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The antihypertensive efficacy of verapamil in the elderly evaluated by ambulatory blood pressure measurement

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Summary: **To assess the efficacy, tolerability and pharmacokinetics of verapamil in the elderly, ten patients with blood pressure > 160/90 mmHg were studied in a randomized double-blind placebo-controlled cross-over trial. Nine patients aged 75 (± 4.9) years completed the study. After titration, doses of verapamil varying from 40 to 120 mg (40 mg in four, 80 mg in one and 120 mg in four patients) twice daily for six weeks were taken. Mean (± SEM) clinic lying blood pressure was reduced on verapamil from 187 ± 6.8/100 ± 4.1 to 167 ± 4.6/86 ± 3.1 mmHg, ((P < 0.001). Mean ambulatory blood pressure was reduced from 174 ± 1.4/95 ± 1.0 to 169 ± 1.3/90 ± 0.8 mmHg, (P < 0.01). Lying heart rate was significantly reduced but glomerular filtration rate, renal blood flow and mental function, were not altered by treatment. The mean plasma half-life of verapamil was 6.9 ± 1.1 hours. Side effects were minimal. We conclude that verapamil is an effective blood pressure lowering agent in the elderly.**

Introduction

Epidemiological studies show that hypertension is an important risk factor for cardiovascular diseases in the elderly.[1] Furthermore the European Working Party on High Blood Pressure in the Elderly (EWPHE) has demonstrated a beneficial effect of lowering BP in patients with hypertension aged over 60 years.[2] However, the efficacy and acceptability of different BP lowering drugs in this age group await clarification.[3] In the EWPHE trial BP was controlled with diuretic therapy alone in 65% of patients,[2] but there was a decrease in glucose tolerance[4] and an increase in serum uric acid[5] and creatinine levels.[6] Beta-adrenoceptor blocking drugs may be less than ideal as treatment in the elderly because of the reduction in stroke volume,[7] a decrease in beta-adrenoceptor-mediated responsiveness[8,9] and some evidence for an increase in the incidence of side effects.[10] Methyldopa though effective in the elderly is associated with drowsiness,[11] a particularly undesirable adverse effect in the aged.

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Verapamil is an effective BP lowering agent in young and middle-aged hypertensives[12–15] and while there is some evidence that verapamil is effective in the elderly,[16] its efficacy has not been fully evaluated. In this study we examined the antihypertensive efficacy, tolerability and pharmacokinetics of verapamil in a group of elderly patients. Because of the possibility that antihypertensive therapy may compromise regional blood flow particularly in the elderly we also assessed mental and renal function by psychometric testing and renal haemodynamic studies.

Patients and methods

Ten patients (seven females), mean age 75 years, range 65–83 years) who had been receiving no therapy for at least one month and with a BP greater than 160/90 mmHg (range 164–225/92–118 mmHg) entered the study. Patients with cardiac conduction defects including sinus bradycardia (< 50 beats per minute), abnormal liver function tests, or elevated serum creatinine levels were excluded. The study protocol was approved by the hospital ethics committee and informed consent was obtained.

Study design

Patients whose mean lying BP remained within the limits 160–240/90–120 mmHg after a four week run-in phase entered an open titration phase. The dose of verapamil (Veramil®—Orion Pharmaceutica) was titrated at weekly intervals (40 to 80 to 120 mg twice a day taken at 09.00 and 18.00 hours) until clinic lying SBP was reduced to less than 160 mmHg or there was a 20% reduction in SBP compared with the average SBP of the run-in phase. Patients then entered a randomised double-blind placebo-controlled cross-over phase using the dose of verapamil as indicated on titration. During this phase they were seen after one, three, five and six weeks in each six week placebo and treatment period for measurement of clinic BP, heart rate and weight, and documentation of side effects. At the end of each treatment period ambulatory BP measurement, renal haemodynamic studies and psychometric testing were carried out.

