Indian J Physiol Pharmacol 1991; 35(4): 232-236

CALCIUM CHANNEL BLOCKERS AND THE CVS REFLEX RESPONSES DURING LOWER BODY SUCTION

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(Received on August 25, 1991)

Abstract : Nine normal men (mean age 27.6 yr) were exposed to continuous lower-body suction pressure (LBSP) of - 20 to - 50 mmHg (for 5 min at each level) on four different occasions after having consumed a single oral therapeutic dose of either diltiazem, nifedipine, verapamil, or a placebo, randomely, in a single blind manner. The suction was applied at 12.30 pm in all experiments, while the medications were administered in such a manner so that their expected peak plasma levels would have been achieved at the time of suction application. The cardiovascular reflex effects commenced at a pressure of -30 mmHg, and peaked at -50 mmHg. The increases in the heart rate for all treatments at -50 mmHg was statistically similar (about 16-20 beats/min). The systolic BP fell by about 9 mmHg for the placebo experiments, and this change was not different from the changes produced by the 3 Calcium channel blocker treatments. The diastolic BP increase was about 3 mmHg. The Cardiac index did not vary significantly. Our results suggest that the commonly used Ca^{++} channel blockers do not adversely affect orthostatic tolerance.

Key words : autonomic reflexes LBSP orthostasis

INTRODUCTION

Drugs which block calcium channels on the cell membrane are now routinely used for the treatment of various cardiovascular disorders, viz., hypertension, ischaemic heart disease and hypertrophic cardiomyopathies (1).

The commonly used Ca^{++} entry blockers in clinical use are diltiazem (a benzothiazepine derivative), nifedipine (a dihydropyridine) and verapamil (a phyenylakyamine) (2). Eventhough all the three drugs have a common mode of action, as these block the slow calcium channels (3,4), the overall cardiovascular effects are determined by an interplay of the direct action of these agents on the myocardium and the peripheral circulation, and the indirect actions induced by autonomic cardiovascular reflex activity excited by them. For example, vasodilatation is produced maximally by nifedipine without affecting myocardial contractility, while verapamil produces effective vasodilatation but depresses contractility (1,4,5). Such dispartate actions may produce a different cardiovascular reflex response to orthostatic stress (6). Even though nifedipine has been associated with orthostatic disturbances (1,6), as yet there is no relative comparison made of the effects the agents have on human cardiovascular reflexes during controlled orthostatic stress. This is particulary important because some individuals who may be on treatment with Ca^{++} channel blockers may have to perform duties where their orthostatic tolerance is taxed. It is possible that an investigation brings forth one of these drugs as the one that least affects cardiovascular reflex stability during orthostatic stress. Lower body subatmospheric pressure (LBSP, lower body suction) is a suitable method for eliciting cardiovascular reflex effects (7), and has been used in this investigation.

METHODS

Nine healthy men (mean (SEM) age 27.6±1.2 yr;

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height 171.0±1.5 cm; weight 65.0±3.1 kg and body surface area 1.74±0.05 m^2) volunteered for the study which was ethically approved. The consent of the subjects was obtained and they were medically examined to ascertain their fitness to participate. All were given a trial exposure to a LBSP of -40 and -50 mmHg for a duration of 5 min in a continuous stepwise fashion, in order to familiarise them with the test procedure, as they were all naive. All withstood the trials without any distress, and their blood pressure and heart rate responses during the LBSP confirmed this objectively.

Protocol : Each subject was exposed to LBSP of -20, -30, -40 and -50 mmHg (each level for 5 min) in a continuous step-up fashion (7,8,9) on four different occasions, after he had taken orally a capsule which contained a single therapeutic dose of either (i) a placebo; (ii) 60 mg Dilitiazem (Dilizem, Torrent) ; (iii) 10 mg Nifedipine (Calcigard Torrent) and (iv) 160 mg Verapamil (Isoptin; Boehringer Knoll). There was a gap of 48 hours between two trials. For all subjects the LBSP was started at 12.30 pm. In order to keep the trials single blind and to ensure that they were exposed to LBSP when the plasma concentration of the drug had reached its peak, the subjects took 3 capsules (one of which contained the prescribed drug, while the other two were placebos) at 8.30 am, 10.30 am and at 12 pm. This was required because diltiazem reaches its peak concentration 30 min after a single oral dose, nifedipine after 2 hours, and verapamil after 4 hours (4,10). Therefore, on the day the subject took verapamil, the 8.30 am capsule contained the drug, while the capsules at 10.30 and 12 pm were placebos. Accordingly, on another occasion, the 10.30 capsule contained the drug (nifedipine) while on another day, the 12 pm capsule contained the third drug. One trial was given where all the 3 capsules contained only the placebo. Only one of the observers (MBD) was aware of the drug combinations which were given randomely.

