Comparison of the Potassium Channel Blocker Tedisamil with the Beta-Adrenoceptor Blocker Esmolol and the Calcium Antagonist Gallopamil in Patients with Coronary Artery Disease

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Summary

Background: Tedisamil is a new bradycardic agent proven to exert anti-ischemic and antiarrhythmic effects by blockade of the different cardiac and vascular K^+ currents.

Hypothesis: It was the aim of the present study to compare the favorable anti-ischemic effects of tedisamil, with two long established representatives in the treatment of coronary artery disease (CAD), namely, the β_1 blocker esmolol and the Ca^{2+} antagonist gallopamil.

Methods: The hemodynamic and neurohumoral effects of the new potassium channel blocker tedisamil, an agent with negative chronotropic and class III antiarrhythmic properties, were compared with the ultra-short-acting β_1 -selective adrenoceptor blocker esmolol and the calcium antagonist gallopamil. A total of 22 patients with angiographically proven CAD and reproducible ST-segment depression in the exercise electrocardiogram was included in two studies with an almost identical design and inclusion criteria. The investigation was carried out using right heart catheterization and bicycle ergometry. A subgroup of 8 patients receiving 0.3 mg/kg body weight tedisamil intravenously (IV) in an open dose-finding study was compared with a group of 14 patients who had received esmolol (IV bolus of 500 μ g/kg, maintenance dose 200 μ g/kg/min) and gallopamil (initial dose 0.025 mg/kg, maintenance dose 0.0005 mg/kg/h) in a second intraindividual comparison.

Results: Tedisamil and esmolol reduced heart rate at rest by 13% ($p < 0.001$), and 6% ($p < 0.05$), and at maximum working levels by 8% ($p < 0.01$) and 9% ($p < 0.05$), respectively. Gallopamil increased heart rate at rest by 7% ($p < 0.05$), with only slight changes occurring during exercise. Corresponding findings for each drug were observed for cardiac output both at rest and during exercise [tedisamil: at rest -10% (NS), max. exercise -8% ; esmolol: at rest -14% (NS), max. exercise -18% (NS); gallopamil: no significant changes]. Compared with tedisamil, stroke volume was reduced by esmolol [at rest and max. workload: -9% (NS)] and gallopamil [rest: -6% (NS), max. exercise: -2% (NS)]. Of the indirect parameters of ventricular function, that is, mean capillary wedge pressure (PCWPm) and right ventricular ejection fraction, only PCWPm demonstrated significant differences between tedisamil and gallopamil ($+18\%$ and -6% at rest, $+17\%$ and -21% during exercise, respectively; $p < 0.001$). Compared with gallopamil, both tedisamil and esmolol were superior in their effects on rate–pressure product, myocardial oxygen consumption, and ST-segment depression, whereas plasma lactate concentration was more reduced by tedisamil and gallopamil. Tedisamil led to a fall in norepinephrine levels in particular.

Conclusion: Tedisamil and esmolol showed almost equipotent anti-ischemic effects at the doses administered. Tedisamil acts mainly by reductions in heart rate, and esmolol, though to a lesser degree, also by reductions in systolic blood pressure. The mechanism of gallopamil is to reduce afterload and to improve coronary perfusion. At the doses applied, however, it has lower antianginal potency compared with tedisamil and esmolol.

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Received: December 17, 1997

Accepted: April 6, 1998

Key words: heart rate reduction, coronary heart disease, tedisamil, gallopamil, esmolol, hemodynamics, vasopressor system

Introduction

Knowledge is still incomplete regarding the complex pathophysiologic relationship between heart rate reduction, coro-

nary perfusion, ventricular contractility, and improvement in myocardial ischemia in patients with coronary artery disease (CAD); yet, the positive effects of reducing heart rates are generally accepted,¹⁻⁴ which led to the development of negative chronotropic substances, beginning with pronethalol, a beta blocker composed by Black and Stephenson⁵ in 1960. The development of this new beta blocker was the foundation of the pharmacologic principle of heart rate reduction in antianginal therapy. Development of specific bradycardiac substances, that might reduce heart rate through direct action on the sinus node, began in the 1980s.⁶ The potassium channel-blocker tedisamil is one representative of this new class. Blockage of outward potassium channels reduces myocellular K⁺ outward current, and the plateau phase of the action potential is prolonged, resulting in increased action potential duration and refractory period, as evidenced by an increased QT interval on the electrocardiogram (ECG).⁷ Studies in the experimental animal^{8, 9} and normal humans¹⁰ confirmed the favorable anti-ischemic effects of tedisamil, and it was the aim of the present study to compare them with two long established representatives in the treatment of CAD.

