ELSEVIER

European Journal of Pharmacology 286 (1995) 71–78

ejp

Effects of semotiadil, a novel Ca^{2+} channel antagonist, on the electrical activity of Langendorff-perfused guinea pig hearts in comparison with diltiazem, amlodipine and nifedipine

Gerhard Stark [a,*], Karin Kasper [a], Ulrike Stark [a], Nobuaki Miyawaki [b], Martin Decrinis [a], Helmut A. Tritthart [c]

[a] *Department of Internal Medicine, Karl-Franzens-University, Graz, Austria*
[b] *Central Research Laboratories, Santen Pharmaceutical Company Ltd, Higashiyodogawa-ku, Osaka, Japan*
[c] *Department of Medical Physics and Biophysics, Karl-Franzens-University, Graz, Austria*

Received 20 February 1995; revised 13 July 1995; accepted 14 July 1995

Abstract

Semotiadil, a new Ca^{2+} antagonist with a high vasoselectivity, in high concentrations depresses AV nodal conduction in a frequency-dependent manner. The aim of the present study was to investigate the effects of semotiadil on intact cardiac conduction and the pacemaker system in comparison with diltiazem, amlodipine and nifedipine. The effects were studied in isolated guinea pig hearts perfused by the method of Langendorff. Both semotiadil and diltiazem decreased markedly the sinus rate in a concentration-dependent manner whereas this was not the case in the presence of amlodipine and nifedipine. Semotiadil (10 μM) markedly prolonged sinus node recovery time and in the presence of diltiazem (10 μM) in 5 out of 7 experiments an intermittent sinus node arrest occurred. Atrioventricular conduction and the effective refractory period of the AV node were most affected by diltiazem and semotiadil. The Ca^{2+} channel blocking compound semotiadil showed the most pronounced rate-dependent effects on the AV node. In the presence of diltiazem the QT interval became even shorter than in untreated hearts. In contrast, semotiadil did not act on the QT interval. In conclusion, as semotiadil exerts a clear rate-dependent effect on AV nodal conduction with a long time constant, it mimics the electrophysiological behavior of a substance of the verapamil type.

Keywords: Semotiadil; Diltiazem; Amlodipine; Nifedipine; Conduction interval; Refractoriness

1. Introduction

Semotiadil fumarate (SD-3211, (+)-(*R*)-2-[5-methoxy-2-[3-methyl[2-[3,4-(methylenedioxy) phenoxy]-ethyl]amino]propoxy]phenyl]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one hydrogen fumarate) was described by Miyawaki et al. (1990) and Nishimura et al. (1990) and differs structurally from all other Ca^{2+} channel antagonists (Fig. 1). Potent and long-lasting Ca^{2+} antagonistic effects are excerted by semotiadil as assessed in both in vivo and in vitro experiments (Kageyama et al., 1991; Miyawaki et al., 1990, 1991; Nakayama et al., 1992; Nishimura et al., 1990; Takada et al., 1991; Yoneyama et al., 1990). Semotiadil is reported to be more vasoselective than diltiazem and verapamil, and more cardioselective than nifedipine and nicardipine (Miyawaki et al., 1991; Nishimura et al., 1990). Against coronary artery contractions semotiadil was 10 times more potent than diltiazem but the negative inotropic effect was only one-third that of diltiazem and the Ca^{2+} antagonistic smooth muscle effects were not reversed by drug washout. Dihydropyridines do not reduce the incidence of reperfusion arrhythmias (Hope et al., 1983; Uematsu et al., 1986) but semotiadil was 7–14 times more potent than bepridil in reducing the incidence of reperfusion-induced premature beats or

* Corresponding author. Department of Internal Medicine, Karl-Franzens-University, Auenbruggerplatz 15, A-8036 Graz, Austria. Tel. 0043-(0)316-385-2012, fax 0043-(0)316-385-3062.

SSDI 0014-2999(95)00433-5

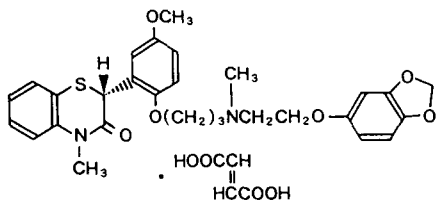

Fig. 1. Chemical structure of semotiadil (SD-3211, (+)-(*R*)-2-[5-methoxy-2-[3-methyl[2-[3,4-(methylenedioxy) phenoxy]ethyl]amino]-propoxy]phenyl]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one hydrogen fumarate).

ventricular fibrillation. In anesthetised open-chest dogs 0.1 mg/kg of semotiadil caused a significant fall in blood pressure, particularly diastolic blood pressure, but no prolongation of AV conduction time. At a higher concentration there was a frequency-dependent depressant effect on the AV conduction time and on the functional refractory period. The classification of the mode of action of semotiadil as a Ca^{2+} antagonistic compound warrants a thorough definition of inhibitory electrophysiological effects in all parts of the cardiac impulse generation and conduction system. In particular, the direct cardiac effects not modified by reflex sympathetic activities are of significance.

