ELSEVIER

European Journal of Pharmacology 380 (1999) 123–128

ejp

www.elsevier.nl/locate/ejphar

Cardiac inotropic vs. chronotropic selectivity of isradipine, nifedipine and clevidipine, a new ultrashort-acting dihydropyridine

Daisuke Segawa [a], Per-Ove Sjöquist [a], Margareta Nordlander [b], Qing-Dong Wang [a], Adrian Gonon [a], Lars Rydén [a,*]

[a] *Department of Cardiology, Karolinska Hospital, S-171 76 Stockholm, Sweden*
[b] *Astra Hässle Research Laboratories, Mölndal, Sweden*

Received 5 July 1999; accepted 23 July 1999

Abstract

Cardiac effects of clevidipine, a new ultrashort-acting dihydropyridine Ca^{2+} channel antagonist were investigated in Langendorff-perfused rat hearts and compared to those of nifedipine and isradipine. The aim was to determine and compare the negative inotropic vs. chronotropic potency of these drugs. The hearts were perfused with oxygenated Krebs–Henseleit buffer at a perfusion pressure of 90 cm H_2O. After stabilization, one concentration of each drug was administered for 45 min followed by a higher concentration for an additional 45 min. The concentrations of each drug in this study were 10^{-9}, 3×10^{-9}, 10^{-8}, 10^{-7}, $10^{-6.5}$ and 10^{-6} M for clevidipine and nifedipine, and 10^{-10}, 3×10^{-10}, 10^{-9}, 10^{-8}, $10^{-7.5}$ and 10^{-7} M for isradipine. Each concentration of each drug was tested in six hearts. Coronary flow, left ventricular dP/dt max, left ventricular systolic pressure and heart rate were recorded when the hearts were beating spontaneously and during pacing at a constant rate for 1 min. Spontaneous heart rate and atrio-ventricular conduction were not affected by clevidipine at any of the concentrations studied, while nifedipine and isradipine caused a concentration-dependent decrease. These two drugs caused atrio-ventricular block at high concentrations. All three compounds reduced cardiac contractility in a concentration-dependent manner. When isradipine was administered, at a given concencentration, heart rate and contractility decreased proportionately. When clevidipine or nifedipine was given, at a given concentration, the proportionate reduction in left ventricular dP/dt max was greater than that in heart rate, resulting in a high inotropic vs. chronotropic selectivity. It is concluded that in contrast to nifedipine and isradipine, clevidipine does not impair atrio-ventricular conduction. Like nifedipine, clevidipine is selective for inotropic vs. chronotropic cardiac effects.

Keywords: Dihydropyridine; Ultra short-acting; Chronotropy; Inotropy; Cardiac selectivity

1. Introduction

The majority of Ca^{2+} channel antagonists used for treatment of cardiovascular disorders like hypertension and angina pectoris belong to three distinct chemical classes: the phenylalkylamines, the benzothiazepines and the dihydropyridines (Fleckenstein, 1983). The former two groups bind to intracellular sites of the L-type Ca^{2+} channel, which they enter through the open channel. The dihydropyridines bind extracellularily or to the inactivated state of the channel (Triggle, 1991). The intracellular binding is facilitated by the repetitive depolarization in atrio-ventricular and myocardial tissues and may explain why phenylalkylamines and benzothiazepines are unselective for myocardial, atrio-ventricular and vascular tissues. Compounds belonging to these groups, e.g., verapamil and diltiazem, can therefore, in addition to their use in patients with hypertension and angina pectoris, also be used for the management of supraventricular arrhythmias with a high ventricular rate (Singh et al., 1983).