Substrate

Tedisamil

The K⁺ channel-blocker tedisamil dihydrochlorid, (Kali-Chemie Pharma GmbH, Hannover, Germany) a bispidine derivate, belongs to the class of specific bradycardiac substances.^{6, 11} Plasma protein binding is 96%, renal clearance is as the unchanged drug, and plasma half-life of the drug is approximately 10 h. Electrophysiologic studies using patch- and voltage-clamp techniques identified its mechanism of ac-

tion as dose-dependent inactivation of cardiac i_{to} (transient outward K⁺ current), i_K (delayed rectifier outward K⁺ current),¹²⁻¹⁴ and adenosine triphosphate (ATP)-dependent K⁺ channels (Fig. 1). As a result, closure rate is increased and mean opening time of the inhibited K⁺ channels is reduced, thus leading to a reduction of the transmembranous myocyte outward K⁺ current and to a prolongation of the repolarization time of the action potential.¹⁵⁻¹⁷ The resulting negative chronotropic property of tedisamil is primarily due to a direct effect on sinoatrial pacemaker cells.^{16, 17} Animal studies in vivo and in vitro showed that tedisamil possesses both anti-ischemic^{8, 9, 18} and class III antiarrhythmic properties.¹⁹ In a first study by our working group of patients with angiographically proven CAD, the favorable antianginal efficacy of tedisamil could be well confirmed.¹⁰ Duchosal and Opie⁸ and Fuchs *et al.*²⁰ reported an inotropic increase in animal studies that could not be confirmed in a clinical study by Thormann *et al.*,¹¹ although a clinically relevant loss in contractility was excluded. Studies with tedisamil thus far published have reported only slight gastrointestinal side effects; vital functional impairment or proarrhythmic effects have not been reported.^{10, 11}

Esmolol

Esmolol hydrochloride (Brevibloc[®] Gensia GmbH, Kamen, Germany), in the following referred to as esmolol, is an ultra-short-acting beta₁-selective adrenoceptor blocker,²¹ similar in structure to metoprolol.²² After IV application, its distribution half-life from plasma to body tissue is 2.0 ± 0.5 min.²³ The distribution volume reaches 3.43 ± 1.42 l/kg. Plasma protein binding of esmolol is 55%. By hydrolytic separation from the methyl ester group, in particular by cytosolic aryl esterase of erythrocytes,²⁴ esmolol is separated into a propionic acid derivative (ASL-8123) and methanol²⁵ with a result-

FIG. 1 Schematic illustration of the effects of tedisamil on potassium channels of cardiac muscle cells.

ing elimination half-life of approx. 9.2 ± 3.5 min.²³ The major route of elimination of the pharmacologically almost ineffective main metabolite ASL-8123 appears to be renal at approximately 70–90%.²⁶ The main effects of esmolol are directed at the sinus node which, along with the atrioventricular (AV) node, is inhibited.²⁷ This results in prolonged sinus cycles and sinus node recovery times as well as in an increase in AV node conduction and AH intervals.²⁷ The pharmacodynamic effects of esmolol are mainly based on a reduction of heart rate and systolic blood pressure.^{28–30} Animal experiments demonstrated a decrease in myocardial oxygen demand³¹ as well as cardioprotective effects due to a significant shortening of the myocardial recovery time after transient ischemia^{32,33} and a significant reduction in infarct size.^{34,35}