The Langendorff-perfused heart is a well-established system to study the direct cardiac effects of Ca^{2+} antagonists. We have described a refined ECG technique (SST-ECG, Stark et al., 1987, 1989) to measure the relevant electrophysiological parameters in all parts of the heart, and this technique has been applied to characterize the mode of action of various compounds (Stark et al., 1988, 1990). It was the aim of the present study to measure the effects of semotiadil in all parts of the cardiac conduction system and to compare its rate and dose dependency with those of amlodipine, diltiazem and nifedipine.

2. Materials and methods

2.1. Animals

62 white guinea pigs of either sex, weighing 200–300 g, given food ad libitum, were divided in four groups of 8, four groups of 6 and one control group of 6 animals. Complete results were obtained from 57 of 62 preparations studied.

2.2. Experimental protocol

Guinea-pigs were injected intraperitoneally with 250 IU of heparin 1 h before being killed by dislocation of the neck. The chest was quickly opened, the heart removed and attached to a modified non-recirculating Langendorff perfusion system (Anton Paar, Graz, Austria). All procedures met the guidelines set by the Committee on Animal Care at our medical center. Tyrode's solution, saturated with a mixture of oxygen (95%) and carbon dioxide (5%) and warmed to 36°C was used as perfusate (in mM: NaCl 132.1, KCl 2.7, $CaCl_2$ 2.5, $MgCl_2$ 1.15, $NaHCO_3$ 24.0, NaH_2PO_4 0.42, D-glucose 5.6). Immediately after the heart had been attached to the Langendorff perfusion system, electrocardiographic (ECG) recordings were taken from the epicardial surface. The perfusion rate was progressively increased until it reached 8 ml/min or a perfusion pressure of 60 cm H_2O so that atrioventricular conduction, a sensitive parameter for acute ischemia in this preparation, was shorter than 65 ms and the spontaneous sinus rate was about 200 beats/min. Each heart was allowed to equilibrate for 30 min. If rhythm irregularities occurred during the equilibration period, the heart was discarded.

Two $FeCl_3$-chloridized silver wire electrodes (wire diameter 0.3 mm, electrode tip diameter 1.5 mm) were placed on the epicardial surface of the heart and were free to move with the contractions. Both electrodes were positioned in the AV-valve plane, anteriorly near to the origin of the interventricular artery and posteriorly between the two auricles, respectively. The unfiltered signals were amplified by a factor of 100 with an instrumentation amplifier (Anton Paar, Graz, Austria) with AC input (fc = 0.72 Hz). His bundle activity was visible in the bipolar recorded ECG signals which were monitored on a digital storage oscilloscope and stored on a tape-recorder sampling at 5 kHz. Details of this high-resolution ECG recording technique have been described in earlier publications (Stark et al., 1989). The ECG signals were further digitised by an analog to digital converter (TL-125, Axon Instruments, USA) and monitored and stored on a personal computer (486/50 MHz) for further analysis.

2.3. Parameters measured

Changes in sinus rate, AV nodal (AH interval), His bundle (HV interval) and intraventricular conduction (QRS interval) as well as the repolarization time (QT interval) were evaluated in four groups (8 experiments in each group) during control conditions and 20 min after the addition of each concentration of semotiadil (10 nM, 0.1 μM, 1 μM, and 10 μM), diltiazem (10 nM, 0.1 μM, 1 μM, and 10 μM), amlodipine (0.1 nM, 1 nM, 10 nM, and 0.1 μM) and nifedipine (0.1 nM, 1 nM, 10 nM, and 0.1 μM). The compounds were continuously injected, by a perfusion pump near the aorta, in the Tyrode's solution to avoid unspecific binding in the perfusion system. At each concentration the atrioventricular, atrial and ventricular effective refractory periods were estimated. In four separate groups (6 experiments in each group) the time constant, characterizing

the prolongation of atrioventricular conduction time after an abrupt increase the pacing rate, was evaluated at a concentration of 100 nM semotiadil, 30 nM diltiazem, 100 nM amlodipine or 10 nM nifedipine.

2.4. Pacing protocol

The time constants of the atrioventricular conduction time prolongation were estimated after an abrupt increase of the pacing rate at a concentration of 100 nM semotiadil, 30 nM diltiazem, 100 nM amlodipine or 10 nM nifedipine, whereby a comparable prolongation of the atrioventricular conduction time during sinus rhythm was induced. Twenty minutes after addition of each drug the atrioventricular conduction time (AVCT) was measured at an atrial pacing cycle length of 240 ms. After 2 min of atrial pacing at an intensity of twice the late diastolic threshold, the pacing cycle length was abruptly shortened from 240 ms to 180 ms, and kept at this new rate for another 2 min. The AVCT was measured continuously, beat to beat, throughout the experiment. To exclude ischemic effects during rapid pacing, in a separate series of 6 experiments the creatine kinase concentration in the coronary effluent was measured before (6.4 IU ± 0.9; mean ± S.E.M.) and immediately after the rapid stimulation period (5.8 IU ± 1.0).

