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The Oral Bioavailability and Pharmacokinetics of Soluble and Resin-Bound Forms of Amphetamine and Phentermine in Man

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Plasma levels of amphetamine and phentermine have been measured in man in a crossover study of the pharmacokinetics of these agents following oral administration of resin-bound and soluble salt formulations. The one-compartment open model with first-order drug absorption was fitted to the data from each subject by nonlinear regression methods and provided an excellent fit. Relative bioavailability of the two salts did not differ for either drug. In both cases the rate constant for absorption was significantly lower and less variable for the resinated compound.

KEY WORDS: absorption; amphetamine; bioavailability; elimination; pharmacokinetics; phentermine; resin-bound drugs.

INTRODUCTION

As one means of controlling their rate of absorption, basic drugs have been incorporated into cation exchange resins (1). The kinetics of release of a drug from the resin particle will determine its concentration in the gastrointestinal tract and, consequently, its rate of absorption into the circulatory system. Some advantages which may be derived by proper choice of resin and drug are prolongation of action, reduction of peak blood concentrations, and a flatter blood concentration curve. A combination of any or all of these effects may aid in obtaining more predictable responses. To be effective, however, a balance must exist between the drug and the resin matrix: the degree of binding to the resin must be sufficiently strong to accomplish the desired objectives but not strong enough to reduce the bioavailability. The work described illustrates a pharmacokinetic approach to investigate

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the equivalent bioavailability of resin-bound amphetamine[3] and phentermine[4] and their respective soluble salts and to show the effect of resination on the rates of absorption of the individual amines in man.

METHODS AND MATERIALS

Drug Formulation

Amphetamine

A combination of one part of *d*-isomer and one part of *dl*-racemic mixture was encapsulated in the prescribed amount either of the salt, amphetamine phosphate or of the resinated product, Biphetamine^R. Identical capsules were used for the two salts and identified by number only.

Phentermine

The prescribed amount of this study was encapsulated either as the salt, phentermine hydrochloride, or as its resinated product, Ionamin^R. Identical capsules were used for both salts and identified by number only.

Drug Administration

To minimize individual variations, a crossover design was employed. A minimum of 2 weeks elapsed time was allowed for drug wash-out prior to exposure to the second drug. Regardless of the drug administered, sequential blood samples were drawn into heparinized tubes over the ensuing 24–72 hr, beginning at 30 min. A minimum of 10 samples was drawn in each experiment. The samples were thoroughly mixed and immediately frozen. The actual time and subject were recorded on each tube and all samples were then transmitted to the Pharmaceutical Division, Pennwalt Corporation, Rochester, New York, where the drug content in blood was measured.

Chemical Measurements

The blood samples were maintained frozen until ready for measurement. The drug was extracted into benzene from a measured volume of blood which had been made alkaline with sodium hydroxide. The organic extract was concentrated by evaporation and an accurately measured amount of internal standard was added. The residue was derivatized with trifluoroacetic anhydride, reconstituted to the known volume, and the drug concentration determined by the gas chromatographic method described by O'Brien *et al.* (2).

[3]Biphetamine^R is the registered trademark of amphetamine bound to the Rohm and Haas IR-120 cation exchange resin.

[4]Ionamin^R is the registered trademark of phentermine bound to the Rohm and Haas IR-120 cation exchange resin.

Pharmacokinetic Theory

If a quantity Q_0 of drug is administered orally and its absorption follows first-order kinetics, the quantity absorbed (Q) at time t is given by the equation

$$Q = Q_0\lambda(1 - e^{-k_1 t}) \quad (1)$$

where λ is the proportion available for absorption and k_1 is the first-order rate constant for absorption. Assuming a one-compartment open model, the plasma concentration (Y) is given by

$$Y = [Q_0\lambda k_1/V(k_1 - k_2)](e^{-k_2 t} - e^{-k_1 t}) \quad (2)$$

where V is the apparent volume of distribution and k_2 is the apparent first-order rate constant for elimination. The assumptions underlying this model have been previously discussed (4,5).

Statistical Fitting Procedure

Each experiment generated several pairs of values for t and Y: Q_0 was known and was expressed as mg kg^{-1}. There are therefore three independent parameters to be estimated: k_1, k_2, and V/λ. These parameters were estimated by fitting equation (2) to the data from each experiment using a modified Gauss–Newton procedure similar to that described in detail in the BMDX series of biomedical computer programs (3), but employing a Wang 600 electronic desk calculator to carry out the computations. Since the error of estimation is approximately independent of the estimate within the relevant concentration range, the regression procedure employed equal weights for all points.

RESULTS

The data were found to be satisfactorily fitted by equation (2) for both resinate and soluble salts of amphetamine and phentermine. For every set of data, regression on a function of the form of equation (2) (analysis of variance) was highly significant ($P < 0.001$ in every case). The standard deviations estimated from the mean residual variances were 2.5 and 2.9 ng/ml for amphetamine and phentermine, respectively. These errors are quantitatively consistent with the reproducibility of the estimation procedure used, and the regression equation is therefore an adequate mathematical model of the kinetic system.