Gallopamil

Gallopamil hydrochloride, in the following referred to as gallopamil, is a methoxy derivative of verapamil and a highly selective blocker of slow Ca^{2+} ion channels. This leads to a strong reduction in the tone of smooth muscle cells in arterial resistance vessels^{36,37} as well as to a decrease in myocardial contractility, conduction formation, and excitation in the sinus and AV node.³⁸ Distribution of gallopamil in the organism is via an open three-compartment model, with the distribution volume found to be 145 l. Concentration-independent plasma protein binding is 90%. Due to its high first-pass metabolism, a bioavailability of only 15% is found, which can be increased to 23% by saturation of hepatic congestion.¹⁵ The main metabolite obtained by N-desacylation is a secondary amine having no pharmacologic activity at the concentrations reached. Pharmacologic studies thus far have yielded no uniform information regarding gallopamil's effect on heart rate, with most studies in patients reporting a decrease^{39–42} or no significant changes.^{39,43–47} A decrease in systolic blood pressures was found in the majority of studies.^{39,44} In animal experiments, gallopamil was reported to lead to dilatation and increased perfusion of coronary artery vessels.^{16,27} In a study including patients with CAD, arteries with eccentric stenoses were significantly dilated in about 50% of cases. Myocardial scintigraphy showed an increase (15–45%) in the blood flow of ischemic myocardial zones^{21,42,48,49} and a redistribution of blood in favor of ischemic areas.⁴⁹ Gallopamil also has cardioprotective properties with reductions in infarct size proven in animal experiments.⁵⁰

Aim of the Study

The new potassium-channel blocker tedisamil was compared, in a first clinical setting, with two other substances with similar rate-reducing effects that have already been firmly established in antianginal therapy. Critical comparison of the different hemodynamic and neurohumoral activities and the resulting anti-ischemic potency of tedisamil, esmolol, and gallopamil should help evaluate their respective advantages and disadvantages in the treatment of exercise-induced myocardial ischemia.

Methods

Clinical Trial Scheme

The data presented were derived from two studies with identical study designs, namely, a tedisamil study using four different dosing groups and an esmolol-gallopamil study. This separation was necessary because this was the first time that tedisamil was investigated in the setting of a phase II study, making a direct comparison with esmolol and gallopamil impossible. As this was a dose-finding study, the dosing group with the best anti-ischemic efficacy could be identified only after completion of the study and then be compared with esmolol and gallopamil. The hemodynamic, anti-ischemic, and neurohumoral effects were evaluated by intra-individual comparison in both studies. The main differences between the two studies are the number of examination cycles (tedisamil: control-, tedisamil-phase; esmolol-gallopamil: control-, esmolol-, and gallopamil-phase) and the number of patients included (tedisamil: 8 subjects/dose level; esmolol-gallopamil: 14 subjects).

The tedisamil study included eight patients for each of the four dosing groups. With strict consideration of clinical efficacy and the occurrence of side effects, the dose regimens were successively increased from an initial dose of 0.1 mg/kg body weight (BW) tedisamil to 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg BW tedisamil intravenously (IV).⁵¹ Anti-ischemic pretreatment with nitrates, calcium antagonists, or beta blockers was withdrawn about 3 to 7 days prior to onset of the study, depending on the respective elimination half-lives.

Introduction of the right heart catheter and termination of all preparations was followed by a pause of 30–45 min. Measurement of all hemodynamic, neurohumoral, and metabolic parameters at rest was then performed. Ergometric exercise testing was started beginning at 25 W with an increase in 25-W steps every 2 min until exercise end points were reached. The hemodynamic parameters and ST-segment depression were assessed at the end of each W step. In addition, neurohumoral and metabolic parameters were measured at the highest exercise level. During the following recovery phase, ST-segment depression and hemodynamics were documented again at the beginning of recovery and after 3 and 6 min. Infusion of tedisamil over 10 min was initiated after a further pause of 30–45 min; subsequent distribution time was 5 min. The study scheme as described previously was repeated with the study parameters being measured at rest, during exercise, and during the recovery phase.

The esmolol-gallopamil study included 14 patients. Esmolol was given as an IV bolus of 500 $\mu\text{g/kg}$ for 1 min with a subsequent maintenance dose of 200 $\mu\text{g/kg/min}$. Gallopamil was administered at an initial dose of 0.025 mg/kg for 3 min and a subsequent maintenance dose of 0.0005 mg/kg/h. Procedure and time of sampling as well as recording of parameters corresponded to the tedisamil study. Esmolol instead of tedisamil was administered after control application and gallopamil after a second recovery time of approximately 30–45 min.