A nonlinear regression analysis (Sigma Plot software package) was performed. $AVCTn = (AVCTss - AVCT0) \times (1 - \exp(-n/\tau))$ where AVCTn, AVCT0, and AVCTss are the AVCT of the nth beat, of the last paced beat at a cycle length of 240 ms, and of the steady state at a pacing cycle length of 180 ms; τ is a time constant expressed as a number of beats. In the presence of semotiadil, diltiazem, amlodipine and nifedipine the frequency-dependent changes of the AVCT were described by a time constant for the initial fast phase and for a following slow phase which was noted only in the presence of drugs. The initial fast phase could be described by a time constant of one beat for the used drugs as well as for control conditions.

2.5. Stimulation protocol for evaluation of the effective refractory period and sinus node recovery time

Under control conditions and 20 min after the addition of each drug concentration the effective refractory period of the atrioventricular, atrial and ventricular myocardium was determined. The stimuli were delivered through Teflon-coated silver wire electrodes placed on the epicardial surface of the left auricle for the measurement of atrial and atrioventricular nodal refractoriness. For evaluation of the effective refractory period of the ventricle the stimulation electrodes were placed on the apex of the right ventricle. The stimulation threshold was evaluated at the beginning of the pacing protocol. A programmable stimulator with separate constant current output delivered rectangular stimuli of 2 ms duration at an intensity of twice the late diastolic threshold. The effective refractory period of the atrioventricular node was evaluated with a conditioning train of ten basic stimuli (S1). The S1–S1 interval was 230 ms and the S1–S2 interval was shortened in steps of 1 ms. After each step the heart was allowed to recover from rapid pacing for 1 s. The longest S1–S1 interval for a stimulus that failed to induce an atrial or ventricular response was defined as atrial effective refractory period (A-ERP) or ventricular effective refractory period (V-ERP) respectively. The longest S1–S2 interval for a stimulus that failed to conduct through the AV node and to produce a His bundle response was defined as the AV nodal effective refractory period (AV-ERP). For the evaluation of the sinus node recovery time (SNRT) the hearts were paced via the right auricle with a pacing rate of 300 beats per minute for 30 s, after which time pacing was stopped. The distance between the last atrial signal induced by a stimulus and the first spontaneously occurring atrial signal was defined as SNRT.

2.6. Expression and statistical analysis of the results

All values are expressed as means ± S.E.M. The data were compared using a Wilcoxon test after a test of homogeneity of variance had been performed on a personal computer using a statistical software package (Statgraphics, version 6.0).

2.7. Drugs used

Semotiadil (Santen Pharmaceutical, Japan) dissolved in dimethyl sulfoxide, diltiazem (Goedecke, Germany), amlodipine (Pfizer, Austria), and nifedipine (Sigma, Germany) dissolved in physiologic saline were prepared before each experiment. The measurements were performed after a perfusion period of 20 min. In pilot experiments ($n = 3$, data not presented in this paper) we have shown that 20 min of perfusion with semotiadil are necessary to get a steady state of the electrophysiological effects. Control measurements were made in the presence of Tyrode's solution. We used one concentration below (×10) and two concentrations above (×10, ×100) the therapeutic drug level for each compound in our experiments.

3. Results

3.1. Effects on sinus rate and conduction intervals

At a concentration of 0.1 μM of semotiadil and diltiazem atrioventricular conduction time (AVCT) was

significantly prolonged. At concentrations higher than 0.1 μM AVCT prolongation was significantly ($P < 0.01$) higher in the presence of diltiazem compared to semotiadil. In 5 out of 7 experiments an intermittent sinus node arrest and third-degree atrioventricular block occurred in the presence of 10 μM diltiazem. AVCT was depressed significantly at a concentration of 0.1 μM nifedipine.

His bundle conduction and intraventricular conduction time remained unaffected by amlodipine and nifedipine also at the highest dosage used. At the highest concentration (10 μM) semotiadil and diltiazem caused a marked prolongation of the His bundle conduction time, whereas the QRS duration was unaffected.