Methods

Clinic BP was measured between 10.00 and 12.00 hours with the Hawksley random zero sphygmomanometer, Korotkoff phase V being taken for DBP. BP and heart rate recordings were made with the patient lying after five minutes rest and standing after two minutes with the arm supported at heart level.[17] Ambulatory BP and heart rate were measured non-invasively at half-hourly intervals using a semi-automated portable recorder, the Remler M2000 (Remler Corp. San Francisco, C.A.).[18] The Remler was operated by the patient from 09.00 to 22.00 hours. All Remler tapes were decoded by one operator.

Glomerular filtration rate and effective renal plasma flow were estimated using plasma clearance of intravenously injected Cr^{51} EDTA and I^{125} hippuran (The Radiochemical Centre, Amersham) respectively. A single injection technique was employed, using 50–75 microCi of each isotope. Samples were taken from a venous cannula in the opposite arm at intervals after injection (5, 10, 15, 30, 40, 50, 60, 80, 100, 140, 170, 180 and 240 minutes). Clearance values were calculated using a two-compartment model.[19] Effective renal plasma flow was corrected for haematocrit to give renal blood flow.

The pharmacokinetics of verapamil and its major metabolite norverapamil were studied at the end of the titration phase from blood samples taken before and at intervals after the last dose (15, 30, 45, 60, 90 minutes two, four, six, 12 and 24 hours). Plasma specimens were stored at −20°C prior to assay. For the high-performance liquid chromatographic assay of verapamil and norverapamil, 1 ml specimens of plasma were made alkaline (0.05 ml of 5N NaOH) and extracted with 5 ml diethyl ether. After removal and evaporation of the organic layers, these were reconstituted in mobile phase (0.1 ml) and chromatographed. The column was 15 cm Sperisorb 5ODS and the mobile phase contained methanol 450 ml, water 50 ml, KH_2PO_4 34 mg, and was adjusted to pH 3 with phosphoric acid. The flow rate was 2.5 ml/min and the drugs were detected by fluorescence at wavelengths 275 nm excitation and 339 nm emission. Retention times for verapamil, norverapamil and internal standard (imipramine) were 3.1, 4.0 and 5.2 minutes respectively. The elimination half-lives of verapamil and norverapamil were calculated from the slope of the line derived by linear least squares regression analysis of the terminal part of the log concentration time curve; the area under the plasma concentration time-curve was calculated by the trapezoidal rule.

Side effects were assessed by asking the patient to report any symptoms experienced during treatment and by the response to a check list of 16 questions put to the patient by the physician.

Psychometric tests used in this study included tests of psychomotor co-ordination, memory, concentration, central nervous system arousal and mood.

Psychomotor Co-ordination This was assessed with the number connection test (NCT) and the peg-board test (PBT) (Perdue Pegboard®—Science Research Association, Inc. Illinois). The NCT is a modified version of the Reitan trail making test[20] in which patients were required to join up, in the correct sequence, a series of encircled numbers, the test being scored as the time to completion. On the PBT, patients were required to transfer a set of small pegs from one row of holes to another using the dominant hand, the score being the time taken to complete the task.

Concentration This was assessed with the digit symbol substitution test (DSST) from the Weschler adult intelligence scale (WAIS).[21] In this test patients are presented with a different code symbol for the numbers one to nine, and asked to write as many symbols as possible on numbered sheets in 90 seconds, the score being the number of correct substitutions.

Memory Short term memory, learning, and delayed recall (DR) performance were measured by means of the 'shopping list test' (SLT)[22] and the analagous 'pictures of objects test' (POT). In the SLT, patients are shown 10 cards, each with the

name of a common grocery item printed on it, one at a time in a fixed order at the rate of one card per second. The number of items remembered after the first presentation of the SLT gives a measure of short term verbal memory. The number of presentations of the set of cards (up to a maximum of five presentations) required before the patient can recall all the 10 items, provides an index of learning ability and is known as trials to criterion (TC). Delayed recall is assessed twenty minutes later by asking patients to recall as many items as possible. Measurement of visual memory (POT) is identical to that used for verbal memory (SLT) except that pictures of common objects are used instead of words. Short term memory was also measured by means of the digit-span test (DST) administered according to the WAIS manual.[21] Patients listen to a series of digits, presented at the rate of one per second, and digit-span is taken as the longest correctly remembered sequence.