Patients

A total of 32 patients was included in the tedisamil study, receiving incremental doses of 0.1, 0.2, 0.3, and 0.4 mg/kg (8 patients/dose). The dose of 0.3 mg produced the most favorable anti-ischemic effects so that the group receiving this dose was chosen for comparison with the group receiving esmolol and gallopamil.

The esmolol-gallopamil study included 14 patients (2 women, 12 men). Seven of these had previous myocardial infarction, 11 had triple-vessel disease, 2 had double-vessel disease, and 1 had single-vessel disease.

Table I illustrates the main clinical and hemodynamic characteristics of the tedisamil and esmolol-gallopamil groups.

Each patient had obtained complete information prior to the respective studies regarding the procedure and aims of the study as well as possible risks and side effects associated with participation in the study, and had given written informed consent.

Inclusion criteria were angiographic documentation of CAD (stenotic degree $\geq 70\%$), and stable CAD with exercise-induced reproducible horizontal or downsloping ST-segment depression (at least 1 mm, 0.08 s after the J point).

Examination Techniques

Examination techniques were identical in both studies. At the beginning of investigation, a 7.5 F Swan-Ganz thermodilution volumetric/ejection fraction catheter (Model 93A-431H-7.5F, American Edwards Laboratories, St. Ana, Calif., USA) was introduced into the cubital vein using the Seldinger technique and placed in the PA/pulmonary capillary position. This was followed by a 30–45 stabilizing phase. Cardiac output and right ventricular ejection fraction were determined using a closed pipe system for cooling measurements (CO set II, Model 93-500, Co. Baxter, Munich, Germany), and a REF-1™ ejection fraction/cardiac output computer (Co. Baxter, Munich, Germany). Right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure were also assessed by means of right heart catheterization according to the procedure described by Swan *et al.*⁵² The recording of pressure curves was done using a pressure transducer (Model Trantec BT800, Co. Baxter-Edwards, Munich, Germany) that connected the catheter to a monitor (Co. Hellige Servomed, Freiburg, Germany) and a recording device (Cardioscript CD, 6000, Co. Schwarzer/Picker, Munich, Germany), via a closed, air bubble-free cleaning system containing saline solution. Mean values were derived from five single measurements.

Systemic blood pressure was measured according to the method of Riva Rocci and Korotkoff with the mean value derived from three measurements. Systemic and pulmonary vascular resistances were calculated by standard formula, and MVO_2 according to the rules of Rooke and Feigl.

Heart rate and ST-segment depression were derived from the ECG; ST segment was assessed from the lead showing the most distinct horizontal or downsloping ST-segment depression prior to drug intake. This reference lead was applied

TABLE I Anthropometric and clinical characteristics of the patient collectives in the tedisamil and esmolol/gallopamil studies

	Tedisamil	Esmolol Gallopamil
Age (years)	56.8 $\pm$ 6.3	63.6 $\pm$ 9.1
Sex	8 M	12 M/2 F
Weight (kg)	85.9 $\pm$ 5.4	78.1 $\pm$ 6.5
Height (cm)	179.3 $\pm$ 4.5	172.1 $\pm$ 6.5
HR (1/min)	72.5 $\pm$ 9.9	64.7 $\pm$ 8.0
BPs (mmHg)	140.6 $\pm$ 9.0	137.1 $\pm$ 13.4
BPd (mmHg)	81.3 $\pm$ 12.2	79.7 $\pm$ 8.0
CO (l/min)	7.5 $\pm$ 1.2	5.9 $\pm$ 1.0
PCm (mmHg)	13.3 $\pm$ 3.4	12.5 $\pm$ 3.5
ST depression (mV)	0.20 $\pm$ 0.15	0.21 $\pm$ 0.08

Abbreviations: HR = heart rate, BPs = systolic blood pressure, BPd = diastolic blood pressure, CO = cardiac output, PCm = mean pulmonary capillary wedge pressure.

throughout the study. A 1:10 magnifier was used to determine ST-segment depression 0.08 s after the J point with mean values derived from 10 cardiac cycles. During recovery, PQ, QRS, and QTc times were also assessed.