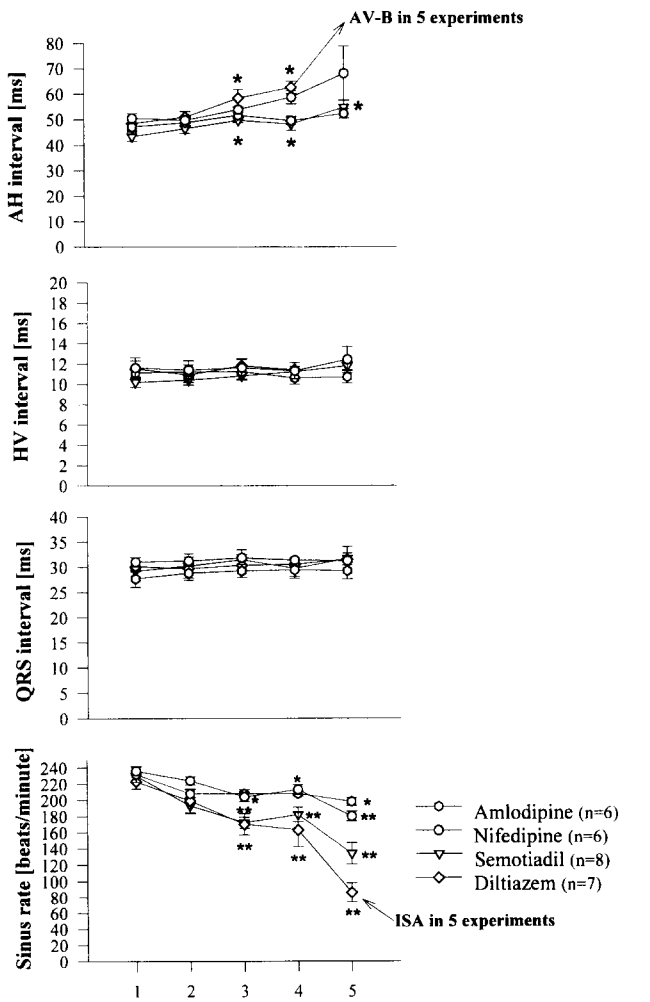

Fig. 2. Effects of semotiadil, diltiazem, amlodipine and nifedipine on sinus rate and conduction intervals. At 10 μM of diltiazem in 5 out of 7 experiments atrioventricular block (3rd degree) and intermittent sinus node arrest occurred. 1 = Control, 2 = 10 nM, 3 = 0.1 μM, 4 = 1 μM, and 5 = 10 μM for semotiadil and diltiazem. 1 = Control, 2 = 0.1 nM, 3 = 1 nM, 4 = 10 nM, and 5 = 0.1 μM for amlodipine and nifedipine. AV-B, atrioventricular block; ISA, intermittent sinus node arrest. Values are means ± S.E.M.; * $P < 0.05$; ** $P < 0.01$.

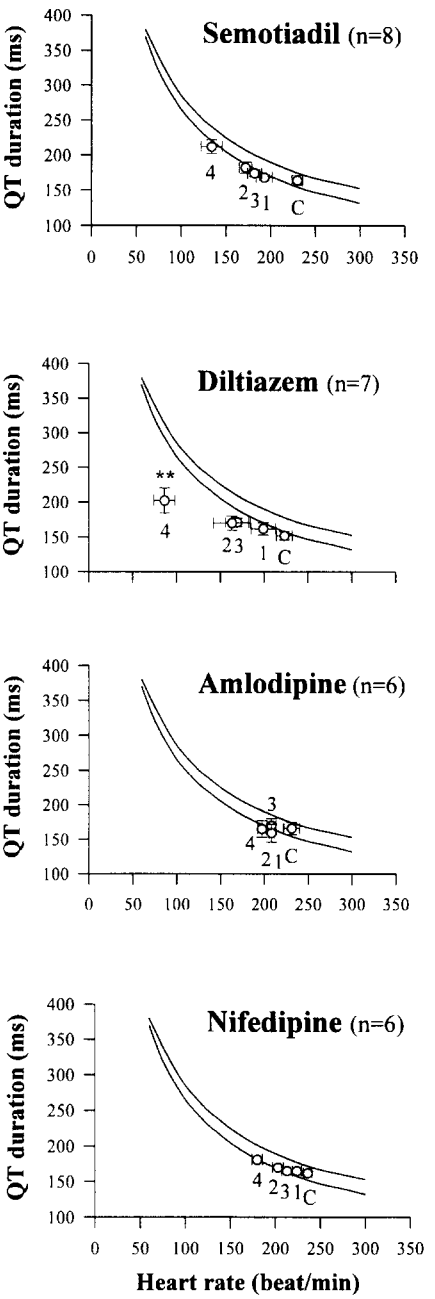

Fig. 3. Changes of the frequency-dependent QT interval in the presence of semotiadil, diltiazem, amlodipine and nifedipine. The area between the two curves indicates the normal behavior of the QT interval in dependence of heart rate in untreated isolated hearts (Stark et al., 1989). 1 = 10 nM, 2 = 0.1 μM, 3 = 1 μM, and 4 = 10 μM for semotiadil and diltiazem. 1 = 0.1 nM, 2 = 1 nM, 3 = 10 nM, and 4 = 0.1 μM for amlodipine and nifedipine. Values are means ± S.E.M.; ** $P < 0.01$.

The sinus rate was significantly depressed by 10 nM semotiadil and 0.1 μM diltiazem. At the highest concentration (10 μM) of both drugs the sinus rate was nearly halved compared to control conditions. In the presence of 10 μM diltiazem in 5 out of 7 experiments an intermittent sinus node arrest occurred. Therefore, the depression of sinus node activity was higher in the

