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NOTES

Pharmacokinetic Linearity of Desipramine Hydrochloride

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Abstract □ The pharmacokinetic linearity of two single oral doses of desipramine hydrochloride was examined in a parallel study involving 30 subjects. Fourteen subjects received 75 mg (3 × 25 mg) of desipramine hydrochloride, and 16 subjects received 150 mg (1 × 150 mg). An open one-compartment model with a lag time to the start of absorption was used to examine the pharmacokinetic linearity. The results of the study suggest that the kinetics are linear in the dose range studied.

Keyphrases □ Desipramine hydrochloride—pharmacokinetic linearity, bioavailability, comparison of two tablet dose levels, humans □ Pharmacokinetic linearity—desipramine hydrochloride, humans □ Tricyclic antidepressants—desipramine hydrochloride, pharmacokinetic linearity, bioavailability, comparison of two tablet dose levels, humans

Tricyclic antidepressants are widely used in the treatment of depression. Recent studies (1–9) showed a relationship between steady-state plasma tricyclic levels and therapeutic response. Several investigations (10–14) were undertaken to find a means of predicting steady-state plasma tricyclic antidepressant concentrations based on plasma levels obtained after a single dose, thus avoiding time-consuming dosage titration to therapeutic plasma levels. These studies indicated that steady-state plasma levels can be predicted accurately by the area under the plasma concentration curve (*AUC*) following a single dose or by a single plasma level obtained 24, 48, or 72 hr after dosing.

This study determined the pharmacokinetic linearity of two single doses of desipramine hydrochloride[1], providing additional evidence that the steady-state predictions are reasonable.

EXPERIMENTAL

Subjects—Thirty healthy male volunteers were randomized into two parallel treatment groups; 14 received 75 mg (three 25-mg tablets) of desipramine hydrochloride and 16 received one 150-mg tablet. The subjects were 19–40 years of age and 47–78 kg. All subjects were within 10% of their ideal weight.

Protocol—Each subject received the prescribed dose at 8:00 am. A 15-ml blood sample (vacuum blood-drawing tubes[2] containing lithium heparin as anticoagulant) was drawn just prior to dosing (time zero) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48, and 72 hr postdosing. No solid food was permitted from 8:00 pm of the preceding day until 12:00 noon of the dose day, at which time a standard lunch was served. A low-fat dinner was served at 6:00 pm; after collection of the 24-hr sample, the subject resumed eating *ad libitum*. A parallel design was employed instead of a crossover design since the elimination half-life for desipramine can be long and variable (15).

Analytical Method—The separated plasma was kept frozen until it was assayed. Desipramine was measured using a GLC–mass spectrometric technique adapted from Pantarotto *et al.* (16). The method involved the addition of the internal standard (nortriptyline) and extraction of the alkalinized plasma with *n*-hexane. The extract was reacted with acetic anhydride and pyridine without prior evaporation. The acetylated extract then was evaporated to dryness, and the residue was dissolved in ethanol. An aliquot was injected into the apparatus with selected-ion monitoring at *m/z* 305 and 308.

Calculations—Pharmacokinetic parameters were computed for each dosage level corresponding to an open one-compartment model with a lag time (17) using:

$$C(t) = \frac{FD}{V}\frac{K_a}{(K_a - K_e)}\left[e^{-K_e(t-L)} - e^{-K_a(t-L)}\right] \qquad \text{(Eq. 1)}$$

where D is the administered oral dose, F is the fraction of the dose absorbed, V is the apparent volume of distribution, K_a is the apparent first-order absorption rate constant, K_e is the first-order elimination rate constant, L is the lag time to the start of absorption, and t is the time

[1] Norpramin, Merrell Dow Pharmaceuticals.

[2] Kimble-Terumo Venoject tubes.

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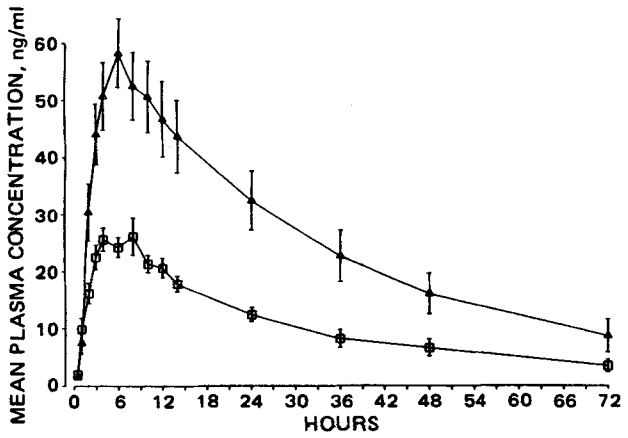

Figure 1—*Concentration of desipramine in plasma (mean ± SE). Key: □, desipramine hydrochloride, 3 × 25 mg; and △, desipramine hydrochloride, 150 mg.*

postdosing. These calculations were performed using the computer program NONLIN (18).

