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PHARMACOKINETICS OF CLONIDINE AND ITS RELATION TO THE HYPOTENSIVE EFFECT IN PATIENTS

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1 The kinetics of clonidine and its relation to the blood pressure response after single intravenous doses of 75 μg–275 μg in hypertensive patients were determined.

2 Clonidine disposition could be described by a two compartment open model and pharmacokinetic parameters show a rapid distribution phase of 20–30 min and a mean plasma clearance of 4.6 ml min^{-1} kg^{-1} (75–200 μg). The half-life of the β-phase was found to be in the range of 7.4–11.4 h. Indications of dose dependent kinetics were obtained.

3 A dose-dependent decrease in blood pressure was obtained.

4 The maximal reduction in MAP (mean arterial blood pressure) was significantly ($P < 0.01$) related to plasma concentrations of clonidine.

5 The reduction in MAP was always related to plasma concentrations of clonidine ($r = 0.88$, $P < 0.01$) when pseudoequilibrium of distribution of the drug was achieved.

Introduction

Clonidine is an α-adrenoceptor agonist with both peripheral and central effects. In man it is used in the treatment of hypertension in doses from 0.075 to 1.5 mg daily (Hoobler & Sagastume 1971; Mroczek, Davidov & Finnerty, 1972). However, the efficacy during chronic treatment seems variable and higher doses (~5.4 mg daily) have recently been reported to fail to produce a hypotensive response in patients (Wing, Reid, Davies, Dargie & Dollery, 1977). The failure after these doses which give plasma concentrations of clonidine above 10 ng/ml or more has been suggested to be due to peripheral α-adrenoceptor stimulation. The initial rise in blood pressure which has been observed by some investigators after bolus intravenous injections of 150–300 μg of the drug (Kroetz, McRaven, Kioschos & Kirkenwall, 1970; Kobinger, 1973) has also been attributed to peripheral α-adrenoceptor stimulation. These studies indicate that the dose of clonidine is of importance for its therapeutic effect. No studies as far have investigated the relationship between the kinetics of clonidine and its hypotensive effect in patients. In the present study we have therefore aimed to elucidate this relationship after intravenous administration of the drug.

Methods

Patients

Thirteen previously untreated patients of both sexes with essential hypertension of WHO stage I-II, attending our hypertension clinic participated. The patients had no other diseases. The untreated mean arterial pressures, based on three separate measurements in the clinic are given in Table 1. The patients were categorized as low–normal renin essential hypertensives on the basis of their plasma renin activity/24 h urinary sodium excretion ratio (Table 1). They were given one or repeated (on separate occasions) doses of the drug. The aims of the study were fully explained to them and all gave their consent to participate.

Procedure

Clonidine hydrochloride was given as a bolus with the patients in the supine position and intravenous cannulae in each arm, one for the injection and one for sampling. Blood pressure response was recorded as mean arterial pressure (MAP) and measured with a scaled mercury sphygmomanometer. The heart rate and blood pressure were both recorded every 15 min for 1 h before the injection, every 2 min (10 min) and every 5 min (50 min) for the hour after the injection and then hourly for 8 h by the same person with the patients still lying. Measurements were also made at 12 and 24 h after the injection. Doses of 75 μg, 100 μg, 150 μg, 200 μg and 275 μg were injected. Venous sampling for clonidine determinations were made immediately before 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 720, 1440 min after the injection. Immediately after the blood samples were drawn they were centrifuged, the internal standard (2,-(2,4-dichlorophenyl-amino)-2-imidazoline) was added and the samples were stored at −40°C until analyzed.

Samples for plasma renin activity were collected into ice cold tubes after the hour of supine rest and analyzed using a standard radioimmunoassay kit. Clonidine was determined by a gas liquid chromatographic procedure as described by Edlund & Paalzow (1977) with a sensitivity of 100 pg/ml and a s.d. less than 15% for single determinations.

Analysis of data

The plasma concentration data for each subject were fitted to a biexponential function by the nonlinear least-square regression program NONLIN 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. Significance of and between observations was obtained by using conventional statistical methods like linear regression analysis, paired *t*-tests for dependent and independent variables.