Central nervous system (CNS) arousal This was assessed by critical flicker frequency (CFF),[23] measured on an activity profiler (Lord Medical Ltd) under standard conditions of illumination. The psychophysical method for obtaining CFF thresholds used was the method of limits. Using this procedure the intensity of the flickering light source is held constant and the frequency is progressively increased (ascending thresholds) or decreased (descending thresholds) until the subject reports a change in his perception of the flicker (i.e. from flicker to fusion or from fusion to flicker). Thresholds are reported in cycles per second (hertz) and the means of six ascending and descending thresholds calculated separately.

Subjective Mood Patients rated their subjective state on bipolar visual analogue scales (VAS), scored as the distance in millimetres from the left hand side of the scale.[24] In order to reduce the VAS data, only scores on alertness, calmness and contentedness are reported.

All assessments were carried out by the same observer under standardised conditions. Patients practised PBT, NCT, DSST, CFFT, and VAS on four occasions prior to the start of the double-blind cross-over stage of the trial, in order to minimise learning effects during the study proper. Equivalent parallel forms of the DSST, NCT, DST, SLT and POT were used to prevent patients learning the material on repeated administration. Paper and pencil test forms were enlarged to facilitate this elderly population.

The ambulatory BP data were analysed using a computer programme designed to pair half-hourly readings on verapamil with readings for the same time of day on placebo. Unpaired data were omitted. Student's paired *t*-test was used for all comparisons and the influence of treatment, order and interaction effects were determined by the method appropriate for cross-over trails suggested by Hills and Armitage.[25] A probability value of less than 5% was taken to be significant.

Results

One patient did not complete the study (see below), leaving six females and three males, mean age 75 years and range 65–83 years. Mean clinic lying BP at the end of the run-in phase was 191/103 mmHg. The daily doses of verapamil at the end of the titration phase were 40 mg (in 4 patients), 80 mg (in 1), and 120 mg (in 4) twice daily. Verapamil reduced both SBP and DBP to a similar extent in the lying and standing positions (Table 1) and there were no order or interaction effects. Heart rate was significantly reduced in the

Table I Clinic blood pressure, heart rate and weight (n = 9)

		Placebo (mean)	*Verapamil (mean)*	*Treatment difference*	*95% Confidence interval*
Lying BP (mmHg)	Systolic	186.9	166.7	20.2**	7.9:32.6
	Diastolic	99.8	86.4	13.2**	5.9:20.4
Standing BP (mmHg)	Systolic	190.0	164.8	24.8***	14.6:34.9
	Diastolic	104.5	91.5	13.1**	6.1:20.3
Heart rate (beats/min)	Lying	82.8	77.8	5.7*	1.8: 9.6
	Standing	89.0	87.3	1.6	−0.6: 3.9
Weight (kg)		66.6	66.3	0.4	−1.5: 0.4

*P < 0.05, **P < 0.01, ***P < 0.001.

Table II Renal haemodynamics (n = 9). GFR = glomerular filtration rate; RBF = renal blood flow

	Placebo (mean)	*Verapamil (mean)*	*Treatment difference*	*95% Confidence interval*
GFR (ml/min)	68.8	65.9	2.3	− 6.2:10.8
RBF (ml/min)	388.2	388.1	− 1.0	− 36.5:34.5

lying position only. Body weight was unchanged with treatment.

Mean ambulatory SBP from 09.00 to 22.00 hours was significantly reduced from 174 to 169 mmHg, (treatment difference, 5.2 mmHg; 95% CI, 1.9: 8.5; $P < 0.01$; 168 paired readings) and DBP from 95 to 90 mmHg (treatment difference 4.4 mmHg; 95% CI, 2.3: 6.4; $P < 0.001$; 169 paired readings) with treatment (Figure 1). Ambulatory heart rate was unaffected. Neither glomerular filtration rate nor renal blood flow were significantly different on active treatment compared with placebo (Table II).