The binding of dihydropyridines to the L-type Ca^{2+} channel is voltage-dependent, which may explain why these Ca^{2+} channel antagonists are selective for vascular smooth muscle, which is more depolarized than cardiac muscle (Triggle, 1991). In clinical use, most dihydropyridines can therefore also be used safely in patients with moderately impaired cardiac performance, but are not use-

* Corresponding author. Tel.: +46-8-5177-2171; fax: +46-8-311-044; E-mail: lry@cardio.ks.se

0014-2999/99/$ - see front matter
PII: S0014-2999(99)00528-2

ful for the treatment of arrhythmias (Packer et al., 1996). Dihydropyridines differ in their vascular vs. myocardial selectivity (Nayler, 1988), with felodipine and isradipine representing highly vascular selective dihydropyridines and nifedipine and amlodipine fairly unselective ones (Cheng et al., 1994; Nayler, 1988). Although still vascular selective at high concentrations, all the dihydropyridines have an inhibitory effect on cardiac contractility and conduction. However, they appear to differ in the potency of their relative inhibitory effects on myocardial contractility and on sinus node depolarization (Hof et al., 1987; Nordlander et al., 1995). Thus, nifedipine has been reported to be more potent in inhibiting myocardial contractility than spontaneous heart rate (Nordlander et al., 1995), while isradipine exhibits the reverse selectivity (Hof et al., 1987).

Clevidipine, butyroxymethyl methyl 4-(2′,3′-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, is a new, ultrashort-acting, vascular selective dihydropyridine Ca^{2+} channel antagonist (Levy et al., 1997; Vuylsteke et al., 1998). With a half-life of less than a minute in blood, clevidipine has proven suitable for rapid blood pressure reductions and control in connection with, e.g., cardiac surgery (Kieler-Jensen et al., 1997; Vuylsteke et al., 1998). The aim of the present investigation was to study cardiac effects of clevidipine, to reveal if it is more potent in inhibiting myocardial contractile function than inhibiting sinus node function; i.e., does clevidipine exhibit an inotropic vs. chronotropic selectivity or not? Isradipine and nifedipine were used as reference agents.

2. Materials and methods

2.1. Drugs

Nifedipine, isradipine and clevidipine were dissolved in 2.6% w/v of solutol (polyethyleneglycol 660-12-hydroxystearate, BASF) and diluted. All drugs were synthesized at the Department of Medicinal Chemistry, Astra Hässle, Mölndal, Sweden.

2.2. Experimental preparations

Male Sprague–Dawley rats weighing about 350 g were anesthetized with an intramuscular injection of a mixture of Hypnorum® (fentanyl citrate 0.315 mg/ml and fluanisone 10 mg/ml, 0.03 ml/100 g body weight) and Dormicum® (midazolam 5 mg/ml, 0.03 ml/100 g body weight). Following heparin (1000 IU/kg) administration through the tail vein to avoid blood clotting, the hearts were excised and immediately soaked in 4°C Krebs–Henseleit buffer solution (NaCl 118 mM, KCl 4.7 mM, $CaCl_2$ 1.5 mM, KH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, $NaHCO_3$ 25.2 mM and glucose 11.0 mM). They were subsequently mounted in a Langendorff circuit and perfused at a perfusion pressure of 90 cm H_2O with oxygenated Krebs–Henseleit buffer solution bubbled with 95% O_2 and 5% CO_2. A water-filled latex balloon connected to a Statham p23Db transducer was inserted into the left ventricular cavity via the left atrium for pressure recordings. The volume of the balloon was adjusted to produce a left ventricular end-diastolic pressure of between 5 and 10 mm Hg. Two electrodes for pacing the hearts were placed on the right ventricular free wall, and they were connected to a stimulator. During the experiments the hearts were beating spontaneously, except for 1 min of pacing at 370 beats/min when coronary flow and cardiac contractility were determined (see Section 2.3). To keep a constant temperature of around 37°C, the hearts were hung in a water-jacket chamber. Heart rate, left ventricular systolic pressure, and the maximum value of the first derivative of left ventricular pressure were continuously recorded on a polygraph (Model-7, Grass Instrument, MA, USA). Coronary flow was measured by weighing the effluent from the Langendorff circuit. The experimental protocol and animal care conformed to the Guide for the care and use of laboratory animals published by US National Institutes of Health (NIH publication number 85-23, revised 1985).

