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Pharmacokinetics and pharmacodynamics of verapamil following sublingual and oral administration to healthy volunteers

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1 The pharmacokinetics and pharmacodynamics of verapamil administered via the oral and sublingual routes were compared in a randomised, two-way cross-over study involving six healthy male volunteers.
2 Administered sublingually, a verapamil 40 mg (Securon®) crushed tablet produced a significantly higher peak plasma concentration ($P < 0.05$), a greater rate of absorption ($P < 0.05$), and greater bioavailability ($P < 0.05$) when compared with orally administered verapamil 40 mg (Securon®).
3 In comparison with oral dosing, PR intervals were significantly ($P < 0.05$) prolonged between 30 and 90 min after sublingual verapamil dosing.
4 Correlations between log plasma verapamil concentration and percentage increase in PR interval were greater after sublingual compared with oral dosing in all volunteers.

Keywords verapamil sublingual pharmacokinetics pharmacodynamics

Introduction

Following an anecdotal report that symptomatic relief of palpitations associated with paroxysmal atrial fibrillation had been obtained after a patient had 'sucked' a standard verapamil tablet it was decided to investigate whether sublingual verapamil offers an alternative method of administering verapamil to the intravenous and oral routes. Verapamil, a type IV antiarrhythmic agent, has been widely used in the form of an intravenous injection in the acute management of supraventricular tachycardias (SVT) such as atrial flutter, atrial fibrillation and atrioventricular re-entrant tachycardia (Dominic *et al.*, 1979; Sung *et al.*, 1980a,b). Oral verapamil is used in the management of chronic atrial fibrillation (Molgaard *et al.*, 1987; Pomfret *et al.*, 1988; Stern *et al.*, 1982) and as a prophylactic measure against paroxysmal SVT (Rinkenberger *et al.*, 1980; Stern *et al.*, 1982).

There have been no reports on the efficacy of sublingual verapamil in patients. However, Woodcock and colleagues (1982) studied this route in healthy volunteers although a direct comparison of its pharmacokinetic and pharmacodynamic effects compared with an equivalent oral verapamil dose was not undertaken. Therefore, the aim of the present study was to determine and compare the pharmacokinetic and pharmacodynamic responses of a standard dose of verapamil administered to healthy volunteers by the oral and sublingual routes.

Methods

Six healthy male volunteers aged 22 to 29 years (mean 25.7 years) participated in an open, randomised, two-way cross-over study. None was taking any prescribed or over-the-counter medication. Subjects were required to undergo appropriate physical, haematological, biochemical, ECG and drugs of abuse screening and had an uneventful medical history. Alcohol and smoking were not permitted for 24 h prior to, and for the duration of, the study. Caffeine-containing products were not allowed from 8 h prior to, and during, each study period. Subjects were required to fast from 23.00 h prior to each study day. Ethics approval was obtained from the local Ethics Committee and informed written consent was obtained from each volunteer.

Volunteers were randomly administered 40 mg rac-verapamil (Securon®, Knoll Ltd, Burgess Hill, Sussex) sublingually and orally, separated by a period of at least 7 days. On each occasion the subjects attended the Clinical Trials Unit, Department of Pharmacology and Therapeutics at the University of Wales College of Medicine, Cardiff at approximately 08.00 h. Volunteers were placed in a supine position for not less than 30 min prior to baseline measurements being made. Supine automated blood pressure (systolic, diastolic, and mean) and heart rate measurements were recorded from a Physiocontrol Lifestat 200 BP Monitor and electro-

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cardiographic (ECG) recordings made using a chart speed of 100 mm s^{-1} (standard lead II) with a Nihon Kohden Cardiofax ECG Monitor. PR intervals, a measure of atrio-ventricular (AV) conduction, were measured manually by taking the mean of five consecutive complexes on the ECG record paper.

A cannula was inserted into the left or right antecubital vein for collection of blood samples. For the oral dose a 40 mg rac-verapamil tablet was swallowed with 200 ml drinking water. In the absence of an available sublingual dosage form a 40 mg oral rac-verapamil tablet was crushed to a fine powder and placed under the subject's tongue. The volunteers were instructed to refrain from swallowing any powder during the dissolution period. Three hours after drug administration via either route, the subjects were provided with caffeine-free food and drink.

