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Detrimental effects of verapamil in patients with primary pulmonary hypertension

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SUMMARY Calcium channel blockade provides a logical approach to the treatment of pulmonary hypertension because these drugs exert direct vasodilator effects in the highly constricted pulmonary circulation. To determine the effectiveness of verapamil in the treatment of primary pulmonary hypertension the haemodynamic effects of the drug were evaluated in seven patients with this disorder; 10 mg was given intravenously to six patients and 120 mg orally to one patient. Verapamil produced a 20% decline in pulmonary vascular resistance and a 27% decrease in mean pulmonary arterial pressure without significant changes in systemic vascular resistance. One patient who received verapamil 480 mg orally daily for three months showed sustained haemodynamic and clinical improvement. Concomitant with its beneficial effects on the pulmonary circulation, however, verapamil produced a pronounced decrease in right ventricular stroke work index (42%) and increase in right ventricular filling pressure (50%), indicating a direct depressant effect of the drug on right ventricular function. In one patient these cardiodepressant effects were sufficiently pronounced to produce severe hypotension and cardiac arrest.

In conclusion, although verapamil appears to exert preferential vasodilator effects on the pulmonary circulation, its negative inotropic effects may be particularly detrimental to patients with primary pulmonary hypertension who have pre-existing right ventricular dysfunction; hence, treatment with verapamil is not recommended in such cases.

Because pulmonary vasoconstriction has been thought to play an important contributory role in the pathophysiology of primary pulmonary hypertension[1-3] several vasodilator drugs have been used in patients with this disorder in an attempt to reduce pulmonary artery pressure and pulmonary vascular resistance.[4] Although occasionally haemodynamic and clinical benefit have followed treatment with various vasodilator agents,[4-7] there remains no satisfactory pharmacological approach to the management of these patients. The major limitation to presently available drugs is that most agents have potent systemic vasodilator effects that exceed the magnitude of their effects on the pulmonary circulation; these systemic effects may result in severe hypotension before any appreciable improvement in pulmonary haemodynamic indices occurs.[4 8 9]

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Because calcium appears to play a critical role in vascular smooth muscle contraction[10 11] calcium channel blockade with nifedipine and verapamil provides a logical approach to the treatment of a variety of conditions characterised by abnormal regional vasoconstriction.[12-15] Calcium channel antagonists appear to exert preferential effects in regional vascular systems that are highly constricted, particularly in the coronary, cerebral, and pulmonary circulations[10 16]; hence, these drugs have proved useful in the treatment of vasospastic angina and in subarachnoid haemorrhage[12-14]; however, there are only preliminary data on the usefulness of calcium channel blockade in pulmonary vasoconstrictive states. Nifedipine attenuates the vasoconstrictor response to hypoxia in several experimental preparations[17 18] and in patients with acute respiratory failure,[19] and several case studies have reported the benefits of short and long term nifedipine treatment in patients with primary pulmonary hypertension.[20-24] In contrast, although verapamil also attenuates hypoxic pulmonary vasoconstriction[18 25 26] there are few data on its effective-

ness in hypoxic or primary pulmonary hypertension.[27] The therapeutic application of verapamil in the treatment of abnormal pulmonary vasoconstriction has theoretical appeal since the drug exerts less pronounced effects on the systemic circulation than does nifedipine[11] and thus may produce less hypotension than do drugs that have pronounced systemic vasodilator actions.

In the present study we evaluated the haemodynamic and clinical responses to verapamil in seven patients with primary pulmonary hypertension, one of whom was treated with the drug for three months and underwent repeat haemodynamic evaluation.

Patients and methods

STUDY POPULATION

We studied seven patients with primary pulmonary hypertension (five women, two men; age range 28–64 (mean 48) years). The diagnosis was established in all patients by right heart catheterisation, which confirmed the pronounced increase in pulmonary artery pressures (mean pulmonary artery pressure >30 mm Hg) and a normal pulmonary capillary wedge pressure (<15 mm Hg). Gated equilibrium scintigraphy showed normal left ventricular function and moderately to severely impaired right ventricular function. All patients has normal ventilation-perfusion scans and normal pulmonary function tests; the diagnosis was confirmed by pulmonary angiography or open lung biopsy or both. All patients had dyspnoea and fatigue on minimal or moderate exertion, but their condition was clinically stable at the time of evaluation.