2.3. Experimental protocol

After 30 min of stabilization, heart rate, left ventricular systolic pressure, left ventricular dP/dt max, and coronary flow were recorded both during spontaneous heart rate and during pacing at a constant rate of 370 beats/min for 1 min. The drug under study was infused at a constant concentration into the perfusion fluid from a side branch of the aortic cannula for 45 min. Care was taken to mix the drugs and perfusion fluid properly. Subsequently, the same compound was infused at higher rate for another 45 min. The following drug concentrations were used: 10^{-9} and 3×10^{-9} ($n=6$), 10^{-8} and 10^{-7} ($n=6$), $10^{-6.5}$ and 10^{-6} M ($n=6$) for clevidipine and nifedipine, and 10^{-10} and 3×10^{-10} ($n=6$), 10^{-9} and 10^{-8} ($n=6$), $10^{-7.5}$ and 10^{-7} M ($n=6$) for isradipine. In control experiments, 2.6% w/v solutol was used ($n=6$), which corresponded to the vehicle used at the maximum drug concentration tested in this study. During infusions, heart rate, left ventricular systolic pressure, left ventricular dP/dt max, and coronary flow were recorded every 5 min while the heart was beating spontaneously. Just before and at the end of each infusion rate, all parameters were recorded both when the heart was beating spontaneously and when paced at a constant rate of 370 beats/min for 1 min.

2.4. Data analysis

Statistical analysis was performed with nonparametric tests because the data obtained in this study were not expected to show normal distribution. The Mann–Whitney test was used for intergroup comparison. A two-tailed

P-value of less than 0.05 was considered statistically significant. All data are presented as mean ± S.D. (standard deviation).

3. Results

3.1. Control experiments and basal values

Control hearts ($n = 6$) perfused with solutol solution for 90 min after an initial stabilization period showed no significant changes in spontaneous heart rate, left ventricular systolic pressure, coronary flow, or left ventricular dP/dt max and exhibited no atrio-ventricular blocks. The basal, predrug, values of coronary flow, heart rate, and left ventricular contractile performance did not differ among the various groups (Table 1).

3.2. Incidence of atrio-ventricular block

The incidence of atrio-ventricular block among the hearts exposed to the various concentrations of drugs differed among groups. In the clevidipine group, no case of atrio-ventricular block was found even at the highest concentration (10^{-6} M) tested. In the nifedipine group, two hearts out of six developed atrio-ventricular block at $10^{-6.5}$ M, and an additional three hearts developed it at 10^{-6} M. In the isradipine group, atrio-ventricular block occurred in one heart out of six at 10^{-8} M, and in additional two hearts at $10^{-7.5}$ M, while all the remaining hearts developed atrio-ventricular block at 10^{-7} M. There were significant differences in the occurrence of atrio-ventricular block between the clevidipine and isradipine groups at 10^{-7} M ($P < 0.05$), between the nifedipine and isradipine groups at 10^{-7} M ($P < 0.05$), and between the clevidipine and nifedipine groups at 10^{-6} M ($P < 0.05$).

3.3. Changes in spontaneous heart rate

Changes in spontaneous heart rate expressed as a percentage of the basal value in the three groups are shown in Fig. 1. In the clevidipine group, heart rate did not change at any concentration. In the nifedipine group, there was no effect on the spontaneous rate at the lower concentrations, but at 10^{-7} M, a decrease in heart rate was obtained and atrio-ventricular block occurred in some hearts. At the highest concentration studied (10^{-6} M), heart rate decreased to 46 ± 19% of control value. In the isradipine group, heart rate decreased at the highest concentrations studied, i.e., 10^{-8}, $10^{-7.5}$ and 10^{-7} M. There were significant differences ($P < 0.05$) in the extent of reduction in heart rate between the clevidipine and isradipine groups at 10^{-8} M and 10^{-7} M, between the nifedipine and isradipine groups at 10^{-8} M and 10^{-7} M, and between the clevidipine and nifedipine groups at $10^{-6.5}$ M and 10^{-6} M.

