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PHARMACOKINETICS AND METABOLISM OF GUANFACINE IN MAN: A REVIEW

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1 The fate of guanfacine has been investigated extensively in animals.

2 Pharmacokinetics and metabolism of [^{14}C]-guanfacine were studied in fourteen subjects given 3 mg orally (seven subjects) and 2.3 mg intravenously. Plasma levels and urinary excretion of radioactivity were measured by liquid scintillation counting. Parent drug was determined by gas chromatography-mass spectrometry. The analytical results were submitted to pharmacokinetic evaluation using the SAAM 26 programme. Metabolites in urine were identified by high pressure liquid chromatography.

3 Guanfacine was rapidly and completely absorbed. Its absolute bioavailability was close to 100%, no evidence of any first-pass effect being found.

4 Its distribution was characterized by low blood levels, low plasma protein binding and a relatively high affinity to the tissues (V_d of 300 l).

5 The elimination half-life of the β-phase was 17 hours. The major route of excretion (80% of the dose) was in the urine. About 1/3 to 1/4 of the total clearance of 11 l/h was renal.

6 The principal metabolite was the 3-hydroxy-derivative of guanfacine conjugated as either *O*-glucuronide or *O*-sulphate. The important fraction (30%) of parent drug found in the urine demonstrates a rather moderate biotransformation of guanfacine in man.

7 The results of an additional study after multiple dosing showed that the measured steady-state plasma levels were in agreement with the values predicted from a single dose experiment and proportional to the daily dosage.

Introduction

The study of the fate of a drug is a multidisciplinary enterprise, as chemists, biochemists, specialists in pharmacokinetics and clinicians are involved in the synthesis of a radiolabelled compound, to develop a highly specific and sensitive bioanalytical method, to perform animal experiments, to isolate metabolites, to elucidate their structures, and to perform pharmacokinetic calculations and clinical investigations.

This review represents the sum of many contributions from members of the Biopharmaceutical Department of Sandoz (Basel): Dr Schreier (labelling), Dr Meier (pharmacokinetics), Dr Laplanche (bioanalytical work), and Mr Galliker (radioactivity determinations). The clinical part of the study was carried out by Dr Beveridge (Department of Experimental Therapeutics of Sandoz, Basel) and Dr Michot (Laufenburg). Some of these data have been partly presented on other occasions (Picard & Bream, 1979; Meier, Beveridge, Laplanche, Kiechel & Ohnhaus, 1978).

Summary of investigations in animals

Chemically guanfacine (pKa of 7.1) is a weaker base than guanethidine (pKa of 8.4) and clonidine (pKa of 7.9). For this reason guanfacine is, at pH 7.4, 67% in the lipid-soluble base form compared with clonidine (24%) and guanethidine (9%). This property, mentioned by Picard & Bream (1979), is possibly the reason for the good and rapid absorption from the intestinal tract which has been demonstrated by studies with [^{14}C]-guanfacine in animals. The distribution in the rat shows the usual pattern of high concentrations in highly perfused organs (kidney, liver) and of low concentrations in blood due to distribution in the tissues. The highest concentrations in the organs were measured at 1.5–2 h after oral administration. After 24 h tissue and blood levels were low or could not be measured. There was no sign of 'retention' of radioactivity in any organ.

Biotransformation was substantial in the rat and slightly less in the dog. A total of 15 metabolites were isolated; the structure of the major ones are represented in Figure 1.