Venous blood samples were collected at 0, 5, 10, 15, 30, 45, 60 and 90 min after drug administration, then hourly up to 8 h. Physiological measurements were also made at these times. Immediately after venesection into BD Vacutainer® lithium heparin tubes, the plasma was separated by centrifugation at 3,000 rev min^{-1} for 10 min at 4° C and then stored at −18° C until assayed. Plasma verapamil and its primary metabolite norverapamil were assayed using a reverse-phase high performance liquid chromatography method developed in our laboratory. The extraction method was a modification of that reported by Kacprowicz and co-workers (1985) and chromatographic conditions were based on those described by Kapur and colleagues (1985).

Pharmacokinetic modelling of the plasma verapamil concentrations was undertaken using a computer program (MK Model 4) based on a non-linear least squares regression analysis (Holford, 1990). The relative bioavailability of verapamil after sublingual and oral administration was calculated from the area under the plasma concentration-time curve, extrapolated to infinity.

Statistical analysis

Results are expressed as mean values (± s.e. mean). Student's paired *t*-test was used to compare data obtained following sublingual and oral administration. Differences were considered significant when $P < 0.05$ at the 2α level of significance.

Results

The mean time at which no trace of white verapamil powder was visible beneath the tongue of the subjects was 18.7 (± 1.8) min. All volunteers ($n = 6$) reported an unpleasant, bitter taste when verapamil was administered sublingually. This persisted for 38.3 (± 11.0) min after dosing. No adverse effects were reported following oral verapamil administration.

There were no significant changes in blood pressure measurements after either oral or sublingual dosing, neither was there any consistent effect on heart rate.

Pharmacokinetics

Curves showing the mean plasma verapamil concentrations following oral and sublingual administration are given in Figure 1. There were found to be significantly greater verapamil concentrations following sublingual administration at 5 ($P < 0.05$), 10 ($P < 0.001$), 15 ($P < 0.05$), 30 ($P < 0.01$), 45 min ($P < 0.05$), 1.0 h, 7.0 h and 8.0 h (all $P < 0.05$) in comparison with concentrations found following oral dosing. Norverapamil was detected in the plasma of all volunteers after oral ($n = 6$) and in the plasma of five volunteers after sublingual ($n = 6$) administration. There were no significant differences between plasma norverapamil concentrations at any time after dosing by either route ($P > 0.05$) (data not shown).

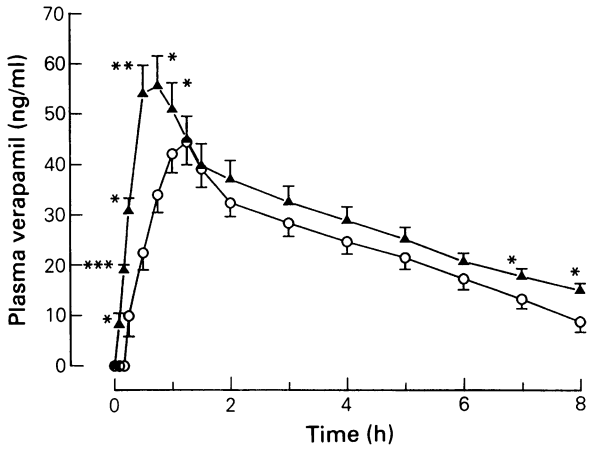

Figure 1 Comparison of plasma verapamil concentrations following sublingual (▲) and oral (○) administration (*$P < 0.05$; **$P < 0.01$, ***$P < 0.001$).

Individual pharmacokinetic parameters for verapamil following the administration by the oral and sublingual routes are presented in Table 1. Sublingual verapamil produced higher plasma verapamil concentrations (C_{max}) ($P < 0.05$) more rapidly (t_{max}) ($P < 0.05$) than after oral dosing. The rate of absorption (*ka*) was faster ($P < 0.05$) and verapamil was first detected in the plasma (t_{app}) sooner ($P < 0.05$) following its administration by the sublingual route. Using the MK Model computer program (Holford, 1990) the plasma verapamil profiles following both sublingual and oral administration were found to be best fitted by a two-compartment open model. For both routes of administration the initial distribution phase ($t_{½\lambda_1}$) of verapamil into peripheral tissues was calculated as having a mean half-life of 0.88 (± 0.20) h (range 0.26–1.80 h) and was followed by the elimination phase ($t_{½\lambda_2}$) with a mean half-life value of 5.29 (± 0.38) h (range 3.56–8.00 h).