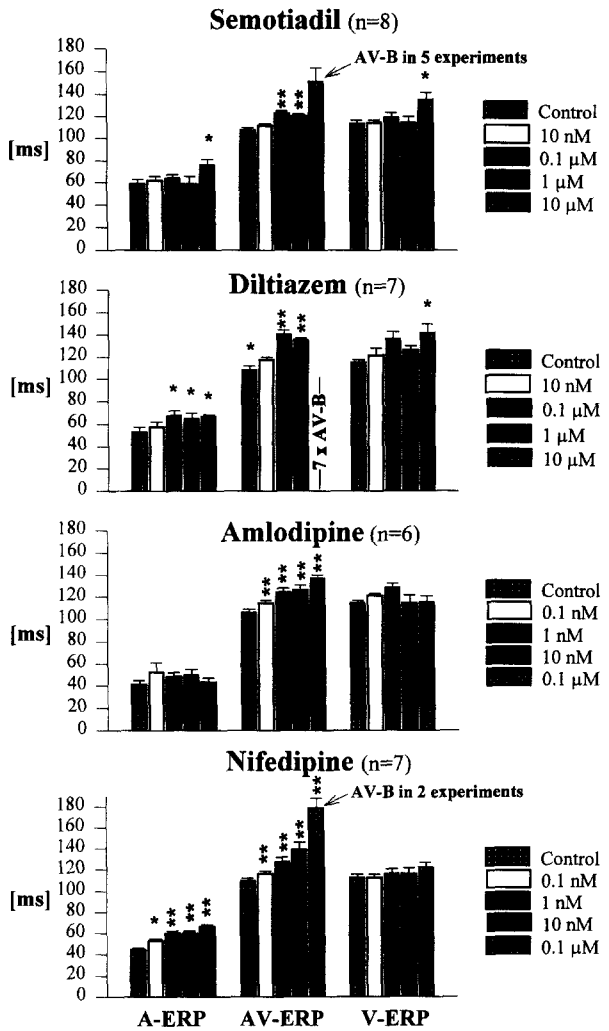

Fig. 4. Effects of semotiadil, diltiazem, amlodipine and nifedipine on atrial (A-ERP), atrioventricular (AV-ERP) and ventricular refractoriness (V-ERP). At the highest concentration of semotiadil (10 μM) in 5 out of 8 experiments, of diltiazem (10 μM) in all experiments and of nifedipine (0.1 μM) in 2 out of 7 experiments an atrioventricular block (3rd degree) occurred during evaluation of the AV-ERP. AV-B, atrioventricular block. Values are means ± S.E.M.; * $P < 0.05$; * * $P < 0.01$.

presence of diltiazem compared to semotiadil at this concentration (Fig. 2).

The repolarization period (QT interval) remained unaffected by semotiadil, amlodipine and nifedipine, whereas in contrast diltiazem induced a concentration-dependent shortening of the QT interval (Fig. 3).

3.2. Effects on refractoriness

Semotiadil caused an increase of the A-ERP only at the highest concentration of 10 μM. Diltiazem also caused an increase of the A-ERP at a concentration of only 0.1 μM. Nifedipine induced only a slight but significant prolongation of the A-ERP at the low concentration of 0.1 nM. Amlodipine did not affect the A-ERP.

The AV-ERP was markedly depressed by 0.1 μM semotiadil and 10 nM diltiazem. Amlodipine and nifedipine depressed the AV-ERP slightly but significantly at a concentration of 1 nM. A third-degree AV block was present during programmed stimulation at the highest concentration of semotiadil (10 μM) in 5 out of 8 experiments and with diltiazem (10 μM) in all experiments. In 2 out of 7 experiments a third-degree AV block occurred in the presence of 0.1 μM nifedipine. No AV block was seen with amlodipine.

The V-ERP remained unaffected by all compounds applied, with the exception of 10 μM of semotiadil and diltiazem, where a significant prolongation could be observed (Fig. 4).

1 μM semotiadil and 1 μM diltiazem were necessary to elicit a significant prolongation of the SNRT. In the presence of 10 nM amlodipine and 0.1 μM nifedipine the SNRT prolongation reached significance. The prolongation of the SNRT was significantly more pronounced ($P < 0.05$) by semotiadil compared to diltiazem at a concentration of 1 μM. However, at a concentration of 10 μM diltiazem in 5 out of 7 experiments an intermittent sinus node arrest occurred and therefore SNRT was not measurable in these cases (Fig. 5).

3.3. Frequency-dependent effects on the AV node

Under control conditions an abrupt change in sinus rate caused by atrial pacing with a S1–S1 interval shortened from 240 to 180 ms did not produce any rate-dependent changes in AVCT. In contrast, in the presence of semotiadil (100 nM), diltiazem (30 nM),

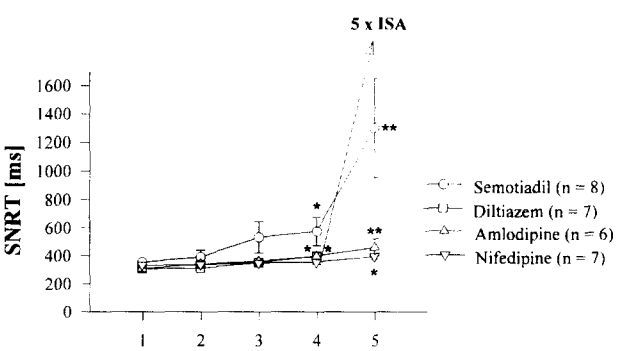

Fig. 5. Effects of semotiadil, diltiazem, amlodipine and nifedipine on sinus node recovery time (SNRT). In the presence of 10 μM diltiazem in 5 out of 7 experiments intermittent sinus node arrest occurred. In these experiments it was not possible to determine the sinus node recovery time (SNRT). 1 = Control, 2 = 10 nM, 3 = 0.1 μM, 4 = 1 μM, and 5 = 10 μM for semotiadil and diltiazem. 1 = Control, 2 = 0.1 nM; 3 = 1 nM, 4 = 10 nM, and 5 = 0.1 μM for amlodipine and nifedipine. ISA, intermittent sinus node arrest. Values are means ± S.E.M.; * $P < 0.05$; * * $P < 0.01$.