On the day of the trial, the subject consumed the 3 capsules as per schedule and was prepared for the LBSP at 12.15 pm. The laboratory temperature was maintained between 25°and 27°C. He was monitored for ECG (CM5 electrode position using disposable chest electrodes) on a cardiac monitor (Truscope; Ind Chem), and his blood pressure was measured using a Hg spygmomanometer. Mean arterial pressure was calculated as 1/3pulse pressure ± diastolic pressure (mmHg). Stroke output was determined by recording of the left ventricular ejection time where Stroke volume = 0.501 LVET (msec) + 0.13 HR-67.2 (11,12). For this the carotid pulse tracing was recorded on a Medicare 4 channel polyrite polygraph (paper speed 50 mm/sec) through a T 303 differential pressure transducer and a Model 201 Universal bioamplifier (Medicare). The variable was expressed as the stroke volume index. The subject was placed inside the lower body suction box, and sealing around the waist and the opening of the box was suitably achieved (for details, refs, 4,5). Graded suction (from -20 to -50 mmHg) in a continuous stepwise fashion was applied using a Euroclean 200 room vacuum cleaner. Physiological variables were measured between the 4th and the 5th min at each suction level, and also in the 5th min after the LBSP application (recovery). The subject was at liberty to call off the experiment anytime during the LBSP, but all our subjects completed their suction exposures without any difficulty.

Statistics : The changes from control (pre-LBSP) in the HR, and the systolic and diastolic blood pressure (SBP and DBP) were calculated for each of the 4 treatments given. The changes in these variables were compared with the changes produced by the placebo treatment using the paired "t" test with $p< 0.05$ as the level of significant change. To compare the relative changes in the variables produced by the calcium channel blockers, the difference in the change between the drug and placebo was compared for the 3 drugs using the ANOVAR.

RESULTS

The typical response of the 8 of our subjects to LBSP ranging from -20 to -50 mmHg for the placebo trials is shown in Fig. 1. The HR increase started at a suction level of -30 mmHg, while the blood pressure altered only at -40 and -50 mmHg. On the other hand there was a near linear decrease in the stroke volume index (SVI ml) which was evident from -20 mmHg.

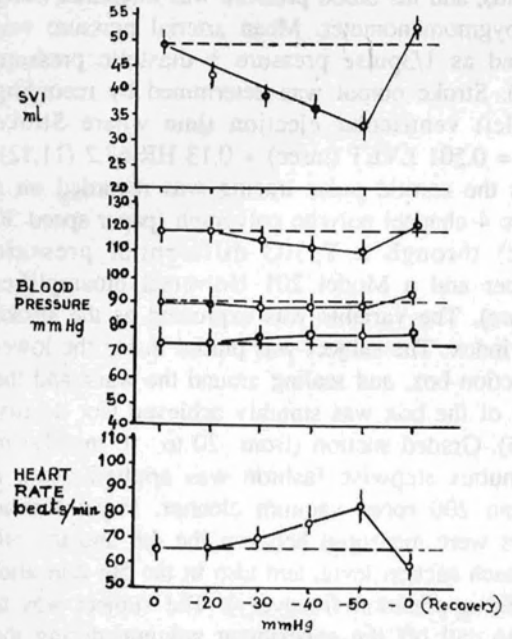

Fig. 1: Depicts the cardiovascular response of eight of our subjects to graded LBSP after placebo treatment. SVI is the stroke volume index (ml).