Exercise testing was performed with patients in supine position, using a regularly calibrated bicycle ergometer (ERG 555, Bosch, Berlin, Germany). Once all resting parameters were obtained, symptom-limited exercise was begun at 25 W and was increased successively by 25 W every 2 min. Hemodynamic and ECG parameters were determined at the end of each exercise step. Exercise testing was terminated in accordance with the World Health Organization (WHO) criteria.

Neurohumoral System

Blood was withdrawn at physical rest and during maximum supine exercise. The samples were drawn from the pulmonary artery through the cardiac catheter into two prechilled edetic acid tubes and one heparin tube. The samples were then centrifuged (4°C, 10 min, 3000 $\times$ g), and the plasma decanted and stored at -20°C until further processing within 4 weeks. Epinephrine, norepinephrine, and dopamine were determined using high-pressure liquid chromatography according to the method described by our working group.⁵³ The atrial natriuretic factor was measured by direct radioimmunoassay (Co. Nichols, Bad Nauheim, Germany).

Blood Gas, Lactate, and Potassium

Blood was withdrawn at rest and during maximum exercise from the pulmonary artery. Blood gas analysis (pH, pCO_2 , pO_2 , BE) was done by an automatic device (Model 995, Co. AVL, Bad Homburg, Germany) using potentiometric and electrochemical techniques. Lactate levels were obtained by full-enzymatic method (Model 704, Co. Hitachi, Mannheim, Germany) and potassium levels by flame photometry (Model 6341, Co. Eppendorf, Hamburg, Germany).

Statistics

Although identical inclusion criteria and an identical trial scheme had been applied in both studies, comparability of basic anthropometric, hemodynamic, and neurohumoral values was ascertained statistically (H test according to Kruskal and Wallis for more than two independent nonparametric samples). After excluding significant differences between the two studies, the tedisamil dose group showing the best hemodynamic and anti-ischemic effects⁵⁴ was compared with the group receiving esmolol and gallopamil. In order to circumvent the problem of different basic values of parameters and the resulting intergroup differences, the percent difference between blank values and drug administration was obtained and again applied to both the H test according to Kruskal and Wallis and the rank test according to Nemenyi. The results were presented as mean and standard error of the mean (SEM) of the percent difference between control and drug admini-

stration ($\bar{X} \pm \text{SEM}$). Two-sided p values were determined for all tests and were presented as [*] $p < 0.05$, [**] $p < 0.01$, [***] $p < 0.001$.

Results

Heart Rate

At rest, tedisamil showed the greatest decrease in heart rate at $-13 \pm 2\%$ ($p < 0.001$, T vs. G), followed by esmolol at $-6 \pm 2\%$ ($p < 0.05$, E vs. G). At the highest workload, esmolol and tedisamil produced similar decreases at $-9 \pm 1\%$ ($p < 0.05$, E vs. G) and $-8 \pm 2\%$ ($p < 0.01$, T vs. G), respectively. Gallopamil, in contrast, increased resting heart rate by $+7 \pm 3\%$ ($p < 0.05$, E vs. G; $p < 0.001$, T vs. G). This trend could no longer be observed during maximum exercise at an increase in heart rate of only $+1 \pm 2\%$ ($p < 0.05$, E vs. G; $p < 0.01$, T vs. G) (Table II).

TABLE II Initial values and percent changes after administration of tedisamil and esmolol or gallopamil at rest and during exercise

