CLONIDINE KINETICS IN MAN—EVIDENCE FOR DOSE DEPENDENCY AND CHANGED PHARMACOKINETICS DURING CHRONIC THERAPY

MARIANNE FRISK-HOLMBERG, LENNART PAALZOW & P.O. EDLUND

Section of Clinical Pharmacology, Department of Medical Pharmacology, and Hypertension Clinic, Uppsala University Hospital, Box 573, Biomedicum, S-751 23 Uppsala, Sweden; Department of Pharmacology, Central Research and Control Laboratory of the National Corporation of Swedish Pharmacies, Box 3045, S-171 03 Solna 3, Sweden.

- 1 Clonidine kinetics were studied in 21 patients with essential hypertension. All received two bolus i.v. injections in the mean dose range of ($0.78\text{--}3.36\ \mu\text{g kg}^{-1}$) and one single oral dose (mean dose $1.7\text{--}2.3\ \mu\text{g kg}^{-1}$) on separate occasions. The kinetics were also studied in some of these patients after multiple therapeutic oral dose (mean dose 1.1 or $1.9\ \mu\text{g kg}^{-1}$) twice daily during a dosage interval after 6–12 months monotherapy with clonidine. The multiple oral dosage was based on the therapeutic response.
- 2 With increasing i.v. doses the rate constants (α , β) decreased and the plasma clearance was reduced by 74% ($9.94\text{--}2.61\ \text{ml min}^{-1}\ \text{kg}^{-1}$) indicating dose-dependent kinetics. The volume of distribution ($V_d\beta$) did not change with dose in contrast to the volume of the plasma compartment (V_c) which was increased at the highest doses.
- 3 The single oral dose kinetics agreed with the i.v. kinetics at comparable dose. The bioavailability was 90%.
- 4 During multiple oral dosing the elimination rate constants decreased compared to the single dose. The plasma clearance increased ($7.18\ \text{ml min}^{-1}\ \text{kg}^{-1}$) compared to the corresponding single dose ($4.17\ \text{ml min}^{-1}\ \text{kg}^{-1}$). The latter change was probably caused by the decrease in bioavailability to about 65%.
- 5 The pharmacodynamic properties of the drug could explain the changes in pharmacokinetics with increased dose and during multiple doses.

Introduction

The kinetics of clonidine after oral doses have not been fully elucidated. Dollery and coworkers have studied the kinetics after single oral doses in a few normotensive and hypertensive patients and also investigated the kinetics after multiple dose administration (Wing *et al.*, 1977; Dollery *et al.*, 1979). The authors claimed that the kinetics after a single dose did not change after 1 week of treatment and were similar in these subjects. We have already described the kinetics of clonidine after bolus i.v. injections of increasing doses ($75\text{--}275\ \mu\text{g}$) to hypertensive patients (Frisk-Holmberg, Edlund & Paalzow, 1978). Clonidine was found to have a rapid distribution phase and a plasma clearance, which decreased from $5.70\ \text{ml min}^{-1}\ \text{kg}^{-1}$ after the lowest, to $2.98\ \text{ml min}^{-1}\ \text{kg}^{-1}$ after the highest dose, indicating dose-dependent kinetics. We suggested that the observed decrease in plasma clearance could be due to the reduction of the rate constant of the β -phase. In the present study we have extended our pharmacokinetic investigations of

clonidine with a special effort to elucidate the possible dose dependency in clonidine disposition and we also investigated the kinetics after single and multiple oral dose to patients with essential hypertension.

Methods

Patients

Twenty-one (6 females, 15 males) previously untreated patients with essential arterial hypertension corresponding to WHO stage I–II participated. The diagnosis was based on three separate (4 weeks apart) blood pressure measurements on the right upper arm at the hypertension clinic. The mean systolic and diastolic blood pressures are given in Table 1. A physical examination including eye fundus inspection, ECG, renogram, chest X-ray, blood and urine

Table 1 Anthropometric data of patients.

