Preliminary investigation of the efficacy of sublingual verapamil in the management of acute atrial fibrillation and flutter

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The antiarrhythmic properties of sublingual verapamil were investigated in seven patients with acute fast atrial flutter ($n = 2$) or fibrillation ($n = 5$). A rapid and significant ($P < 0.05$) reduction in the ventricular rate was achieved in all seven patients. The ventricular rate at peak plasma verapamil concentration ($\pm$ s.d.) was significantly slower than on admission (101.6 ± 11.3 and 159 ± 5.3 beats min^{-1} respectively, $P < 0.01$). The ventricular rate remained controlled for over 4 h. Sublingual verapamil was rapidly absorbed with the maximum peak plasma concentration (153.3 ± 15.5 ng ml^{-1}) being achieved after 1.21 ± 0.18 h. Side-effects of sublingual verapamil were limited to one report of a bitter taste. The sublingual administration of verapamil may provide an alternative method for the control of acute fast atrial fibrillation and flutter in selected patients.

Keywords atrial fibrillation and flutter sublingual verapamil antiarrhythmic pharmacokinetics

Introduction

Intravenous verapamil is a recognised and effective treatment for certain acute supraventricular tachycardias [1–7]. Oral verapamil has been used successfully (in combination with pindolol) for terminating re-entrant supraventricular tachycardias [8] but to our knowledge there are no reports of oral verapamil being used alone for the acute management of such arrhythmias. However, oral verapamil is widely used for the prophylaxis of some paroxysmal supraventricular arrhythmias [9] although its efficacy has recently been questioned [10]. Administered sublingually or buccally to healthy volunteers, verapamil has been previously shown to have characteristics intermediate between those seen following intravenous-bolus and oral administration [11–15].

An anecdotal report inferred that a patient with chronic paroxysmal atrial fibrillation obtained greater symptomatic relief of palpitations after sucking a conventional oral verapamil tablet rather than swallowing it. Since there were no reports in the literature demonstrating the antiarrhythmic efficacy of verapamil after administration by the sublingual route in patients, this was investigated further. In this

preliminary study, 80 mg verapamil was administered sublingually to five patients presenting with acute atrial fibrillation and to two patients with acute atrial flutter to investigate (a) the effectiveness of sublingual verapamil in controlling the ventricular response to such arrhythmias and (b) the acceptability of the treatment to patients.

Methods

Six patients with symptoms of palpitations, breathlessness and chest pain were urgently admitted to hospital via their general practitioner. The remaining subject was an in-patient with a history of angina pectoris and a recent cerebrovascular accident. The patients (three male and four female) were aged between 62 and 76 years (mean 69.6 ± 2.2 years). All patients underwent haematological and biochemical screening, a chest radiograph and 12-lead electrocardiogram (ECG) prior to being admitted to the study. Patients with unstable or potentially unstable illnesses (e.g. myocardial infarction, left ventricular

failure, sick sinus syndrome, heart block) were excluded, as well as those whose poor physical condition prevented compliance with the sublingual technique. Approval for the study was granted by the local Ethics Committee. Informed consent was obtained from the patient prior to inclusion in the open trial.

A cannula for venous access was inserted. In the absence of a sublingual dosage form, patients were administered two crushed verapamil 40mg tablets ('Securon', Knoll Limited, Burgess Hill, Sussex RH15 9NE) to provide a total dose of 80mg. The crushed tablets were then given to the patient to retain under their tongue until the powder had been absorbed. Patients were asked to refrain from swallowing the powder during the dissolution period which lasted for approximately 20 min. Venous sampling, blood pressure and ECG recordings for heart rate and rhythm were made immediately before and at 10, 20, 30, 45, 60, 90 min and 2, 3 and 4 h after the administration of verapamil. Once the patient's acute arrhythmia had been controlled, conventional anti-arrhythmic treatment was prescribed as appropriate.

Immediately after venous collection into lithium heparin tubes, the blood was centrifuged and the separated plasma stored at -18°C until assayed. The plasma was extracted by a previously reported method [16] and the plasma concentrations of verapamil, and its primary metabolite norverapamil, were determined by a high performance liquid chromatography method based on that described by Kapur and colleagues [17].