Tables I and II summarize the estimates of the kinetic parameters obtained for both salts for amphetamine and phentermine, respectively. Several features of these data deserve comment. Only one of the parameters showed a significant difference between the resinate and soluble salt forms—

Table I. Summary of Arithmetic Means ± Standard Errors of Estimates of Pharmacokinetic Parameters of Amphetamine Phosphate and Resinate in Healthy Subjects

Dose (mg)	Salt	n	Parameters		
			k_1 (hr^{-1})	k_2 (hr^{-1})	V/λ ($1\ kg^{-1}$)
12.5	Phosphate	6	1.514 ±0.439	0.0605 ±0.0103	4.23 ±0.48
	Resinate	6	0.651 ±0.144	0.0425 ±0.0111	5.06 ±0.36
20	Phosphate	6	1.026 ±0.144	0.0776 ±0.0102	3.30 ±0.36
	Resinate	6	0.299 ±0.053	0.0958 ±0.0143	3.00 ±0.34

the rate constant for absorption. This was larger for the soluble salt than for the resinate for both drugs at both dose levels, although for the lower dose of amphetamine the difference fell short of significance at the 5% level ($0.10 > P > 0.05$). For both drugs at both dose levels, this rate constant was also significantly more variable for the soluble salt than for the resinate (variance ratio). None of the other parameters showed significant differences in variability or mean value.

For the soluble salts, none of the parameters showed a significant difference between the two dose levels for either drug. For the resinate, the

Table II. Summary of Arithmetic Means ± Standard Errors of Estimate of Pharmacokinetic Parameters of Phentermine Hydrochloride and Resinate in Healthy Subjects

Dose (mg)	Salt	n	Parameters		
			k_1 (hr^{-1})	k_2 (hr^{-1})	V/λ ($1\ kg^{-1}$)
15	Hydrochloride	6	0.614 ±0.100	0.0293 ±0.0038	3.30 ±0.17
	Resinate	6	0.295 ±0.014	0.0283 ±0.0024	3.30 ±0.17
30	Hydrochloride	8	0.738 ±0.192	0.0316 ±0.0024	3.52 ±0.33
	Resinate	8	0.236 ±0.021	0.0280 ±0.0031	3.81 ±0.29

rate constant for absorption was for both drugs lower at the higher dose level ($0.05 > P > 0.01$), while, in the case of amphetamine only, the ratio V/λ was lower ($P < 0.01$) and the rate constant for elimination was larger ($0.02 > P > 0.01$) following 20 mg than after 12.5 mg. The functional importance of these differences is not obvious: one possible explanation is that the pharmacological actions of the drugs may influence their own disposition.

It has been shown that amphetamine delays gastric emptying (6), reduces intestinal motility (7), and delays the absorption of some other agents (8); the prolonged presence of amphetamine or phentermine in the small intestine may delay absorption by causing mucosal vascoconstriction.

Figure 1 shows blood concentration curves following hydrochloride and resinate salts of phentermine which are reconstituted from the mean parameter values presented in Table II, to illustrate graphically the effect of resination. It is evident that the resinate yielded a lower, later, and flatter peak than did the soluble salt, and the tail of the curve was somewhat higher following the resinate.

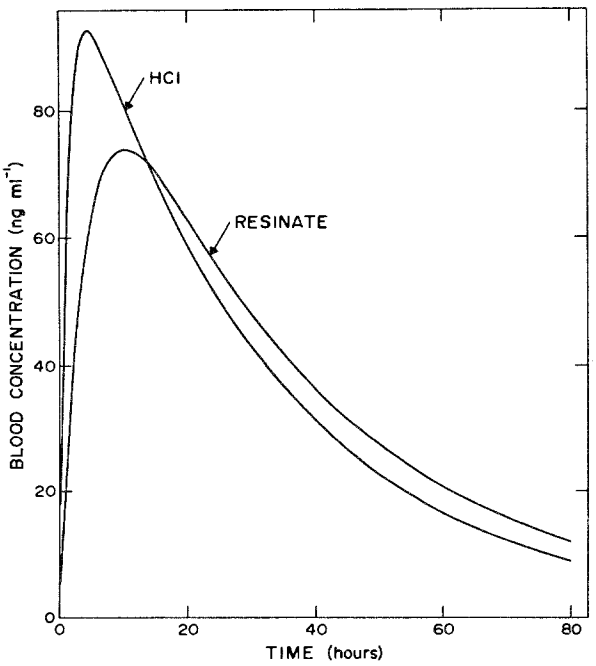

Fig. 1. Blood concentrations of phentermine following 0.375 mg kg^{-1} of the hydrochloride or resinate salts, calculated from the mean values of k_1, k_2, and V/λ for 30 mg kg^{-1} summarized in Table II.

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