Greater antihypertensive efficacy of the calcium channel inhibitor verapamil in older and low renin patients

FRITZ R. BÜHLER, U. LENNART HULTHÉN, WOLFGANG KIOWSKI AND PETER BOLLI

Department of Medicine and Department of Research, University of Basel, Switzerland

Summary

1. The calcium slow channel inhibitor verapamil was administered as monotherapy (240–270 mg; mean 427 mg/day) on the average for 93 days to 43 patients with essential hypertension; 11 with low, 24 with normal and eight with high renin sodium index.

2. Verapamil reduced blood pressure from 171 ± 16/108 ± SD 6 mmHg to 152 ± 14/93 ± 9 (both P < 0.001); in 25 of the 43 patients a diastolic pressure ≤95 mmHg was achieved. Two patients each reported vertigo, sleeplessness and constipation.

3. The fall in mean blood pressure after verapamil was directly related to age (r = 0.759, P < 0.001), pretreatment mean blood pressure (r = 0.701, P < 0.01) and plasma noradrenaline concentration (r = 0.400, P < 0.05), and inversely related to plasma renin activity (r = −0.551), P < 0.001). These correlations were also significant for diastolic blood pressure. Accordingly, the antihypertensive response to verapamil was greatest in older and low renin patients.

4. This greater blood pressure decrease with verapamil in older and low renin patients suggests a greater calcium influx-dependent vasoconstriction in these patients, which seems to be directly related to the activity of the sympathetic nervous system.

Key words: calcium, renin, sodium, verapamil.

Introduction

Intracellular sodium concentration has been reported by several investigators to be increased in essential hypertension [1, 2]. This increased intracellular sodium concentration was found to be associated with a decreased total sodium efflux rate constant in leucocytes from patients with essential hypertension [2]. The sodium efflux rate constant was particularly diminished in patients with low activity of the renin–angiotensin–aldosterone system [3], known to occur more frequently in hypertensive subjects of greater age [4]. Elevated intracellular sodium is considered to lead to increased arteriolar tone by raising intracellular free calcium [5], which is the final determinant of tension development in the vascular smooth muscle cell [6]. Accordingly, drugs inhibiting calcium influx, e.g. verapamil and nifedipine, were shown to be potent vasodilators [7, 8]. Although the antihypertensive effect of verapamil was reported more than a decade ago [9, 10], only recently has this aspect gained due attention [11]. In normotensive subjects neither verapamil nor nifedipine lowered blood pressure [10, 12]. This discrepancy in the effect on blood pressure between hypertensive and normotensive subjects tallies with recent findings of an enhanced vasodilatation in the forearm to intra-arterially administered verapamil in patients with essential hypertension [13]. The vasodilator response to verapamil was directly related to basal plasma adrenaline and, with higher dosages being associated with a fall in blood pressure, indirectly related to basal plasma renin activity.

In the present study we investigated the antihypertensive effect of verapamil in patients with essential hypertension in relation to age, plasma renin activity and plasma catecholamine concentration.

Patients and methods

The study population consisted of 43 patients with essential hypertension, 20 females and 23
males aged 20–86 (mean 53) years with a casual diastolic blood pressure between 100 and 120 mmHg (Korotkoff V) measured on at least three occasions during 4 weeks’ placebo treatment. Blood pressure was measured in both arms after 5 min in the sitting position, with a standard mercury sphygmomanometer. The mean value of the two measurements was used for analysis. Heart rate and body weight were recorded at each visit. The patients were classified according to their renin sodium index into low (n = 24) and high (n = 8) renin patients [14]. In 28 of the patients plasma catecholamines were determined after 30 min in the supine position [15].

Verapamil (120 mg in a slow release preparation) was given twice daily initially. Aiming at a diastolic pressure of ≤95 mmHg, the dosage was increased when necessary at 2 week intervals up to a maximal dosage of 240 mg three times daily. The final dosage varied between 240 and 720 (mean 427) mg/day, which was continued for 41–240 (mean 93) days. Only spontaneously reported unwanted effects were recorded. Mean blood pressure was calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure. The statistical evaluation was performed with paired and unpaired Student’s t-test and linear regression analysis. The level of significance was taken as P < 0.05. Results are given as means ± SD.

Results

Verapamil lowered blood pressure from 171 ± 16/108 ± 6 mmHg to 152 ± 14/93 ± 9 mmHg (both P < 0.001). In 25 of the 43 patients a diastolic pressure of ≤95 mmHg was achieved. There was no significant change in heart rate (81 ± 8 before and 75 ± 7 beats/min on verapamil) and body weight (77 ± 13 before and 76 ± 12 kg on verapamil). In none of the patients was reflex tachycardia or sodium and fluid retention observed. Transient vertigo and sleeplessness was reported by two patients each. Persistent constipation occurred in two other patients, which led to discontinuation of verapamil (480 mg/day for 77 days) in one of them.