Parameter	Tedisamil		Initial value	Esmolol	Gallopamil
	Initial value	$\Delta\%$		$\Delta\%$	$\Delta\%$
Rest					
HR (1/min)	72.5±9.9	-13	64.7±8.0	-6	+7
BPs (mmHg)	145.0±27.7	+5	136.8±13.5	-1	-6
BPd (mmHg)	90.6±13.5	+3	79.5±7.9	+4	-3
RAm (mmHg)	9.3±2.9	+14	9.4±3.6	-3	-8
PAm (mmHg)	20.5±3.7	+1	20.4±4.3	+3	+1
PCm (mmHg)	13.3±3.4	+18	12.5±3.5	+5	-6
SVR (dyn·s·cm ⁻⁵)	1079±248	+17	1241±243	+20	-1
PVR (dyn·s·cm ⁻⁵)	78.9±20.0	+3	109.3±37.0	+23	+18
CO (l/min)	7.52±1.17	-10	5.91±1.01	-14	0
SV (ml)	104.5±16.0	+3	91.7±13.4	-9	-6
RV-EF (%)	44.8±7.5	+8	39.5±8.4	-2	-9
RPP (mmHg/min)	10411±1858	-9	8850±1440	-7	+1
MVO ₂ (ml/min/100 g)	9.48±1.52	-7	8.13±8.13	-9	-2
ST depression (mV)	0.011±0.023	+4	0.004±0.015	+1	+4
Exercise					
HR (1/min)	114.8±17.8	-8	107.4±15.3	-9	+1
BPs (mmHg)	182.5±28.3	-2	175.7±9.4	-9	-4
BPd (mmHg)	96.9±11.3	+2	91.8±12.7	+1	+4
PAm (mmHg)	43.0±11.2	+7	45.4±9.5	+3	-16
PCm (mmHg)	30.1±8.9	+17	31.0±9.3	-1	-21
SVR (dyn·s·cm ⁻⁵)	589±179	+3	805±184	+19	+5
PVR (dyn·s·cm ⁻⁵)	82.5±29.3	-7	104.6±36.5	+42	+6
CO (l/min)	13.9±2.97	-8	11.57±3.09	-18	-1
SV (ml)	115.1±22.1	0	107.6±22.9	-9	-2
RV-EF (%)	42.8±7.3	+2	41.1±11.8	-14	-4
RPP (mmHg/min)	21059±5104	-9	107.6±1140	-17	-2
MVO ₂ (ml/min/100 g)	18.40±4.52	-8	16.79±2.97	-19	-3
ST depression (mV)	0.205±0.052	-46	0.210±0.080	-54	-35

Abbreviations: RAm = mean right atrial pressure, PAm = mean pulmonary artery pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, SV = stroke volume, RV-EF = right ventricular ejection fraction, RPP = rate-pressure product, MVO₂ = myocardial oxygen consumption. Other abbreviations as in Table I.

FIG. 2 Percent changes of heart rate and systolic blood pressure at rest, during maximum exercise, and in the recovery phase compared with initial values after administration of esmolol, gallopamil, and tedisamil (* $p < 0.05$; ** $p < 0.01$). □ = Esmolol, ■ = gallopamil, ■ = tedisamil.

While tedisamil and esmolol showed no significant differences, they were found to be distinctly different compared with the heart-rate increasing effects of gallopamil (Fig. 2).

Peripheral Blood Pressure

With one exception, the three drugs demonstrated no significant difference in their effect on peripheral blood pressures.

The strongest decrease in systolic blood pressure was produced by gallopamil ($-6 \pm 3\%$, $p < 0.05$, G vs. T), followed by esmolol ($-1 \pm 2\%$), while tedisamil led to an increase by $+5 \pm 2\%$ ($p < 0.05$, G vs. T). At the highest workload, esmolol ranked first (NS), followed by gallopamil and the attenuated effect of tedisamil (Fig. 2, Table II).

Mean Right Atrial Pressure, Pulmonary Artery Pressure, and Pulmonary Capillary Wedge Pressure

Esmolol ($-3 \pm 5\%$), gallopamil ($-8 \pm 5\%$), and tedisamil ($+14 \pm 14\%$) had only a slight effect on mean right atrial pressure at rest without showing significant differences (Table II).

Tedisamil and esmolol both produced a slight pressure increase in the lung circuit although the effect of esmolol was less pronounced. Gallopamil, in contrast, produced a partly distinct pressure decrease (Fig. 3).

Tedisamil increased mean pulmonary arterial pressure (PAPm) by $+9 \pm 6\%$ prior to (NS), and by $+7 \pm 6\%$ during maximum workload (NS). The respective values for esmolol

FIG. 3 Percent changes of mean pulmonary artery pressure (PAPm), mean pulmonary capillary wedge pressure (PCm), cardiac output (CO), and stroke volume (SV) at rest and during maximum exercise compared with initial values after administration of esmolol, gallopamil, and tedisamil (* $p < 0.05$; ** $p < 0.01$). □ = Esmolol, ■ = gallopamil, ■ = tedisamil.