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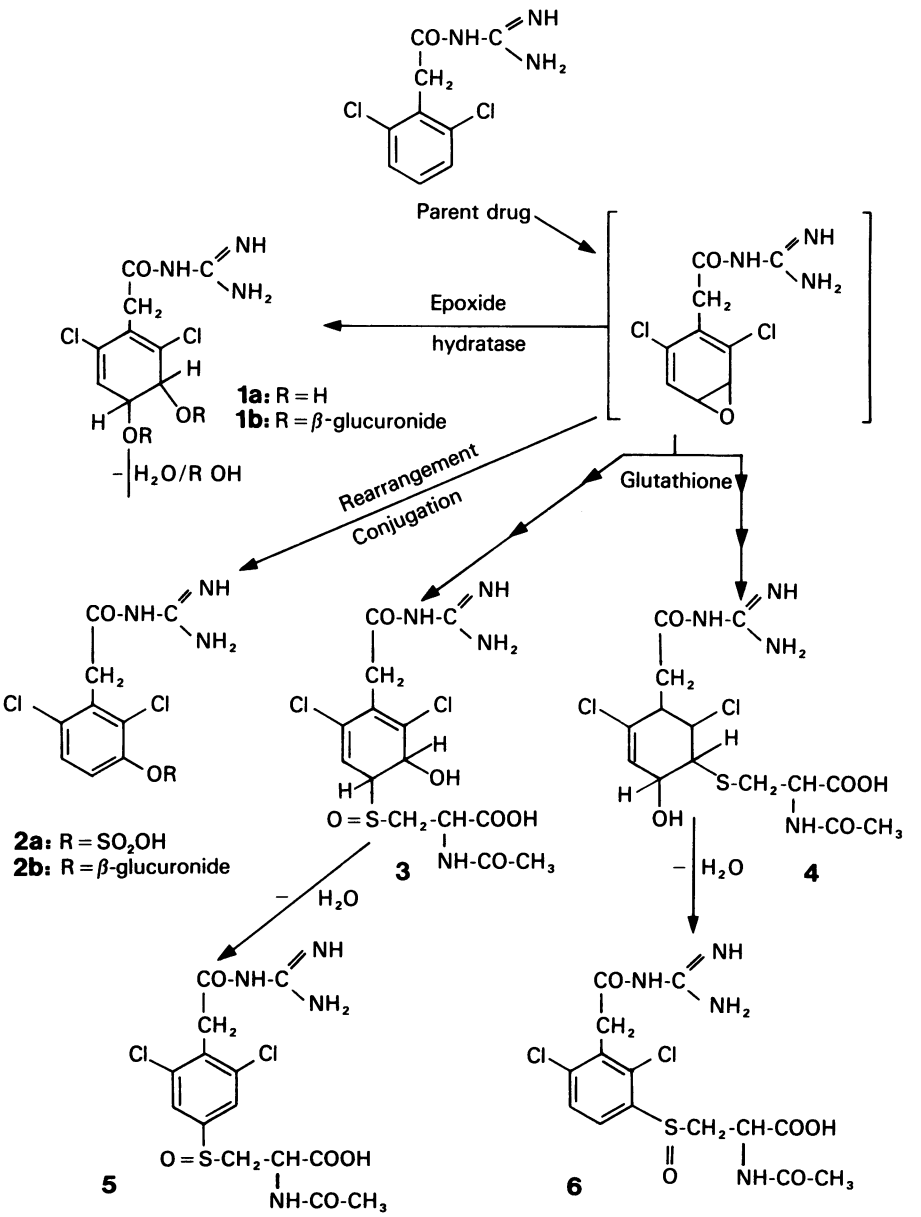

Figure 1 Structure of major metabolites and proposed biotransformation pathways for guanfacine in rat, dog and man.

The excretion was mostly by the urinary route, 75% of the dose being recovered in dog urine, independent of the route of administration. After 24–48 h only very low amounts ($\leq 1\%$) were excreted in both rats and dogs.

Additional specific studies in the rat have demonstrated an unimportant enterohepatic circulation and no tendency of cumulation after multiple dosing. Low concentrations of radioactivity (75% of those in plasma) could be shown in the milk of lactating rats. In pregnant animals guanfacine crossed the placental barrier: highest concentrations were found in the intestinal tract of the foetus.

Protein binding studies have been carried out using equilibrium dialysis at 37°C and pH 7.4 in a wide range of concentrations showing that guanfacine is