Pharmacokinetic modelling was applied to the plasma verapamil data using a computer programme based on non-linear least squares regression analysis [18]. Statistical comparisons were made by means of Student's paired *t*-test. Results are expressed as the mean $\pm$ 1 standard deviation (s.d.).

Results

Sublingual verapamil was effective in reducing and controlling the ventricular rate in all seven patients who presented with either fast atrial fibrillation ($n = 5$) or fast atrial flutter ($n = 2$). A statistically significant reduction in the mean ventricular rate ($P < 0.05$) was first observed 30 min after initial dosing which corresponded to a mean verapamil plasma concentration of $121.3 \pm 56.4 \text{ ng ml}^{-1}$. The heart rate at peak plasma verapamil concentration was significantly lower ($P < 0.01$) than on admission (101.6 ± 11.3 and $159.6 \pm 5.3 \text{ beats min}^{-1}$, respectively) representing a mean reduction of $35.4 \pm 18.1\%$. In addition, the mean heart rates were also significantly lower (when compared with the rate on admission) at 30 and 45 min ($P < 0.05$) and likewise at 1h, 1.5h, 2h, 3h, 4h ($P < 0.01$) following the administration of sublingual verapamil. The heart rate vs time curve is shown in Figure 1.

The ventricular rates of all patients ($n = 7$)

Figure 1 Mean ($\pm$ s.d.) heart rate vs time following sublingual administration of 80 mg verapamil (Securon[®]) sublingually to patients with fast atrial flutter and fibrillation ($n = 7$).

* $P < 0.05$, ** $P < 0.01$.

remained controlled and significantly lower after 30 min than those measured on admission and remained so for the duration of the study period ($P < 0.05$). Four of the seven patients reverted to sinus rhythm on completion of the study. Sublingual verapamil was well-tolerated with adverse effects limited to one report of a bitter taste.

Verapamil rapidly appeared in the plasma following sublingual administration being detected $12.6 \pm 1.8 \text{ min}$ after dosing. A mean peak plasma verapamil concentration of $153.3 \pm 15.5 \text{ ng ml}^{-1}$ was attained $1.21 \pm 0.18 \text{ h}$ after dosing. Elimination of verapamil followed a biphasic pattern with the half-lives of the distribution and slower elimination phases being 1.40 ± 0.47 and $5.30 \pm 1.05 \text{ h}$, respectively. Mean values for some of the pharmacokinetic parameters derived from the plasma verapamil data are given in Table 1 together with those from other studies [11–14] where the sublingual or buccal routes have been used for the administration of verapamil.

Norverapamil, the primary metabolite of verapamil, was first detected in the plasma of patients after $0.92 \pm 0.34 \text{ h}$ at a concentration of $12.8 \pm 6.9 \text{ ng ml}^{-1}$. The mean peak plasma norverapamil concentration of $42.7 \pm 15.1 \text{ ng ml}^{-1}$ was recorded after $2.71 \pm 0.55 \text{ h}$.

Discussion

Verapamil is a calcium channel antagonist commercially available and currently licensed as a racemic mixture of equal proportions of the (+)- and (-)-isomers for the management of angina, hypertension and certain supraventricular arrhythmias [19–21]. Its antiarrhythmic actions are due to the blocking of the slow-inward calcium channel at the sino-atrial (SA) and atrioventricular (AV) nodes. Administered intravenously it is highly effective in

Table 1 Comparison of the means of some pharmacokinetic parameters determined from patient and volunteer studies

Reference	[11]	[11]	[14]	[14]	[13]	[13]	[12]	[12]	[12]	Present study
Volunteer	Healthy subject	Healthy subject	Healthy subject	Healthy subject	Healthy subject	Healthy subject	Healthy subject	Healthy subject	Healthy subject	Patient
Dose (mg)	120	20	80	20	40	40	5	40	60	80
Route	oral	buccal	oral	sublingual	sublingual	oral	intravenous	sublingual	sublingual	sublingual
<i>n</i>	7	7	6	6	6	6	7	4	3	7
<i>C</i> _{max} * (ng ml ⁻¹)	335.6 (103–741)	48 (32–72)	125.6 (± 151.5)	26 (± 12.9)	59.17 (± 13.62)	48.58 (± 10.71)	39.1 (± 13.3)	72.3 (± 46.4)	107.0 (± 36.6)	153.29 (± 40.88)
<i>t</i> _{max} (h)	1.15 (0.5–2.0)	0.975 (0.58–1.25)	1.33 (± 0.73)	1.185 (± 0.3)	0.58 (± 0.13)	1.125 (± 0.26)	NS NS	1.50 (± 0.77)	1.02 (± 0.36)	1.21 (± 0.47)