	Number of patients	Age (years)	Weight (kg)	Mean supine arterial blood pressure (mm Hg)			
				systolic untreated	systolic treated*	diastolic untreated	diastolic treated*
Female	6	42 ± 17	59 ± 27	155 ± 5	137 ± 2	100 ± 5	85 ± 7
Male	15	43 ± 14	79 ± 26	160 ± 10	145 ± 5	100 ± 10	95 ± 4
Total	21	46 ± 8	76 ± 22	160 ± 10	140 ± 4	100 ± 10	90 ± 5

*After 6–12 months' chronic dosage on clonidine 75 µg twice daily or 150 µg twice daily (7 patients, 3 females and 4 males).

analysis, and creatinine clearance were performed. Renal function was within normal limits for all patients. None of the patients had any clinical or biochemical evidence of other diseases and none was taking any known enzyme-inducing or other medication including contraceptives. The aim of the study was fully explained to the patients and all gave their consent to participate. The study was approved by the ethic committee of the University Hospital.

Procedure

Single i.v. dose: Of 21 patients, 13 received two separate i.v. bolus injections (one low dose <150 µg and one high dose >150 µg; one patient received the same dose twice) of clonidine in doses from 0.51–3.81 µg kg⁻¹. Eight of the patients only volunteered for one injection (<150 µg).

Single and multiple oral dose: Ten of the 13 patients participated in the single oral dose and seven of these patients in the chronic oral dose study.

After an overnight fast the patients arrived at the hospital in the morning at 07.00 h and remained for 12 h. All doses were given at the hospital.

Venous sampling for clonidine determinations was done before dosing and 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, 720 and 1440 min (not chronic doses). After the oral dose the 5, 10, 45 min samples were not taken. The patients returned to the hospital the following morning for the last 24 h blood sampling.

The blood samples were centrifuged immediately after they were drawn and the internal standard (2-(2,4-dichlorophenyl-amino)-2-imidazoline) was added to the samples and the samples were stored at -40°C until analysed by a gaschromatographic method (Edlund, 1979). The sensitivity was 50 pg/ml and the recovery using this method was 40–60% for concentrations in the range of 0.1–1 ng/ml. Clonidine was administered as clonidine hydrochloride (Catapresan, Boehringer Ingelheim AB FRG) and all doses are expressed as the salt. The compliance of the patients during the chronic study was estimated by tablet counting and patient reliability.

Analysis of data

Plasma concentration-time data for each subject were fitted to biexponential equations by the non-linear least square regression program, NONLIN, and run on an IBM 370 computer. The individual data points were given the weight 1/y and the mean values the reciprocal of the coefficient of variation, respectively. Secondary kinetic parameters such as AUC, clearance and volumes of distribution were calculated from the obtained coefficients and exponents according to Wagner (1975).

Multiple dose data, considering different doses and dosing interval, were fitted to multiexponential functions by the special subroutine of DFUNC as described by Elfving & Metzler (1978). The bioavailability was obtained by comparing the AUC during a dosage interval during multiple dosage with the AUC after the same dose as a bolus i.v. injection for each patient. The mean values were then calculated. Significance between observations was obtained by using conventional statistical methods like *t*-test and analysis of variance. Values are given as means ± s.d. if not stated otherwise.

Results

Single i.v. dose

The individual concentration-time profiles of clonidine in doses of 0.78 to 3.86 µg kg⁻¹ were best fitted to a biexponential decay and the mean plasma concentration-time curves are shown in Figure 1. The mean values of the kinetic parameters at different doses are given in Table 2. The rate constants α and β decreased with increasing dose. The decreases were significant ($P < 0.01$) after the 3.36 µg kg⁻¹ dose compared to 0.78 µg kg⁻¹. The half-life of the β -phase was increased two-fold to 12.8 ± 2 h after the highest dose of 3.36 µg kg⁻¹ compared to that after the lowest dose 6.2 ± 2.3 h. The total plasma clearance similarly decreased by ~74% from 9.94 to 2.61 ml min⁻¹ kg⁻¹ (Table 2). The AUC increased in a linear manner

