The Dog as a Quantitative Model for Evaluation of Nondisintegrating Sustained-Release Tablets

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Abstract □ Beagle dogs were evaluated as a possible model for the preliminary evaluation of nondisintegrating sustained-release tablets. A quantitative comparison of the rate and extent of absorption of the drug from sustained- and nonsustained-release dosage forms in man and dog was obtained. The data suggest that the dog is a satisfactory model to screen dosage forms for possible human testing. The specific limitations of the model are discussed.

Keyphrases □ Dog, quantitative model—nondisintegrating sustained-release tablet evaluation □ Sustained-, nonsustained-release dosage form, rate, extent of absorption—studied, compared, man, dog □ Absorption, sustained-, nonsustained-release dosage forms—rate, extent studied in man, dog, comparison

It is an accepted practice to screen dosage forms of a new drug in animals, whose general physiology approaches that of man, before submission of an Investigational New Drug (IND) Application permits use of these dosage forms in humans. The literature contains little information comparing data on the rate and extent of drug absorption obtained in animals during the development of a dosage form to similar data obtained in humans. This is especially true when one looks for reports on the development of sustained-release dosage forms. Rosen *et al.* (1) reported the plasma levels of radioactivity obtained in man and beagle dogs following administration of dextroamphetamine-^{14}C. The compound was administered in a pelleted sustained-release form and as a t.i.d. dosage regimen in nonsustained-release pellets. From a comparison of the similarities in plasma levels and urinary excretion obtained in the two species, they concluded that dogs could be used to assist in the selection of pelleted sustained-release formulations worthy of objective human testing.

With any sustained-release dosage form, the production of a sustained, essentially unchanging, plasma level of drug is desired. The mechanism for attaining this condition is assumed to be the development of a steady state, in which the amount of drug absorbed per unit of time is essentially equivalent to the amount of drug eliminated in the same period of time. The condition might also be described as zero-order absorption and equivalent pseudo-zero-order elimination, where the product of the clearance rate for plasma and the steady-state plasma concentration are represented by a zero-order rate constant for elimination.

The relationship between the first-order rate constant for plasma loss and clearance rate is:

$$\text{clearance rate} = (k_e)(V_D) \qquad \text{(Eq. 1)}$$

where k_e is the first-order rate constant for plasma loss (elimination), and V_D is the apparent volume of distribution of the drug. Most pharmacokinetic models use weight of drug rather than concentrations. Therefore, for the case of a steady-state plasma or body-compartment level:

$$A \xrightarrow{k_0} B \xrightarrow{k_e} C \qquad \text{(Eq. 2)}$$

where A is the amount of drug in the gut, B is the amount of drug in the plasma or body compartment, C is the amount of drug eliminated, k_0 is a zero-order absorption-rate constant, and k_e is a first-order elimination-rate constant;

$$\frac{dB}{dt} = 0 = k_0 - k_e B \qquad \text{(Eq. 3)}$$

One can relate this to plasma concentration by

$$k_0 = k_e (V_D)(C_B) \qquad \text{(Eq. 4)}$$

where C_B is the plasma concentration of drug, and V_D is its apparent volume of distribution. Absorption under these conditions must equal the product of the elimination-rate constant (k_e) and the amount of drug in the plasma or the product of the clearance rate ($k_e \cdot V_D$) and the concentration of drug in the plasma, *i.e.*, C_B. The first-order rate constant obtained from a semilog plot of C_B *versus* t is k_e, since the equation used:

$$\log (C_B) = \frac{-k_e t}{2.303} + \log C_{B0} \qquad \text{(Eq. 5)}$$

can be rewritten as

$$\log B = \frac{-k_e t}{2.303} + \log B_0 \qquad \text{(Eq. 6)}$$

Table I—Plasma Levels of Radioactivity Obtained following Oral Administration of Various Dosage Forms of Aminorex Fumarate to Dogs

Hours	3.93 mg. Aminorex Base (as Fumarate Salt) in a Capsule	20-mg. Sustained-Release Tablet of Aminorex Base (as Fumarate Salt)[a]
0.5	6[b] (2)[c]	50 (8)
1	214 (11)	164 (6)
1.5	—	228 (11)
2	202 (19)	281 (10)
3	202 (35)	320 (22)
4	188 (33)	368 (22)
5	175 (40)	408 (54)
6	164 (29)	416 (50)
7	146 (33)	—
8	128 (35)	364 (60)
9	118 (28)	—
24	29 (17)	—
Average wt., kg.	7.5	12.1
No. of animals	2	3

[a] Dosage form H of *Reference 2*. [b] Values given as micrograms aminorex (base)/liter (± *SD*). [c] Included only to give indication of the range of values obtained.

This rearrangement affects the intercept of the line described by Eq. 5 but not the slope. The equation obtained, Eq. 6, is identical to that obtained on integration of the rate equation for Eq. 2 after absorption is complete.