*C*_{max} – maximum measured plasma concentration (* – dose-related parameter); *t*_{max} – time of maximum measured plasma concentration; NS – not stated. (Figures in brackets represent ranges or standard deviations).

controlling and terminating certain types of supraventricular arrhythmias [1–7]. To our knowledge there have been no published reports of the use of sublingual verapamil or oral verapamil alone for the acute management of such arrhythmias. Intravenous verapamil offers the advantage over oral dosing due to the delay associated with disintegration, dissolution and subsequent absorption of drug after administration by the latter route. Also, verapamil undergoes extensive first-pass hepatic metabolism [22] which is not observed following intravenous administration, with this phenomenon occurring to a greater extent with the more biologically active (-)-isomer [23, 24].

Previous work with healthy volunteers has shown that the pharmacokinetic profile of sublingual verapamil is intermediate between those obtained after intravenous and oral administration [11–15]. Also, sublingual administration reduces the extensive first-pass metabolism seen with oral verapamil. It has also been shown to be more effective at prolonging the PR-interval in healthy subjects than oral verapamil at equivalent plasma concentrations. For comparative purposes, previously reported pharmacokinetic parameters are provided in Table 1. Clearly, all the studies used only small numbers of subjects (*n* = 3–7) and therefore, no firm conclusions can be drawn from the results. However, the data indicate the need to conduct larger, well-controlled trials to confirm these initial findings.

In the present study, the mean time to reach maximum plasma concentrations was 1.21 h after sublingual dosing. This compares with the range from 0.58 to 1.5 h reported in the other studies [11–15]. The greater bioavailability observed with sublingual verapamil when compared with an equivalent oral dose [13] was attributed to the extensive first-pass hepatic metabolism of verapamil after oral dosing. However, the possibility exists in that study as well as in the present one that a proportion of the sublingual dose may have been swallowed and subsequently subjected to first-pass metabolism. The rapid and significant reduction in ventricular rate seen in this study would be difficult to attribute to absorp-

tion from the gastro-intestinal tract. There may have been some absorption due to swallowing of a fraction of the dose but it is considered unlikely that any such verapamil would have contributed significantly to its rapid effect.

In two previous studies [12, 13] it was found that all volunteers who received a sublingual dose of verapamil experienced a bitter taste sensation whereas in the present study this side-effect was reported by only one of the seven subjects. A possible explanation is that patients who are experiencing rapid ventricular rates are more likely to welcome a reduction in heart rate and may not notice a bitter taste as inconvenient or unpleasant.

To our knowledge this is the first reported study of the successful use of sublingual verapamil for treatment of patients with acute atrial fibrillation or flutter. We have found it simple to administer, well tolerated by patients and rapidly absorbed. In fast atrial flutter and fibrillation the ventricular rate was rapidly controlled in all seven patients. Further placebo-controlled trials and comparator studies with intravenous verapamil using larger numbers of patients are required to establish whether there is a role for sublingual verapamil in the management of some patients with atrial fibrillation or flutter. The sublingual route is more convenient to patients and to medical staff and is considerably less expensive to administer. However, sublingual verapamil is not as effective nor as rapid as intravenous verapamil and therefore, the intravenous route is likely to remain the one of choice in the hospital environment for the majority of patients. However, sublingual verapamil might be administered to selected patients in the domiciliary setting where intravenous administration is not an option. This could be of benefit to patients with infrequent episodes of documented paroxysmal atrial flutter and fibrillation, and perhaps other appropriate supraventricular tachycardias. The administration of sublingual verapamil, by producing rapid control of the ventricular rate and its associated symptoms would overcome the inconvenience and side-effects of long-term, prophylactic, oral anti-arrhythmic medication.

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