Results

Kinetic analysis of plasma concentration data

The individual concentration profiles of clonidine in doses from 75 μg–275 μg were best fitted to a biexponential decay and the mean curves are shown (see Figure 1). This suggests that the distribution of clonidine in the body can be described by a two compartment open model. In Table 2 are shown the mean values of individual kinetic parameters. The half-life for the α-phase was 2.4–2.8 min in the dose interval 100–200 μg and for the β-phase 7.4–9.2 h. These values were not significantly lower than those obtained after the 75 and 275 μg dose although the mean of the latter were different.

In Table 3 the volume of distribution, $V_d\beta$, mean plasma clearance and dose normalized areas under the plasma curve (AUC) for dose interval 75–275 μg are tabulated. The AUC in the doses 75–200 μg averaged 256.3 ± 44.4 min μg ml^{-1} and was increased about 1.5 times when the dose was increased to 275 μg. A continuous increase of the areas was observed from 150 μg to 275 μg (Table 3).

Table 1 Patient data.

Patient	*Age (years)*	*Plasma renin activity (ng ml^{-1} h^{-1})*	*Urinary sodium excretion (mmol/l)*	*MAP (initial) (mm Hg)*	*Clonidine dose i.v. (μg)*
KB	52	3.9/127		113	150
LS	40	1.38/176		114	150, 200
CB	50	1.32/155		113	75, 75
IE	42	2.3/284		121	75, 150
MP (F)	37	1.84/103		116	150, 275
RB	48	1.68/197		112	150
GL	44	0.68/85[2]		116	150
ML (F)	52	0.2/175[2]		120	75, 150
AT (F)	33	0.1/168[2]		116	100, 150
GL	60	1.39/238		121	150, 275
BG	49	1.63/179		128	100, 200
GB	38	0.65/144[2]		112	150
SA	52	0.5/246		121	150, 275
Group mean	46 ± 8			118 ± 6	

[1] F = female
[2] Patient categorized as low renin essential hypertensive.

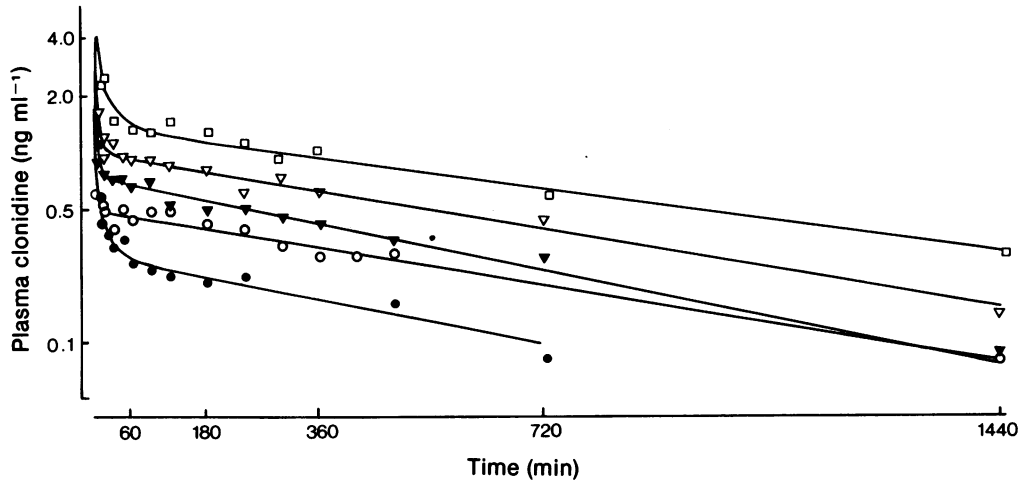

Figure 1 Plasma concentration (mean of group) – time curves for clonidine after i.v. administration of 275 μg □, 200 μg ▽, 150 μg ▼, 100 μg ○ and 75 μg ●.

