# Biopharmaceutic Factors that Influence Effects of Anticholinergic Drugs: Comparison of Propantheline, Hexocyclium, and Isopropamide

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**Abstract** □ The antisecretory (determined from salivary flow rates) and antimotility (determined from riboflavin absorption) effects of usually recommended doses of propantheline, hexocyclium, and isopropamide were compared in four adult volunteers. Both propantheline and hexocyclium significantly decreased salivary flow and increased riboflavin absorption. Although the usual dose of propantheline was about twice as effective as the usual dose of hexocyclium in suppressing salivary flow, these doses produced comparable effects on riboflavin absorption. Isopropamide had little or no effect on either the salivary flow rate or riboflavin absorption. Propantheline and hexocyclium elicited little effect on salivary flow when administered after a meal. Prolonged-release dosage forms of these drugs produced effects comparable to those produced by much smaller doses in conventional tablets and gave no indication of providing prolonged anticholinergic effects.

**Keyphrases** □ Propantheline—antisecretory and antimotility effects compared to hexocyclium and isopropamide, humans □ Hexocyclium—antisecretory and antimotility effects compared to propantheline and isopropamide, humans □ Isopropamide—antisecretory and antimotility effects compared to propantheline and hexocyclium, humans □ Antisecretory effects—propantheline, hexocyclium, and isopropamide compared, humans □ Antimotility effects—propantheline, hexocyclium, and isopropamide compared, humans □ Anticholinergic agents—propantheline, hexocyclium, and isopropamide, antisecretory and antimotility effects compared, humans

Anticholinergic agents are among the most widely prescribed drugs for GI disorders (1). Their principal therapeutic effects are inhibition of gastric acid production and reduction of GI motility. Direct evaluation of the anticholinergic effects of a drug is difficult and causes discomfort to the patient, but relatively simple and noninvasive methods are available to evaluate such effects indirectly.

The antisecretory effect of anticholinergics is relatively nonspecific; suppression of gastric acid output is accompanied by a reduction in the secretion of pancreatic juice and saliva (1). Studies in which gastric acid and salivary secretions were measured simultaneously after administration of an anticholinergic drug indicated parallel decreases in flow rates (2). With the salivary flow rate as an index of anticholinergic response, the bioavailability of propantheline was reduced when the drug was given after a meal or in a sustained-release tablet compared to the bioavailability after administration of conventional tablets to fasted subjects (3).

Changes in GI motility can alter significantly the bioavailability of certain drugs. For example, propantheline increased the absorption of riboflavin in healthy volunteers (4) and of digoxin in patients (5), presumably by increasing the residence time of the drug at optimal absorption sites in the GI tract. Hence, changes in the absorption of such drugs may be a useful index of the antimotility effect of anticholinergic drugs.

The present study was undertaken to compare the effects of recommended doses of certain anticholinergic drugs on secretory activity, as reflected by the salivary flow rate, and GI motility, as reflected by riboflavin absorption in healthy volunteers, and to determine the influence of food and dosage form on these effects.

**Table I—Suppression of Salivary Secretion (Milliliters)**

| Treatment | Subject M | B | W | A | Mean ± *SD* |
|---|---|---|---|---|---|
| **Conventional Dosage Forms** | | | | | |
| Propantheline, 15 mg | 175 | 284 | 171 | 216 | 212 ± 52 |
| Hexocyclium, 25 mg | 104 | 184 | 102 | 60 | 112 ± 52 |
| Isopropamide, 5 mg | 0 | 58 | 58 | 3 | 30 ± 33 |
| **Conventional Dosage Forms with Food** | | | | | |
| Propantheline, 15 mg | — | — | 18 | 0 | — |
| Hexocyclium, 25 mg | 3 | 17 | 18 | 33 | 18 ± 12 |
| **Prolonged-Release Dosage Forms** | | | | | |
| Propantheline, 30 mg | 38 | 246 | 64 | 225 | 143 ± 107 |
| Hexocyclium, 75 mg | 100 | 149 | 88 | 174 | 128 ± 41 |

## EXPERIMENTAL

Four male volunteers, 21–29 years of age and weighing 59–75 kg, were in apparent good health and gave informed consent.

The following drugs were studied: propantheline bromide[1], 15 mg; isopropamide iodide[2], 5 mg; and hexocyclium methylsulfate[3], 25 mg. Propantheline[4], 30 mg, and hexocyclium[5], 75 mg, prolonged-acting dosage forms also were studied. Riboflavin 5′-phosphate was obtained commercially[6].