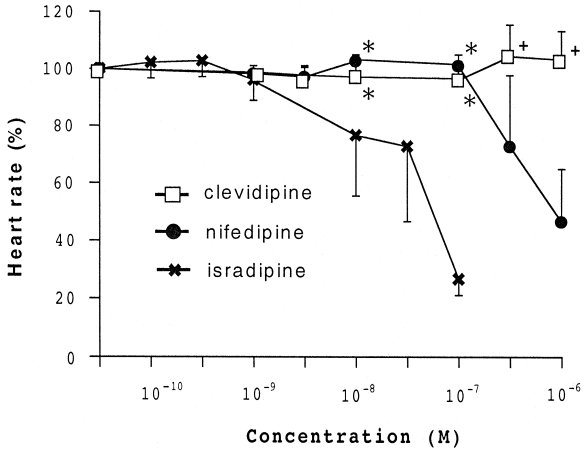

Fig. 1. Changes in spontaneous heart rate caused by increasing concentrations of clevidipine, nifedipine, and isradipine. Data are expressed as percentage of the basal values, which are given in Table 1. Values are mean ± S.D. * $P < 0.05$ vs. isradipine, + $P < 0.05$ vs. nifedipine.

Table 1
Basal (pre-drug) values

	n	Coronary flow (ml/min)	Heart rate (bpm)	dP/dt (mm Hg/s)	LVSP (mm Hg)
Vehicle	6	12.8 ± 1.5	315 ± 8	3808 ± 332	118 ± 12
Clevidipine	18	13.1 ± 1.5	319 ± 31	3447 ± 494	115 ± 12
Nifedipine	18	12.7 ± 1.6	317 ± 42	3553 ± 466	110 ± 17
Isradipine	18	13.8 ± 1.5	306 ± 39	3736 ± 348	112 ± 11

Data are given as mean ± S.D. Left ventricular dP/dt max, (dP/dt), left ventricular systolic pressure (LVSP). All measurements except heart rate were done during cardiac pacing at 370 beats/min.

3.4. Changes in left ventricular dP / dt max

Changes in left ventricular dP/dt max in the three groups are shown in Fig. 2. The values are expressed as a percentage of the basal value. In the clevidipine group, contractility did not change until 10^{-8} M, but after that it decreased gradually as the concentrations increased. At the highest concentration, left ventricular dP/dt max decreased to 48 ± 10% of the control value. In the nifedipine group, the contractility did not change until 10^{-8} M, but thereafter it decreased markedly. At the highest concentration of nifedipine studied, left ventricular dP/dt max decreased to 10 ± 3% of the control value. Isradipine at lower concentrations had little effect on the contractility, at concentrations above 10^{-9} M it decreased. At the highest concentration, left ventricular dP/dt max in the isradipine group decreased to 41 ± 22% of the control value. Regard-

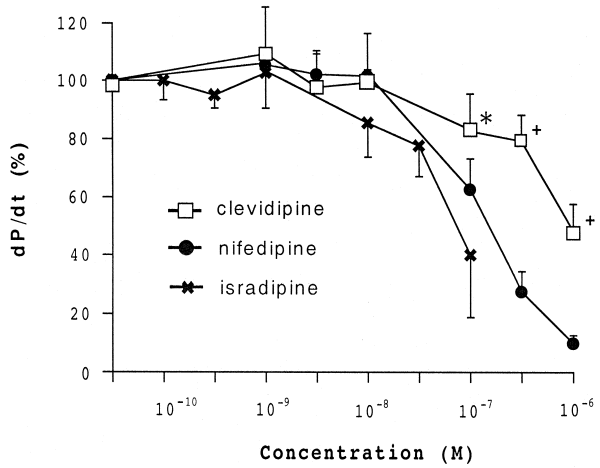

Fig. 2. Changes in left ventricular dP/dt max (dP/dt) caused by increasing concentrations of clevidipine, nifedipine, and isradipine recorded during cardiac pacing. Data are expressed as percentage of the basal value and given as mean ± S.D. $^{*}P < 0.05$ vs. isradipine, $+ P < 0.05$ vs. nifedipine.

ing the extent of left ventricular dP/dt max reduction, there were significant ($P < 0.05$) differences between the clevidipine and nifedipine groups at 10^{-7}, $10^{-6.5}$ and 10^{-6} M, and between the clevidipine and isradipine groups at 10^{-7} M.