Blood pressure effects

Intravenous doses of clonidine from 75–275 μg produced a dose dependent decrease in both systolic and diastolic blood pressures in these hypertensive patients as is seen in Figure 2 where the maximal blood pressure response (MAP_{max}) is plotted against logarithm of the dose. A highly significant relation between dose and blood pressure reduction was obtained ($r=0.97$, $P<0.01$). Analysis of regression gave a significant slope ($P<0.001$) and analysis of variance revealed no significant difference from regression ($P<0.05$). No blood pressure increase was observed after these doses using the described technique. The maximal response occurred between 0.5–1 h post injection. The blood pressure reduction after the higher doses of 200–275 μg was still observed 24 h after administration. No relation between the renin status of the patients and the degree of blood pressure decrease was found. The heart rate was also reduced after the injections but no relation between maximal heart rate reduction and dose was obtained (Table 4).

Relation between clonidine plasma concentration and blood pressure reduction

A positive correlation was found between the maximal change in MAP and the logarithm of the plasma concentrations of clonidine as is seen in Figure 3 ($r=0.86$, P 0.01). At concentrations of 0.9 ng/ml the decrease in MAP was 16 mm Hg and at concentrations of 2.2 ng/ml the blood pressure decrease was 34 mm Hg (patient SA) and at concentrations of 0.2 ng/ml the blood pressure decrease was 6 mm Hg and at concentrations of 0.5 ng/ml the decrease was 11 mm Hg (patient IE).

Table 2 Pharmacokinetic parameters (mean ± s.d.) for clonidine after intravenous doses of 75 μg, 100 μg, 150 μg, 200 μg and 275 μg. $C_p = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$

Dose (μg i.v.)	*A (ng/ml)*	*α (min⁻¹)*	*$T_{\frac{1}{2}}\alpha$ (min)*	*B (ng/ml)*	*β (min⁻¹)*	*$T_{\frac{1}{2}}\beta$ (h)*
75	0.451 ±	0.066 ±	10.5 ±	0.286 ±	0.00146 ±	7.9 ±
$n=4$	0.0061	0.017	2.7	0.023	0.00041	2.2
100	0.240 ±	0.251 ±	2.8 ±	0.490 ±	0.00125 ±	9.2 ±
$n=2$	0.521	0.425	4.7	0.018	0.00022	1.6
150	2.077 ±	0.261 ±	2.6 ±	0.734 ±	0.00157 ±	7.4 ±
$n=11$	0.697	0.061	0.6	0.025	0.00017	0.8
200	2.703 ±	0.285 ±	2.4 ±	0.993 ±	0.00131 ±	8.8 ±
$n=2$	1.428	0.092	0.7	0.035	0.00022	1.5
275	2.806 ±	0.066 ±	15.1 ±	1.389 ±	0.0010 ±	11.4 ±
$n=3$	1.463	0.038	6.0	0.178	0.00036	4.1

n = number of patients.

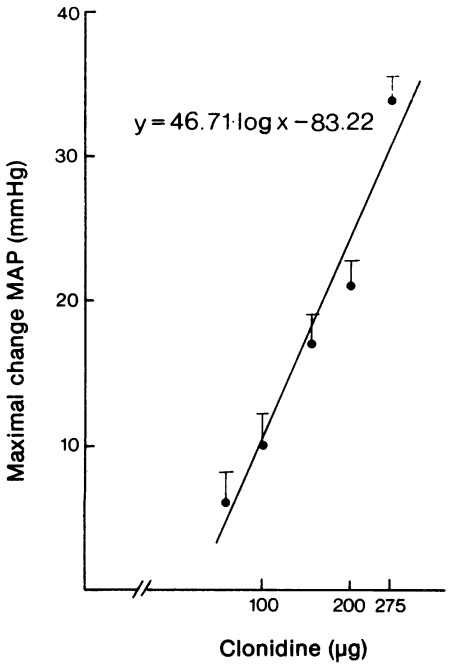

Figure 2 Relationship between blood pressure response (expressed as maximal change in mean arterial blood pressure (MAP, mean of group ± s.d.) and dose of clonidine (log scale). $r = 0.972$, $P < 0.01$.

Figure 4 illustrates the relationship between the log mean plasma concentrations of clonidine and the mean blood pressure reduction plotted after the different doses (75–275 μg) at all points of time during pseudoequilibrium of distribution. This phase was considered to be present after a point of time corresponding to seven times $T_{\frac{1}{2}}\alpha$ (Table 2). A significant positive correlation ($r = 0.86$, $P < 0.02$) was obtained in the concentration interval studied.