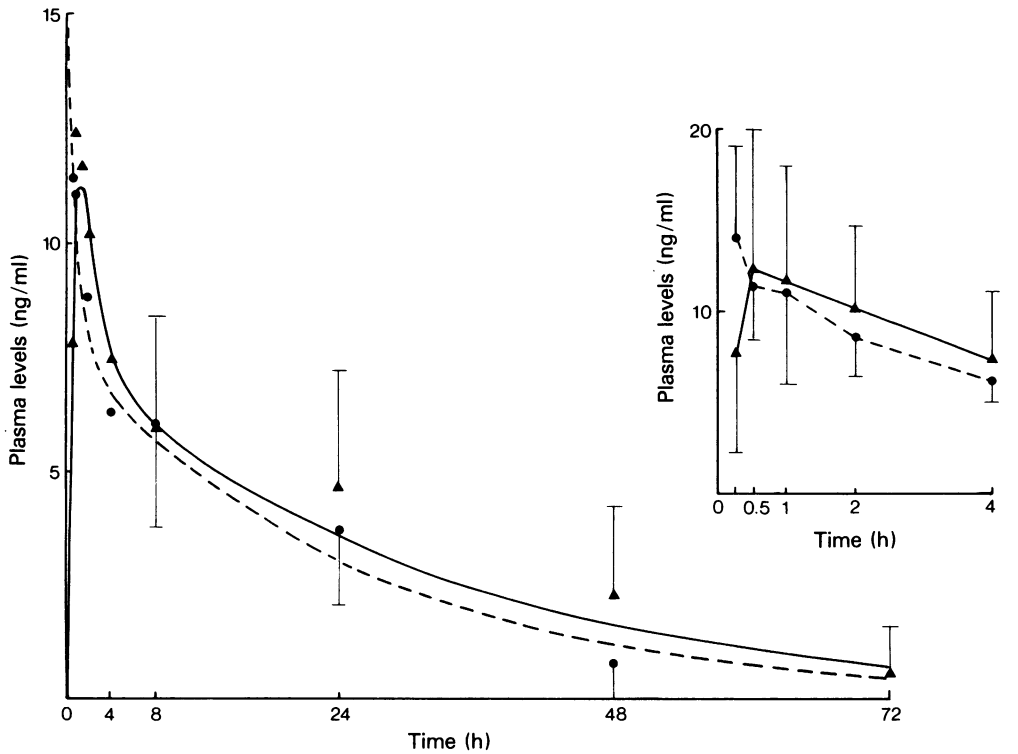

Figure 2 Experimental and calculated plasma concentration of the parent drug in man after administration of guanfacine 2.3 mg intravenously (●, n=7) and 3 mg orally (▲, $n=6$). Vertical lines indicate mean ± s.e. mean. Insert displays values obtained in the 0–4 h time period.

moderately bound to both the red cells and the plasma proteins. In man and rat more guanfacine is bound to the red cells (about 60%) than to the plasma proteins (20–30%). In human plasma only 64% of total guanfacine is bound. The binding to erythrocytes has led to *in vivo* investigations in man mentioned later.

A 'lag-time' in the rat between the maximum blood level (1.5 h after oral administration) and the concentration maximum in the brain (4 h after administration) is of interest and will be mentioned again later, as guanfacine has a central site of action. In spite of substantial biotransformation in the rat, the parent drug has been demonstrated to be the major constituent of the radioactivity in the brain. All these results in animals have been documented in detail (Beveridge, Kiechel, Meier & Schreier, 1977).

Investigations in man: Single dose experiments and metabolism

Methods

The radioactive label was introduced into the carbonyl group of the acetamide chain of guanfacine by reaction of 2,6-dichlorobenzylchloride with sodium [^{14}C]-cyanide (Schreier, unpublished observations). This label had been shown to be stable to biotransformation processes in animals. Liquid dosage forms were prepared and administered to 14 patients (six men) with a mean age of 73 yr and a mean body weight of 59 kg. Two evenly distributed groups of seven patients were formed for the studies with the oral dose of 3 mg or the intravenous dose of 2.3 mg guanfacine. Plasma, erythrocytes and urine samples were analyzed for total radioactivity (parent drug plus metabolites), and also using gas chromatography-mass spectrometry (parent drug) as described by Laplanche & Morin (1978). The metabolites in urine were separated using high pressure liquid chromatography and quantified using on-line radioactivity detection (Kiechel & Delaborde, unpublished results).

Results of single-dose pharmacokinetics

The plasma level curves of parent drug are displayed in Figure 2 and demonstrate a great similarity of the plasma levels after intravenous or oral administration. Similar results were obtained for the

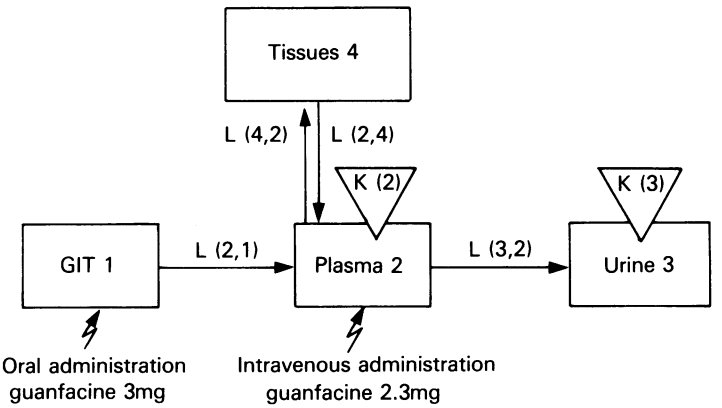

Figure 3 Two-compartment open model used for the kinetic calculations based on guanfacine data in man. L (x, y) are first order rate constants; K (2) is the reciprocal distribution volume (l^{-1}); K (3) is the fraction eliminated unchanged in urine at $t=\infty$.

cumulative urinary excretion. If the difference in dose is taken into consideration the absolute bioavailability of guanfacine in man is approximately 100%.