amlodipine (100 nM), and nifedipine (10 nM) AVCT increased progressively as a logarithmic function of the beat number (Fig. 6). The above concentrations were those causing comparable AVCT prolongation during sinus rhythm. At a pacing cycle length of 180 ms the rate-dependent slowing of conduction was most pronounced in the presence of diltiazem ($P < 0.05$) compared to all other drugs (Table 1).

The time constant of the rate-dependent AVCT prolongation was longest ($P < 0.01$) in the presence of semotiadil compared to all other drugs (Table 1). In the presence of nifedipine the onset of AVCT prolongation after the abrupt increase in pacing rate was so fast and only followed by a slow and minor prolongation that a meaningful calculation of the time constant was not possible.

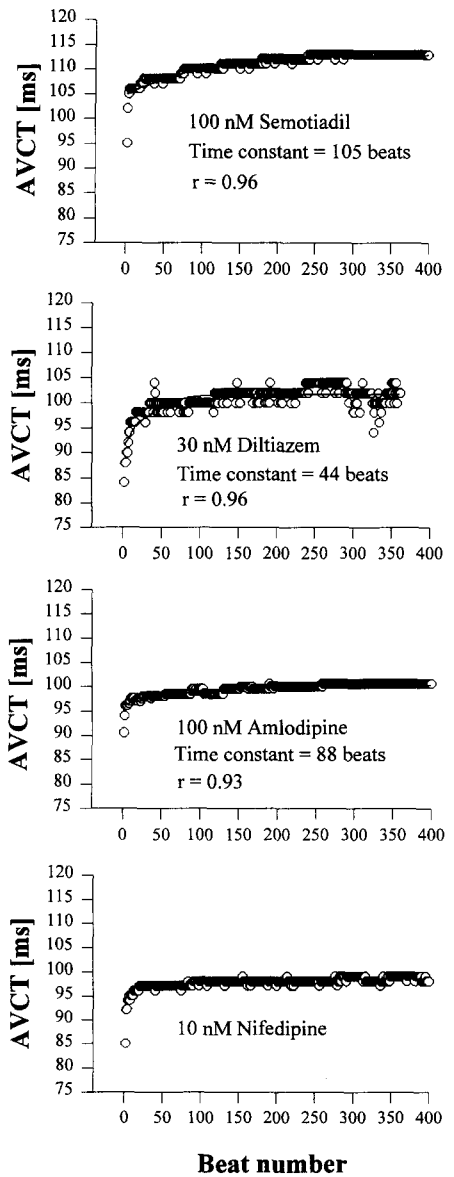

Fig. 6. Beat-to-beat plots of atrioventricular conduction time (AVCT) during atrial pacing in the presence of semotiadil, diltiazem, amlodipine and nifedipine. At beat 0, the pacing cycle length was shortened abruptly from 240 to 180 ms. Onset time constant for the best nonlinear regression fit is expressed in beats.

Table 1
Time constant for drug-induced changes in atrioventricular conduction time

Parameter	Semotiadil	Diltiazem	Amlodipine	Nifedipine
n	6	6	6	6
r	0.96±0.01	0.92±0.01	0.89±0.02	
Magnitude (ms)	15.4±1.4	22.7±2.5	13.3±0.9	17.8±1.8
τ (beats)	128±9	72±11	77±10	< 20

Values are means±S.E.M.; n, number of experiments with analyzable kinetic data; r, nonlinear correlation coefficient; τ, time constant; magnitude, drug-induced prolongation of atrioventricular conduction time after abrupt decrease in pacing cycle length from 240 to 180 ms.

4. Discussion

It is well known that semotiadil is a highly selective vasodilator (Nishimura et al., 1990; Takada et al., 1991). The relative specificity of semotiadil for coronary vasodilation rather than for cardiodepression is greater than that of diltiazem, but less than that of dihydropyridines (Miyawaki et al., 1991; Nishimura et al., 1990). Semotiadil is distinctly different from dihydropyridine Ca^{2+} antagonists in depressing AV nodal function in coronary vasodilator doses; the dose that produced a 15% increase in AV conduction time was very close to the dose that doubled coronary blood flow (Yoneyama et al., 1990). In this respect, semotiadil resembles verapamil and diltiazem (Taira, 1987). Because of the direct effects of semotiadil on the AV node it seems to be of interest to study the electrophysiological properties of this substance on the intact cardiac pacemaker and conduction system and to compare them to those of other potent vasodilators such as diltiazem, amlodipine and nifedipine.

