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Rate and Extent of Absorption of Clonidine from a Transdermal Therapeutic System

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Abstract—The in-vivo performance of a clonidine transdermal therapeutic system (TTS 3·5 cm^2, 2·5 mg) was assessed in 12 healthy normal volunteers. Particular attention was paid to the rate and extent of absorption of clonidine from the TTS dosage form by reference to a 2 h i.v. infusion of clonidine. The absolute bioavailability of clonidine from the TTS dosage form was found to be approximately 60% with clonidine being released from the TTS at a relatively reproducible and consistent rate of 4·32 $\mu g\ h^{-1}$ over a 7-day period.

Transdermal delivery of drugs for systemic therapy is now widely recognised as feasible, on the basis of performance of ointment preparations of nitroglycerin, anti-inflammatory agents and hormones. Over recent years techniques have been developed to facilitate reproducible and reliable drug administration via this route (Chandrasekaran & Shaw 1977; Shaw & Chandrasekaran 1981).

Clonidine has been used for many years in the treatment of mild to moderate hypertension with more recent indications in the management of migraine and post-menopausal flushing. It is rapidly absorbed following oral administration, with the maximum plasma concentrations being achieved within 30 min of dosing, and is eliminated with a half-life of 5–13 hr (Lowenthal 1980). It is currently given orally once (0·3 mg) or twice a day, and because of its pharmacokinetic properties, this regimen results in quite wide fluctuation in its plasma concentration, even at steady state. Many of the side-effects associated with clonidine therapy have been related to its high peak plasma concentration that is associated with oral therapy (Lowenthal 1980) and consequently a dosage form capable of minimizing the marked fluctuations in its plasma concentration and maintaining steady state over a prolonged period would be desirable.

Success has been achieved in the administration of drugs such as nitroglycerin and scopolamine transdermally via transdermal therapeutic systems (TTS), with a view to maintaining a constant plasma concentration of the respective drug over a pre-determined time span (Chandrasekaran & Shaw 1977; Good 1983; Karim 1983; Keith 1983). Clonidine meets many of the criteria required for successful transdermal delivery, being pharmacologically potent with a suitable degree of lipophilicity. Consequently, clonidine has been successfully formulated and used in a transdermal therapeutic system with the aim of delivering the drug at a constant rate over a 7-day period, providing once-a-week therapy (McMahon 1983; Weber et al 1984).

To ensure that the TTS dosage form, and not the skin, controls the administration of drug to the systemic circulation, it is important that the TTS delivers less drug per unit area than the skin is capable of absorbing. The rate of release of drug from the TTS is thus a determinant in the successful performance of the dosage form.

The present study was undertaken to assess the pharmacokinetic characteristics of clonidine delivered transdermally via a TTS. Specifically, the study was undertaken to assess the rate and extent of absorption of clonidine from the TTS dosage form, by reference to a short duration constant-rate intravenous infusion of the drug.

Methods

Subjects

The study was undertaken with 12 healthy normotensive volunteers (6 male, 6 female) whose average height, weight and age were 175·2 cm (163–190), 69 kg (49–85) and 27 yr (24–40), respectively. All volunteers were judged healthy as a result of full physical, biochemical and haematological examination carried out before and after the study. Full informed consent was given by all volunteers before their entering the study, which had previously been passed by an independent ethics committee.

Study design

The study was of a randomized two-way crossover design. All volunteers entered the study simultaneously and all successfully completed the investigation. Each volunteer received either a 2 h constant-rate intravenous infusion of 150 μg of clonidine or a 3·5 cm^2 transdermal therapeutic system (TTS) containing 2·5 mg of clonidine base.