HAEMODYNAMIC MEASUREMENTS

After all medications had been withheld for at least 12 hours right heart catheterisation was performed with a triple lumen, flow directed catheter for measuring right heart pressures, and cannulation of the radial artery used for measuring systemic arterial pressures. Haemodynamic measurements were made with the zero reference level at the midaxillary line with the patient supine. Left ventricular filling pressure was measured as the mean pulmonary capillary wedge pressure. Cardiac output was determined by the thermodilution method with a bedside cardiac output computer after injection of iced saline solution. Heart rates were derived from a continuously recorded electrocardiogram. All patients were breathing room air throughout the study.

DRUG ADMINISTRATION

Before drug administration mean systemic arterial pressure, heart rate, mean pulmonary capillary wedge pressure, mean right atrial pressure, and cardiac output were measured repeatedly (with a variation of <10%) until a stable haemodynamic state was achieved. Six patients then received 5 mg of verapamil intravenously followed by a additional 5 mg intravenously 10 minutes later; haemodynamic indices were measured every five minutes for 30 minutes after drug administration. One patient received a single dose of 120 mg of verapamil orally, after which haemodynamic indices were measured every 30 minutes for three hours.

After completion of the intravenous study, long term treatment with oral verapamil (480 mg daily) was started in one patient, who underwent repeat haemodynamic evaluation after three months; at that time, the haemodynamic effects of verapamil were assessed at peak drug effect, and 48 hours after drug withdrawal. This patient received no other medications during this period.

DATA ANALYSIS

Mean systemic and pulmonary artery pressures were determined by electronic filtration. Derived haemodynamic variables were calculated according to the following formulae: cardiac index (CI) = CO/body surface area (l/min/m^2); stroke volume index (SVI) = CI/HR (ml/beat/m^2); RV stroke work index (RVSWI) = SVI$\times$0·0136$\times$(MPAP$-$MRAP) (g m/m^2); systemic vascular resistance (SVR) = 80$\times$(MAP$-$MRAP)/CO (dyn s cm^{-5}); and pulmonary vascular resistance (PVR) = 80$\times$(MPAP$-$PCW)/CO (dyn s cm^{-5}), where CO is cardiac output, HR heart rate, MAP mean systemic arterial pressure, PCW pulmonary capillary wedge pressure, MPAP mean pulmonary artery pressure, MRAP mean right atrial pressure, and RV right ventricular.

The responses to verapamil at peak drug effect were compared with control values by the *t* test for paired data. Group data were expressed as mean (1 SD).

Results

HAEMODYNAMIC EFFECTS

The individual haemodynamic responses to verapamil in the seven patients with primary pulmonary hypertension are shown in Table 1. Verapamil produced a decrease in pulmonary vascular resistance in each patient in our study (range 10–32%); overall, mean pulmonary vascular resistance declined from 1344 to 1078 dyn s cm^{-5} ($p<0·025$). In contrast, the small decrease in systemic vascular resistance after verapamil (1619 to 1469 dyn s cm^{-5}) was not significant, and the decline in pulmonary vascular resistance exceeded the changes seen in the systemic circulation in all but one patient.

Table 1 *Individual haemodynamic responses to verapamil in patients with primary pulmonary hypertension*

