide
Mean	6.50	18.00	13.00
SD	2.71	1.91	3.41
CV, %	41.69	10.61	26.23

Analysis of Variance

Source of Variation	Degrees of Freedom	Sum of Squares	Mean of Squares	F^a Ratio
Among dosage forms	2	199.5	99.75	13.14
Error	6	45.22	7.59	
Total	8	244.72		

[a] Significance at the 5% level.

Table IV—Desorption of Tolbutamide, Tolazamide, and Acetohexamide from Antacids

	Mean Drug Desorbed ± *SD* (n = 3), %		
Drug	Magnesium Trisilicate	Magnesium Oxide	Aluminum Hydroxide
Acetohexamide	5.17 ± 1.72	8.36 ± 1.12	10.50 ± 1.76
Tolazamide	6.50 ± 2.76	12.20 ± 1.45	13.50 ± 0.87
Tolbutamide	5.20 ± 1.42	8.50 ± 0.38	10.80 ± 0.36

Analysis of Variance

Source of Variation	Degrees of Freedom	Sum of Squares	Mean of Squares	F^a Ratio
Among dosage forms	2	38.98	19.49	3.54
Error	6	33.02	5.50	
Total	8	71.99		

[a] Significance at the 5% level.

showed that there was a significant difference ($p < 0.05$) among the tested dosage forms (Table II). There was a significant difference (least significant difference procedure, $p < 0.05$) between the mean blood glucose level when acetohexamide was administered alone and when it was administered with either magnesium trisilicate or aluminum hydroxide (Table II). Similarly, statistical comparison of the data in Table III indicated that there was a significant difference (analysis of variance, $p < 0.05$) among the tested tolazamide dosage forms as to the 2-hr mean blood glucose levels. There was also a significant difference (least significant difference procedure, $p < 0.05$) between the mean blood glucose level when tolazamide was administered alone and when it was administered with either magnesium trisilicate or aluminum hydroxide.

Figure 3 shows the plots of drug adsorption onto magnesium trisilicate (1% w/v). Preliminary experiments showed that equilibrium was attained within 6–24 hr, depending on the drug, its concentration, and the antacid. Antacid adsorption of the drugs followed the sequence magnesium trisilicate > magnesium oxide > aluminum hydroxide. These antacids adsorbed 95, 50, and 17.5% of tolbutamide, respectively. The extent of drug adsorption to antacids followed the sequence acetohexamide > tolbutamide > tolazamide. The three drugs possess varying relative polarity, and the extent of adsorption was increased with the more polar drug. This finding is concordant with the reported (10) conclusion that, for a given solvent, the more soluble solutes generally were adsorbed less strongly than the less soluble ones.

Table IV summarizes the extent of adsorption of the three drugs from the respective medium used for dissolution. These data illustrate a strong adsorption of the three drugs to magnesium trisilicate; only 5.17, 5.20, and 6.5% were desorbed from acetohexamide, tolbutamide, and tolazamide, respectively. The same sequence occurred with aluminum hydroxide and magnesium oxide. Analysis of variance of the data in Table IV showed that there was no significant difference among the tested antacids as to the extent of adsorption of the three hypoglycemics.

Statistical analysis of the data in Table IV (least significant difference procedure, $p < 0.05$) indicated that tolbutamide was adsorbed more significantly to magnesium trisilicate than to aluminum hydroxide. There appeared to be no significant differences between the extent of tolbutamide adsorption to magnesium trisilicate and magnesium oxide nor to aluminum hydroxide and magnesium oxide. Tolazamide was adsorbed more strongly to magnesium trisilicate than to the other two antacids. Acetohexamide exhibited a significantly higher adsorption to magnesium trisilicate than to aluminum hydroxide; however, no significant difference existed between the extent of its adsorption to magnesium oxide and magnesium trisilicate nor between its adsorption to aluminum hydroxide and magnesium oxide.

These results indicate that the tested antacids reduce the hypoglycemic activity of acetohexamide, tolazamide, and tolbutamide. The dissolution rates of the three oral hypoglycemics in the presence of the antacids, with the exception of magnesium trisilicate, increased (0.5–1 hr), plateaued, and then decreased. Increased dissolution in the 1st hr did not rise continually due to uptake of the dissolved drug by the antacid. Again, the earlier increased dissolution does not reflect increased hypoglycemic activity due to direct adsorption of drug by antacid decreasing the amount of free drug available for systemic absorption. Magnesium trisilicate, which showed the highest adsorption capacity for the three oral hypoglycemics, induced the paramount suppression in their hypoglycemic activity. Furthermore, the powerful adsorption of the drugs by this antacid, as indicated by minor desorption, illustrates this suppression.

From the present study, it may be concluded that the hypoglycemic activity of acetohexamide, tolazamide, and tolbutamide will be decreased considerably if these drugs are separately coadministered with the tested antacids. The extent of reduction will vary with the antacid.