Administration

Intravenous clonidine. The contents of an ampoule containing 150 μg intravenous clonidine (1 mL), as the hydrochloride, were diluted with 9 mL of sterile water. The resulting 10 mL solution was infused intravenously via an antecubital vein at a constant rate over 2 h, by means of a constant rate infusion pump (Graseby Medical Syringe Driver, type MS16A, Graseby Medical, Graseby Dynamics, Watford, UK). The stopwatch was started on commencement of the infusion and the weight of the syringe filled and after use was recorded (Sartorius 1712 MP8) to estimate accurately the

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volume of infusate administered. The syringe pump was connected to an infusion set, 21G, (Mediwing, Argyle) inserted in an antecubital vein. The subject remained supine throughout the infusion and blood sampling was performed on the opposite arm.

Clonidine TTS. The application site was a non-hairy area of intact skin on the upper outer arm. Before application the site was cleaned by wiping with a Mediswab (70% isopropanol BP disposable swab) and then wiped dry with a gauze swab. An overlay adhesive was applied over the system. The clonidine TTS was applied at 0800 h on Day 1 and it and the overlay were removed at 0800 h on Day 8 of the TTS phase. Subjects were requested to refrain from immersing the clonidine TTS in water, but there were no other restrictions on their daily routine.

The blood sampling schedule associated with the i.v. phase, commencing at the start of the infusion, was 0, 15, 30 and 45 min and then 1, 1·5, 2, 3, 4, 5, 8, 12, 24, 30, 36, 48, 60 and 72 h. In addition to a blank (pre-drug) urine sample, urine samples associated with the i.v. infusion phase were collected over timed intervals totalling 84 h. Blood sampling relating to the TTS phase was 0, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 h. The TTS was removed after 168 h. Urine samples were again collected over timed intervals, but this time totalling 264 h. Following the blood and urine sampling schedule associated with each phase, a one week washout period was allowed before administration of the alternate regimen. All plasma and urine samples were stored at −20°C before analysis. The used TTS dosage forms and overlay were wrapped in silver foil following removal and stored at 4°C until analysed for residual clonidine.

Clonidine analysis

Plasma and urine concentrations of clonidine were analysed by radioimmunoassay (Arndts et al 1981; Farina et al 1986) by E G and G Mason Research Institute, Boston, USA. Clonidine remaining in the used TTS dosage form was analysed by HPLC by Boehringer Ingelheim, Germany.

Pharmacokinetic data analysis

The disposition kinetics arising from the i.v. dose were adequately described by a mono-exponential model. The elimination rate-constant (k) was obtained by non-linear least squares regression (Gomeni 1984). Total clearance (CL) was calculated according to equation 1:

$$CL = \frac{Dose}{AUC} \quad (1)$$

where Dose is the administered intravenous dose of clonidine and AUC is the area under the plasma clonidine concentration-time profile between time zero and infinity. The AUC was calculated using the linear trapezoid approximation between times 0 and t, the last experimental observation. The additional area between time t and infinity was calculated from C_t/k, where C_t was the predicted plasma clonidine concentration at time t. This additional area never contributed more than 2% to the total AUC.

The elimination half-life ($t_{\frac{1}{2}}$) of clonidine was calculated from equation 2:

$$t_{\frac{1}{2}} = \frac{0{\cdot}693}{k} \quad (2)$$

The volume of distribution (V_z) was calculated using equation 3:

$$V_z = \frac{CL}{k} \quad (3)$$

No attempts were made to model the plasma clonidine concentration-time data from the TTS application. The AUC was as defined and calculated as for the i.v. dose.

The amount of clonidine excreted into the urine unchanged (Ae(∞)) following either i.v. or TTS administration was calculated by summing the amounts of unchanged drug excreted in the timed urine collection periods.

Clonidine renal clearance (CL_R) was calculated for both the i.v. and TTS data according to equation 4:

$$CL_R = \frac{Ae_{o,t}}{AUC_{o,t}} \quad (4)$$

where Ae and AUC are as previously defined but measured over an identical time interval, which in practice was approximately 264 and 84 h for the TTS and i.v. doses respectively.