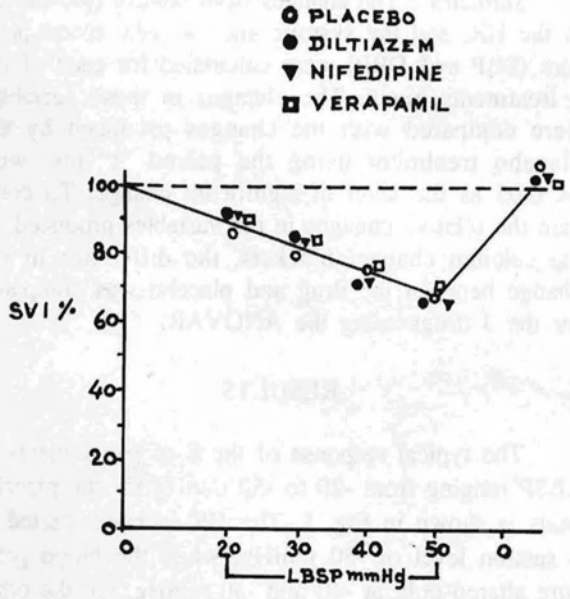

Fig. 2: Depicts the percentage reduction in the SVI (ml) in 9 subjects to graded LBSP after they had ingested a single oral dose of the placebo, and the calcium channel blockers.

The change in the various variables brought about by the application of LBSP for the 4 treatments is depicated in Table I. The maximum changes in all the variables were produced at -50 mmHg suction. Compared with the change produced by the placebo treatment, none of the three drugs used produced changes which were significantly different from each other as shown by using ANOVAR (Table II). However, verapamil produced changes which were closest to those produced by the placebo. The SVI decreased similarly for all treatments when LBSP was applied (Fig. 2).

TABLE I: The table gives the mean and ± SE values for the heart rate (HR; beats/min), the systolic blood pressure (BP; mmHg), the diastolic pressure (DBP; mmHG), and the mean arterial pressure (MAP; mmHG) for nine subjects before being subjected to LBSP. The subjects had been given a single oral dose of a placebo (Plac), diltiazem (Dilt), Nifedipine (Nif) and verapamil (Vera) as described in the methods. ANOVAR did not reveal any significant difference between the 4 treatment effects.

		PLAC	DILT	NIF	VERA
HR	X	67.3	67.0	73.7	65.9
	SE	2.7	2.4	2.9	2.5
SEP		118.9	118.7	117.3	113.8
		2.3	3.0	3.9	3.4
DBP		74.0	73.6	68.7	72.0
		3.5	3.6	3.8	3.0
MAP		89.1	88.6	88.0	86.6
		2.6	2.7	2.9	2.6

TABLE II: Shows the mean changes (±SE) from control in the heart rate (HR), systolic blood pressure (SBP), and the diastolic pressure (DBP) of 9 males subjected to graded LBSP (-20 to -50 mmHg) after treatment with placebo (Plac; diltiazem (Dilt); nifedipine (NIF); and verapamil (Vera).

	LBSP	PLAC	DILT	NIF	VERA
HR	-20	1.44±1.68	2.22±1.33	1.67±1.28	2.22±0.99
	-30	4.89±2.06	8.56±1.94	5.00±1.59	3.88±1.74
	-40	9.67±2.53	12.33±2.65	10.44±2.14	8.55±2.27
	-50	19.67±4.32	15.44±2.51	16.33±2.78	16.89±2.34
SBP	-20	-2.89±1.29	-3.33±0.75	-4.00±1.97	-2.89±1.06
	-30	-5.11±1.01	-6.44±0.93	-7.56±2.05	-2.67±1.00
	-40	-6.89±1.67	-9.11±1.29	-9.11±1.60	-6.22±1.68
	-50	-9.11±2.06	-10.89±1.95	-11.11±2.03	-9.56±1.94
DBP	-20	0.89±1.06	-1.11±1.16	-2.00±0.67	1.11±1.89
	-30	2.67±1.49	-1.11±0.59	2.67±3.13	2.44±1.79
	-40	3.33±1.60	-1.78±0.78	3.33±2.81	2.00±2.13
	-50	3.11±2.61	2.44±1.63	3.11±2.71	0.33±2.24

No gross ECG rhythm abnormalities were observed. Occassional incidence of inversion of the T wave was observed on the monitor. However, there were no accompanying HR or BP irregularities, nor did the subjects have any untoward symptoms. Subjects No. 2 developed a passing episode of pre-syncope at the 5th min of -50 mmHg, which however did not stop him from completing the test. He had taken verapamil on that occasion. He did not have such an episode on any other ocassion, nor did any of the other subjects who had taken verapamil, develop any disturbances during LBSP.