Figure 1 Plasma concentration-time curves after single bolus injections of clonidine (■ $0.78 \mu\text{g kg}^{-1}$, □ $1.27 \mu\text{g kg}^{-1}$, ● $1.79 \mu\text{g kg}^{-1}$, ○ $2.35 \mu\text{g kg}^{-1}$, ▲ $3.36 \mu\text{g kg}^{-1}$). Each point represents the mean $\pm$ s.d. The curve of the best fit obtained by least square analysis is given.

with dose except for the highest dose (Table 2). The volume of distribution ($V_d\beta$) averaged 3.45 l kg^{-1} and did not seem to change with dose, in contrast to the volume of the plasma compartment (V_c) which was increased for the doses 3.36 and $2.35 \mu\text{g kg}^{-1}$ compared to 1.27 and $1.79 \mu\text{g kg}^{-1}$.

Single oral dose

Two single oral doses from mean 1.77 and $2.33 \mu\text{g kg}^{-1}$ were given to 10 patients on separate occasions (Table 3). The elimination rate constants (K_e) corresponded to those found after the bolus i.v. injections (β). The absorption rate constant (K_a) was the same at both oral doses with a half-life of $\sim 0.5 \text{ h}$ and thus the absorption of clonidine should be complete within 2.5 h . The maximal plasma concentration occurred 1.5 – 2.5 h after dose. The volume of distribution and plasma clearance (Table 3) corresponded to those found after corresponding i.v. doses. The bioavailability (F) ranged from 88 – 96% and the extent of absorption therefore seemed to be near complete (Table 3).

Multiple oral dose

Seven of the patients were treated for 6 months or more with clonidine in a mean daily dose of 1.08 or $1.94 \mu\text{g kg}^{-1}$ twice daily. All patients responded and the choice of dose was based on the therapeutic effect in the individual patient (Table 1). The mean values of pharmacokinetic parameters during a dosage inter-

val are shown in Table 3. The elimination rate constant (K_e) decreased compared to the single dose study. The biological half-life thus increased from 8.0 h to 14.3 h in the chronic situation. An interesting observation was that during the chronic treatment the absorption rate constant K_a decreased significantly ($P < 0.01$) after the highest dose of $1.94 \mu\text{g kg}^{-1}$. This is both in comparison to the single oral doses and to the lower oral dose during chronic treatment. The volume of distribution was unchanged compared to the values after single oral dose. An increase of the plasma clearance was also found during chronic treatment compared to the single dose. An almost complete bioavailability (F) after single oral dose was consequently reduced to about 65% during the chronic situation (Table 3). This decrease in F was also obvious from the individual patient data (Table 4). The listed patients obtained the same single and multiple oral dose.

Discussion

The present results support our previous suggestion (Frisk-Holmberg *et al.*, 1978) of a dose-dependent disposition of clonidine.

After increasing i.v. doses of clonidine the disposition rate constants (α , β) and the plasma clearance decreased. The decrease of the latter is reflected by the change in β since the volume of distribution was not changed in the dosage range studied. Single oral dose kinetics agreed with the single i.v. kinetics. The

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d.) after increasing bolus intravenous injections of clonidine:

$$C_p = A \cdot e^{-\alpha t} + B e^{-\beta t}; AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

$$V_d \beta = \frac{\text{Dose}}{\beta \cdot AUC}; Cl = V_d \beta \cdot \beta = \frac{\text{Dose}}{AUC}$$

