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The Haemodynamic Effect of Verapamil

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Summary. The haemodynamic effect of verapamil has been studied in twelve patients during diagnostic cardiac catheterisation. The dose administered was 0.1 mg/kg body-weight given as an i. v. injection followed immediately by continuous infusion of 0.005 mg/kg body-weight per minute for thirty minutes. The total amount of verapamil administered varied between 13.0 and 21.6 mg. Brachial and pulmonary artery pressure, cardiac output, stroke volume, heart rate and peripheral vascular resistance were studied as well as atrioventricular conduction. — In patients in sinus rhythm no significant haemodynamic effects were observed, despite a significant increase in the atrioventricular conduction time. One patient developed second degree atrioventricular block, and several others showed first degree blocks. Two digitalized patients with atrial fibrillation were examined. Their results differed as they showed significant decreases in ventricular rate, blood pressure and cardiac output despite some increase in stroke volume. — On the basis of these results it was concluded that verapamil does not seem to have any haemodynamically unfavourable effects in the doses used. However, until further experience has been gained, verapamil should be used with caution in patients with atrial fibrillation who have already been digitalized. Verapamil should also be used with great care in persons with disturbed atrioventricular conduction and should not be given at all to patients with AV block of the second and third degree.

Key-words: Verapamil, haemodynamics.

In 1962, Haas and Hartfelder [9] reported that verapamil (α-isopropyl-α-((N-methyl-N-homo)veratryl)-γ-aminopropyl) 3.4-dimethoxyphenylacetonitrilehydrochloride)[1] dilated the coronary arteries. It was originally considered to have a β-receptor-blocking effect [10], but this has not been confirmed by subsequent investigations [8, 18, 21].

In large doses verapamil directly impairs myocardial performance [5, 18]. In addition, deterioration in atrioventricular conductivity has been demonstrated after administration of verapamil, and it may also depress the sino-atrial node [6, 21].

Verapamil has been shown experimentally to protect against chloroform, ouabain and aconitine-induced arrhythmias [11, 17], presumably by a quinidine-like effect [16]. Verapamil also has some local anaesthetic activity [20].

Clinical studies have shown that verapamil has a benefical effect on anginal pain [12, 14, 19, 23]. The drug has been used orally for prolonged treatment and it has also been administered parenterally in order to stop acute anginal pain, even in the presence of acute cardiac infarction [7, 13]. Verapamil has alo been used for the treatment of various types of cardiac arrhythmias [2, 3, 4, 6]. Although verapamil is widely used in cardiological practice, little is known about its mechanism of action, and there have been few studies of its haemodynamic effects. The present report is a detailed investigation of the circulatory changes produced by acute treatment with standard therapeutic doses of verapamil.

Material and Methods

Twelve patients, eleven of whom were men, were studied during diagnostic cardiac catheterisation. Their ages lay between 18 and 59 years, the mean was 39 years. Ten patients were in sinus rhythm, and two had atrial fibrillation. Summarised clinical data are shown in Table 1.

All patients were informed about the investigation and had agreed to take part in the study.

The investigations were carried out in the mornings on fasting, non-premedicated patients who stayed in the supine position all the time. Any prior treatment with digitalis or diuretics was continued. None of the patients had received any anti-arrhythmic drugs during the 24 hours before the study. The serum electrolytes in all cases were normal on the day of the investigation.

Right heart catheterisation (Cournand catheter no. 7 or 8), and percutaneous catheterisation of a brachial artery (polyethylene catheter PE 205) were carried out in all patients, and in two (patients 4 and 6, Table 1) transseptal catheterisation was also performed. An infusion cannula (Stille 70 × 1,45 mm) was inserted percutaneously in an arm vein and was used for the administration of verapamil. Only local anaesthetics were used (Carbocain® 0.5%, AB Bofors, Sweden). Blood pressures were measured with pressure trans-

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1 Isoptin®

ducers (EMT 35) and were recorded on a Mingograph 81 (AB Elema-Schönander, Sweden) at the same time as the ECG. Cardiac output was determined by the dye dilution method using an Atlas densitometer (Atlas-Werke, Bremen) and the indicator dye indocyanine green (Cardiogreen®). Peripheral vascular resistance was expressed as the relationship between the mean blood pressure in the brachial artery and the cardiac output.