Haemodynamic index	*Case Nos*							*Mean (SD) value*	*p value*
	1	*2*	*3*	*4*	*5*	*6*	*7*		
Mean arterial pressure (mm Hg)									
Control	82	114	102	85	65	69	79	85·1 (17·5)	<0·01
Verapamil	69	109	75	76	56	50	73	72·6 (18·9)	
Heart rate (beats/min)									
Control	104	79	95	79	90	109	103	94·1 (12·1)	NS
Verapamil	100	89	90	81	67	95	89	87·3 (10·7)	
Mean pulmonary artery pressure (mm Hg)									
Control	60	61	121	68	42	41	50	63·3 (27·4)	<0·05
Verapamil	38	56	66	53	35	33	42	46·1 (12·4)	
Pulmonary capillary wedge pressure (mm Hg)									
Control	7	12	14	6	10	2	2	7·6 (4·7)	<0·05
Verapamil	13	12	16	8	13	2	4	9·7 (5·2)	
Mean right atrial pressure (mm Hg)									
Control	10	14	19	5	11	17	4	11·4 (5·7)	<0·01
Verapamil	23	18	26	9	16	23	5	17·1 (7·8)	
Cardiac index (l/min/m^2)									
Control	2·05	2·80	1·39	2·23	3·52	1·42	2·14	2·22 (0·75)	NS
Verapamil	1·23	2·77	0·81	2·38	3·24	1·37	1·90	1·96 (0·88)	
Stroke volume index (ml/beat/m^2)									
Control	19·7	35·4	14·6	28·2	39·1	13·0	20·8	24·4 (10·1)	NS
Verapamil	12·3	31·1	9·0	29·4	48·4	14·4	21·3	23·7 (13·8)	
Pulmonary vascular resistance (dyn s cm^{-5})									
Control	1194	728	3658	1046	488	1224	1067	1344 (1054)	<0·025
Verapamil	939	658	2920	709	364	1008	950	1078 (842)	
Systemic vascular resistance (dyn s cm $^{-5}$)									
Control	1623	1479	2838	1350	808	1569	1667	1619 (611)	NS
Verapamil	1728	1361	2861	1055	663	915	1700	1469 (730)	
Right ventricular stroke work index (g m/m^2)									
Control	13·4	22·6	20·3	24·2	16·5	4·2	13·0	16·3 (6·9)	<0·01
Verapamil	2·5	16·1	4·9	17·6	12·5	2·0	10·7	9·5 (6·4)	

The fall in pulmonary vascular resistance after verapamil resulted primarily from a pronounced decrease in mean pulmonary artery pressure with the drug (63·3 to 46·1 mm Hg, $p<0·05$) since there was little overall change in cardiac index. Part of the lack of improvement in cardiac index occurred because heart rate decreased substantially in some patients (>10 beats/min in three patients), but the overall fall in heart rate (−7 beats/min) was not significant, and thus, there were no overall changes in stroke volume index (24·4 to 23·7 ml/beat/m^2). Verapamil produced a significant increase in mean right atrial pressure (11·4 to 17·1 mm Hg, $p<0·01$), however, and a decrease in right ventricular stroke work index (16·3 to 9·5 g m/m^2, $p<0·01$).

Although there were no overall changes in cardiac index, two patients had a pronounced decrease in cardiac index after verapamil (−0·82 and −0·58 l/min/m^2), and these two patients also showed the most pronounced changes in mean pulmonary artery pressure (−22 and −55 mm Hg), mean right atrial pressure (+13 and +7 mm Hg), and right ventricular stroke work index (−10·9 and −15·4 g m/m^2 respectively) seen in our seven patients.

Additional haemodynamic effects after verapamil administration included a moderate decrease in mean arterial pressure (85·1 to 72·6 mm Hg, $p<0·01$) and a small increase in pulmonary capillary wedge pressure (7·6 to 9·7 mm Hg, $p<0·05$).

CLINICAL EFFECTS

Four patients tolerated intravenous verapamil well without adverse effects, but three patients experienced unfavourable clinical reactions. One patient had severe dyspnoea immediately after verapamil administration while systemic oxygen saturation decreased from 85 to 79%, and she improved after receiving supplemental oxygen treatment. The one patient who showed a decrease in systemic vascular resistance that exceeded the fall in pulmonary vascular resistance experienced chest pain and dyspnoea as mean arterial pressure declined to 50 mm Hg; these effects were short lived, and the patient improved without specific treatment. In one of the two patients who had a pronounced decrease in cardiac index and right ventricular stroke work index intravenous verapamil administration rapidly produced hypotension, loss of consciousness, and cardiac arrest; the patient improved rapidly with cardiac compression and intravenous noradrenaline and calcium chloride administration.