Table III summarises the pharmacokinetic findings. The mean elimination half-life for verapamil was 6.9 ± 1.1 hours. Pre-dose and maximum post-dose (C_{max}) concentrations of verapamil increased with increasing doses of the drug. Times to C_{max}, did not differ substantially between doses. Areas under the plasma concentration-time curves over a dose interval (AUC 0–12 hours, final dose) were dose-related. Data for norverapamil were similar in trend. Note, however, that the values of norverapamil half-life are apparent values and probably over-estimate the elimination half-life because of continuing formation of norverapamil from verapamil during the verapamil elimination process.

No impairment of mental function was found on any of the performance indices measured (Table IV). These findings were not influenced by either order or interaction effects, confirming that

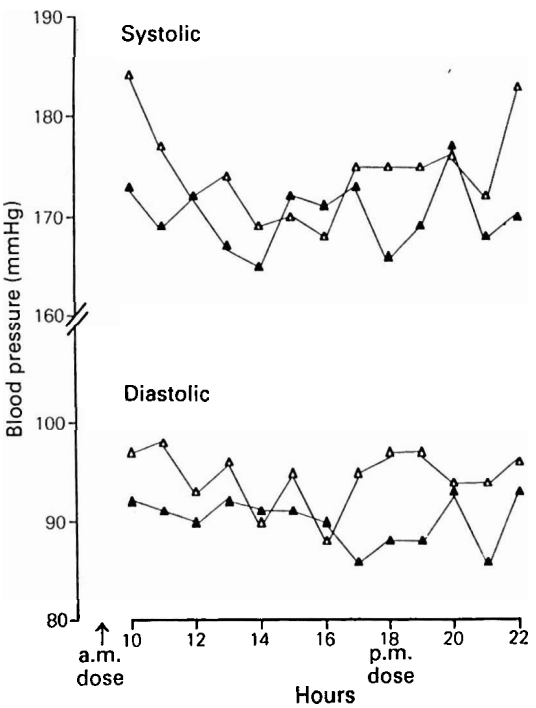

Figure 1 Curves derived from the means of hourly values of ambulatory systolic and diastolic blood pressure on placebo (Δ) and verapamil (▲) after 6 weeks of treatment (n = 9).

Table III Verapamil and norverapamil pharmacokinetics

	40 mg twice daily (n = 4)		*Verapamil dose 80 mg twice daily (n = 1)*		*120 mg twice daily (n = 4)*	
Parameter	*Verapamil*	*Norverapamil*	*Verapamil*	*Norverapamil*	*Verapamil*	*Norverapamil*
t 1/2 B (hr)	5.1 ± 2.6	16.5 ± 17.0	4.4	11.0	10.1 ± 0.7	14.6 ± 3.6
AUC 0–12 (ng/ml/hr)	507.0 ± 275.2	1133.1 ± 328.7	2345.0	4148.1	1914.2 ± 285.4	3778.2 ± 1325.5
C_{min} (ng/ml)	15.5 ± 27.8	43.3 ± 24.7	25.0	92.0	68.3 ± 29.6	210.8 ± 128.3
C_{max} (ng/ml)	133.0 ± 50.9	162.5 ± 20.6	344.0	493.0	349.0 ± 80.4	500.0 ± 215.8
t_{max} (hr)	1.2 ± 0.4	1.3 ± 0.6	1.5	6.0	1.6 ± 0.8	3.3 ± 2.2

Data are mean ± SD; t 1/2 B = elimination half-life; AUC, 0–12 = area under plasma concentration-time curve during a dose interval; C_{min} = pre-dose drug plasma concentration; C_{max} = peak drug plasma concentration; t_{max} = time to C_{max}.

Table IV Psychometric test scores (n = 9)