the duration of the P-Q interval were measured. The patients then received verapamil 0.1 mg per kg body-weight given as an i.v. injection over two minutes, followed immediately by an i.v. infusion of verapamil 0.005 mg per kg body-weight per minute, the drug being in solution in 5.5% glucose. The rate of infusion was held constant by an infusion pump (Watson-Marlow MHRE 72). The total amounts of verapamil administered are shown in Table 1. The brachial and pulmonary artery

Table 1. *Details of patients studied showing age, sex, weight, diagnosis, heart rhythm and dose of verapamil*

Pat. no.	Age yrs.	Sex	Weight kg	Diagnosis	Heart rhythm	Digi-talis	Amount of verapamil administered (mg) injec-tion	infusion	total
1	25	male	70	Innocent murmur	Sinus	—	7.0	9.8	16.8
2	43	male	70	Pulmonary hypertension	Sinus	—	7.0	9.8	16.8
3	23	male	82	Innocent murmur	Sinus	—	8.2	11.5	19.7
4	21	male	78	Aortic stenosis	Sinus	—	7.8	10.9	18.7
5	18	male	77	Innocent murmur	Sinus	—	7.7	10.8	18.5
6	59	male	76	Aortic stenosis	Sinus	—	7.6	10.6	18.2
7	59	female	64	Cardiomyopathy	Sinus	+	6.4	9.0	15.4
8	51	male	90	Mitral stenosis + insufficiency	Atrial fibrillation	+	9.0	12.6	21.6
9	45	male	73	Innocent murmur	Sinus	—	7.3	10.2	17.5
10	52	male	72	Coronary heart disease	Sinus	+	7.2	10.1	17.3
11	54	male	78	Mitral stenosis	Atrial fibrillation	+	7.8	10.9	18.7
12	19	male	54	Innocent murmur	Sinus	—	5.4	7.6	13.0

Table 2. *Haemodynamic changes after verapamil administration in nine patients with sinus rhythm*

	Mean value ± S.E. before Verapamil	Mean value ± S.E. after 5 minutes	Mean value ± S.E. after 30 minutes	Mean difference before and after 5 minutes	Mean difference before and after 30 minutes
Brachial artery pressure (mmHg)					
systolic	132 ± 8	126 ± 8	125 ± 6	-4.1 N.S.	-7.1 $p < 0.05$
diastolic	76 ± 3	75 ± 3	72 ± 3	-1.1 N.S.	-3.9 N.S.*
mean	95 ± 3	90 ± 4	91 ± 4	-4.3 $p < 0.02$	-3.7 N.S.
Pulmonary artery pressure (mmHg)					
systolic	23 ± 2	25 ± 2	26 ± 2	$+2.6$ $p < 0.005$	$+2.7$ $p < 0.001$
diastolic	10 ± 1	12 ± 1	13 ± 1	$+1.7$ $p < 0.005$	$+2.6$ $p < 0.005$
mean	15 ± 2	17 ± 1	18 ± 1	$+1.8$ $p < 0.01$	$+2.8$ $p < 0.001$
Heart rate (minute)	75 ± 3	83 ± 3	80 ± 3	$+8.2$ $p < 0.05$	$+5.4$ N.S.
Cardiac output (litres/minute)	8.0 ± 0.6	—	8.7 ± 0.6	—	$+0.7$ $p < 0.025$
Stroke volume (ml)	109.4 ± 9.7	—	108.1 ± 7.7	—	-1.3 N.S.
Peripheral vascular resistance (units)	12.5 ± 1.2	—	10.8 ± 0.7		-1.7 N.S.

* N.S. = not significant

After completion of the diagnostic catherterisation the patient rested for 30 minutes, and then the brachial and pulmonary artery pressures, cardiac output, heart rate, stroke volume, peripheral vascular resistance and

pressures and the ECG were monitored continuously on an oscilloscope. At 5 and 30 minutes after the start of the injection, recordings were made and the pressures calculated, as well as the heart rate, P-Q interval

and the corrected Q-T time. The cardiac output, stroke volume and the peripheral vascular resistance were determined after fifteen and thirty minutes.