The absolute bioavailability (F) of clonidine from the TTS was calculated using 3 approaches utilising urinary or plasma data alone or in combination:

(1) *Urine alone*

Amount absorbed $= Ae(\infty)_{TTS}/fe_{i.v.}$

where

$fe_{i.v.} = Ae(\infty)_{i.v.}/Dose_{i.v.}$

$$F = \frac{\text{Amount absorbed}}{Dose_{TTS}} = \frac{Ae(\infty)_{TTS}}{Ae(\infty)_{i.v.}} \cdot \frac{Dose_{i.v.}}{Dose_{TTS}}$$

which simplifies to give

$$F = \frac{fe_{TTS}}{fe_{i.v.}} \quad (5)$$

where $fe_{i.v.}$ and fe_{TTS} are the fraction of the respective i.v. and TTS doses of clonidine excreted into the urine unchanged and $Dose_{TTS}$ is calculated from the difference between the initial amount of clonidine in the TTS and the analytically determined residual amount.

(2) *Plasma alone*

Amount absorbed = CL.AUC

$$F = \frac{\text{Amount absorbed}}{Dose_{TTS}} = \frac{CL_{TTS} \cdot AUC_{TTS}}{Dose_{TTS}}$$

$$= \frac{AUC_{TTS}}{Dose_{TTS}} \cdot \frac{Dose_{i.v.}}{AUC_{i.v.}}$$

assuming $CL_{TTS} = CL_{i.v.}$

(3) *Plasma plus Urine*

Amount absorbed $= CL_{NR} \cdot AUC_{TTS} + Ae(\infty)_{TTS}$

where $CL_{NR} = CL_{i.v.} - CL_{R\,i.v.}$

$$\therefore F = \frac{\text{Amount absorbed}}{Dose_{TTS}} = \frac{CL_{NR} \cdot AUC_{TTS} + Ae(\infty)_{TTS}}{Dose_{TTS}}$$

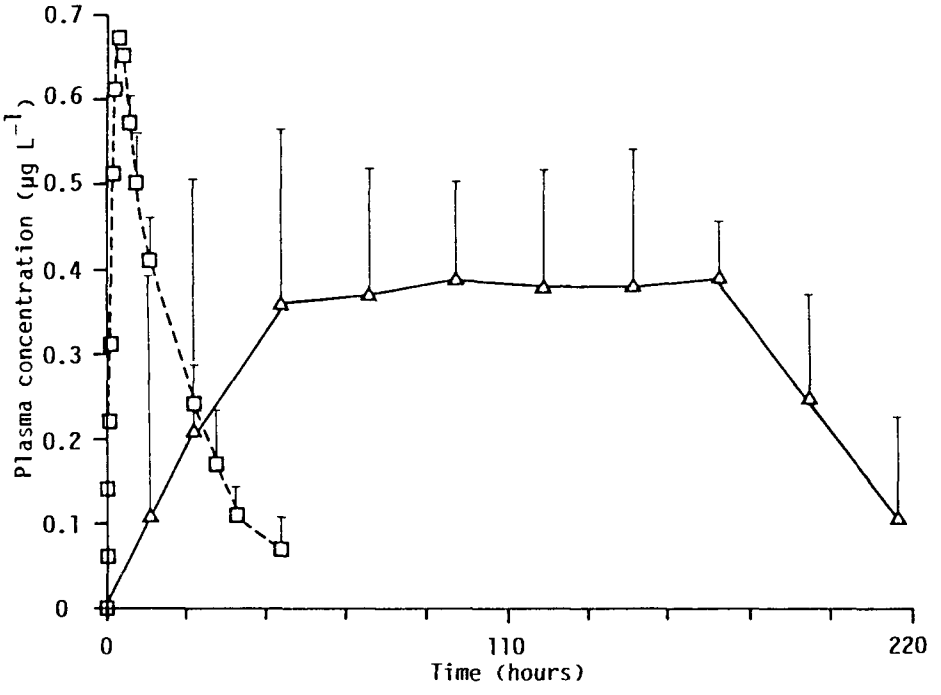

FIG. 1. Average plasma clonidine concentration-time profiles following the administration of a 2h i.v. infusion of clonidine (0·15 mg) or the application of a 3·5 cm^2 TTS dosage form (2·5 mg clonidine) to 12 normal healthy volunteers.

assuming $CL_{NR.TTS} = CL_{NR,i.v.}$
where CL_{NR} is the non-renal clearance and CL_R is the renal clearance of clonidine associated with either of the two formulations.