3.5. Changes in coronary flow

Clevidipine caused a modest increase in coronary flow at lower concentrations (Fig. 3), while there were no particular changes by nifedipine and isradipine. Cornary flow tended to decrease at higher concentrations in all groups, with a somewhat more pronounced effect by nifedipine. Thus, there was a difference in the extent of reduction in coronary flow between the clevidipine and nifedipine groups that could be documented as statistically significant ($P < 0.05$) for three of the concentrations studied (Fig. 3).

3.6. Changes in left ventricular systolic pressure

At concentrations up to 10^{-8} M, all three drugs exerted only a minor effect on left ventricular systolic pressure without any significant differences between the groups (Fig. 4). At higher concentrations, left ventricular systolic pressure decreased in all groups. In the isradipine group, left ventricular systolic pressure decreased markedly, and at 10^{-7} M, there were significant differences between the clevidipine and isradipine groups and between the nifedipine and isradipine groups. Clevidipine was the least potent compound in reducing left ventricular systolic pressure among the three drugs studied. At $10^{-6.5}$ or 10^{-6} M, left ventricular systolic pressure in the clevidipine group was significantly higher than that in the nifedipine group.

3.7. Ratio between extent of reduction in heart rate and in left ventricular dP / dt max

To enable within-drug comparison of effects on spontaneous heart rate and left ventricular dP/dt max, changes in both variables are shown in Fig. 5A–C. As illustrated, relative potency between inotropic and chronotropic effects was highest for clevidipine, as this drug did not reduce heart rate, while isradipine is equally potent in reducing both variables and is thus unselective in its cardiac effect. Nifedipine, like clevidipine, is inotropic vs.

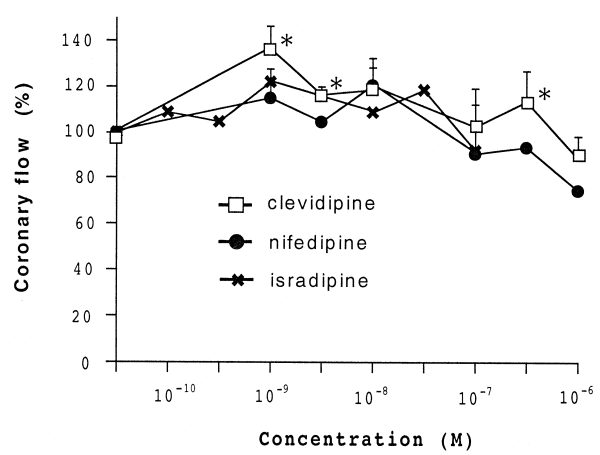

Fig. 3. Changes in coronary flow caused by increasing concentrations of clevidipine, nifedipine, and isradipine. Data are determined during cardiac pacing at 370 beats/min and expressed as percentage of the basal value given as mean ± S.D. $^{*}P < 0.05$ vs. nifedipine.

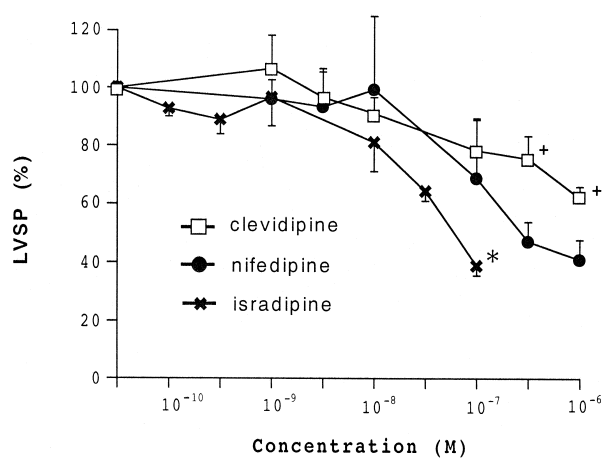

Fig. 4. Changes in left ventricular systolic pressure (LVSP) caused by increasing concentrations of clevidipine, nifedipine and isradipine. Data are expressed as percentage of the basal value and given as mean ± S.D. $^{*}P < 0.05$ vs. nifedipine or clevidipine, $+ P < 0.05$ vs. nifedipine.