Discussion

In the present study after intravenous doses of 75–275 μg the plasma concentrations of clonidine declined in a biexponential manner indicating that the distribution of this drug can be described by a two-compartment open model. After doses of 100–200 μg a rapid distribution phase of approximately 20–30 min was followed by a slow elimination phase with a mean plasma clearance of ~4 ml min^{-1} kg^{-1} and a half-life for the decline of the terminal plasma concentration curve in the range of 7.4–9.2 h. The interpatient variability was low and the pharmacokinetic parameters are in agreement with those which have been reported from studies on volunteers using a different method for analysis of clonidine (Davies, Wing, Reid, Neill, Tipett & Dollery, 1977). In the doses from 150 μg to 275 μg the areas under the plasma concentration curve were increasing

Table 3 Pharmacokinetic parameters for clonidine after intravenous doses of 75 μg, 100 μg, 150 μg, 200 μg and 275 μg. Each number represents the mean of individual data

Dose (μg i.v.)	*AUC[1] (min μg ml^{-1}) (Dose normalized)*	$V_{d\beta}$[2] *(l/kg)*	*Mean plasma[3] clearance (ml min^{-1} kg^{-1})*
75 $n=4$	202.4	3.91	5.70
100 $n=2$	295.0	3.12	3.91
150 $n=11$	237.6	3.10	4.86
200 $n=2$	289.6	3.06	3.99
275 $n=3$	386.7	2.95	2.98

n = number of patients
AUC is the area under the plasma concentration curve
$V_{d\beta}$ is the volume of distribution

[1] $AUC = \frac{A}{\alpha} + \frac{B}{\beta}$

[2] $V_{d\beta} = \frac{Dose}{\beta \cdot AUC}$

[3] $V_{d\beta} \cdot \beta$

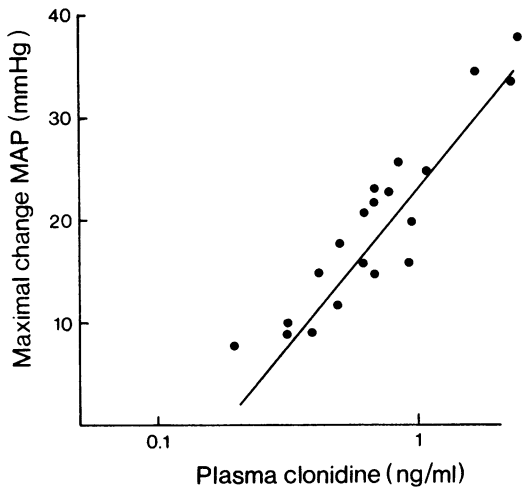

Figure 3 Relationship between individual maximal blood pressure response (expressed as maximal change in mean arterial blood pressure (MAP)) and the plasma concentration of clonidine (log scale). $r=0.86$, $P<0.01$, slope 12.99, intercept 4.99.

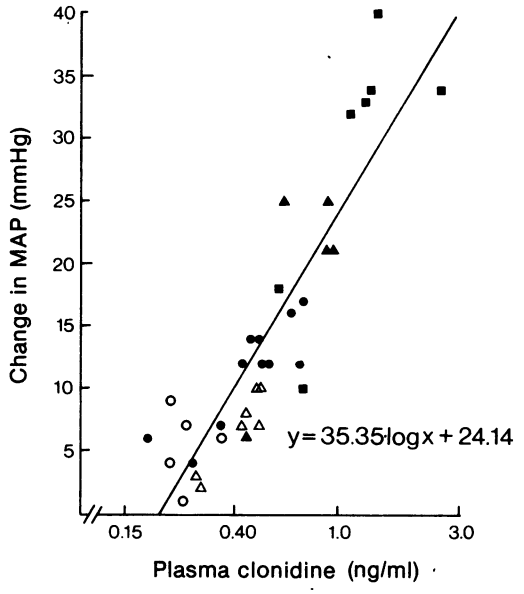

Figure 4 Relationship between reduction of blood pressure (MAP) mean of group and mean plasma concentrations of clonidine (log scale) after different doses 75 μg (○), 100 μg (△), 150 μg (●), 200 μg (▲), and 275 μg (■), and at all points of time during pseudoequilibrium of distribution, $r=0.89$, $P<0.02$.