The rate of input of clonidine from the TTS dosage form into the body was obtained by numerical deconvolution of the TTS plasma clonidine concentration-time data with respect to the i.v. data. As the i.v. clonidine plasma concentration-time profiles were adequately described using a single compartment model, the Wagner-Nelson method (Wagner & Nelson 1964) was used.

The amount of clonidine absorbed from the TTS and the amount remaining to be absorbed, were expressed as a fraction of the cumulative amount of clonidine absorbed up to the final plasma clonidine concentration-time point. The rate of clonidine absorption was determined from the differential fraction absorbed multiplied by the total amount of clonidine absorbed.

Table 1. Average pharmacokinetic parameters defining the input and disposition of clonidine from a TTS (3·5 cm^2; 2·5 mg clonidine) formulation and pharmacokinetics following a 2 h i.v. infusion of 0·15 mg of clonidine to 12 healthy adult volunteers.

Parameter	Mean	S.D.	CV (%)
Clonidine absorption rate in-vivo ($\mu g\ h^{-1}$)	4·32	1·68	38·8
Clonidine release rate in-vitro ($\mu g\ h^{-1}$)*	11·6	2·86	24·6
Clonidine released from TTS (mg)	1·23	0·48	38·7
Maximum plasma concentration (C_{max}; μgL^{-1})	0·53	0·35	66·0
Time to C_{max} (t_{max}; h)	125	47·7	38·2
Bioavailability (F%) [Based on urinary data]	63·0	17·1	27·2
Bioavailability (F%) [Based on plasma data]	56·8	11·5	20·3
Bioavailability (F%) [Based on plasma and urinary data]	63·3	13·1	20·7
Renal clearance (CL_{RTTS}; Lh^{-1})	6·67	1·96	29·7
Intravenous dose			
Maximum plasma clonidine concentration (C_{max}; μgL^{-1})	0·69	0·10	14·5
Time to reach C_{max} (t_{max}; h)	3·32	0·65	19·6
Elimination rate constant (k; h^{-1})	0·054	0·011	20·4
Elimination half-life ($t_{\frac{1}{2}}$; h)	13·3	2·80	21·1
Clearance (CL; $L\ h^{-1}$)	10·6	2·20	20·9
Renal clearance ($CL_{R\ i.v.}$; Lh^{-1})	6·13	1·86	30·3
Volume of distribution (V_2; L)	197	33·6	17·1

*Data supplied by Boehringer Ingelheim

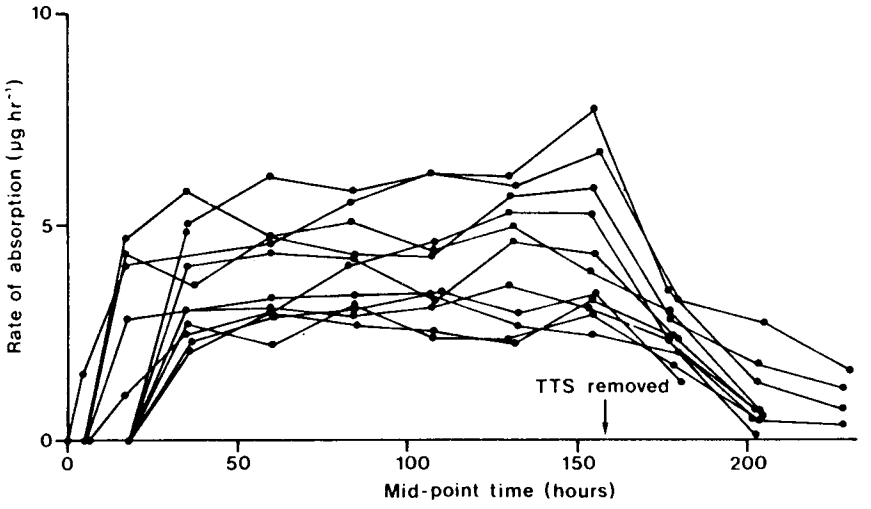

FIG. 2. In-vivo rate of absorption of clonidine from a 3·5 cm^2 TTS dosage form with respect to time following its application to 12 (subject 6 not represented) normal healthy volunteers.