Pretreatment mean blood pressure was positively correlated with the age of the patient (r = 0.382; P < 0.05). The change in mean blood pressure to verapamil was directly correlated with pretreatment mean blood pressure (r = 0.701; P < 0.001) as well as with the age of the patient (r = 0.759; P < 0.001) (Fig. 1). Pretreatment diastolic blood pressure was not related to the age of the patient, but nevertheless the decrease in diastolic blood pressure to verapamil was directly related to pretreatment diastolic blood pressure (r = 0.491; P < 0.001) as well as age (r = 0.690; P < 0.001). Pretreatment mean blood pressure and diastolic blood pressure were not related to plasma catecholamines or plasma renin activity but there was a positive correlation between age and plasma noradrenaline (r = 0.391; P < 0.001) and a negative correlation between age and plasma renin activity (r = −0.589; P < 0.001). The decrease in mean blood pressure to verapamil was directly correlated to pretreatment plasma noradrenaline (r = 0.400, P < 0.05) and indirectly to pretreatment plasma renin activity (r = −0.551; P < 0.001). These relations were also significant when the decrease in diastolic pressure was used for analysis (r = 0.435, P < 0.05, and r = −0.539, P < 0.001 respectively).

Diastolic blood pressure ≤95 mmHg was reached in 10/11 patients with a low, in 15/24 with a normal and in 0/8 with a high renin sodium index (Fig. 1).

Discussion

Verapamil lowered blood pressure to ≤95 mmHg diastolic in more than 50% of the patients. The fall in pressure was greater with increasing age and increasing pretreatment blood pressure. The better antihypertensive response to verapamil with increasing age cannot be accounted for by a higher pretreatment pressure in the older patients, since pretreatment diastolic blood pressure was unrelated to age.
The better antihypertensive effect of verapamil in older patients may explain the negative correlation found between plasma renin activity and the decrease in blood pressure to verapamil, as it is well known that plasma renin activity decreases with age [4]. A greater intracellular correlation found between plasma renin activity and the decrease in blood pressure to verapamil, as indicated by the study on leucocyte sodium efflux by Edmondson & MacGregor [3], could form a pathophysiological basis for the greater antihypertensive response to inhibition of calcium influx by verapamil in low renin patients.

The greater antihypertensive effect in the low renin patients may be further explained by a less reactive increase in renin to the verapamil-induced fall in blood pressure in these patients. This would be in accordance with the findings that the increase in plasma renin activity directly relates to basal plasma renin activity after administration of the vasodilators minoxidil and nifedipine [16, 17] and also with the observation that the antihypertensive response to prazosin was negatively correlated to basal plasma renin activity [18].

The direct relationship found between the fall in blood pressure to verapamil and basal plasma noradrenaline concentration could partly be ascribed to a rise in plasma noradrenaline with increasing age [19]. A greater antihypertensive response to verapamil with increasing sympathetic activity is in accordance with the observation that in the forearm the vasodilatory response to intra-arterial verapamil directly correlated to plasma adrenaline and, to some extent, to plasma noradrenaline in patients with essential hypertension [13]. In analogy, α-adrenoceptor blockade with prazosin and phentolamine induced an increase in forearm blood flow, which positively related to plasma adrenaline and noradrenaline respectively in hypertensive patients [20, 21]. Accordingly, calcium influx-dependent, in addition to α-adrenoceptor-mediated, vasoconstriction appears to be closely related to the activity of the sympathetic nervous system in essential hypertension.

The present findings may be of relevance for the antihypertensive treatment strategy. In the past treatment of hypertension was mainly based on a diuretic agent, which proved to be particularly effective in the older and low renin patients [22]. In the last decade 'β-blockers' have become first line drugs showing greater efficacy in the younger and high renin patients [4, 23]. In a recent extension of the present study we found that the antihypertensive efficacy of verapamil was similar to that of diuretics and β-blockers. However, whereas verapamil and diuretics were most potent in the older and low renin patients, β-blockers lowered blood pressure to a greater extent in the younger and high renin patients [24]. These data provide the basis for a new treatment concept for patients with essential hypertension, proposing as the first line drug a calcium channel blocker for the older and a β-blocker for the younger patients, thereby offering the possible prospect of cardioprotection for all hypertensive patients [11].

Acknowledgments
We are indebted for the supply of verapamil 120 mg retard to Dr E. Vogt, Knoll AG, Liestal, Switzerland. This work was supported by the Swiss National Research Fund 3.807.080.

References


Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. *Life Sciences*, 19, 1161–1174.