The statistical analyses were made by t-testing paired differences using an Olivetti Programma 101.

Results

The results in the patients in sinus rhythm and atrial fibrillation will be considered separately. One of the former patients was excluded because she vomited during the experiment (no. 7, Table 1), and the results from the remaining nine are shown in Table 2. Brachial artery pressure fell slightly after the administration of verapamil. The differences, however, were significant only with regard to the mean pressure after five and the systolic pressure after thirty minutes. In the pulmonary artery, there were slight but statistically significant increases in the systolic, diastolic and mean pressures. The patient with pulmonary hypertension did not differ from the others in this respect. The slight increase in heart rate was significant only after five minutes. Cardiac output after both fifteen and thirty minutes was significantly increased by 0.7 l/min. No significant alterations of stroke volume and peripheral vascular resistance were observed. Before the administration of verapamil to these nine patients the P-Q interval varied between 0.12 and 0.18 seconds (mean value 0.16). Five minutes after commencement of the injection the interval had increased in four patients, in two of them markedly (0.23 and 0.33 seconds, respectively). After thirty minutes, six of the nine patients had longer P-Q intervals than before the verapamil, and, of these six four had first degree atrioventricular block (P-Q intervals of 0.23, 0.23, 0.22 and 0.37 seconds respectively). In one patient a short episode of nodal rhythm was observed. The mean value of the P-Q interval after thirty minutes was 0.20 seconds, which was significantly longer than before verapamil ($p<0.02$) administration. The duration of the QRS complex was unchanged in all patients, nor were there any changes in the corrected Q-T time.

The effects of verapamil on the two patients in atrial fibrillation are shown in Table 3. The various parameters for these patients were calculated before and 30 minutes after the administration of the drug.

There was a pronounced decrease in the brachial artery pressure as well as the heart rate. Cardiac output fell. Peripheral vascular resistance increased in one patient by 0.4, and decreased in the other by 2.7 units.

The remaining patient (no. 7, Table 1) became nauseated one minute after the verapamil injection began and vomited. Haemodynamic factors might have been affected by vagal reactions and her results have therefore also been reported separately (Table 3). Prior to the administration of verapamil this patient had a P-Q interval of 0.20 seconds. This increased steadily, and, sixteen minutes after beginning the injection, was 0.40 seconds. During the last minutes of the verapamil infusion, second degree atrioventricular block of the Wenckebach type developed. This persisted for six minutes after the infusion was stopped, and then the P-Q interval gradually became normal.

In the two patients in whom left atrial pressure was measured (nos. 4 and 6, Table 1), after thirty minutes this had increased by 1 and 5 mmHg respectively (resting values 10 and 2 mmHg). The pulmonary vascular resistance was unaltered.

Table 3. *Haemodynamic findings in the three patients not included in Table 2 (two patients had atrial fibrillation and one vomited during the study)*

Pat. no.	BA pressure, mmHg		PA pressure mmHg		Heart rate and rhythm beats/min		Cardiac output L/min		Stroke volume ml	
	before	after	before	after	before	after	before	after	before	after
8	111/65 81	94/52 68	22/11 15	23/11 17	AF 90	AF 60	5.8	4.7	64	78
11	121/75 93	93/56 65	25/12 16	26/12 18	AF 78	AF 60	5.3	4.4	68	73
7	188/89 134	153/72 96	30/14 20	38/15 23	SR 72	AVII 60	4.0	4.5	56	75

BA = brachial artery
PA = pulmonary artery
AF = atrial fibrillation
SR = sinus rhythm
AV II = atrio-ventricular block of the second degree

Side effects. Patient no. 7 became sick and vomited during the injection of verapamil. No other side effects were observed.