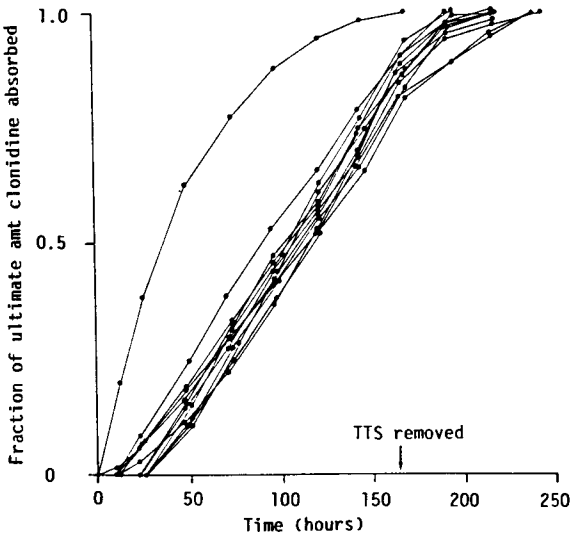

FIG. 3. Fraction of the ultimate amount of clonidine absorbed from a 3·5 cm^2 TTS dosage form with respect to time following application to 12 normal healthy volunteers.

Results

The average plasma clonidine concentration-time profiles relating to both the TTS and i.v. infusion are shown in Fig. 1. The mean pharmacokinetic parameters defining the disposition of clonidine from both routes of administration are shown in Table 1.

Based upon intravenous infusion data, the elimination half-life ($t_{\frac{1}{2}}$) and total clearance (CL) of clonidine were found to be $13{\cdot}3 \pm 2{\cdot}8$ h and $10{\cdot}6 \pm 2{\cdot}2$ Lh^{-1}, respectively. The volume of distribution (V_z) was $197 \pm 33{\cdot}6$L, the fraction of the i.v. clonidine dose excreted into the urine unchanged ($fe_{i.v.}$) was $0{\cdot}61 \pm 0{\cdot}10$ and the maximum plasma clonidine concentration (C_{max}) $0{\cdot}69 \pm 0{\cdot}09$ μgL^{-1} which was achieved $3{\cdot}32 \pm 0{\cdot}65$ h (t_{max}) after the commencement of the i.v. infusion.

The amount of clonidine released from the TTS (the dose) was found to be $1{\cdot}23 \pm 0{\cdot}48$ mg, approximately half that specified to be contained within the dosage form (2·5 mg).

The maximum plasma clonidine concentration observed with the TTS dosage form was $0{\cdot}53 \pm 0{\cdot}35$ μgL^{-1} achieved $125 \pm 47{\cdot}7$ h after application. Clonidine renal clearance assessed from the TTS data was $6{\cdot}7 \pm 2{\cdot}0$L h^{-1}, a value in close agreement with that obtained following i.v. administration ($6{\cdot}1 \pm 1{\cdot}9$L h^{-1}). The value for the absolute bioavailability of clonidine from the TTS dosage was $63{\cdot}0\% \pm 17{\cdot}1$ based upon urinary data alone, $56{\cdot}8\% \pm 11{\cdot}5$ based upon plasma data and $63{\cdot}3\% \pm 13{\cdot}1$ from combined plasma and urinary data.

Fig. 2 shows a plot of the rate of clonidine absorption from the TTS with respect to time. It was found to take approximately 2 days for the absorption process to stabilize at an average rate of $4{\cdot}3 \pm 1{\cdot}7$ μgh^{-1}.

The cumulative absorption of clonidine from the TTS system (expressed as the fraction of the ultimate amount of clonidine absorbed) is shown in Fig. 3. The absorption of clonidine from the TTS was found to be relatively consistent and linear within the group studied. One volunteer was a noticeable outlier.