DISCUSSION

The calcium channel blockers used in this study produce their action by blocking slow calcium channels (5), and yet they are thought to produce cvs effects which are qualitatively and quantitatively different (6). One of the possible mechanisms which may be involved in producing this differential action is that the barorecptor sensitivity may be differently affected by the various medications in question (6). It is this hypothesis that prompted us to take up the present study. In many daily life situations, particularly during the military service, a number of activities involve repeated exposure to orthostatic stress, which in turn affects baroreceptor activity.

The pre-LBSP values for the HR and the DBP for the nifedipine experiments were somewhat lower (though not statistically significant) as compared with the values for these variables for the other three treatments (Table I). Nifedipine is a potent vasodilator (13), and the slightly higher heart rate could have been due to reflex response to the lower blood pressure. As such, nifedipine is thought to potentiate the baroreflex mediated sympathetic nerve activity (SNA) (14). Verapamil too is thought to increase resting heart rate while diltiazem may decrease it (15), but this was not observed in the present study. Nor did the resting blood pressure differ with the 4 treatments.

Application of lower-body subatmospheric pressure (lower-body suction) produces a controlled sequestration of the central blood volume (7,16), and therefore this technique was chosen to elicit CVS reflexes in this study. Under normal situations, HR is affected only at a pressure of about -30 mmHg suction and beyond, while forearm blood flow alters at a pressure as low as -10 mmHg (7). If nifedipine can potentiate baroreceptor mediated SNA (14), even low grades of suction may affect the response in a manner not normally seen. Also, the other medications used may have similar effects. The response of the subjects given the placebo treatment was similar to that seen in normal male subjects (as reported elsewhere) for a suction pressure range of 0-20 to -50 mmHg (9) (Fig.1).

Even though effect of baroreceptor induced SNA has been previously investigated (14), the workers had applied suction of only -5 to -15 mmHg. At this level of LBSP, only the low pressure to cardiovascular receptors are deactivated (17). Further in that study the CVS effects of LBSP were compared with those produced after the administration of Na-nitroprusside, a potent peripheral vasodilator, and not with the effects produced by any other calcium channel blockers. Those workers also pointed out that it is the afferent (baroreceptor) part of the reflex that is responsible for the results. Because of the low level of LBSP applied in that study (14), no comments were offered on whether nifedipine affects the arterial baroreceptor induced neuro-effector changes. In the present study LBSP ranging from -20 to -50 mmHg was applied in order to see if the arterial baroreceptor induced CVS reflexes are altered by the commonly used calcium channel blockers.

Keeping in view the available information on calcium channel blocking agents, it was hypothetised that nifedipine may in fact enhance the baroreceptor induced CVS reflex tachycardia. Millard et al (6) had suggested that this agent may induce orthostatic intolerance. This effect would have been noticeable during the high grade of suction applied (-50 mmHg) in the present study which however did not produce any untoward effects. Nor were the changes produced in the various variables by the 4 grades of suction different from those produced by the placebo trials (Table II). Pre-load may decrease after nifedipine treatment, but is likely to be unaltered after verapamil and diltiazem. On the other hand, all the three agents reduce after-load (5). This has perhaps contributed to the similar reduction in the SVI with all

the treatments. However, the placebo induced reduction in the SVI was not different to the other three (Fig. 2).

The present study, suggests that none of the 3 popularly used calcium channel blockers, after a single oral therapeutic dose, adversely affect orthostatic tolerance. A wide variation in the plasma level of diltiazem after a single oral dose has been reported (19). This may also be applicable to the other medications used. May be because of this the drugs did not produce any noticeable effects on CV reflex status. It may be worth while to also study, whether any changes different from the present study, may be observed, if the drugs are used over longer periods.

ACKNOWLEDGEMENTS

We acknowledge the co-operation of our subjects.

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