One patient was treated with oral verapamil 120 mg four times daily for three months (Table 2). After 48 hours verapamil produced a 26% increase in stroke volume index, a 36% decrease in mean pulmonary artery pressure, and a 37% decrease in pulmonary vascular resistance, compared with pretreatment values, with minimal change in systemic arterial pressure or systemic vascular resistance. After three months'

Table 2 *Short and long term haemodynamic effects of verapamil in a patient with primary pulmonary hypertension treated for three months*

Haemodynamic index	*Control values*	*After verapamil (mg)*			
		120 orally (first dose)	*480/day for 48 h*	*480/day for 3 m*	*48 h after withdrawal*
Mean arterial pressure (mm Hg)	79	73	73	79	85
Heart rate (beats/min)	103	89	73	79	99
Mean pulmonary artery pressure (mm Hg)	50	42	32	44	59
Pulmonary capillary wedge pressure (mm Hg)	2	4	5	8	3
Mean right atrial pressure (mm Hg)	4	5	9	9	3
Cardiac index (l/min/m^2)	2·14	1·90	1·91	1·93	2·14
Stroke volume index (ml/beat/m^2)	20·8	21·3	26·2	24·4	21·6
Pulmonary vascular resistance (dyn s cm^{-5})	1067	950	673	889	1248
Systemic vascular resistance (dyn s cm^{-5})	1667	1700	1595	1728	1827

treatment, the patient's dyspnoea and fatigue had moderately improved, and exercise duration on a bicycle ergometer (150 kpm/min (24·5 W) for three minutes followed by increments of 150 kpm/min (24·5 W) every three minutes until exhaustion) increased from 6·3 to 7·8 minutes. Repeat haemodynamic evaluation after three months' treatment and again 48 hours after withdrawal of verapamil showed sustained effects of the drug with decreases in mean pulmonary artery pressure and pulmonary vascular resistance similar to those during the start of treatment; however, there was evidence of mild progression of the underlying pulmonary vascular disease during the course of follow up.

Discussion

Calcium channel blockade provides a logical approach to the treatment of patients with pulmonary hypertension. In so far as vasoconstriction plays an important role in these patients and appears to be critically dependent on intracellular calcium,[4 10 11] calcium channel antagonism may serve to ameliorate the haemodynamic abnormalities and produce clinical benefits. This approach is of particular interest since calcium channel blocking drugs appear selectively to dilate constricted vessels[16] and may exert preferential effects on the pulmonary circulation.[10] Nifedipine attenuates hypoxic pulmonary vasoconstriction experimentally and clinically,[17–19] and preliminary results with both short and long term treatment in patients with primary pulmonary hypertension have been highly favourable.[20–24] Nevertheless, nifedipine exerts potent systemic vasodilator effects in addition to those in the pulmonary circulation,[11] and this could lead to severe hypotension if the diseased pulmonary vascular bed is not responsive to calcium channel blockade. In addition, nifedipine may activate the sympathetic nervous system,[28] which may exacerbate the pulmonary hypertension by increasing venous return to the right heart and by increasing right ventricular contractility.[29 30] Lastly, long term nifedipine treatment may be accompanied by peripheral oedema[31]; such fluid retention may confuse the clinical picture of right heart failure, which so commonly complicates the course of chronic pulmonary hypertension.