Bioavailability was found to be significantly greater (1.59 ± 0.07 fold; $P < 0.001$) following sublingual dosing than after oral administration of verapamil.

Pharmacodynamics

PR intervals measured after the administration of oral and sublingual verapamil are shown in Figure 2. There was a significantly greater increase in the PR interval at 30 ($P < 0.05$), 45 ($P < 0.01$), 60 ($P < 0.01$) and 90 min ($P < 0.01$) after sublingual dosing, than observed after oral verapamil, although not at other times. When percentage increase in PR interval and the corresponding log plasma concentration values were correlated for

Table 1 Pharmacokinetic parameters of verapamil following oral and sublingual verapamil administration to volunteers

Subject	*1*	*2*	*3*	*4*	*5*	*6*	*Mean*	*± s.e. mean*
Oral								
ka (h^{-1})	1.99	2.00	2.00	2.67	1.33	1.60	1.93	0.45
t_{max} (h)	1.25	1.00	1.00	0.75	1.5	1.25	1.13	0.26
C_{max} (ng ml^{-1})	65	37	56	47	49	38	48.58	10.71
t_{app} (h)	0.50	0.17	0.25	0.25	0.25	0.50	0.27	0.10
AUC(0–8) (ng ml^{-1} h)	300	158	294	282	185	191	234	63.75
AUC(0–∞) (ng ml^{-1} h)	1661	711	1623	1845	792	975	1268	497.19
$t_{½\lambda_1}$ (h)	0.43	1.32	0.46	2.21	0.26	0.65	0.89	0.75
$t_{½\lambda_z}$ (h)	4.93	3.92	5.00	6.25	3.56	4.55	4.70	0.95
Sublingual								
ka (h^{-1})	3.72	2.87	2.67	2.67	4.00	4.00	3.32	0.65
t_{max} (h)	0.50	0.50	0.75	0.75	0.50	0.50	0.58	0.13
C_{max} (ng ml^{-1})	68	56	81	49	57	43	59.20	13.62
t_{app} (h)	0.17	0.08	0.08	0.08	0.08	0.08	0.10	0.03
AUC(0–8) (ng ml^{-1} h)	422	199	381	339	275	238	310	86.14
AUC(0–∞) (ng ml^{-1} h)	2668	1058	2314	2651	1488	1632	1971	674.77
$t_{½\lambda_1}$ (h)	0.34	0.36	1.00	1.51	1.80	0.17	0.86	0.68
$t_{½\lambda_z}$ (h)	6.94	4.67	4.33	6.17	8.00	5.18	5.88	1.42

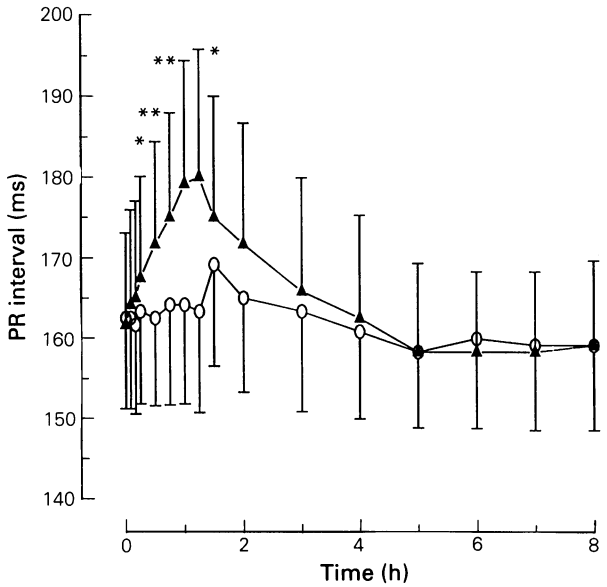

Figure 2 Comparison of PR intervals following sublingual verapamil (▲) and oral verapamil (○) administration (*$P < 0.05$; **$P < 0.01$).

individual subjects using logarithmic linear regression, there was a closer correlation between the two measurements following sublingual dosing than after oral administration in all volunteers.

