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Determination of the steady-state volume of distribution using arterial and venous plasma data from constant infusion studies with procainamide

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The apparent steady-state volume of distribution (V_{ss}) of a drug is an important pharmacokinetic parameter. It can be estimated by the following general equation (Chiou 1982a):

$$V_{ss} = \frac{\int_0^\infty X_t\,dt}{\int_0^\infty C_t\,dt} \quad (1)$$

where X_t is the amount of drug in the body and C_t its concentration in plasma at time t, after a dose. Equation 1 is independent of the site of elimination and the route and rate of drug administration. It is also applicable to blood sampling at any site of the body. When a constant infusion is given intravenously and drug elimination is assumed to be proportional to the total body clearance, CL, equation 2 is obtained (Chiou 1982a):

$$V_{ss} = \frac{\int_0^\infty (A_t - CL\,AUC_{0\to t})\,dt}{AUC_{0\to\infty}} \quad (2)$$

where A_t is the total amount of drug infused into the body at time t, CL is the apparent total plasma clearance and AUC is the area under the plasma curve.

* Correspondence.

Until recently, relatively little attention has been directed toward the differentiation between arterial and venous (A–V) plasma concentration in pharmacokinetic analysis (Chiou & Lam 1982; Chiou et al 1981). Since the elimination of a drug is assumed to be directly proportional to its concentration in plasma, the potential effect of the plasma source on the kinetic parameters of drugs remains to be assessed. We now report the preliminary results of the influence of A–V differences on the determination of V_{ss} using the infusion method and attempt a rationale for such phenomena.

Method

Three pigmented male rabbits were anaesthetized with urethane 1·0 g kg^{-1} i.p., and the right carotid artery and the jugular vein catheterized with polyethylene tubing. A third catheter was placed in the sacral part of the vena cava via the right femoral vein, the tip of the cannula being positioned at the junction of the femoral branch (confirmed post mortem). The animals were allowed to recover overnight.

Infusion solutions prepared by dissolving varying amounts of procainamide HCl in 0·9% NaCl (saline) infused into the jugular vein by means of a constant infusion

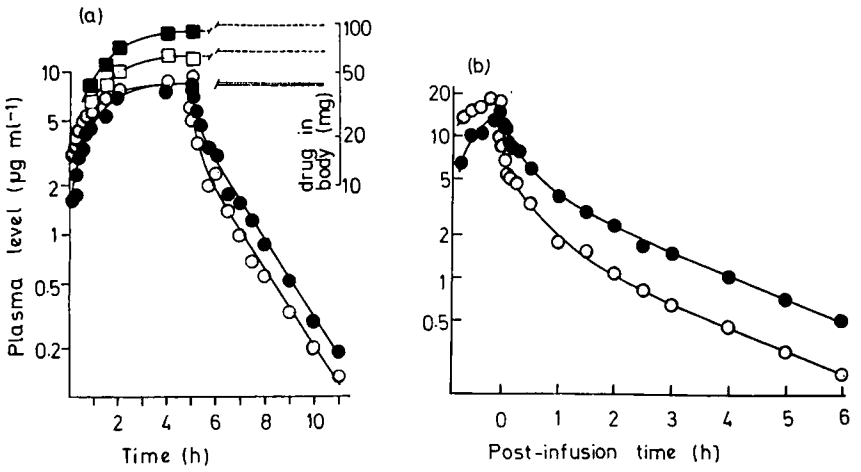

FIG. 1. Arterial (○, ...) and venous (●, ...) plasma procainamide levels during and after constant intravenous infusion of procainamide HCl in (a) rabbit no. 1 over 5 h (the response from rabbit no. 2 was very similar), and (b) rabbit no. 3 over 54 min. The top curves in (a) are the calculated amount of procainamide in the body from arterial (□) and venous (■) data. Dotted lines were obtained assuming the attainment of steady-state.

pump. A short-term infusion (54 min) was conducted in one rabbit and a long-term infusion (5 h) in two rabbits. Arterial and venous blood were collected simultaneously from carotid artery and femoral vein at predetermined times during and after the infusion. Blood samples were centrifuged immediately and plasma procainamide levels were assayed by a slightly modified h.p.l.c. method (Gadalla et al 1978).

In view of the apparent parallel terminal phase between arterial and venous data, the terminal rate constants were assumed to be the same and were estimated by a least squares regression analysis program (Metzler et al 1974). AUC was calculated by using the linear trapezoidal rule during the infusion period, the logarithmic trapezoidal rule for the post-infusion period, as recommended by Chiou (1978), and extrapolation after the last sampling point:

$$AUC = \sum_{i-1}^{m-1} \frac{Cp_{i+1} + Cp_i}{2}(t_{i+1} - t_i) + \sum_{i=m}^{n-1} \frac{Cp_{i+1} - Cp_i}{\ln(Cp_{i+1}/Cp_i)}(t_{i+1} - t_i) + \frac{\hat{C}p_n}{k} \quad (3)$$

where k is the elimination rate constant of the terminal phase, and $\hat{C}p_n$ is the computer estimated concentration of the last sampling point: The CL was estimated by dividing the total procainamide base infused by $AUC_0 \rightarrow \infty$, and V_{ss} was calculated according to equation 2.