Both semotiadil and diltiazem decreased markedly the sinus rate and prolonged the SNRT in a concentration-dependent manner compared to the two dihydropyridines amlodipine and nifedipine.

The highest concentration of diltiazem (10 μM) caused in 5 out of 7 experiments an intermittent sinus node arrest. This was not the case in the presence of semotiadil at this concentration. Therefore, the sinus node was most depressed by diltiazem compared to all other substances used in this study. However, semotiadil also has to be used with caution for patients with sick sinus syndrome.

The atrial effective refractory period was slightly but significantly prolonged by semotiadil, diltiazem and nifedipine. The most pronounced prolongation of the A-ERP was reached at the highest concentration of

semotiadil (10 μM), which may be explained by its sodium antagonistic activity (Fukuchi et al., 1990). However, because of the small increase in the A-ERP caused by semotiadil, diltiazem and nifedipine, this effect may be of questionable biological significance at clinically used drug concentrations.

Atrioventricular conduction time was most affected by diltiazem compared to all other compounds studied. The marked prolongation of AVCT in the presence of 10 μM diltiazem was also present when the sinus rate was low (86 $\pm$ 12 beats/min). Therefore, at this concentration during programmed stimulation (S1–S1 = 230 ms) for evaluation of AV nodal refractoriness in all experiments a third-degree AV block was induced. Semotiadil mimicked the effects of diltiazem on AVCT and AV-ERP. Amlodipine and nifedipine led also to a concentration-dependent prolongation of the AVCT whereas in contrast to semotiadil and diltiazem, the sinus rate was only slightly affected by the two dihydropyridines. To further characterize the effects on the AV node of the compounds studied the time constant of their rate-dependent inhibitory effect on AVCT was calculated after the heart rate was changed abruptly. Alterations in basic frequency resulted in complex changes in drug dissociation between beats and of drug association during successive activations. The degree to which the time dependence of drug-induced conduction changes paralleled effects on the corresponding inward Ca^{2+} current is still unclear. In canine cardiac Purkinje fibers, there is a close relation between the recovery time constant for effects on V_{max} and conduction (Nattel, 1986). The precise relation between the time dependence of measures of inward current and conduction in the presence of antiarrhythmic drugs is still uncertain. Nonetheless, considerable evidence shows that, at least for drugs that alter sodium conductance, the frequency dependence of inward current changes is closely related to use-dependent changes in conduction (Hondeghem and Katzung, 1977; Morady et al., 1985). This phenomenon might also explain the slowing of atrioventricular conduction during an abrupt increase of the heart rate in the presence of Ca^{2+} channel blocking substances. The Ca^{2+} channel blocking substance semotiadil showed the most pronounced rate-dependent effects on the AV node, as indicated by a very long time constant comparable to that of verapamil (Stark et al., 1993). In the presence of nifedipine the AVCT prolongation during an abrupt increase of the heart rate occurred within a few beats, which made it impossible to calculate a time constant. The rate-dependent effect of amlodipine and diltiazem on the AV node was characterized by approximately the same short time constant. Therefore, under clinical situations, semotiadil, due to its high rate-dependent effect on AV nodal conduction, may be equally as effective as verapamil in controlling the ventricular rate during atrial flutter or fibrillation (Stark et al., 1995).

Both semotiadil and diltiazem caused a marked prolongation of the His bundle conduction time, indicating an unspecific sodium antagonistic effect of both substances at a concentration of 10 μM. According to this effect the V-ERP was also significantly prolonged by both substances at this high concentration (Henry, 1980).

The QT interval in untreated hearts is inversely proportional to the heart rate. A decrease in heart rate elicited by the effects of Ca^{2+} antagonists should lead to a prolongation of the QT interval. With diltiazem the heart rate decrease did not cause the expected prolongation of the QT interval. With increasing concentrations of diltiazem, the QT interval became even shorter than in untreated hearts. In contrast, semotiadil did not act on the QT interval at the used concentrations. This effect is comparable to that of verapamil (Stark et al., 1988).

In conclusion, semotiadil and diltiazem strongly influenced the whole cardiac conduction and pacemaker system, whereas the two dihydropyridines (amlodipine and nifedipine) did not show such strong effects, especially not on the sinus node and atrioventricular node. Due to a marked prolongation of the sinus node recovery time, caused by semotiadil, this compound should be used with caution in patients with sick sinus syndrome. As semotiadil exerted a clear rate-dependent effect on AV nodal conduction with a long time constant and did not affect the rate-dependent QT interval, it mimics the electrophysiological effects of a substance of the verapamil type.

Acknowledgements

The authors wish to thank the Austrian Research Foundation (P10239) for supporting this work.

References

Fukuchi, M., T. Uematsu, S. Nagashima and M. Nakashima, 1990, Antiarrhythmic effects of a benzothiazine derivative (SD-3211) and its stereoisomer (SA3212) in anaesthetized rats and isolated perfused rat hearts compared with bepridil, Naunyn-Schmied. Arch. Pharmacol. 341, 557.