Mean dose ($\mu\text{g kg}^{-1}$)	A^3 (ng ml^{-1})	α (min^{-1})	B^3 (ng ml^{-1})	β (min^{-1})	$T_{1/2} \beta$ (h)	AUC ($\text{ng ml}^{-1} \text{ min}$)	Cl ($\text{ml min}^{-1} \text{ kg}^{-1}$)	$V_d \beta$ (l kg^{-1})	V_c (l kg^{-1})
0.78 ± 0.32 (0.5-1) ¹ $n^2 = 6$	0.26 ± 0.11	0.225 ± 0.039	0.19 ± 0.02	0.0019 ± 0.0007	6.18 ± 2.28	78.4 ± 20.9	9.94 ± 5.15	5.32 ± 2.72	2.23 ± 0.85
1.27 ± 0.2 (1.01-1.50) ¹ $n = 7$	0.78 ± 0.18	0.301 ± 0.037	0.38 ± 0.02	0.0015 ± 0.0003	7.63 ± 1.62	319 ± 48	3.98 ± 0.6	2.63 ± 0.39	0.86 ± 0.11
1.79 ± 0.31 (1.51-2.00) ¹ $n = 9$	0.83 ± 0.12	0.218 ± 0.017	0.33 ± 0.01	0.0013 ± 0.0002	9.25 ± 1.18	485 ± 49	3.69 ± 0.37	2.96 ± 0.3	0.86 ± 0.08
2.35 ± 0.51 (2.01-3.00) ¹ $n = 7$	0.33 ± 0.05	$0.136 \pm 0.012^{**}$	0.29 ± 0.01	0.0010 ± 0.0002	11.33 ± 1.79	675 ± 80	3.48 ± 0.41	3.42 ± 0.4	$1.61 \pm 0.19^{**}$
3.36 ± 0.35 (3.01-3.81) ¹ $n = 6$	0.19 ± 0.04	$0.046 \pm 0.007^{**}$	0.34 ± 0.02	$0.0009 \pm 0.0001^{**}$	12.83 ± 2.02	1290 ± 171	$2.61 \pm 0.24^{**}$	2.9 ± 0.3	$1.89 \pm 0.18^{**}$

¹Figures in brackets denote dose range.² n = number of patients receiving the dose.³= dose normalized to $1.00 \mu\text{g kg}^{-1}$.^{**}($P < 0.01$) denotes value significantly different from value after 0.78 and $1.27 \mu\text{g kg}^{-1}$ dose.

elimination half-life was also in agreement with that previously found by us (Frisk-Holmberg *et al.*, 1978) and others (Wing *et al.*, 1977; Dollery *et al.*, 1979) studying hypertensive patients. The bioavailability after the single oral doses was high, ~90%.

The area under the curve (AUC), however, changed in a linear manner with increasing dose despite the decrease in the constants α and β . As is apparent from Table 2 the reason for this could be the simultaneous decrease of the coefficients A and B of the exponential terms since AUC equals the sum of A/α and B/β . The first coefficient A equals the ratio $\text{Dose} \cdot (\alpha - k_{21})/V_c(\alpha - \beta)$ and B equals $\text{Dose} \cdot (k_{21} - \beta)/V_c(\alpha - \beta)$ and changes are therefore possible both in the rate constants of distribution to and from tissues as well as in the volume of distribution. The latter V_c was in fact also increased at the highest dose of clonidine.

In an extensive study on the pharmacokinetics of clonidine in animals we have earlier found a nonlinear pharmacokinetic behaviour of clonidine (Paalzow & Edlund, 1979). This was suggested to be a consequence of a change of the tissue perfusion caused by a vasoconstriction since it is known that clonidine at higher concentrations, as a postsynaptic α -adrenoceptor agonist, produces vasoconstriction (Schmitt, 1977). A decreased ability of clonidine to distribute

into tissues from the blood stream will lead to an increase of V_c with increasing dose, which was found in the present study.

During chronic oral administration, the kinetics of clonidine changed. The plasma clearance increased and the bioavailability (F) decreased in comparison to the single oral dose (Table 3 and Table 4). The marked decrease in bioavailability is regarded as the main reason for the increase in plasma clearance since elimination rate constant K_e decreased and V_d remained unchanged. The decrease of K_e could be caused by the same factors as those discussed previously.