Results

The plasma procainamide level profiles of the infusion studies are shown in Fig. 1a and b. During the infusion period, the arterial plasma levels rose rapidly and appeared to reach almost to the steady state at 5 h in the long-term infusion studies (Fig. 1a). Venous plasma levels, however, were lower at all times but approached the arterial curve at the end of infusion. After the infusion stopped, both curves declined polyexponentially with venous plasma levels being higher than the arterial counterparts. The mean venous-to-arterial ratios during the terminal phase averaged 1·9 among the studies (Fig. 1a and b. It is thus evident that the source of blood sampling has direct influence on the characteristics of plasma procainamide levels. Table 1 lists some of the relevant information and pharmacokinetic parameters of the individual rabbits. The mean V_{ss} estimated from venous data was 1·5 times higher than that from arterial data.

The reason for the differences in V_{ss} estimation based on different plasma data can be better understood by examination of equation 2. The amount of drug remaining in the body at time t during the infusion is equal to the amount of drug infused less the amount eliminated:

$$X_t = A_t - TBC \int_0^t C_t\,dt \quad (4)$$

Since venous plasma levels over the infusion period were

Table 1. Summary of constant infusion studies and calculated pharmacokinetic parameters.

Rabbit (kg)	Infusion rate mg h⁻¹	Duration of infusion	Type of data	AUC μg ml⁻¹ min	TBC ml min⁻¹	V_{ss} L kg⁻¹
No. 1 (2·9)	92·4	5 h	A	2558	156	2·7
			V	2490	161	4·1
No. 2 (3·0)	52·4	5 h	A	2024	113	2·7
			V	2103	109	3·9
No. 3 (3·15)	244·0	54 min	A	1269	150	2·7
			V	1492	127	4·1

* A and V stand for arterial and venous, respectively.

consistently lower than their arterial counterparts, the estimated amount eliminated will then be smaller and result in a larger estimated amount of drug remaining in the body. This will be the case even at the attainment of the steady state as shown in Fig. 1a. As a result, estimated V_{ss} values from venous data are higher than from arterial data. The dotted lines in Fig. 1a, would be obtained if the infusion continued to the steady state.

From a physiological point of view, the driving force for drug distribution and elimination lies mainly in the arterial blood (Chiou 1981, 1982a; Chiou & Lam 1982; Chiou et al 1981), hence the use of arterial plasma data is more appropriate to describe the disposition kinetics of drugs. The results of the present study have demonstrated the uptake and release of procainamide by the leg (assumed to be a non-eliminating tissue) during infusion and post-infusion periods, respectively. V_{ss} determination from arterial plasma, therefore, better reflects the 'true' apparent distribution volume of procainamide in these rabbits. The inclusion of an additional non-eliminating tissue from a venous sampling site simply increases this volume term by a factor of 1·5. Similar magnitudes of difference due to the use of arterial or venous plasma data in the determination of the V_{ss} of propranolol in dogs and rabbits have also been recently reported (Lam & Chiou 1981).

In the light of the potential effect of the A–V difference on the determination of V_{ss} and the difficulty and risk involved in sampling the systemic arterial blood, new equations employing venous plasma and urinary excretion data have been recently proposed for V_{ss} determination (Chiou & Lam 1981; Chiou 1982a). In other words, the determination of V_{ss} using these new equations is theoretically independent of the source of blood or plasma employed.

Finally, the observed A–V differences are not unique in this study; they have been reported for many compounds in animal and human (Chiou et al 1981; Orskov & Christensen 1969; Slot 1965; Tucker & Mather 1979). Their implications in the determination and in the physiological significance of the apparent volume of distribution at the pseudo-distribution equilibrium (Chiou 1981), and the total body clearance (Chiou 1982b) have been recently discussed.

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Cocaine-induced release of noradrenaline in rat tail artery

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The ability of cocaine to potentiate contractile responses to nerve stimulation and to exogenous noradrenaline has been demonstrated in isolated blood vessel preparations (see Vanhoutte et al 1981 for review). The mechanism of this potentiation is generally believed to involve inhibition of the neuronal uptake process resulting in an increase in the effective concentration of noradrenaline in the vicinity of the adrenoceptors.

Recently, we observed that isolated strips of rat tail artery contract in response to increasing concentrations of cocaine (Webb et al 1980). These contractions were blocked by phentolamine and were reduced after acute adrenergic denervation with 6-hydroxydopamine, suggesting that cocaine causes release of noradrenaline from adrenergic nerve endings. The present experiments were designed to test this interpretation.

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Adult, male albino rats (Sprague-Dawley, 350–400 g) were killed by cervical dislocation and tail arteries isolated, stored in physiological salt solution (PSS), and cut helically into strips (1·0 mm × 10 cm) under a dissecting microscope. After dissection, the preparations were incubated for 4 h in PSS containing 3×10^{-7} M [7-^{3}H] noradrenaline (spec. act. = 8·8 Ci mmol^{-1}; Amersham/Searle, Arlington Heights, IL). At the end of the incubation period, the strips were rinsed in fresh PSS and mounted for superfusion as described previously (Vanhoutte et al 1973; Lorenz & Vanhoutte 1975).

The arterial strips were suspended in a moist tunnel-shaped chamber maintained at 37 °C. The preparations were superfused at 3 ml min^{-1} by a constant flow roller pump with PSS. A three-way stopcock, upstream from the pump, allowed rapid switching from control solution to a