Each subject received a single dose of each drug in the form of a conventional or prolonged-action tablet on the morning after an overnight fast. Food was withheld for an additional 3–4 hr after drug administration. All subjects were asked not to ingest any drugs or vitamins for at least 72 hr before and after each experiment.

The flow rate of mixed saliva was determined immediately before drug administration and at 30-min intervals thereafter for 6 hr in the manner described previously (3). During the study, on a nondrug day, normal salivary flow rates were determined in each fasting subject over the same time period.

Single doses of propantheline, 15 mg, or hexocyclium, 25 mg, were also taken immediately after a standard breakfast consisting of 60 g of cornflakes and 500 ml of milk, and salivary flow rates were determined. Normal salivary flow rates were determined on a nondrug day following the standard breakfast.

Each volunteer received an amount of riboflavin 5′-phosphate equivalent to 150 mg of riboflavin/$m^2$ of body surface area. The vitamin was dissolved in 200 ml of water and taken orally in the morning on an empty stomach. No food was permitted for 3 hr. This study was carried out on two occasions. In other experiments, the subjects received propantheline, 15 mg, isopropamide, 5 mg, or hexocyclium, 25 mg, 1 hr before ingestion of the vitamin solution. Urine was collected for 24 hr. Total riboflavin was determined fluorometrically (6); the data were corrected for normal

[1] Pro-Banthine, various lots, Searle.
[2] Darbid, lot 14D62, Smith Kline & French.
[3] Tral, lot 28-521-AF-22, Abbott.
[4] Pro-Bantheline P.A., lot 875-503, Searle.
[5] Tral Gradumet, lot 43-555-AF-26, Abbott.
[6] Roche Chemical Division.

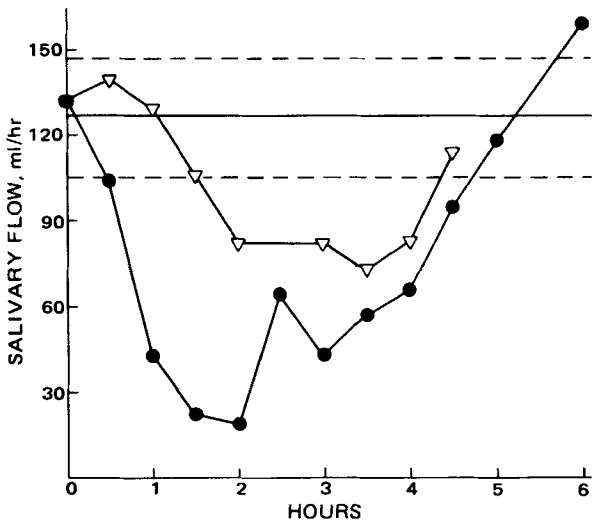


**Figure 1**—*Comparison of effects of propantheline, 15 mg (●), and hexocyclium, 25 mg (▽), on salivary flow in a healthy volunteer. The horizontal solid line indicates the mean normal salivary flow rate, and the broken lines denote the mean ± 1* SD.

physiological riboflavin excretion, which was determined from 24-hr blank collections of urine.

## RESULTS AND DISCUSSION

The effect of various treatments on the salivary flow rate was estimated by determining the total area under the response (salivary flow) *versus* time curve over 6 hr as described previously (3) (Table I).

Administration of propantheline, 15 mg, in a conventional tablet under fasting conditions resulted in the most pronounced suppression of the salivary flow rate. Hexocyclium also reduced salivary flow but produced only about one-half the effect, on the average, of propantheline. Propantheline tended to evoke a more rapid and intense response after a single dose than did hexocyclium (Fig. 1).

Single 5-mg doses of isopropamide had little or no effect on the salivary flow rate (Table I). These findings are consistent with earlier reports indicating that doses of 10 mg (maximum recommended) or more are necessary to inhibit salivary flow and gastric acid secretion (1, 7).

Neither propantheline nor hexocyclium had much effect on salivary flow when administered after a standard breakfast (Table I). The fact that food decreases or abolishes the anticholinergic effect is a clinically relevant observation, since these drugs are usually prescribed to be taken