			Placebo (mean)	*Verapamil (mean)*	*Treatment difference*	*95% Confidence interval*
PBT		(seconds to completion)	41.8	38.2	3.6	− 2.4: 9.1
NCT		(seconds to completion)	96.3	88.6	7.7	− 13.6:28.5
DSST		(number correct/90 seconds)	15.7	15.9	− 0.3	− 2.6: 2.0
SLT	TC	(number of presentations)	4.3	3.6	0.7	− 0.7: 1.5
	DR	(number of items recalled)	6.3	6.0	0.3	− 0.8: 1.8
POT	TC	(number of presentations)	3.3	3.3	0.0	− 1.5: 1.5
	DR	(number of items recalled)	8.6	8.6	0.0	− 1.0: 1.2
DST		(longest sequence recalled)	6.1	6.0	0.1	− 0.7: 0.8
CFF	Ascending	(Hertz)	26.7	26.1	0.7	− 2.8: 2.6
	Descending	(Hertz)	27.4	27.8	− 0.4	− 2.4: 1.3
VAS	1. Alert–Drowsy	(mm)	4.6	9.0	− 4.6	− 19.6:10.1
	2. Happy–Sad	(mm)	11.0	13.7	− 2.7	− 21.0:15.1
	3. Calm-Excited	(mm)	2.6	18.2	− 15.7	− 53.4:18.1

PBT = peg board test; NCT = number connection test; DSST = digit symbol substitution test; SLT = shopping list test; TC = trials to criterion; DR = delayed recall; POT = pictures of objects test; DST = digit span test; CFF = critical flicker frequency; VAS = visual analogue scale.

the learning plateau was achieved in the pre-study phase.

One patient with a history of epilepsy left the study because of a grand mal seizure which occurred in the double-blind phase while on placebo. Two patients reported headaches and one complained of leg cramps on verapamil.

Discussion

Verapamil exerts its BP lowering effect by reducing peripheral resistance, without causing reflex tachycardia, an increase in plasma renin activity or fluid retention,[12] as occurs with other vasodilator drugs such as hydralazine.[26] In this study verapamil in an averge dose of 80 mg twice daily lowered BP effectively in elderly hypertensives with few side-effects. Reductions in lying and standing BP were similar and postural hypotension did not occur. Heart rate was significantly reduced only in the lying position. The effects of verapamil in these elderly patients are similar to those found in studies of younger hypertensives, the main difference being that doses in the range, 80 to 240 mg/day controlled BP in this study whereas considerably higher doses, up to a total of 720 mg, were used to obtain control in the younger patients.[12–14,16]

Mean ambulatory BP was significantly lower on verapamil from 09.30 to 22.00 hours, although this effect seemed to wane six hours after the 09.00 hrs dose (Figure 1). These findings are similar to those of Hornung *et al.*,[27] who showed that twice-daily verapamil achieved significant reduction in intra-arterial BP consistently throughout the day and night in younger hypertensives (mean age 49.3 years) using a higher average dose of verapamil (165 mg twice daily).

Renal haemodynamics were unchanged in the face of a fall in BP in keeping with animal studies[28] and data in younger subjects.[29–31] The maintenance of renal function in patients who might be expected to have decreased renal perfusion[32,33] suggests that verapamil may have a useful role in this age group.

The elimination half-life for verapamil of 6.9 ± 1.1 hours is similar to that of 6.7 ± 2.0 hours reported in a younger population after 3 days on verapamil.[34] An average peak verapamil plasma concentration of 280 ± 56.0 ng/ml after 160 mg of verapamil was reported in the same study,[34] whereas our values after 120 mg were higher at 349.0 ± 80.4 ng/ml. This difference may be due to a reduction in first pass metabolism of verapamil in the elderly as has been observed with propranolol[35] and labetalol.[36]

The possibility that antihypertensive agents might have adverse effects on mental function has been investigated in several studies. Beta-adrenoreceptor blocking drugs have central effects which can be demonstrated by psychomotor tests.[37] Solomon *et al*[38] comparing mental function in patients on diuretic therapy alone with patients taking methyldopa or propranolol, showed impairment of verbal memory with methyldopa and propranolol but not with diuretic therapy. Lichter *et al*,[39] using tests of memory similar to those used in the present study, showed a significant memory impairmant with atenolol but not enalapril. The absence of impairment in mental function in the presence of BP reduction with verapamil is of particular relevance to the elderly. It would appear

from the evidence to date that impairment of mental function is more closely related to the drug used than to a reduction in BP.

In conclusion twice-daily verapamil lowers BP with few side effects in elderly hypertensives. The ambulatory data show that the BP lowering effect is reasonably well maintained throughout the interval between doses. Thus, verapamil in the present formulation appears both safe and effective as monotherapy in the management of the elderly hypertensive patient.

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