TABLE III Initial values of metabolic markers of ischemia and plasma catecholamines and percent changes after administration of tedisamil and esmolol or gallopamil at rest and during exercise

Parameter	Tedisamil		Initial value	Esmolol	Gallopamil
	Initial value	$\Delta\%$		$\Delta\%$	$\Delta\%$
Rest					
Lactate (mmol/l)	1.28 ± 0.43	−14	1.12 ± 0.48	+4	−4
K ⁺ (mmol/l)	4.10 ± 0.40	+1	3.96 ± 0.31	+1	0
Adrenaline (pg/ml)	34.4 ± 19.7	−36	64.7 ± 36.6	+3	+20
Noradrenaline (pg/ml)	248.0 ± 59.8	−29	358.8 ± 141.0	−7	+9
Dopamine (pg/ml)	24.0 ± 8.6	+11	39.2 ± 23.1	+7	−6
Exercise					
Lactate (mmol/l)	3.04 ± 1.31	−21	3.66 ± 1.84	+4	−16
K ⁺ (mmol/l)	4.32 ± 0.28	−4	4.18 ± 0.31	+2	+1
Adrenaline (pg/ml)	39.0 ± 22.4	−4	98.7 ± 63.3	+29	+62
Noradrenaline (pg/ml)	446.8 ± 273.0	−29	779.9 ± 420.5	+10	−10
Dopamine (pg/ml)	23.8 ± 10.6	+2	38.0 ± 19.0	−9	+8

and gallopamil at rest and during exercise were $+3 \pm 3\%$ (NS) or $+3 \pm 4\%$ (NS), and $+1 \pm 4\%$ or $-16 \pm 4\%$, respectively.

The behavior of mean pulmonary capillary (PC) wedge pressure further clarified the different effects of tedisamil and gallopamil. While tedisamil produced an increase of $+18 \pm 8\%$ (NS) at rest and $+17 \pm 8\%$ under maximum workload ($p < 0.001$, T vs. G), the respective values for gallopamil demonstrated a decrease of $-6 \pm 6\%$ (NS) and $-21 \pm 4\%$, respectively ($p < 0.001$, T vs. G). The influence of esmolol was rather unremarkable at $-5 \pm 6\%$ (NS) prior to, and $-1 \pm 6\%$ during maximum workload ($p < 0.05$, G vs. E) (Fig. 3, Table III).

Systemic and Pulmonary Vascular Resistance

Systemic resistance was increased most strongly after esmolol. A corresponding increase was found after tedisamil at rest, which showed, however, almost complete regression during exercise. Gallopamil led to a slight pressure increase at maximum workload only and was otherwise found neutral. A significant difference between esmolol and gallopamil was seen only at resting conditions. Esmolol here produced an increase of $+20 \pm 4\%$ ($p < 0.05$, E vs. G) in systemic vascular resistance (SVR), while gallopamil induced no changes at all. This difference was also maintained during maximum workload, although it was not significant (Table III).

The distinct increase in pulmonary vascular resistance (PVR) observed after administration of esmolol by far exceeded that following administration of gallopamil and tedisamil. At an increase at rest of $+23 \pm 11\%$ (NS), this value was surpassed by another 19%, thus reaching $+42 \pm 9\%$. Although only the latter was significantly different from gallopamil ($p < 0.05$) and tedisamil ($p < 0.01$), the differences in effect and strength could not be denied. While gallopamil likewise increased PVR, tedisamil produced a slight increase at rest and a decrease of $-7 \pm 10\%$ during maximum workload.

Cardiac Output, Stroke Volume, and Right Ventricular Ejection Fraction

The three substances could be clearly differentiated in their effects on cardiac output (CO). The volume-reducing properties of esmolol were strongest with a decrease of $-14 \pm 3\%$ at rest (NS) and $-18 \pm 3\%$ during exercise ($p < 0.05$, E vs. G). The reduction after tedisamil was less pronounced at $-10 \pm 4\%$ at rest (NS) and $-8 \pm 6\%$ during maximum workload (NS). No relevant changes in CO were seen after gallopamil (Fig. 3, Table II).