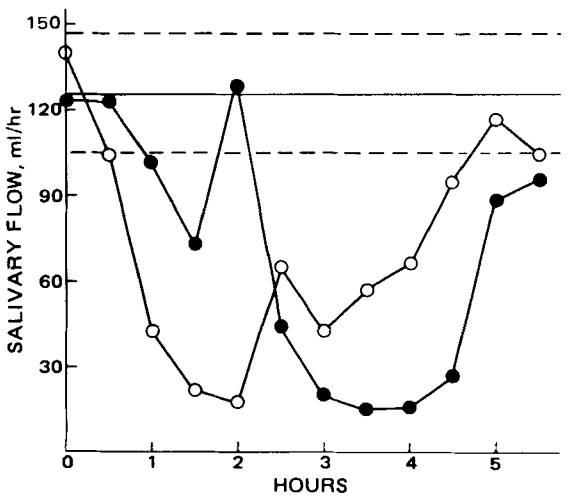


**Figure 2**—*Comparison of effects of different dosage forms of propantheline on salivary flow in a healthy volunteer. Key:* ○, *propantheline, 15 mg, in a conventional tablet; and* ●, *propantheline, 30 mg, in a prolonged-release dosage form. See Fig. 1 for additional details.*

**Table II—Urinary Excretion of Riboflavin (Percent of Dose)**

| Treatment | Subject M | B | W | A | Mean ± *SD* |
|---|---|---|---|---|---|
| First control study | 1.0 | 2.0 | 3.0 | 2.7 | 2.0 ± 0.6 |
| Second control study | 1.2 | 2.2 | 2.1 | 1.6 | |
| Propantheline, 15 mg | 4.2 | 3.4 | 3.8 | 3.2 | 3.6 ± 0.5[a] |
| Hexocyclium, 25 mg | 3.7 | 3.8 | 5.4 | 3.2 | 4.0 ± 1.0[a] |
| Isopropamide, 5 mg | 1.5 | 3.3 | 2.0 | 3.8 | 2.6 ± 1.1 |

[a] Significantly different from control value, $p < 0.05$, paired $t$ test.

with meals. Maximal effects are likely to occur when the drug is given 1 to 2 hr before a meal. However, under these conditions, the degree of salivary suppression may be sufficient to interfere seriously with mastication and swallowing. If an anticholinergic is to be given immediately before or after a meal, larger doses than those currently recommended are required.

The present study continues to raise serious questions regarding the value of prolonged-release dosage forms of anticholinergic drugs. Previously, one lot of propantheline, 30 mg, failed to affect salivary flow (3). A newer lot, marketed after a major recall, was investigated during this study and was improved, but it was still less bioavailable than the conventional tablets. The prolonged-release form of propantheline produced effects comparable to the conventional dosage form in two subjects and less than the conventional form in the two others, even though the prolonged-release tablet contained twice as much drug (30 *versus* 15 mg) (Table I). In subjects showing comparable salivary suppression after either the conventional tablet or the prolonged-release tablet, the only difference in the effects produced by each was a delay in onset of salivary suppression after the prolonged-release form (Fig. 2). In no instance was there an indication of prolonged activity compared to that observed with the conventional tablet.

In general, the total salivary suppression and the time course of this effect resulting from 75 mg of hexocyclium in a prolonged-release dosage form were comparable to those observed after a 25-mg dose in a conventional tablet (Table I). The commercially available prolonged-release dosage forms of propantheline or hexocyclium appear to offer no advantage over considerably smaller doses in conventional dosage forms.

The effect of propantheline, hexocyclium, or isopropamide on riboflavin absorption is shown in Table II. Cumulative riboflavin excretion, corrected for excretion of endogenous and dietary riboflavin, was used as an index of the extent of absorption of the vitamin after the test dose. Excretion of apparent riboflavin in the absence of a test dose averaged 1.14 mg/24 hr in this panel of subjects. This result is in excellent agreement with a value of 1.0 mg/24 hr previously observed in five other subjects (4). A control study was carried out at the beginning of the investigation and a second one at the end of the investigation, several months later. Excretion of riboflavin ranged from 1 to 3% of the test dose. No significant differences were noted between the results of the first and second control studies.

Both propantheline and hexocyclium increased the extent of riboflavin absorption by about twofold. These statistically significant increases probably reflect the inhibitory effect of these drugs on gastric emptying and the intestinal transit rate. Although, at the usually recommended doses, propantheline was more effective than hexocyclium in reducing salivary flow, no difference in their effect on riboflavin absorption was noted. A 5-mg dose of isopropamide, which had little effect on salivary flow, failed to increase riboflavin absorption significantly.

The findings that propantheline and hexocyclium exert a quantitatively different effect on the salivary flow rate (probably reflective of changes in gastric acid output) but a quantitatively comparable effect on riboflavin absorption (probably reflective of changes in GI motility) suggest that a degree of selectivity in pharmacological response may be obtained through careful selection of anticholinergic drugs.