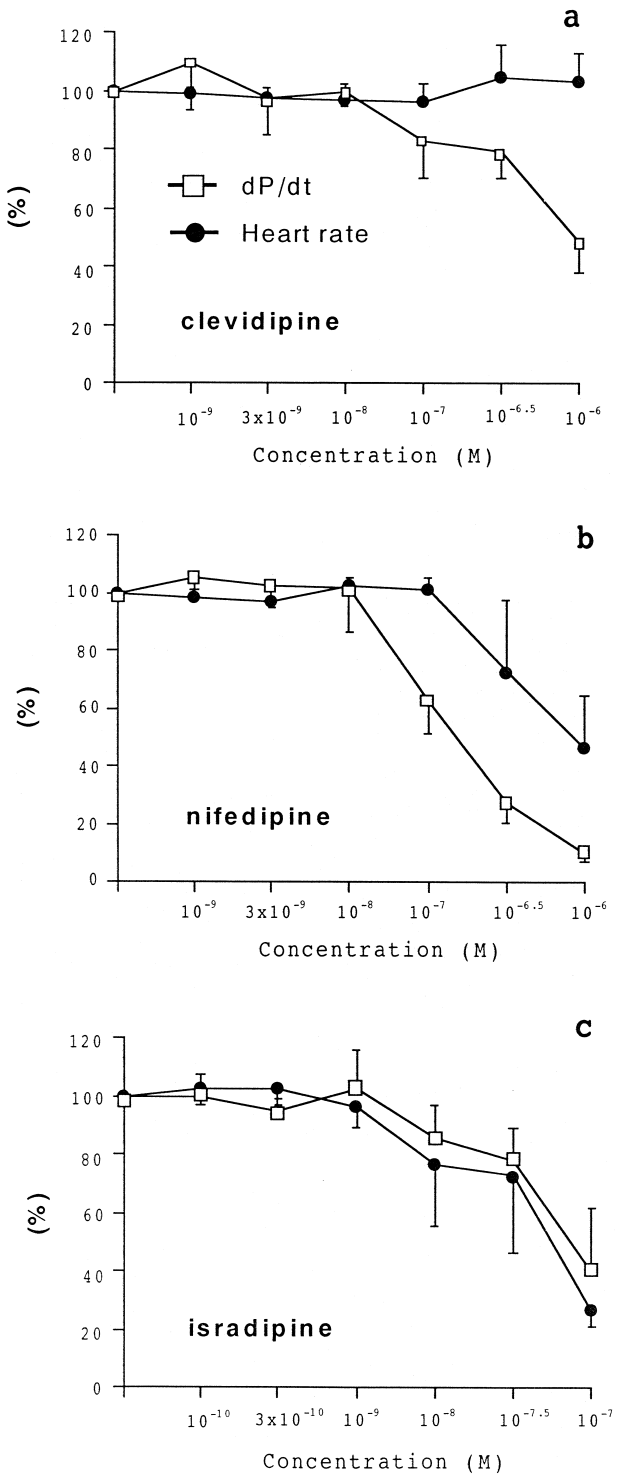

Fig. 5. Changes in spontaneous heart rate and left ventricular dP/dt (dP/dt) max caused by increasing concentrations of clevidipine, nifedipine, and isradipine. Left ventricular dP/dt max was recorded during cardiac pacing at 370 beats/min. Data are expressed as percentage of the basal value and given as mean ± S.D.

chronotropic selective. As revealed by Fig. 5, the order of inotropic vs. chronotropic selectivity was clevidipine > nifedipine > isradipine.

4. Discussion

The results of the present study demonstrate that the three dihydropyridine Ca^{2+} channel antagonists — nifedipine, isradipine and clevidipine — have different relative effects on myocardial contractility, sinus node function and atrio-ventricular conduction, when investigated in vitro in Langendorff-perfused rat hearts. Clevidipine and nifedipine are more selective for inhibition of myocardial contractility than for inhibition of spontaneous heart rate, while this is not the case for isradipine. Commonly, selectivity ratios are calculated as the difference in, e.g., ED_{50} or ED_{25} of a drug for two effects (Hof and Scholtysik, 1983). The lack of effect on spontaneous heart rate at the highest concentration of clevidipine studied did not allow such calculations in the present study. However, from Fig. 5, it is evident that the rank order of inotropic vs. chronotropic selectivity is clevidipine > nifedipine > isradipine.