Inspection of the data suggests that the kinetics of guanfacine are best described by a two-compartment model (Figure 3). The SAAM 26 program by Bermann & Weiss (1975) was used for data fitting. If the two compartments have some physiological reality the question of the site of the guanfacine receptors is of relevance. The pharmacological action might be more closely related to either the time course of concentration in the central plasma or in the tissue compartment.

The summary of the calculated parameters collected in Table 1 demonstrates a rapid absorption (0.7 h) and distribution into the tissues and a long half-life of elimination corresponding to the β-phase (17.7–21.4 h). The clearance of 11 l/h is 1/3 to 1/4 renal, the non-renal clearance being mainly metabolic.

The absolute bioavailability based on the comparison of the oral and intravenous results for either the cumulated urinary excretion or the area under the plasma level curve (Table 1) is close to 100% which, for guanfacine indicates a complete absorption and the lack of any first-pass effect. The large apparent volume of distribution (V_d of about

Table 1 Kinetic parameters of guanfacine in man after oral administration of 3.0 mg ($n=6$) and intravenous administration of 2.3 mg ($n=7$) [^{14}C]-labelled drug

Parameter	*Oral administration* (*Mean ± s.e.m. n=6*)	*Intravenous administration* (*mean ± s.e. mean, n=7*)
Dose (mg)	*3*	*2.3*
α h^{-1}	1.19 ± 0.13	1.13 ± 0.24
β h^{-1}	0.0324 ± 0.0046	0.0391 ± 0.0041
$T_{\frac{1}{2}}$ invasion	0.722 h	—
$T_{\frac{1}{2}}$ elimination	21.4 h	17.7 h
Cl_T total clearance	11.1 l/h = 185 ml/min	11.3 l/h = 188 ml/min
renal clearance	2.7 l/h = 45 ml/min	2.6 l/h = 43 ml/min
non-renal clearance	8.1 l/h = 140 ml/min	8.7 l/h = 145 ml/min
AUC (0–∞)	272 ± 128 µg l^{-1} h^{-1}	204 ± 57 µg l^{-1} h^{-1}
C_u (0–∞)	24.4 ± 3.2%	23.1 ± 4.2%
Bioavailability:		
Urinary data	106%	100% (definition)
Plasma data	102%	100% (definition)
$V_C = 1/K(2)$	110 l	144 l
$V_d\beta = Clt/\beta$	343 l	289 l
$V_{SS} = V_C$ L $\frac{(2.4)+L(4.2)}{L(2.4)}$	347 l	276 l

Parameters were calculated based on the determination of parent drug using gas chromatography-mass spectrometry in plasma and urine.

300 l) confirms the affinity of guanfacine for the tissues demonstrated already in animals and explains the low plasma levels in spite of the very good bioavailability.

The rate constants of transfer from plasma to the tissues and from the tissues to plasma which have been calculated based on the two-compartment model and the plasma and urinary data enable one to simulate the concentration profile of guanfacine in the tissue compartment.

A lag-time of 3–4 h between the concentration maxima in the blood (Cp maximum at 1–2 h after administration) and the tissue compartment (maximum at 5–6 h after administration) was found. This delay might be of importance considering the variations with time of the pharmacological action of the drug and possibly the reported lag for the onset of action or side-effects. It is noteworthy as mentioned in the summary on animal experiments that in the brain of the rat the maximum concentration of unchanged guanfacine appears about 2.5 h later than in blood. This observation supports indeed, the use of the 'hypothetical' tissue compartment in the two-compartment model and might bear some relevance to the observations in man.

From the radioactivity data collected during the experiment, it can be deduced that the absorption is complete, as respectively 82 and 85% of either the oral or the intravenous dose were excreted with urine in 4 days. It confirms the results obtained for the parent drug (Table 1).