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# General Class of Multiparticulate Dissolution Models

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**Abstract** □ The dissolution of multiparticulate systems under sink and nonsink conditions can be described rigorously according to a generally applicable formula on the basis of the single-particle dissolution model and the initial particle distribution. The kinetic model for log-normal systems dissolving under sink conditions is extended to nonsink conditions as a specific example. The equation presented describes a general class of multiparticulate models for various values of the dispersion parameter and the dissolution capacity coefficient.

**Keyphrases** □ Dissolution model—multiparticulate systems under sink and nonsink conditions, generally applicable equations derived □ Models, dissolution—multiparticulate systems under sink and nonsink conditions, generally applicable equations derived □ Multiparticulate systems—dissolution model under sink and nonsink conditions, generally applicable equations derived

Characterization of dissolution behavior is often facilitated by the use of an appropriate mathematical model that enables the process to be summarized in terms of one or more parameters such as the dissolution rate constant. Since most dissolution tests are performed under nonsink conditions, the kinetics under such conditions are of interest. Various nonsink dissolution equations for multiparticulate systems have been derived (1–4), but they are based on monodisperse systems which are rarely met in practice (5).

A proper characterization of dissolution behavior must account for the particle-size distribution. This paper provides a general and rigorous description of dissolution under nonsink conditions on the basis of a single-particle dissolution model and the initial particle distribution. Log-normal powders are considered as a specific example. The equation presented describes a large class of multiparticulate dissolution models for various values of the dispersion parameter and the dissolution capacity coefficient.

## THEORY

A previous publication (6) showed how the dissolution kinetics of a multiparticulate system can be rigorously described theoretically when the single-particle dissolution equation is known together with the initial particle-size distribution. Although equations for the general case (Eqs. 12 and 13 in Ref. 6) were derived assuming sink conditions, they can also be applied to nonsink dissolution.

In the current context, sink condition is defined as interparticle independent dissolution[1]. This condition may be closely approximated in a noncumulating, open, flow-through system (7). A nonsink condition is defined as the condition in a solute-cumulating, closed system, where the particles are exposed to the same bulk concentration of solute. Dissolution according to the latter definition implies agitation that is intense enough to give a homogeneous bulk solute concentration and to suspend the dissolving particles freely in the vehicle.

The only difference between the mathematical description of the two systems is that, for nonsink conditions, dissolution is influenced by the bulk concentration of solute; therefore, the single-particle dissolution equation contains an additional time-dependent variable. Since this variable is a function of the total dissolution behavior of the system, mathematical analysis leads to an integral equation describing multiparticulate nonsink dissolution kinetics.

These principles can be illustrated on the basis of the well-known Noyes–Whitney kinetics (8) for log-normal powders and spherical particles without loss of generality. The choice of a log-normal distribution to approximate the initial particle distribution appears appropriate considering previous investigations (7, 9, 10).

**Single-Particle Dissolution Equation**—Consider a single spherical particle, in a polydisperse system, dissolving under nonsink conditions according to the Noyes–Whitney model:

$$dw/dt = -k_1 s(c_i - c) \doteq -k_2 w^{2/3}[c_s - (W_0 - W)/V] \quad \text{(Eq. 1)}$$

where $w$ is the weight of the particle, $s$ is its surface area, and $c_i$ is the interfacial solute concentration which, in most cases, is close to the solubility concentration, $c_s$. Let it be assumed that $k_1$ and $k_2 = 4\pi(4/3\pi\rho)^{-2/3}k_1$ ($\rho$ = density) are constants not dependent on the particle diameter. Such an assumption is reasonable, since it leads to the well-established cube root model (1) under sink conditions ($c = 0$). If the single-particle dissolution kinetics are different from the Noyes–Whitney kinetics (11) or if $k$ (Eq. 1) is not constant, then the multiparticulate kinetics can still be treated similarly to the cases considered below. The bulk solute concentration, $c$ (Eq. 1), is, according to the definition of nonsink conditions, equal to the ratio of the amount of powder dissolved, $(W_0 - W)$, to the vehicle volume, $V$.

It is useful to introduce the dissolution capacity coefficient defined by:

$$\alpha = [(c_s V - W_0)/W_0]^{1/3} \doteq [(c_i V - W_0)/W_0]^{1/3} \quad \text{(Eq. 2)}$$

Equation 1 then integrates to yield:

$$w = \left[ w_0^{1/3} - \frac{3k_2 W_0 \alpha^3}{V} t - \frac{3k_2 W_0}{V} \int_0^t \frac{W}{W_0} dt \right]^3 \quad \text{(Eq. 3)}$$

For comparison with earlier derivations (6, 12), it is convenient also to

[1] This definition is different from the usual definition, which defines a sink condition as a condition where the solute bulk concentration does not increase beyond a small fraction (10–15%) of the solubility concentration.