It should be realized from this discussion that in any animal species, one could not, *a priori*, expect the plasma level profile obtained following administration of a sustained-release dosage form to be identical to the profile expected in humans. Even if one assumes equivalent absorption rates (since this would hopefully be determined by the dosage form), the rate constants for elimination would have to be similar in the animal and man in order to obtain similar plasma level profiles.

It was hoped that an animal model, specifically the purebred beagle dog, could be used as a rapid, concise means of evaluating sustained-release formulations of various drug entities. Dosage forms for *in vivo* screening would be selected on the basis of having dissolution characteristics (2) similar to those observed for sustained-release tablets of aminorex fumarate (*Reference 2*, dosage form H). The aminorex tablet had been shown (2) to produce prolonged, relatively stable plasma levels of total drug and satisfactory clinical response.

Because the aminorex dosage form had never been evaluated in dogs, the following question arose. Is the beagle dog an acceptable model for the evaluation of this type (3) of nondisintegrating sustained-release dosage form? To test the proposed animal model for its ability to mimic the absorption profiles observed for nondisintegrating sustained-release tablets in human subjects, this study was designed. In this study, the plasma-level profiles and sustained-release properties of tablets of aminorex fumarate (*Reference 2*, dosage form H) in beagle dogs are compared with results obtained several years ago in human subjects (2).

EXPERIMENTAL

Human Protocol (2)—Four to five subjects were each administered one 20-mg. sustained-release tablet of aminorex-^{14}C base (as the fumarate salt) (*Reference 2*, dosage form H), or 7.5 mg. of aminorex-^{14}C base (as the fumarate salt) dissolved in 200 ml. of water and followed by a 100-ml. water wash. The drug was administered before breakfast, following an overnight fast. No food was consumed for at least 2 hours after dosing, but water was permitted *ad lib.* Blood samples were withdrawn at time intervals dictated by the dosage form.

Animal Protocol—Three male, 1-year-old, purebred beagle dogs were each administered one 20-mg. sustained-release tablet of aminorex-^{14}C base (as the fumarate salt) (*Reference 2*, dosage form H). Two dogs were given capsules containing 3.93 mg. of aminorex-^{14}C base (as the fumarate salt). The same procedure as described under *Human Protocol* was followed.

Assay Method—The plasma samples were assayed by dissolving 100 μl. of plasma in a toluene scintillator containing 10% Beckman[1] Biosolve B. The samples were counted directly in a Beckman[1] LS 200 B ambient temperature scintillation spectrometer. Efficiencies were determined by the external standard method.

RESULTS

The plasma levels of radioactivity, expressed as their equivalent in micrograms per liter of aminorex, are given in Table I. The data in humans have been presented previously (2) but are repeated here for comparison. These data are plotted in Fig. 1.

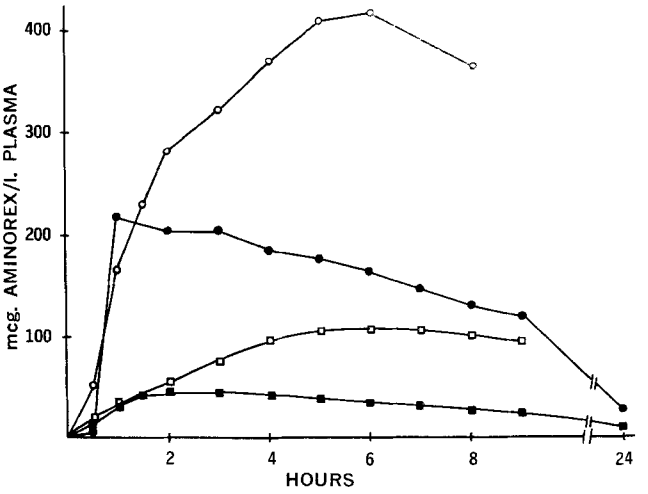

Figure 1—*Plasma levels of radioactivity, expressed as micrograms of aminorex, obtained following oral administration of aminorex fumarate. Key: ■, 7.5 mg. as a solution to human subjects; □, 20-mg. sustained-release tablet to human subjects; ●, 3.93-mg. capsule to dogs; and ○, 20-mg. sustained-release tablet to dogs.*

The data were evaluated using the method of Wagner and Nelson (4) and the approach reported previously (2). The use of plasma levels of total radioactivity instead of intact drug is compatible with the proposed model if the plasma loss of radioactivity is first order over the time period of interest. Application of this model (2) permits one to calculate the absorption rate of the drug from various dosage forms.