The calculated apparent volume of distribution is smaller for the metabolites than for unchanged guanfacine, a possible consequence of their more hydrophilic character. The erythrocytes seem to bind mostly parent drug and not the metabolites, as the concentrations of radioactivity (parent drug plus metabolites) in plasma are much higher than in erythrocytes, whereas for parent drug similar values were found for both media as demonstrated below. In the experiment with [^{14}C]-guanfacine 3 mg orally the maximum of the plasma radioactivity was 35 ng/ml equivalents of guanfacine-base, whereas for the erythrocytes only 14 ng/g equivalents were measured.

The simultaneous determination of parent drug, in plasma and erythrocytes has been carried out by Weiss, Lavene, Safar, Simon, Loria, Georges & Milliez (1979). It confirms the hypothesis based on the inspection of the radioactivity determinations described above. The concentrations of parent drug are somewhat higher in the red blood cells than in plasma, higher than expected from the haematocrit value. This result is in agreement with the *in vitro* protein binding studies.

Finally, the excretion of the sum of the metabolites (total radioactivity) does not seem to be rate-limiting. The plasma concentrations and urinary excretion data showed for most subjects only one clear exponential in the decay. The elimination half-lives were estimated to be 14.8 and 18.3 h, slightly shorter than for the parent drug, the concentrations of which were better defined by a two-compartment model. No slowly excreted radio-activity related to a metabolite of guanfacine has been found. The sum of parent drug and metabolites is almost exclusively excreted by the urinary route independently of the route of administration and represents as indicated above more than 80% of the dose.

Biotransformation

The proposed metabolic pathway of guanfacine in animals and man is displayed on Figure 1, which illustrates the major known metabolites which have been isolated. (Kiechel & Delaborde, unpublished observations). The key-intermediate is an epoxide, the existence of which has been postulated based on product analysis. Indeed, the dihydrodiol *1a* and its glucuronide *1b* have both been isolated with, in addition, the oxidized pre-mercapturic acid derivative *3* and the mercapturic acid derivatives *5* and *6*. Jerina & Daly (1974) have indicated that the occurrence of such end-products presupposes the existence of an epoxide intermediate. This type of intermediate has been demonstrated in the route of biotransformation of halogenated benzene derivatives (Lindsay, Smith, Shaw & Foulkes, 1972).

For the formation of *2b* and *2a* different alternatives can be proposed. A direct oxidation of the benzene ring is unlikely based on the available information on other aromatic substitutions. Rearrangement of the postulated epoxide intermediate or the loss of water from a dihydrodiol followed by the conjugation reaction are more likely. A survey of the structures of the metabolites reveals the metabolic stability of the guanidino-group.

To analyze the urinary metabolites in man a separation method using high pressure liquid chromatography has been developed using a reverse phase silicagel material which allows injection of 'raw' urine samples on to the column followed by on-line radioactivity monitoring of the effluent. A number of advantages characterize this method, such as high speed, high resolution, no sample handling, no work up, and no loss. A typical chromatogram of a 'crude' urine sample is displayed in Figure 4.

The urinary metabolites have been quantified in all 0–24 and 24–48 h samples for both groups of patients to whom guanfacine had been given by the oral and intravenous route. No difference in the quantitative distribution nor in the type of metabolites was observed by comparing the two time periods or the two routes of administration, an observation possibly related to the absence of a first-pass effect and to the clearance of parent drug being the rate limiting step. The glucuronide and sulphate of 3-OH guanfacine

