model was better and in one case the data could not be fitted satisfactorily to a three-compartment model. We therefore conclude that the simplest model consistent with our data is the two-compartment open model.

We have found our adaptation of the method rapid, sensitive and convenient such that large numbers of biological samples can be handled simultaneously.

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Steady state plasma concentration of clonidine and its relation to the effects on blood pressure in normotensive and hypertensive rats

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In a previous study it was found that clonidine given intravenously as bolus doses of less than 20 $\mu g\ kg^{-1}$ produced a dose-dependent hypotensive response in conscious normotensive rats. When the intravenous dose was increased, an initial short hypertensive phase became more and more dominant and in doses from 40–500 $\mu g\ kg^{-1}$ a clear dose-dependent increase of blood pressure was obtained. The subsequent fall in blood pressure was delayed up to 2 h in the dose of 500 $\mu g\ kg^{-1}$ (Paalzow & Edlund 1978). Obviously, in a certain dose range clonidine produces a hypotensive response, while in a higher dose-range the hypertensive effects dominate. It has been suggested that the hypotensive response of clonidine is induced by an inhibition of the sympathetic outflow from the brain (Schmitt et al 1968; Klupp et al 1970; Kobinger 1973; Haeusler 1974). The intial rise in blood pressure after i.v. bolus doses which has been observed both in man and in animals, has been suggested to be due to a stimulation of peripheral α-adrenoceptors (Schmitt et al 1971, 1973; Finch 1974; Ozawa et al 1977) as well as due to a central mechanism (Trolin 1975). We have aimed to evaluate the relationship between the steady state plasma concentrations of clonidine and the effects on arterial blood pressure in conscious normotensive and spontaneous hypertensive rats (SHR).

Male Sprague Dawley normotensive rats, 162–315 g, and SHR/Okamoto rats, 191–287 g, were used. Blood pressure was recorded in conscious rats through an indwelling carotid arterial catheter (Silastic o.d. 0·025 in) exteriorized at the back of the neck and connected to a pressure transducer (Statham P23DC) writing on a Grass Polygraph.

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Blood pressure was expressed as mean arterial blood pressure. Clonidine was infused through a catheter in the jugular vein exteriorized together with the arterial catheter. The two consecutive intravenous infusions technique described by Wagner (1975) was used to rapidly attain steady state plasma concentrations of clonidine. Variables needed for a given drug to be used in this technique are plasma clearance and half-life. These data were obtained from a previous study (Paalzow & Edlund 1979). The first more rapid infusion lasted for 30 min; this was then abruptly changed to a lower rate, which was maintained for the 2 h experiment. 15 min after the end of the first infusion, steady state plasma concentrations of clonidine were obtained and to check that these were maintained and in agreement with theoretically calculated values, plasma concentrations were determined from blood samples withdrawn from the jugular vein. Clonidine concentrations were assayed by gas liquid chromatography according to Edlund & Paalzow (1977). The initial infusion rate (Q_1) is given by equation 1 and the final rate (Q_2) by equation 2.

$$Q_1 = \frac{Q_2}{1 - e^{-\beta \cdot 30}} \quad (\text{ng min}^{-1}\,\text{kg}^{-1}) \qquad (1)$$

$$Q_2 = \frac{\text{Dose} \cdot C_{pss}}{A/\alpha + B/\beta} \quad (\text{ng min}^{-1}\,\text{kg}^{-1}) \qquad (2)$$

A, B, α, β are the coefficients and exponents of the bi-exponential equation describing the disposition of clonidine in plasma after an intravenous bolus dose (Edlund & Paalzow 1977; Paalzow & Edlund 1979).

In normotensive rats, a steady state value above 0·5 ng ml^{-1} was needed to obtain a decrease in blood

pressure (Fig. 1). Maximal blood pressure decrease was obtained at 0·80 ng ml^{-1} with a decrease of 17·5 ± 2·5% (s.e.) with a range of 15·1–20·0 mm Hg.

With increasing concentration of clonidine the blood pressure lowering became less pronounced and at 5·5 ng ml^{-1} only a 3·8 ± 1·8% decrease was obtained. 9·0 ng ml^{-1} gave an increase in blood pressure of 15·5 ± 3·4%. The data obtained on the relation between effect on blood pressure and steady state concentration of clonidine were fitted by a non-linear least square regression program (BMDP5R) to a polynomial equation. The predicted and observed values can be seen in Fig. 1. From his equation it can be calculated that for at least a 10% decrease in arterial blood pressure (usually about 10 mm Hg) the steady state plasma concentration should be in the range of 0·6–4·0 ng ml^{-1}.

The same kind of blood pressure response was obtained in SHR rats (Fig. 2), but, a higher plasma concentration was needed and the maximal blood pressure reduction was obtained at 2·6 ng ml^{-1}, with a decrease of 21·2 ± 8·2% (s.e.). The range which produced at least a 10% decrease in blood pressure was also found to be higher (1·0–5·0 ng ml^{-1}). The difference between the normotensive and hypertensive rats was not marked.

The present results show that clonidine has a narrow range of plasma concentrations for its hypotensive effects in the rat. Wing et al (1977) have also reported that patients not responsive to oral clonidine treatment had plasma concentrations above 10 ng ml^{-1}. These data are in accordance with the range of steady state concentrations for optimal effect in the present study in rats. In patients, with hypertension, we earlier reported that a dose-dependent decrease of blood pressure is obtained after i.v. administration of 75–275 μg as bolus doses and a corresponding linear effect relationship to the logarithm of the plasma concentrations in the range 0·5–3·0 ng ml^{-1} clonidine (Frisk-Holmberg et al 1978). Consequently, there is evidence that the therapeutic "window" obtained in rats could be the same in man.

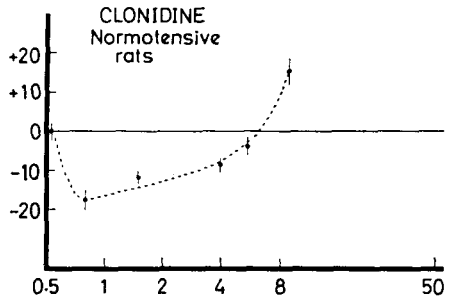

FIG. 1. Effects on blood pressure at different steady state plasma concentrations in the normotensive rat. Each point is a mean of 2–5 determinations, vertical bars show the standard error. Ordinate: change in mean blood pressure (%). Abscissa: Cp_{ss} (ng ml^{-1}).

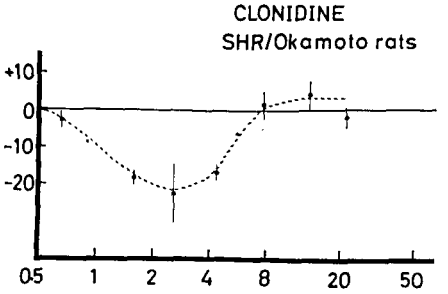

FIG. 2. Effects on blood pressure at different steady state plasma concentration in the hypertensive rat. Each point is a mean of 2–4 determinations, vertical bars show the standard error. Ordinate: change in mean blood pressure (%). Abscissa: Cp_{ss} (ng ml^{-1}).

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