Henry, P.D., 1980, Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem, Am. J. Cardiol. 46, 1047.

Hondeghem, L.M. and B.G. Katzung, 1977, Time-and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels, Biochim. Biophys. Acta 472, 373.

Hope, F.G., R.J. Marshall and E. Winslow, 1983, The effects of nifedipine, tetrodotoxin and bepridil on reperfusion-induced arrhythmias in the rat isolated perfused heart, Br. J. Pharmacol. 78, 33P (abstract).

Kageyama, M., K. Nishimura, T. Takada, N. Miyawaki and H. Yamauchi, 1991, SD-3211, a novel bezothiazine calcium antagonist, alone and in combination with a beta-adrenoceptor antagonist, produces antihypertensive effects without affecting heart rate and atrioventricular conduction in conscious renal hypertesive dogs, J. Cardiovasc. Pharmacol. 17, 102.

Miyawaki, N., T. Furuta, T. Shigei, H. Yamauchi and T. Iso, 1990, Electrophysiological properties of SD-3211, a novel putative Ca^{2+}-antagonist, in isolated guinea-pig and rabbit hearts, J. Cardiovasc. Pharmacol. 16, 769.

Miyawaki, N., T. Furuta, T. Shigei, H. Yamauchi and T. Iso, 1991, Cardiovascular characterization of SD-3211, a novel benzothiazine calcium channel blocker, in isolated rabbit hearts, Life Sci. 48, 1903.

Morady, F., L.A. DiCarlo, R.B. Baermann and R.B. Krol, 1985, Rate-dependent effects of intravenous lidocaine, procainamide, and amiodarone on intraventricular conduction, J. Am. Coll. Cardiol. 6, 179.

Nakayama, K., Y. Morimoto and Y. Tanaka, 1992, Calcium antagonistic and binding properties of semotiadil (SD-3211), a benzothiazine derivative assessed in cerebral and coronary arteries, J. Cardiovasc. Pharmacol. 20, 380.

Nattel, S., 1986, The relationship between frequency-dependence of local anesthetic drug effects on V_{max} and conduction in canine Purkinje fibers, Clin. Res. 34, 329A.

Nishimura, K., N. Miyawaki, H. Yamauchi and T. Iso, 1990, Tissue selectivity of novel calcium antagonist sesamodil fumarate in isolated smooth muscles and cardiac muscles. Arzneim.-Forsch. Drug Res. 40, 244.

Stark, G., U. Huber, E. Hofer and H.A. Tritthart, 1987, Continuous ECG measurements of intracardiac activity from the surface of Langendorff-perfused guinea pig hearts, Basic Res. Cardiol. 82, 437.

Stark, G., U. Stark and H.A. Tritthart, 1988, Modulation of cardiac impulse generation and conduction by nifedipine and verapamil analyzed by a refined surface ECG technique in Langendorff perfused guinea pig hearts, Basic Res. Cardiol. 83, 202.

Stark, G., U. Stark and H.A. Tritthart, 1989, Assessment of the conduction of the cardiac impulse by a new epicardiac surface and stimulation technique (SST-ECG) in Langendorff perfused mammalian hearts, J. Pharmacol. Methods 21, 195.

Stark, G., U. Stark, A. Lueger, K. Stoschitzky, E. Pilger, H.A. Tritthart et al., 1990, Changes of the cardiac electrophysiological parameters by (*R,S*)-propafenone and its (*R*)-and (*S*)-enantiomers evaluated in Langendorff perfused guinea pig hearts, Eur. J. Pharmacol. 183, 1766.

Stark, G., F. Sterz, U. Stark, M. Bachernegg, M. Decrinis and H.A. Tritthart, 1993, Frequency-dependent effects of adenosine and verapamil on atrioventricular conduction in isolated guinea pig hearts, J. Cardiovasc. Pharmacol. 21, 955.

Stark, G., C. Schulze-Bauer, U. Stark, K. Kasper, M. Decrinis and H.A. Tritthart, 1995, Comparison of the frequency-dependent effects on the atrioventricular node of verapamil, amiodarone, digoxin, and diltiazem in isolated guinea pig hearts, J. Cardiovasc. Pharmacol. 25, 330.

Taira, N., 1987, Differences in cardiovascular profile among calcium antagonists, Am. J. Cardiol. 59, 24B.

Takada, T., N. Miyawaki, K. Nishimura et al., 1991, Cardiohemodynamic effect of a novel calcium antagonist, SD-3211, in the dog, Arch. Int. Pharmacodyn. Ther. 309, 75.

Uematsu, T., N.S. Cook, R.P. Hof, S. Vozeh and F. Follath, 1986, Effects of the enantiomers of the dihydropyridine derivative 202-791 on contractility, coronary flow and ischemia-related arrhythmias in rat heart, Eur. J. Pharmacol. 123, 455.

Yoneyama, F., H. Yamada, K. Satoh and N. Taira, 1990, Cardiac versus coronary dilator effects of SD-3211, a new nondihydropyridine calcium antagonist, in isolated, blood-perfused dog hearts, Cardiovasc. Drug Ther. 4, 1469.