The distributions of F/V, K_a, K_e, and L for the two dose groups were compared statistically by the Mann–Whitney U test (19). The elimination half-life, $t_{1/2}$, was calculated as $0.693/K_e$. No analysis was performed on $t_{1/2}$ since the results would be identical to those reported on K_e using this statistical method. If the kinetics of the compound are linear in the dose range studied, the distributions of F/V, K_a, K_e, and L are expected to be the same for both dose groups.

The AUC (nanogram hours per milliliter) was calculated using the trapezoidal rule. Statistical analysis of the AUC, C_{max} (nanograms per milliliter), and t_{max} (hours) data was performed on the logarithms of the values using a two-sample t-test. Homogeneity of variance was verified by Cochran's test (20). The mean AUC and C_{max} values for the 150-mg group were expressed as a percentage of the 75-mg group mean by taking the antilog of the difference in log means. If the kinetics are linear in the dose range studied, the expected 150-mg mean would be ~200% of the 75-mg mean for AUC and C_{max} but equal to the 75-mg mean for t_{max}.

RESULTS

The mean plasma concentrations are displayed for the two dose groups in Fig. 1, and the relevant pharmacokinetic data are listed in Table I.

The lag time estimated for the 75-mg dose ranged from 0 to 0.78 hr, while that for the 150-mg dose ranged from 0.39 to 0.77 hr. A statistically significant longer lag time for the 150-mg group resulted. However, this result probably has no clinical significance since maintenance therapy is required with tricyclic antidepressants.

The apparent K_a calculated from this data ranged from 0.210 to 1.733 hr for 29 of the 30 subjects; the other subject had an estimated apparent K_a of 13.548. There was no statistically significant difference in the apparent K_a values for the two groups, but the value from the one individual resulted in a relatively high mean and standard error for the apparent K_a of the 75-mg dose. If the value for this subject is deleted, the corresponding values are 0.69 ± 0.13 (mean ± SE).

The half-lives estimated for 28 of the 30 subjects ranged from 9.76 to 34.65 hr; the other two half-lives were 4.85 and 69.30 hr. There was no statistically significant difference in the half-lives between the two groups. These half-lives agreed quite well with the previously reported half-lives of 17.1 ± 5.3 hr (mean ± SD, range 12.5–24.7 hr) following a 1-mg/kg dose of desipramine (29.75 ± 4.89 mg, mean ± SD) (11) and of 20.0 ± 1.5 hr (mean ± SD, range 12–30) following a 100-mg dose of desipramine (21).

There were no statistically significant differences among F/V, K, or t_{max} for the two dose groups.

The 150-mg dose produced significantly higher mean AUC and C_{max} values than did the 75-mg dose. The mean AUC for the 150-mg group, when expressed as a percentage of the 75-mg mean, was 219% with 95% confidence limits of 151–318%. The corresponding mean ratio for C_{max} was 199% with 95% confidence limits of 150–263%.

These results indicate that the kinetics of desipramine hydrochloride are linear in the 75–150-mg range and provide additional evidence that the earlier steady-state predictions based on levels after a single dose are meaningful.

Table I—Pharmacokinetic Parameters (Mean ± *SE*)

Parameter	75 mg (n = 14)	150 mg (n = 16)
F/V, $ml^{-1} \times 10^3$	0.45 ± 0.05	0.47 ± 0.04
K_a, hr^{-1}	1.61 ± 0.93[a]	0.50 ± 0.06
K_e, hr^{-1}	0.048 ± 0.008	0.040 ± 0.004
$t_{1/2}$, hr	19.7 ± 4.0	18.4 ± 1.8
L[b], hr	0.46 ± 0.05	0.62 ± 0.03
AUC[c], ng hr/ml	771.7 ± 87.3	1854.0 ± 307.0
C_{max}[c], ng/hr	30.7 ± 3.2	60.9 ± 5.9
t_{max}, hr	6.1 ± 0.7	5.9 ± 0.5

[a] Values are 0.69 ± 0.13 when one subject is deleted. [b] $p < 0.02$. [c] $p < 0.001$.

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