The mechanisms for the decreased bioavailability during chronic dosing could be several: enhanced drug metabolism and/or a decrease of the rate and/or extent of absorption. Results from previous studies in man (Darda & Förster, 1978) and animal (Rehbinder & Deckers, 1969) and from liver perfusion experiments in rats with clonidine (Paalzow & Edlund, 1979) do not indicate an increase of the metabolic rate. On the other hand clonidine as an α -adrenoceptor agonist might inhibit the gastrointestinal motility and the gastric emptying and thus decrease absorption. Recently it has also been reported that clonidine depresses the small intestinal transit to 20–30% of the control values in the rat (Renwart,

Table 3 Pharmacokinetic parameters after single and chronic¹ oral treatment with clonidine:

$$C_p = \frac{F \cdot \text{Dose} \cdot K_a}{V_d \cdot (K_a - K_e)} (e^{-k_e t} - e^{-k_a t})$$

$$AUC = \frac{F \cdot \text{Dose} \cdot K_a}{V_d \cdot (K_a - K_e)} \left(\frac{1}{k_e} - \frac{1}{k_a} \right); Cl = \frac{\text{Dose}}{AUC}$$

$$F = \frac{AUC_0 \cdot \text{Dose}_{iv}}{\text{Dose}_0 \cdot AUC_{iv}}$$

Mean dose ($\mu\text{g kg}^{-1}$)	K_a (min^{-1})	K_e (min^{-1})	$T_{1/2}$ (h)	V_d (l kg^{-1})	AUC ($\text{ng ml}^{-1} \text{min}$)	Cl ($\text{ml min}^{-1} \text{kg}^{-1}$)	F(%)
1.77 $\pm$ 0.4 (1.51–2.00) ² $n^3 = 7$	0.022 $\pm$ 0.006	0.0015 $\pm$ 0.0004	7.98 $\pm$ 2.12	2.88 $\pm$ 0.29	424 $\pm$ 42	4.17 $\pm$ 0.42	88 $\pm$ 9
2.3 $\pm$ 0.5 (2.01–3.00) ² $n = 3$	0.021 $\pm$ 0.011	0.0012 $\pm$ 0.0009	9.38 $\pm$ 2.35	2.94 $\pm$ 0.77	635 $\pm$ 73	3.62 $\pm$ 0.54	96 $\pm$ 11
1.08 ¹ $\pm$ 0.2 (1.01–1.5) ² $n = 3$	0.047 $\pm$ 0.007	0.0008 $\pm$ 0.0005*	15.2 $\pm$ 6.10	2.81 $\pm$ 1.62	172.2 $\pm$ 32	6.27 $\pm$ 1.25	64 $\pm$ 11**
1.94 ¹ $\pm$ 0.1 (1.5–2.0) ² $n = 4$	0.014 $\pm$ 0.001**	0.0008 $\pm$ 0.0004*	14.3 $\pm$ 6.21	2.93 $\pm$ 1.56	270.0 $\pm$ 54	7.18 $\pm$ 1.79	52 $\pm$ 10**

¹Twice daily regimen > 6 months.

²Figures in brackets denote dose range.

³ n = number of patients receiving the dose.

*($P < 0.05$) **($P < 0.01$) denote value significantly different from single dose (1.77 $\mu\text{g kg}^{-1}$) value.