Discussion

It has been demonstrated in healthy male volunteers that the sublingual administration of verapamil results in more rapid absorption, higher peak plasma verapamil concentrations, greater bioavailability and greater prolongation of PR intervals than an equivalent dose of verapamil administered orally. The sublingual route may therefore provide a suitable method of administering verapamil to patients with certain acute supraventricular arrhythmias who would otherwise receive verapamil intravenously.

The handling of verapamil after both oral and sublingual administration has been found to be be consistent with a two-compartment open pharmacokinetic model with first order absorption (Holford, 1990). This observation,

and the plasma distribution and elimination half-lives of oral and sublingual verapamil in this study are in agreement with those reported previously (Asthana *et al.*, 1984; Dominic *et al.*, 1981; Eichelbaum *et al.*, 1984; McAllister & Kirsten, 1982; Reiter *et al.*, 1982; Schomerus *et al.*, 1976; Woodcock *et al.*, 1982). Verapamil administered sublingually has been shown to exhibit intermediate pharmacokinetic characteristics between those of intravenous and oral administration (Woodcock *et al.*, 1982).

The greater relative bioavailability of verapamil following sublingual administration observed in the present study is doubtless associated with the fact that following oral dosing verapamil undergoes extensive first-pass metabolism (Eichelbaum *et al.*, 1979; Eichelbaum & Somogyi, 1984). The possibility exists that a portion of the sublingual verapamil dose may have been swallowed and subsequently subjected to first-pass metabolism. However, due to the rapid absorption and efficacy of sublingual verapamil in prolonging the PR interval, it is considered unlikely that any swallowed verapamil would have contributed significantly to this effect.

The greater pharmacodynamic response and greater correlation between plasma concentration and percentage increase in PR interval observed with sublingual verapamil, even at equivalent plasma verapamil concentrations, is in agreement with the findings of Woodcock and colleagues (1982). This may be associated with the fact that currently available verapamil formulations are comprised of a racemic mixture of equal amounts of the dextro (d or +) and laevo (l or −) isomers. The (−)-isomer of verapamil has been shown to be up to 18 times more potent than the (+)-isomer at prolonging the PR interval in healthy volunteers (Echizen *et al.*, 1985a,b). The elimination half-lives of the two isomers have been shown to be similar but the systemic clearance of the more active (−)-verapamil is twice that of (+)-verapamil (Eichelbaum *et al.*, 1984). Stereoselective metabolism of the more active (−)-isomer has been postulated by several workers (Echizen *et al.*, 1985a,b; Eichelbaum *et al.*, 1984; Vogelgesang *et al.*, 1984). This would result in lower plasma, and hence myocardial (−)-verapamil levels following oral compared with intravenous, buccal or sublingual administration and possibly explains the difference in pharmacodynamics observed in this study at equivalent plasma rac-verapamil concentrations. The systemic bioavailability of (−)-verapamil has also been shown to be less than that of (+)-verapamil (Hoon *et al.*, 1986). Correlation of plasma concentrations of (+)- and (−)-verapamil with the pharmacological response, such as PR interval prolongation, would require measurement of the individual isomers. Although Earle & MacKichan (1987) have reported the successful separation and measurement of verapamil isomers *in vitro* no limits of detection were cited.

Padrini and co-workers (1985) analysed verapamil in samples of right atrial appendage of patients and found that the relationship between plasma and myocardial tissue verapamil concentrations may be related by a non-linear function reflecting specific and non-specific tissue binding, further complicating the correlation between plasma verapamil concentrations and pharmacodynamic response. Norverapamil, the primary metabolite detected after oral and sublingual administration, possesses only 20% of the vasodilator activity of verapamil but exhibits no antiarrhythmic activity (Neugebauer, 1978) and is therefore not expected to contribute to the antiarrhythmic effect of verapamil. Such factors make a precise interpretation of the relationship between the pharmacokinetics and pharmacodynamics of rac-verapamil difficult to determine.

The data presented demonstrate that at equivalent plasma verapamil concentrations, sublingual administration produces a greater pharmacodynamic response, as judged by AV node conduction, compared with oral dosing. This suggests that the sublingual administration of verapamil may offer an additional and alternative method for the management of certain acute or paroxysmal SVTs, particularly as sublingual verapamil offers significant advantages in terms of ease of dosing over intravenous administration.

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