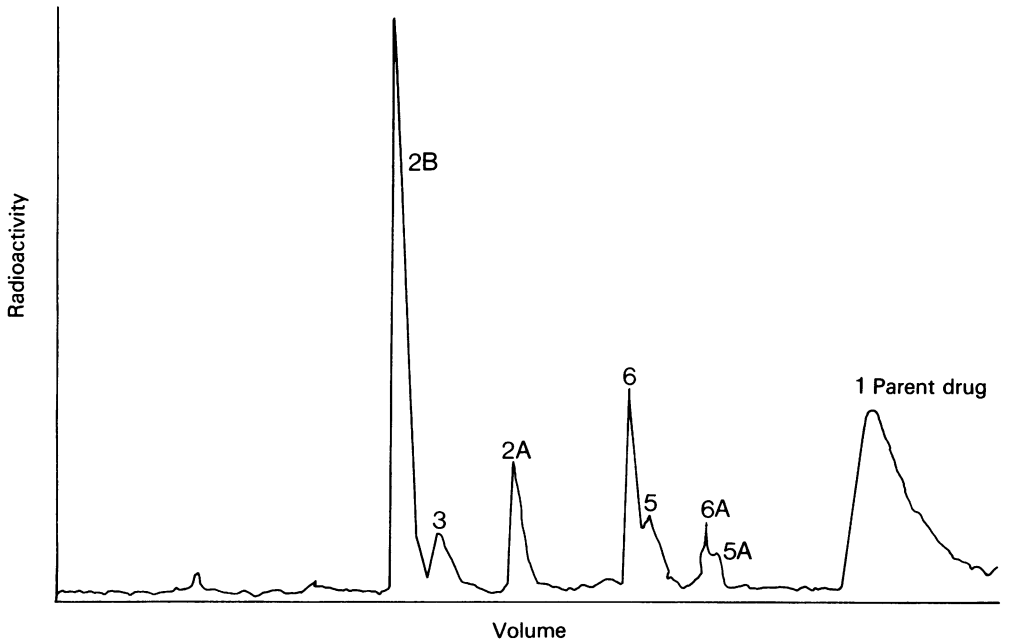

Figure 4 High pressure liquid chromatographic elution curve of a 0–24 h human urine sample on Lichrosorb 10 μm C-18 after oral administration of 3 mg [^{14}C]-guanfacine to subject H.O. Numbers refer to identified metabolites (see Figure 1).

represent about 50% of the amounts excreted in urine in 48 h and are the major metabolites. The oxidized mercapturic acid derivatives are the only other metabolites of some importance.

The mean relative abundance of [^{14}C]-guanfacine and its metabolites in the 0–24 h human urine samples after oral or intravenous administration of the [^{14}C]-labelled drug is displayed in Table 2, illustrating some of the aspects discussed above. The high percentage (=30%) of parent drug found after both routes of administrations is evident. Some interpatient variations in the amounts of parent drug and metabolites excreted in urine are revealed by the variation of the calculated means.

Comparing the biotransformation in animals and man a number of similarities in the amounts of parent drug excreted, in the amounts of metabolites formed and in the metabolic pathways can be observed. Metabolites *2a, 2b, 3* and *6* were found in both human and rat urine. In the second species they represented about 10% of the urinary radioactivity. The parent drug, however, was not found in large amounts in the rat but 20% of the dose was excreted in the urine of the dog, the other animal species studied.

Considering metabolites in dog urine, *3* and *6* were characterized in low quantities. But the finding of about 20% of the dose of *1a* indicates the likely

Table 2 Mean ± s.d. relative abundance of [^{14}C]-guanfacine and its metabolites in human urine samples after oral administration of 3 mg or intravenous administration of 2.3 mg [^{14}C]-guanfacine ($n=7$)

Metabolite (*see Figure 1*)	*Percentage in urine after oral administration* (*0–24 h*)	*Percentage in urine after intravenous administration* (*0–24 h*)
Parent drug 1	27.6 ± 15.7	31.7 ± 13.3
2a	7.7 ± 5.2	10.7 ± 5.2
2b	34.5 ± 15.4	33.1 ± 8.7
3	2.6 ± 1.2	2.4 ± 1.4
5	4.5 ± 3.3	3.2 ± 2.4
6	12.5 ± 9.0	9.8 ± 4.0
5a + 6a	3.4 ± 1.6	4.3 ± 3.1

formation of an intermediate epoxide in this species as in man and in the rat.

Investigations in man: Multiple dosing

In another study (Weiss *et al.*, 1979) with guanfacine in 19 hypertensive patients after single and repeated oral doses, the questions of the linearity of the kinetics in the therapeutic dose range and of the fate of guanfacine after multiple dosing have been investigated. A gas-chromatographic method (Guerret, Lavene, Longchampt & Kiger 1979) was used for determinations of parent drug in plasma, red blood cells and urine.

After single oral doses of 2 and 4 mg, $29.9 \pm 2.5\%$ and $34.3 \pm 5.4\%$ were excreted as the parent drug in the urine over the 0–72 h period. The related AUCs were 86 ± 10 and 164 ± 10 ng ml^{-1} after the two doses, demonstrating the linearity of the kinetics in this dose range and no change in bioavailability. As the populations were not the same (nine and ten patients, respectively) the ratio of plasma level maxima was not exactly equal to 2 (3.5 and 8.3 ng/ml) and the time to the maxima showed a slight difference (2.6 and 3.1 hours).