The present findings demonstrate an inotropic vs. chronotropic selectivity of clevidipine and confirm previous in vitro findings with nifedipine of greater inhibitory potency on myocardial contractility than on spontaneous depolarization in the sinus node (Nordlander et al., 1995). This suggests that the Ca^{2+} channels of the sinus node cells and those in contracting myocardial tissue could have different physicochemical properties, and can thus be blocked relatively selectively by dihydropyridines which appear to be able to discriminate between them (Hof and Scholtysik, 1983). A reverse selectivity of isradipine could, however, not be demonstrated in the present study, since spontaneous heart rate and left ventricular dP/dt max were almost equally reduced at the concentrations studied. This is in contrast to a previous study (Hof et al., 1984), in which isradipine was approximately 50 times more potent in inhibiting spontaneous rate than the force developed in isolated right and left guinea pig atria, respectively. The difference in the results obtained could possibly be explained by the difference in the rate of contraction in the two studies. In the present study, the isolated perfused hearts were paced at 370 beats/min during measurements of the effects on contractile force, while they were beating spontaneously at rates varing between 240 and 360 beats/min. In the previous study (Hof et al., 1984), the isolated left guinea pig atria were paced to 60 beats/min during measurement of contractile force, in contrast to the right atria, which had a spontaneous rate of 112 beats/min before determination of the effects of isradipine on sinus node function. Binding of Ca^{2+} channel antagonists to Ca^{2+} channels has been claimed to be use- or frequency-dependent (Opie, 1990). The higher rate of myocardial contraction before measurements of the effects of isradipine on the spontaneous rate of the isolated guinea pig right atria would therefore enhance the affinity of isradipine to the spontaneously beating atrial tissue, as compared to the paced left atrial preparation used for determination of

contractile force. This would result in a higher potency of isradipine in inhibiting spontaneous heart rate than in inhibiting contractile force, as described by Hof et al. (1984). In the present study, the spontaneous heart rate of the isolated perfused rat heart and that during pacing for determination of contractile force did not differ substantially. The reason for applying electrical pacing at a frequency of 370 beats/min in the present study was that at lower frequencies there was an escape to a higher spontaneous rate. Furthermore, in order to compare variables of left ventricular contractility, a constant heart rate is required. In the present study, pacing electrodes were applied on the right ventricle. Although right atrial pacing is thought to be more physiologically acceptable compared to ventricular pacing, it cannot drive the heart when atrio-ventricular blocks occur, as they did in the hearts receiving the higher concentrations of nifedipine and isradipine in the present study.

In this study, each concentration of the drugs was administered for 45 min to allow equilibration. The time-course for inhibition of contractile force and heart rate varies among the dihydropyridines, but effects of long-acting drugs also come close to maximum within 45 min (Nordlander et al., 1995). The concentrations used were based on previous experiments with nifedipine (Nordlander et al., 1995). The same concentrations of nifedipine and clevidipine were used. Since with both dihydropyridines cardiac contractility was depressed by more than 50% at the highest concentration tested (1 μM), this was considered a maximal concentration devoid of secondary, nonspecific effects. Isradipine was investigated at lower concentrations, since at concentrations above 10^{-7} M, cardiac contractility was reduced by more than 50% and atrio-ventricular blocks occurred in all hearts according to pilot experiments preceding this study. Thus, from our results, it appears as if isradipine totally blocks atrio-ventricular conduction at a concentration which depresses left ventricular dP/dt max about 60%. At the highest concentration of clevidipine which depressed left ventricular dP/dt max about 50%, there were no atrio-ventricular block. Thus, clevidipine appears to lack potential to inhibit electrical conductance, while isradipine and nifedipine induce atrio-ventricular block at high concentrations. The clinical implication of these findings is that clevidipine is devoid of risk for atrio-ventricular block when used for acute blood pressure reduction, while there might be a higher risk when isradipine is used at high doses.