and the mean plasma clearance decreasing, particularly in the dose of 275 μg. This could indicate dose dependent kinetics of clonidine which from the available data can be interpreted as derived from a decreasing rate constant of the β-phase, since the volume of distribution did not change significantly (Table 2). However, more data are needed to establish dose-dependent kinetics of this drug.

In the dosage interval used clonidine produced a dose dependent decrease in blood pressure and the response after the 275 μg dose is in agreement with published findings (Brod, Horback, Just, Rosental & Nicolescu, 1972). No blood pressure increase was observed in our study. This is in contrast to the reports (Kroetz *et al.*, 1970; Lund-Johanssen, 1976) where moderate pressure increases have been recorded after i.v. doses of 150 μg and 300 μg. A fallacy in the earlier studies might have been that the patients were not in complete homeostasis before the injection and were taking other antihypertensive drugs and no dose titration was done. On the other hand we might in our study have missed the pressure increase but since the latter has been reported to last for approximately 2 min and appear in close connection to the injection that option seems less probable.

Table 4 Maximal heart rate reduction (mean ± s.d.) after varying doses of clonidine

Clonidine (μg)	*Heart rate (beats/min)*
275	10 ± 4
200	9 ± 3
150	11 ± 5
100	8 ± 3
75	9.7 ± 5

The plasma concentrations of clonidine were correlated to the maximal blood pressure decrease. After the distribution phase of approximately 20–30 min the plasma concentrations of clonidine were also significantly related to the blood pressure reduction. This shows that when pseudoequilibrium of distribution of clonidine is obtained in the body a significant correlation exists between plasma levels and the pharmacological effect, in this case blood pressure reduction. This relationship is of interest since it has been hard to establish correlations between such a complex integrated response as the blood pressure reduction and antihypertensive drug concentrations. In responsive patients, however, it has been shown that a relation exists between pressure reduction and plasma levels, e.g. β-adrenoceptor blockers like propranolol (Leonetti, Mayer, Morganti, Terzoli, Zancetti, Bianchetti & Morselli, 1975) and alprenolol (Collste, Frisk-Holmberg, Haglund, Orme, Rawlins & Östman, 1976).

A central action has been suggested as the mechanism for the hypotensive effect of clonidine

(Kobinger, 1973). Animal studies also indicate that clonidine penetrates the blood brain barrier rapidly and more quickly than the physiological adjustment leading to a blood pressure decrease (Paalzow & Edlund, 1978, unpublished observations). For this highly lipid soluble drug it is possible that a correlation exists between the brain concentration of clonidine and its hypotensive effect. However, in the present study the maximum decrease of blood pressure was obtained about 30–60 min after intravenous administration. This might indicate a delay in time of response rather than a gradual increase of clonidine concentration in the brain. When pseudoequilibrium of distribution is obtained in the body, the plasma concentration should theoretically be a representative measure of the relative levels of clonidine in different type of tissues. Our results show that the clonidine levels also are directly related to the hypotensive effect during such an equilibrium. It has also been shown that other centrally mediated effects of clonidine like the sedation are related to its plasma concentrations (Davies *et al.*, 1977).

In the concentration interval 0.1–2.2 ng/ml found in our study no blood pressure increases were observed. The blood pressure increase might be obtained only when plasma concentrations higher than those found in our study are present. Such concentrations would be obtained after high doses like those given by others (Wing *et al.*, 1977).

Taken together the present findings and earlier reports could explain the therapeutic variability of clonidine and indicate that clonidine has a therapeutic 'window'. Low plasma concentrations will then give a hypotensive response which when high concentrations (at present unknown) are obtained is opposed by the peripheral (vasoconstrictor) α-adrenoceptor agonistic effect. Therefore close monitoring of plasma levels of clonidine might be of value for effective therapy.

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