Discussion

Administration of verapamil to animals has produced a decrease in blood pressure which seems initially to be explained by a fall in peripheral vascular resistance, as the cardiac output remains unchanged. The effects of the drug have, however, been dependent on the dose administered. Larger amounts of verapamil appear to have a myocardial depressive effect as they have caused a fall in cardiac output, stroke volume and blood pressure [21, 22]. In man, there have been few studies of the haemodynamic response to verapamil administered parenterally in therapeutic doses. A slight fall in blood pressure and some indication of a negative inotropic effect have been reported in the form of a drop in cardiac output and stoke volume [7, 13, 15]. Definite conclusions could not be drawn from these studies, since they relied on indirect methods of measurement, and in some instances the patients were not in a "steady state" before administration of the drug.

Our purpose was to investigate the effects of therapeutic amounts of verapamil with respect to both single injections and the total amount administered during the period of observation. We administered verapamil as an i.v. injection followed immediately by an i.v. infusion, as greater reliance can be placed on consistency of the drug's effects by this means than after a single injection. The serum concentrations of verapamil were not measured, and we were unable to find reports of any such studies in man. In animals the serum concentration falls rapidly after injection, which has been attributed to binding to serum proteins [1].

As our experimental conditions included continuous monitoring of the ECG and brachial and pulmonary artery pressures transient post injection effects of the drug could not have been missed. As such phenomenas were not found, it is considered that suitably representative times were chosen for study of the effects of verapamil. Although a time response curve was not estimated we consider that the speed of infusion used was effective. This is shown by the fact that almost all the changes which occured after the injection persisted during the infusion period, and, in some cases they even increased (A-V conduction time and pulmonary artery pressure). The marked differences in the results from the patients in sinus rhythm and from the two with atrial fibrillation have led us to consider the two groups separately.

There is no information available about the influence of verapamil on pulmonary artery pressure. The increase in pulmonary artery pressure observed in this series can be disregarded from the practical point of view, although it is still interesting. Theoretically, this result could be accounted for either by an increased pulmonary vascular resistance or reduced performance of the left ventricle with increasing left atrial filling pressure. The results from the two patients in whom the left atrial pressure and the pulmonary vascular resistance were examined were inconclusive. In patients in sinus rhythm there was some increase in cardiac output after verapamil, which makes it improbable that the dose of verapamil being used could have a negative inotropic effect. The slight tendency for lower brachial artery pressures observed in this study is of no clinical importance. There was no reduction of peripheral vascular resistance unlike the changes observed in animal experiments.

Our results accord well with what has been observed previously about the inhibitory effect of verapamil on the atrioventricular conductivity [15]. Vagal influence can not be ignored as a partial cause in the patient who developed a Wenkebach block. However, the second degree AV block did not appear in direct relation to the period of vomiting, but was only seen ten minutes later, and lasted for six minutes after the drug had been withdrawn, after which the conduction process returned to normal.

The pronounced rate-decreasing effect which verapamil had in the patients in atrial fibrillation is a further example of impairment of atrioventricular conduction. In these patients there was a much greater fall in brachial artery pressure then in those with sinus rhythm. Also, the cardiac output in the former group became much lower despite some increase in the stroke volume. Both of these patients were digitalized, and had normal ventricular rates and good left ventricular function. The unfavourable haemodynamic effects of verapamil in these two patients seem to have been caused by the change in heart rate. Although only two patients with atrial fibrillation were examined, and so no definite conclusion can be drawn, our observations indicate the need for caution when treating such cases with parenteral verapamil. The circumstances may be different in cases of rapid and irregular atrial fibrillation in whom lowering of the ventricular rate may be important in improving diastolic filling of the ventricles.

References

1. Appel, W.: α-Isopropyl-α-((N-methyl-N-homoveratryl)-γ-aminopropyl(-3.4-dimethoxyphenylacetonitril, sein Nachweis in biologischem Material und sein Verhalten im Blut. Arzneimittel-Forsch. **12**, 562–566 (1962).
2. Atterhög, J.-H.: Verapamil vid hjärtarrythmier. Opusc. med. **14**, 127–135 (1969).
3 Bender, F.: Isoptin zur Behandlung der tachykarden Form des Vorhofflatterns. Med. Klin. **62**, 634–636 (1967).
4. Bender, F., Reploh, H.D.: Behandlung von Kammertachykardien mit Isoptin. Med. Klin. **63**, 715–717 (1968).
5. Benfey, B.G., Greef, K., Heeg, E.: Evaluation of sympathetic betareceptor blockade by recording the rate of ventricular pressure rise in cats. Brit. J. Pharmacol. **30**, 23–29 (1967).
6. Diewitz, M., Lange, B.M.: Zur Behandlung tachykarder Rhythmusstörungen mit Verapamil. Med. Klin. **64**, 1699–1707 (1969).