Clevidipine had minor effects on cardiac contractility at concentrations of less than 10^{-8} M. Higher concentrations caused a decrease in cardiac contractility and a minor reduction in coronary flow. However, the coronary flow was not reduced below the control level. It is therefore unlikely that the negative inotropic effects of higher concentrations of clevidipine would result from a decrease in coronary flow.

In conclusion, clevidipine decreased cardiac contractility, but had a minor effect on spontaneous heart rate and did not bring about atrio-ventricular block, in the concentrations studied. This was in contrast to isradipine and nifedipine. The rank order of the degree of selectivity for inotropic vs. chronotropic cardiac effects was therefore: clevidipine > nifedipine > isradipine.

Acknowledgements

This study was supported by grants from the Swedish Heart and Lung Foundation, the Swedish Medical Research Council (grant number: 45521) and from Karolinska Institutet.

References

Cheng, C.P., Noda, T., Nordlander, M., Ohno, M., Little, W.C., 1994. Comparison of effects of dihydropyridine calcium channel antagonists on left ventricular systolic and diastolic performance. J. Pharmacol. Exp. Ther. 268, 1232–1241.

Fleckenstein, A., 1983. History of calcium antagonist. Circ. Res. 52, 13–16.

Hof, R.P., Scholtysik, G., 1983. Effects of the calcium antagonist PY 108-068 on myocardial tissues in vitro and on reflex tachycardia in vivo. J. Cardiovasc. Pharmacol. 5, 176–183.

Hof, R.P., Scholtysik, G., Loutzenhiser, R., Vuorela, H.J., Neumann, P., 1984. PN 200-110, a new calcium antagonist: Electrophysiological, inotropic, and chronotropic effects on guinea pig myocardial tissue and effects on contraction and calcium uptake of rabbit aorta. J. Cardiovasc. Pharmacol. 6, 399–406.

Hof, R.P., Salzmann, R., Siegl, H., 1987. Selective effects of PN 200-110 (isradipine) on the peripheral circulation and the heart. Am. J. Cardiol. 59, 30B–36B.

Kieler-Jensen, N., Jolin-Mellgård, Å., Nordlander, M., Ricksten, S.E., 1997. Myocardial circulatory and metabolic effects of clevidipine after coronary artery bypass grafting (CABG). Br. J. Anaesth. 78, A12, Suppl. 2.

Levy, J.H., Huraux, C., Nordlander, M., 1997. Treatment of perioperative hypertension. In: Epstein, M. (Ed.), Calcium Antagonists in Clinical Medicine. Hanely and Belfus, Philadelphia, pp. 345–358.

Nayler, W.G. (Ed.), 1988. Calcium Antagonists. Academic Press, London, 113–129.

Nordlander, M., Abrahamsson, T., Åkerblom, B., Thalén, P., 1995. Vascular versus myocardial selectivity of dihydropyridine calcium antagonists as studied in vivo and in vitro. Pharmacol. Toxicol. 76, 56–62.

Opie, L.H., 1990. Clinical use of calcium channel antagonist. In: Drugs. Kluwer Academic Publishers, Boston.

Packer, M., O'Connor, M., Chali, J.K., Pressler, M.L., Carson, P.E., Belkin, R.N. et al., 1996. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N. Engl. J. Med. 335, 1107–1114.

Singh, B.N., Nademanee, D., Baky, S., 1983. Calcium antagonists used in the treatment of cardiac arrhythmias. Drugs 25, 125–138.

Triggle, D.J., 1991. Sites, mechanisms of action, and differentiation of calcium channel antagonists. Am. J. Hypertens. 4, 422S–429S.

Vuylsteke, A., Milner, Q.J., Ericsson, H., Mur, D., Dunning, J., Latimer, R.D., 1998. Therapeutic dose rates and pharmacokinetics of clevidipine in patients undergoing coronary artery bypass surgery. Br. J. Anaesth. 80 (2), A11.