Discussion and Conclusions

The pharmacokinetic parameters defining the disposition of clonidine were in good agreement with those previously reported (Lowenthal 1980; MacGregor et al 1985). There was no evidence of any sex differences in the disposition of clonidine associated with either dosage form. Although clonidine was administered as a constant rate i.v. infusion over a 2 h period, the average time taken to reach maximum plasma clonidine concentration was 3·3 h. The reason for the lag in reaching the peak concentration is unclear. There was

no evidence that the drug had been injected into tissues rather than given intravenously. Although speculative, a possible explanation is that, as clonidine is very lipophilic, some of the drug at the injection site diffuses into local tissue which it is subsequently released relatively slowly back into the systemic circulation.

Some credence is given to the idea of clonidine forming localized tissue depots from observations relating to the TTS formulation, where the absorption process can still be observed even after removal of the TTS (Fig. 2). Comparison of the area under the curve associated with the observations made after removal of the TTS with the preceding AUC indicates, however, that on average less than 10% of the dose is "absorbed" after removal of the transdermal dosage form.

Differing approaches to the assessment of bioavailability were undertaken to minimize the effects of variability in parameters used to assess F in any one chosen method. The major parameters used in the assessment of bioavailability relate to the elimination processes; both renal and non-renal. As the values for F, and also the variability of this parameter, were similar for all three approaches to its calculation, this may indicate that the renal elimination of clonidine is as variable as the non-renal route contrary to the general belief that non-renal elimination is much more variable than renal elimination.

From the assessment of bioavailability, approximately 40% of the dose of clonidine released from the TTS dosage form does not enter the systemic circulation. The reason for this loss in availability is unclear. One possible explanation is that drug leaked from around the edge of the TTS. Analysis of the gauze overlay did not, however, show the presence of appreciable amounts of clonidine. Cleansing of the application site following removal of the TTS may also have been a source of drug loss. Unfortunately, the used cleaning pads were not assayed for drug. A more speculative explanation would be first-pass transdermal metabolism of clonidine; there is no evidence, however, for this phenomenon within the literature.

Although there is no evidence of non-linearity in the pharmacokinetics of clonidine, the plasma clonidine concentrations and time profiles differ quite markedly between the i.v. and TTS dosage forms. If a pharmacokinetic non-linearity did exist, this could potentially compromise the assessment of bioavailability of clonidine from the TTS dosage form by reference to an i.v. bolus dose.

The in-vivo performance of the TTS dosage form within this group of volunteers appeared to be good showing relatively stable plasma clonidine concentrations over the study period resulting from a constant rate of clonidine input from the dosage form. The cumulative absorption of clonidine from the TTS dosage form was found to be linear and relatively consistent within the group. The average rate of absorption of clonidine from the TTS dosage form ($4{\cdot}32 \pm 1{\cdot}68$ $\mu g h^{-1}$) was much lower than the observed in vitro rate of relase of clonidine from this formulation ($11{\cdot}6 \pm 2{\cdot}86$ $\mu g h^{-1}$). This observation could indicate that transdermal penetration is a significant rate-limiting step in the release of clonidine from the TTS formulation.

The in-vivo performance of the dosage form was in good agreement with claims made on the labelling of Catapres-TTS-1 (0·1 mg. day^{-1} over one week).

One volunteer (subject 6) showed a marked deviation in his cumulative absorption profile from the other members of the group. The rate of absorption of clonidine was much higher (to such a degree that the data relating to this individual are not shown in Fig. 2) in this individual ($8{\cdot}14$ $\mu g h^{-1}$) than in the other subjects ($3{\cdot}97 \pm 1{\cdot}22$ $\mu g h^{-1}$). Although it was known that this particular volunteer was an active athlete, retrospective questioning indicated that he had maintained training schedule throughout the study period. His increased rate of absorption of clonidine perhaps reflects an increased perfusion of the musculature underlying the site of application.

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