7. Doschtschizin, W.L., Arschakuni, R.O., Zarow, E.I.: Primjenenije Isoptina pri grundnoj žabje i naruschenijach ritma ssérdza. Kardiologija **8**, 32—40 (1967).
8. Fitzgerald, J.D., Barett, A.M.: What is a β-blocker? Lancet **1967 II**, 310.
9. Haas, H., Hartfelder, G.: α-Isopropyl-α-((N-methyl-N-homoveratryl)-γ-amino-propyl)-3.4-dimethoxy-phenylacetonitril, einer Substanz mit coronargefäß-erweiternden Eigenschaften. Arzneimittel-Forsch. **12**, 549—558 (1962).
10. Haas, H.: Zum Wirkungsmechanismus des α-Isopropyl-α-((N-methyl-N-homoveratryl)-γ-aminopropyl)-3.4-dimethoxyphenolacetonitrils, einer Substanz mit coronargefäßerweiternden Eigenschaften. Arzneimittel-Forsch. **14**, 461—468 (1964).
11. Haas, H., Busch, E.: Antiarrhythmische Wirkungen von Verapamil und seinen Derivaten im Vergleich zu Propranolol, Pronetalol, Chinidin, Procainamid und Ajmalin. Arzneimittel-Forsch. **18**, 401—407 (1968).
12. Hanley, C., Lebowitz, W.B.: Iproveratril in angina pectoris. St Vincent's Hosp. med. Bull. **9**, 1—5 (1967).
13. Hofmann, H.: Klinische Untersuchungen zur Wirkung von Iproveratril bei Koronarinsuffizienz und zur sympatikolytischen Beeinflussung der Myokardfunktion. Zschr. inn. Med. **23**, 357—364 (1968).
14. Kaltenbach, M., Zimmermann, D.: Zur Wirkung von Verapamil auf die Angina pectoris und die adrenergischen β-Rezeptoren des Menschen. Dtsch. med. Wschr. **93**, 25—28 (1968).
15. Knoch, G., Schlepper, M., Witzleb, E.: Untersuchungen an Gesunden und Koronarkranken Patienten mit Isoptin. Med. Klin. **58**, 1485—1489 (1963).
16. Melville, K.I., Shister, H.E., Huq, S.: Iproveratril: experimental data on coronary dilatation and antiarrhythmic action. Can. med. Ass. J. **90**, 761—770 (1964).
17. Melville, K.I. & Benfey, B.C.: Coronary vasodilatory and cardiac adrenergic blocking effects of iproveratril. Canad. J. Physiol. Pharm. **43**, 339—342 (1965).
18. Nayler, W.G., McInnes, I., Swann, J.B., Prices, J.M., Carson, V., Race, D., Lowe, T.E.: Some effects of iproveratril (isoptin) on the cardiovascular system. J. Pharmacol. exp. Ther. **161**, 247—261 (1968).
19. Neumann, M., Luisada, A.A.: Double blind evaluation of orally administered iproveratril in patients with angina pectoris. Amer. J. med. Sci. **251**, 552—556 (1966).
20. Rodrigues-Pereira, E., Viana, A.P.: The actions of verapamil on experimental arrythmias. Arzneimittel-Forsch. **18**, 175—179 (1968).
21. Ross, G., Jorgensen, C.R.: Cardiovascular actions of iproveratril. J. Pharmacol. exp. Ther. **158**, 504—509 (1967).
22. Ross, G., Jorgensen, C.R.: Effects of iproveratril and nitroglycerin in the heart and coronary circulation of dogs. Amer. Heart J. **76**, 74—78 (1968).
23. Sandler, G., Clayton, G.A., Thornicraft, S.G.: Clinical evaluation of verapamil in angina pectoris. Brit. med. J. **3**, 224—227 (1968).

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