The linearity was confirmed by the determinations at steady state, which, depending on the $T_{1/2}$ of the β-phase (16–23 h), was reached in approximately 4 days. The daily dose in the investigated population ranged from 2–6 mg daily. The plasma levels were proportional at steady state to these administered amounts. Some inter-individual variations were, however, observed.

The results of the single-dose experiments after 2 and 4 mg indicated that the kinetics of guanfacine

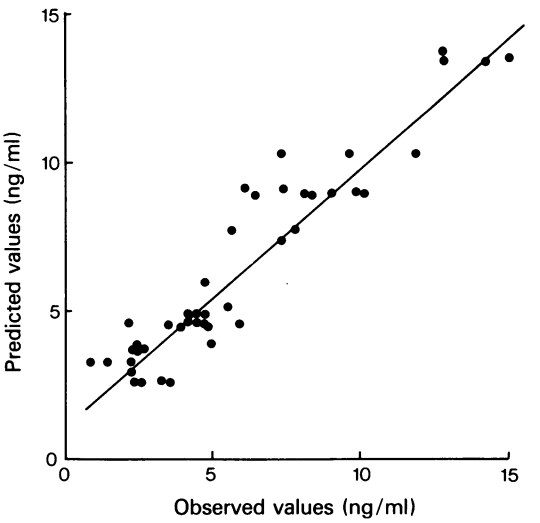

Figure 5 Relationship between observed steady-state plasma levels and predicted values deduced from individual parameters of a single-dose experiment. From Weiss *et al.* (1979). $y = 0.868x + 1.241$; $r = 0.948$; $P < 0.001$.

were well described by a two-compartment open model, in agreement with the interpretation of the radioactivity study. Based on these results a simulation at steady state could be performed and the simulated levels compared with the actual values found either 1 week (and/or at different days until 2 months) after the beginning of the study. The observed plasma levels were in good agreement with predicted values confirming that the chosen kinetic model was suitable for describing the fate of

Table 3 Comparison of the kinetic parameters from the study with [^{14}C]-labelled guanfacine in man and the data from Weiss *et al.* (1979)

Parameter	*Study I* (*Beveridge* et al. *1977*)	*Study II* (*Weiss* et al. 1979)
Number of subjects	5	19
Dose level (mg)	3	2 and 4 in 9 and 10 patients
Mean age (yr)	74 (66–81)	42 (23–59)
Mean weight (kg)	64 (44–86.5)	76 (59–89)
Creatinine clearance (ml/min)	62 ± 10 ($n = 5$)	98 ± 6
$T_{\frac{1}{2}}$ (β)	21.4 h	15.8 and 22.8 h*
$V_d\beta$	343 l	456 l
Total clearance	11.1 l/h = 185 ml/min	25.4 l/h = 424 ml/min
Renal clearance	2.7 l/h = 45 ml/min	6 l/h = 100 ml/min
Parent drug in urine	21.9%	29.9 and 34.3%*
C_p (max)	≤ 4 ng ml^{-1} mg^{-1}	1.7 and 2 ng ml^{-1} mg^{*-1}
Time of C_p (max)	1–1.5 h	3 h

*Results of 2 and 4 mg dose experiments, respectively.

guanfacine in man. No evidence of autoinduction of the metabolism nor abnormal accumulation with respect to initial kinetic parameters was observed (Figure 5; Table 3).

It may be of interest to compare the oral study with [^{14}C]-guanfacine and with non-labelled material (Weiss *et al.*, 1979) performed in different populations. The first group consisted mainly of old patients (mean age 74 yr) with a mean body weight of 64 kg receiving oral doses of 3 mg. Their creatinine clearance was approximately 60 ml/minute. The second was a group of adults (mean age 42 yr) with a mean body weight of 76 kg receiving respectively oral doses of 2 and 4 mg. The mean creatinine clearance was 98 ± 6 ml/minute. For the older population the renal and non-renal clearances were both diminished but there seemed to be a decrease in the volume of distribution due partially to the different body weights. However, considering the $t_{1/2}$ of the βphase the values were 21.4 h for the group of aged patients and 15.8 and 22.8 h for the two adult groups. It can be tentatively concluded from the comparison that in older subjects it does not seem to be neccessary to change the frequency of dosage to maintain the same duration of effect.

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