Discussion

This study has shown that nadolol binding, in common with other basic drugs, is dependent on the circulating levels of serum α-1 acid glycoprotein (Piafsky 1980). However this factor alone explains only a small portion, <10% ($r^2 = 0.09$), of the variance in nadolol binding. It is therefore unlikely that in the variety of diseases associated with increased α-1-acid glycoprotein, nadolol binding would be changed to a clinically relevent extent. In any case the degree to which nadolol is bound to serum proteins is so small that even total displacement of the drug from its binding sites or a doubling of the drugs binding would have minimal clinical effect.

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The pharmacokinetic profile of carbidopa in dogs

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A pharmacokinetic study of carbidopa in beagle dogs has been carried out after intravenous (4 mg kg^{-1}) and oral (75 mg) administration. An open model of three compartments was the best approach for the pharmacokinetic profile of carbidopa administered intravenously. The estimated biological $t_{\frac{1}{2}}$ was 5 h and the plasma clearance 0·0053 (litre kg^{-1}) min^{-1}. The oral absorption of carbidopa was almost complete and the absolute bioavailability (F) was 88%.

Carbidopa (L-(−)-α-hydroazino-3,4-dihydroxy-α-methylhydrocinnamic acid monohydrate) is an aromatic amino acid decarboxylase inhibitor (Porter et al 1962) widely used in association with L-dopa in the therapy of Parkinson's disease (Calne et al 1971). The drug is also used in association with L-5-hydroxytryptophan for the treatment of myoclonus (Chadwick et al 1975) and certain types of depression (Praag 1981). Although the disposition and metabolism of carbidopa in several animal species are known (Vickers et al 1974; 1975) there are not, to our knowledge, published studies on the pharmacokinetic profile of this drug. We report here the pharmacokinetic profile of carbidopa after intravenous and oral administration in the beagle dog.

Materials and methods

Four male beagle dogs (11–16 kg) were used. Carbidopa (Synthesized by LASA Laboratorios. Span. Pat. 486030 and 493201) was administered intravenously at a fixed dose of 4 mg kg^{-1} and, by mouth, using tablets of 75 mg manufactured in our laboratories for the purpose of this study. The time between the i.v. and oral administration was a week. Blood (4 ml) was withdrawn from a cephalic vein immediately before the administration of carbidopa (blank sample) and at different times up to 10 h after the drug administration.

The plasma was immediately separated and stored at −20 °C until analysis. The determination of carbidopa in plasma was by a spectrophotofluorimetric method (Vickers & Stuart 1973). Plasma blank and samples were evaluated using an internal standard calibration curve for each administration. Two and three compartment models were fitted to the plasma concentrations obtained after the intravenous administration of carbidopa with a weighted nonlinear least square regression method that uses Marquardt's algorithm. The data were weighted according to equation 1

$$W_i = \frac{1}{y_i^2} \qquad (1)$$

where W_i is the weight and y_i is the value of the i^{th} observation. In order to determine the simplest exponential equation consistent with the data, the 'F' test proposed by Boxenbaum et al (1974) was used. In the same way a biexponential equation was fitted to the plasma concentrations obtained after the oral administration.

The values of AUC (area under curve) were calculated from the fitted equations and the bioavailability (F) of carbidopa was assessed from equation 2

$$F = \frac{AUC_{oral}}{AUC_{i.v.}} \times \frac{D_{i.v.}}{D_{oral}} \qquad (2)$$

where $D_{i.v.}$ is the i.v. administered dose and D_{oral} the corresponding oral dose.

Results and discussion

An open model of three compartments (lowest F value 19·9 $P < 0.05$) was the best approach for the pharmacokinetic profile of carbidopa administered intravenously (4 mg kg^{-1}) to the beagle dog. According to this model the relevant pharmacokinetic parameters (mean values ± s.e.m., n = 4) are summarized in Table 1.

The biological half-life ($t_{1/2}$, π) of carbidopa was 5 h and the volume of distribution in the central compartment (Vc) was 0·17 (litre kg^{-1}) min^{-1}. The total plasma clearance was 0·0053 litre kg^{-1}. The pharmacokinetic parameters obtained after the oral administration of carbidopa are shown in Table 2. The absorption of

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Table 1. Pharmacokinetic parameters of a three compartment model for carbidopa administered intravenously (4 mg kg^{-1}) in the beagle dog.

Parameter	Mean value ± s.e.m.	Unit
Initial concentration (Co)	23·9 ± 2·4	μg ml^{-1}
Coefficient of alpha phase (Ao)	25·3 ± 2·4	"
Coefficient of beta phase (Bo)	8·0 ± 0·7	"
Coefficient of pi phase (Po)	0·6 ± 0·2	"
Disposition constant of alpha phase (α)	0·209 ± 0·030	min^{-1}
Disposition constant of beta phase (β)	0·017 ± 0·001	"
Disposition constant of pi phase (π)	0·0031 ± 0·0009	"
Biological t½π	294·8 ± 82·5	min
Volume of distribution in the central compartment (Vc)	0·17 ± 0·02	litre kg^{-1}
Total plasma clearance	0·0053 ± 0·0006	(litre kg^{-1}) min^{-1}
Area under curve (AUC$^{0\to\infty}$)	779·13 ± 82·09	(μg ml^{-1}) min^{-1}

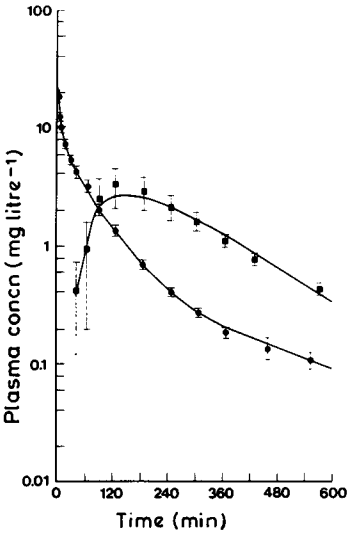

FIG. 1. Representative mean plasma concentrations of carbidopa after 4 mg kg^{-1} i.v. (●) and 75 mg by mouth (■) in the beagle dog.

Table 2. Pharmacokinetic parameters of carbidopa administered orally (75 mg) in the beagle dog.

Parameter	Mean value ±s.e.m.	Unit
Bioavailability	0·88 ± 0·8	—
Peak concentration (C_{max})	3·1 ± 1·1	μg ml^{-1}
Time to peak (T_{max})	158·6 ± 23·0	min
Lag time (to)	41·9 ± 7·5	min
Apparent absorption rate (Ka)	0·018 ± 0·004	min^{-1}

carbidopa was almost complete and the absolute bioavailability (F) was 88%. The peak concentration (C_{max}) was 3 μg ml^{-1} and the corresponding time (T_{max}) 2·5 h. Assuming that the absorption process follows first order kinetics, the absorption t½ was 40 min.

The mean plasma concentrations obtained after intravenous and oral administration of carbidopa are shown in Fig. 1.

The biological t½ estimated for carbidopa in the present study (t½, π = 5 h) was higher than that reported previously by Vickers et al (1974) in the same species (t½ = 1 h). Those authors made incomplete pharmacokinetic analyses of their data and the reported biological t½ of carbidopa was most probably underestimated.

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