Verapamil may provide a therapeutic alternative to nifedipine for the management of pulmonary hypertension. Compared with nifedipine the drug appears to exert less pronounced effects on systemic vascular resistance,[11] neutralises the reflex increase in sympathetic tone resulting from systemic vasodilatation,[28] and rarely produces peripheral oedema.[13] In a similar way to nifedipine, verapamil attenuates acute hypoxic pulmonary vasoconstriction in experimental studies[18 25 26] and may lessen the magnitude of secondary right ventricular hypertrophy after chronic hypoxia.[32 33] There are, however, few reports of the use of verapamil in hypoxic pulmonary hypertension in man. Furthermore, preliminary work by Landmark and colleagues[27] with verapamil in nine patients with primary pulmonary hypertension has largely been unfavourable. These investigators found that the injection of 0·15 mg/kg of verapamil directly into the pulmonary artery produced only small decreases in pulmonary artery pressure and no change in pulmonary vascular resistance or cardiac output. Although an occasional patient showed notable pulmonary vasodilatation, others had pronounced decreases in cardiac output and right ventricular stroke work, one of whom had severe dyspnoea and hypotension after drug administration. Because of the lack of appreciable pulmonary vasodilator effects, Landmark *et al* doubted that long term verapamil treatment would be beneficial in patients with primary pulmonary hypertension.

Our results in seven patients with primary pulmonary hypertension extend the findings of Landmark *et al*. In contrast to these earlier observations,[27] we found that verapamil produced significant decreases in pulmonary vascular resistance that exceeded those in systemic resistance; these favourable pulmonary vasodilator effects were accompanied by pronounced

decreases in mean pulmonary artery pressure. Long term treatment with oral verapamil in one patient produced notable haemodynamic and symptomatic improvement that was sustained for three months. Unfortunately, despite these benefits, cardiac index failed to increase in most of our patients despite the decrease in resistance to right ventricular systolic ejection because verapamil treatment was accompanied by decreases in right ventricular stroke work and increases in right ventricular filling pressure; these haemodynamic responses indicated that the drug exerted a direct negative inotropic effect on right ventricular function, independent of its pulmonary vasodilator action. This is consistent with the known cardiodepressant effects of verapamil that result from its ability to block transmembrane calcium transport in the myocardium.[34 35] Although such negative inotropic effects are usually offset by the drug's ability to reduce ventricular afterload,[28] this neutralisation does not appear to be sufficient in patients with compromised ventricular function, who are particularly sensitive to verapamil's negative inotropic action[35]; this may be especially true if the degree of pulmonary vasodilatation is limited by obliterative pulmonary vascular disease.[8] Hence, in our patients with a severely reduced right ventricular ejection fraction due to chronic pressure overload, right ventricular performance deteriorated after verapamil treatment. Two of the seven patients showed pronounced cardiodepressant effects, one of whom experienced cardiogenic shock and arrest, which required the intravenous administration of pressors and calcium chloride to restore circulatory homeostasis. Although the clinical importance of the negative inotropic effects of verapamil in patients with pre-existing left ventricular dysfunction is well established,[35] this is the first report to document the potential dangers of verapamil in patients with underlying right ventricular failure.

Two other patients experienced adverse reactions with intravenous verapamil that were not related to the drug's negative inotropic action. One patient, who showed pronounced systemic vasodilator effects but minimal effects on the pulmonary circulation, experienced severe hypotension associated with chest pain and dyspnoea after receiving verapamil. Another patient had severe dyspnoea associated with a pronounced decrease in systemic oxygen saturation (to 79%). Both reactions have been seen with other vasodilator drugs in patients with pulmonary hypertension[8 19] and appear to be secondary to the pronounced systemic vasodilator effects that may occasionally accompany treatment (and produce hypotension) and to the dilatation of transpulmonary shunts (which may produce hypoxaemia).[7 8]

In conclusion, despite its preferential vasodilator effects on the pulmonary circulation, we do not recommend verapamil for treating patients with primary pulmonary hypertension. Although an occasional patient's condition may improve during short and long term treatment with the drug, most patients will experience major depressant effects on right ventricular performance, and this may have serious cardiovascular consequences. Calcium channel blockade may be a useful approach to the management of primary pulmonary hypertension, but its application requires the development of a drug with selective pulmonary vasodilator effects and without appreciable negative inotropic action. Since verapamil may be given to patients with chronic pulmonary hypertension for the treatment of atrial tachycardias (in patients with severe mitral stenosis) or for the treatment of exertional angina (in patients with chronic obstructive lung disease), we advise caution with its use in any patient with severe right ventricular dysfunction.

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