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Stereospecific Radioimmunoassays for *d*-Pseudoephedrine in Human Plasma and Their Application to Bioequivalency Studies

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Abstract □ Antiserum to *d*-pseudoephedrine was raised in New Zealand White rabbits in response to immunization with a conjugate of bovine serum albumin and *d*-pseudoephedrine-*N*-3-propionic acid. The hapten was prepared by reaction of methyl acrylate with *d*-pseudoephedrine, followed by ester hydrolysis. Sodium boro[^{3}H]hydride reduction of *dl*-ephedrone gave [α-^{3}H]-*dl*-ephedrine, and a Welsh rearrangement with acetic anhydride followed by deacetylation gave [α-^{3}H]-*dl*-pseudoephedrine, which was used as a radioligand in radioimmunoassay procedures for direct plasma analyses. Three sensitive radioimmunoassay procedures were developed, two using [^{3}H]pseudoephedrine as the radioligand and either adsorption on coated charcoal or polyethylene glycol precipitation for separation of antibody-bound from free radioligand. The third method used an [^{125}I]tyrosine methyl ester analog of pseudoephedrine and charcoal separation, preceded by extraction and derivatization of pseudoephedrine with methyl acrylate. All three assays could detect ≤2.5 ng of pseudoephedrine/ml. The antiserum was stereospecific, showing low cross-reactivities with *l*-pseudoephedrine and *d*- and *l*-ephedrines. *d*-Norpseudoephedrine and some other related compounds also had low cross-reactivity in these radioimmunoassay procedures. Excellent agreement was found between pseudoephedrine concentrations in human plasma determined by radioimmunoassay and by a standard GLC method. The utility of radioimmunoassay was illustrated by application of one of these procedures to an assessment of the bioequivalence of immediate- and sustained-release pseudoephedrine formulations in normal volunteers. A sustained-release preparation containing 120 mg of pseudoephedrine hydrochloride given every 12 hr was shown by *AUC* comparisons to be bioequivalent to an immediate-release tablet (containing 60 mg of pseudoephedrine hydrochloride) given every 6 hr.

Keyphrases □ Radioimmunoassay—*d*-pseudoephedrine, human plasma, bioequivalency studies, immediate- and sustained-release tablets □ *d*-Pseudoephedrine—radioimmunoassay, bioequivalency studies, immediate- and sustained-release tablets □ Bioequivalency studies—radioimmunoassays of *d*-pseudoephedrine in human plasma, bioequivalency studies, immediate- and sustained-release tablets □ Adrenergics—radioimmunoassays for *d*-pseudoephedrine in human plasma, bioequivalency studies, immediate- and sustained-release tablets

d-Pseudoephedrine was first isolated from the Chinese plant *Ma Huang* by Chou and Read (1) in 1926, and studies of its pharmacology started soon thereafter (2, 3). Although pseudoephedrine is in widespread use as a proven, clinically effective nasal decongestant (4–6), little published information is available on its disposition and pharmacokinetics in human plasma following administration of therapeutic doses. Studies have examined kinetics chiefly from the viewpoint of urinary excretion (7–9), which is liable to be influenced by alterations in urinary pH (8). Such indirect studies were necessitated by the lack of methods sufficiently sensitive to detect the relatively low circulating concentrations of pseudoephedrine in plasma following therapeutic doses.

Reported GLC procedures (7, 10, and 11) were capable of detecting only 0.3–0.5 μg of pseudoephedrine/ml. Even with nitrogen detection, Bye *et al.* (12) were able to lower the sensitivity limit only to 25 ng/ml. Kuntzman *et al.* (8) reported a procedure that involved esterification of isolated pseudoephedrine with tritiated acetic anhydride followed by separation and quantitation of the resulting radioactive product. Although capable of detecting 50 ng of pseudoephedrine/ml of plasma, this method is still relatively insensitive and time consuming. A study (13) of plasma pseudoephedrine levels relative to efficacy, using a GLC method for drug determination, was able to determine plasma concentrations up to 6 hr following a 60-mg oral dose of pseudoephedrine hydrochloride.

This report describes the development of a specific antiserum to pseudoephedrine and its application to three specific radioimmunoassay procedures for the drug. Two procedures are direct and employ a tritium-labeled radioligand; the third requires extraction and derivatization of the drug prior to assay but employs a γ-labeled radioligand. The sensitivity limits of these procedures are <2.5 ng of pseudoephedrine/ml in all cases. Their use for drug disposition studies following oral administration of both immediate- and sustained-release pseudoephedrine preparations is illustrated.

EXPERIMENTAL

Melting points[1] are uncorrected. ^{1}H-NMR spectra[2] were obtained in deuterochloroform with tetramethylsilane as the internal standard unless otherwise indicated. Low-resolution mass spectra[3] were obtained by

[1] Thomas-Hoover apparatus, Arthur H. Thomas Co., Philadelphia, Pa.
[2] Model R-24A, Perkin-Elmer Corp., Norwalk, Conn.
[3] Model MAT 731 or CH5DF, Varian Associates, Palo Alto, Calif.

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