The plasma half-life of radioactivity in human subjects (2) was 7.7 hr. The plasma half-life of radioactivity in dogs was calculated from Fig. 2. The half-life, determined by linear-regression analysis, was 7.4 hr. By using these values for plasma half-lives, the absorption rates of the various dosage forms in human subjects and dogs could be calculated. The equation used to generate the data was:

$$A_t/V = k \int_0^t C_p\, dt + C_p \qquad \text{(Eq. 7)}$$

where A_t is the amount of the dose absorbed at time t, V is the apparent volume of distribution of the drug, k is the plasma elimination-rate constant for radioactivity, $\int_0^t C_p\, dt$ is the area under the

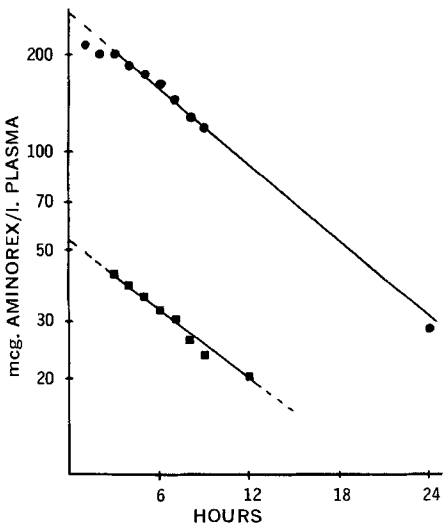

Figure 2—*First-order plot of plasma levels of radioactivity, expressed as micrograms of aminorex, obtained following oral administration of 7.5 mg. as a solution (■) to human subjects or 3.93 mg. in a capsule (●) to dogs.*

[1] Beckman Instruments Inc., Fullerton, CA 92634.

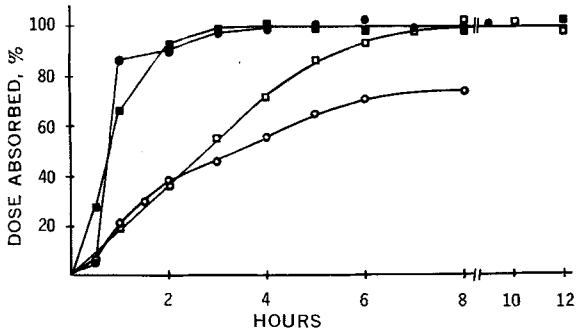

Figure 3—*Absorption of aminorex fumarate following administration to human subjects and to dogs. Key:* ■, *7.5 mg. as a solution to human subjects;* □, *20-mg. sustained-release tablet to human subjects;* ●, *3.93-mg. capsule to dogs; and* ○, *20-mg. sustained-release tablet to dogs.*

plasma level curve up to time t, and C_p is the plasma concentration at time t. The percent of the dose absorbed (Fig. 3) is calculated relative to the most readily available and (assumed) completely absorbed dosage form, in this case the solution or gelatin capsule of the drug.

DISCUSSION

From the data given in Fig. 2, it can be seen that the half-life of radioactivity for aminorex is very similar in dog and man. The values are 7.4 and 7.7 hr., respectively. The rate of absorption of aminorex fumarate (from readily available dosage forms) by man and dog is very similar (Fig. 3). A slight (15–30 min.) lag time in absorption is seen for the capsules in the dog. This lag is attributed to the time required for the capsule to disintegrate and release its contents.

Although the sustained-release tablets prolonged the absorption period of aminorex in both man and dog, the rates of absorption differed. The rates were equivalent for the first 2 hr. Following this time, absorption in man continued at a steady rate of ~18% of the dose/hour. The absorption by dogs did not continue at a steady rate but instead decreased. The data of Fig. 3 also indicate that the dog only absorbed 70–80% of the administered dose of aminorex from the sustained-release tablets. Human subjects absorbed 100% of the administered dosage form.

The reason for the reduced rate of absorption in dogs has not been established. However, in a subsequent experiment with nondisintegrating sustained-release tablets, an examination of the dogs' feces provided interesting information. In two of the four dogs used in the study, the tablet was expelled in the 6th hr. In the remaining two dogs, the tablets were found in the 8–12-hr. fecal sample. These results suggest that the dosage form may traverse the gut faster in dogs than in man. If, in the present study, rapid intestinal transit (6–8 hr.) occurred, this would account for the termination of absorption of aminorex at approximately 6–8 hr. A reduced rate of absorption or dissolution in the lower portions of the gut would account for the reduced absorption rate observed in the dog after the 2nd hr.

Although the rate and extent of absorption of aminorex were reduced in the dog, coincidentally the plasma level profile produced (Fig. 1) was not as divergent from man as might first appear. The plasma level curves obtained for the sustained-release tablet in man and dog are similar in their general shape. The rate of change in plasma level is amplified in the dog because of the much higher levels obtained. Such a result would not have been expected if the elimination constants in man and dog had not been similar.

CONCLUSIONS

The use of purebred beagle dogs as model animals for the preliminary evaluation of nondisintegrating sustained-release dosage forms would appear to be pharmacokinetically justifiable with certain limitations. The model should only be used to determine if a given dosage form has affected the rate of absorption, relative to some readily available dose, of the drug under study. The model should not be used to extrapolate the rate and/or extent of absorption observed to that expected in humans. Decisions as to the ability of the sustained-release product to provide satisfactory plasma levels in human subjects should not be made solely on the basis of the results of studies using the animal model. The authors have shown that both the rate and extent of absorption differed when the same dosage form was studied in the animal model and in man. The aminorex dosage form was 100% absorbed by human subjects; however, only 70–80% absorption was observed in the animal model. Clearly, incomplete absorption by the model system cannot be considered to reflect, with any accuracy, similar incomplete absorption in man.

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