Table 4 Biological availability (F) for individual patients who received the same single oral and multiple dosage

$\frac{\text{AUC oral}}{\text{AUC i.v.}}$		
Patient and dose of clonidine ($\mu\text{g/kg}$)	Single oral dose (%)	Multiple oral dose (%)
M.L. 1.07 (♀)	94.6	72.9
C.W. 1.76	78.2	69.9
M.P. 1.92 (♀)	88.0	55.3
S.A. 1.92	91.8	54.7
A.T. 2.59 (♀)	77.4	72.0
Mean $\pm$ s.d	86.0 $\pm$ 3.5	64.9 $\pm$ 4.1**

** $P < 0.01$

Klepper & Rush, 1980). A vasoconstriction of the absorptive intestinal areas (clonidine is a base with a pK_a 8.05 (Struyker-Boudier *et al.*, 1975) could also contribute to the reduction of the rate and/or the

extent of absorption. Still other possibilities exist. The blood pressure reduction (= the therapeutic effect) as such, could contribute to the observed change in kinetics. At present it is not known how physiological changes (e.g. change from a hypertensive to a normotensive condition) influence drug kinetics.

Thus, the pharmacodynamic properties of clonidine appear to be a plausible explanation for the change in kinetics found both with increased single i.v. dose and during multiple oral dosing. The present findings further support our concept (Frisk-Holmberg *et al.*, 1978) that clonidine therapy should be monitored carefully.

We are grateful to Marianne Sundblad, RN, who participated in the hypertension care.

The work was supported by a grant from the Swedish Medical Research Council B-79 04X 541 401 and Boehringer Ingelheim, FRG.

References

- DARDA, S., FÖRSTER, H.S. & STAHL, H. (1978). Metabolischer Abbau von clonidin. *Arzneim-Forsch. (Drug Res.)*, **28**, 255–259.
- DOLLERY, C.T., DAVIES, D.S., DRAFFAN, G.H., DARGIE, M.B., DEAN, C.R., PHIL, D., REID, J.L., CLARE, R.A. & MURRAY, S. (1979). Clinical pharmacology and pharmacokinetics of clonidine. *Clin. Pharmac. Ther.*, **19**, 11–17.
- EDLUND, P.O. (1979). Determination of clonidine in human plasma by glass capillary gas chromatography with electron-capture detection. *J. Chromatogr.*, **187**, 161–169.
- ELFVING, G.L. & METZLER, C.M. (1978). Reported at 125th Annual Meeting of APhA (Academy of Pharmaceutical Sciences), Montreal.
- FRISK-HOLMBERG, M., EDLUND, P.O. & PAALZOW, L. (1978). Pharmacokinetics of clonidine and its relation to the hypotensive effect in patients. *Br. J. clin. Pharmac.*, **6**, 227–232.
- PAALZOW, L. & EDLUND, P.O. (1979). Pharmacokinetics of clonidine in the rat and cat. *J. Pharmacokin. Biopharm.*, **7**, 481–494.
- REHBINDER, D. & DECKERS, W. (1969). Untersuchungen zur Pharmacokinetic und Metabolismus des 2-(2,6-dichlorphenylamino)-2-imidazolinhydrochlorid (ST 155). *Arzneim-Forsch. (Drug Res.)*, **19**, 169–176.
- RENWART, M.I., KLEPPER, M.S. & RUSH, B.D. (1980). Clonidine delays small intestinal transit in the rat. *J. Pharmac. exp. Ther.*, **212**, 487–490.
- SCHMITT, H. (1977). The pharmacology of clonidine and related compounds. In *Antihypertensive Agents*, Handbook of experimental Pharmacology, ed. Gross, F. **39**, 299–378. Berlin: Springer Verlag.
- STRUYKER-BOUDIER H.A.J., de BOER, J., SMEETS, G., ZIEN, E.S. & van ROSSUM, J. (1975). Structure activity relationships for central and peripheral adrenergic activities of imidazoline derivatives. *Life Sci.*, **17**, 377–386.
- WAGNER, J. (1975). *Fundamentals of clinical pharmacokinetics*. Hamilton (Ill): Drug Intelligence Publications.
- WING, L.M.H., REID, J.L., DAVIES, D.S., NEILL, E.A.M., TIPPET, P. & DOLLERY, C.T. (1977). Pharmacokinetic and concentration-effect relationships of clonidine in essential hypertension. *Eur. J. clin. Pharmac.*, **12**, 463–469.

(Received December 31, 1980)