Stroke volume showed the greatest reduction after esmolol: $-9 \pm 3\%$ at rest and during exercise. Gallopamil ranked second with a decrease of $-6 \pm 4\%$ and $-2 \pm 5\%$, respectively. Tedisamil ranked last, showing only a slight increase at rest and no change at maximum workload.

Right ventricular ejection fraction was slightly decreased after esmolol and gallopamil. No or only slight changes were seen after tedisamil (Fig. 4, Table II).

FIG. 4 Percent changes of right ventricular ejection fraction at rest and during maximum exercise compared with initial values after administration of esmolol, gallopamil, and tedisamil. □ = Esmolol, ■ = gallopamil, ■ = tedisamil.

FIG. 5 Percent changes of myocardial oxygen consumption (MVO₂) and ST-segment depression at rest and during maximum exercise compared with initial values after administration of esmolol, gallopamil, and tedisamil (** $p < 0.01$). □ = Esmolol, ■ = gallopamil, ■ = tedisamil.

Myocardial Oxygen Consumption and Rate-Pressure Product

The most pronounced improvement in MVO₂ was achieved after esmolol therapy. Furthermore, tedisamil was superior to gallopamil, and significant differences were again seen between esmolol and gallopamil only ($p < 0.01$) (Fig. 5, Table II).

The rate-pressure-product showed the strongest decrease after administration of esmolol. The effects of tedisamil were somewhat more attenuated, whereas gallopamil produced practically no changes (Table II).

ST-Segment Depression

The greatest depression of the ST segment was produced by esmolol ($-54 \pm 5\%$). The anti-ischemic effects of tedisamil and gallopamil were less pronounced ($-46 \pm 11\%$ and $-35 \pm 6\%$, respectively) (Fig. 5, Table II).

Metabolic Parameters of Ischemia and Neurohumoral System

Although the changes in lactate concentration were not significantly different, the greatest reduction could be seen

after tedisamil, followed by gallopamil and esmolol (Fig. 6, Table II).

Potassium levels and pH values showed only very modest variations at interdrug and control-related comparison. A significant difference in effect could thus not be established (Table II).

The changes in catecholamine levels demonstrated considerable interdrug variation without, however, producing significant differences (Table III). Tedisamil was found to reduce norepinephrine and epinephrine levels. Esmolol and gallopamil showed nonuniform reactions with regard to norepinephrine and dopamine levels, but both drugs led to an increase in epinephrine levels (Fig. 6).

Electrocardiographic Parameters

PQ and the QRS complex were without significant differences for any of the drugs. The increase in QT and QTc duration, in contrast, was significantly greater after tedisamil ($p < 0.01$, T vs. E, and $p < 0.001$, T vs. G) compared with esmolol and gallopamil. Tedisamil led to a QT prolongation of $+19 \pm 5\%$, whereas the values remained largely unaltered after both esmolol and gallopamil.

FIG. 6 Percent changes of plasma lactate levels and plasma catecholamines at rest and during maximum exercise compared with initial values after administration of esmolol, gallopamil, and tedisamil. □ = Esmolol, ■ = gallopamil, ■ = tedisamil.

Discussion

The rationale for this study was to undertake a first comparison between the newer K⁺ channel blocker tedisamil and two other substance groups that are well established in the pharmacologic therapy of CAD, that is, beta blockers and calcium antagonists of the verapamil type. Bearing critically in mind the nonrandomized scheme of patient allocation to the two studies and the different numbers of patients included, comparability, nevertheless, appears to have been maintained.

No statistically significant differences could be confirmed in regard to the most important anthropometric, hemodynamic, and neurohumoral baseline data of the patient collectives of either study. The design and course of study were identical in both investigations.

As previously reported by our working group,⁵⁴ tedisamil induced the most pronounced hemodynamic and anti-ischemic effects at a dose of 0.3 mg/kg compared with doses of 0.1–0.4 mg/kg BW IV and was thus the dose chosen for the present comparison.

Tedisamil and esmolol showed no difference in their negative chronotropic effect with the exception that tedisamil produced a greater reduction in heart rate at rest. Both substances were found to have comparable bradycardiac properties at the doses applied. Gallopamil, in contrast, showed no heart rate-reducing effect despite its classification as calcium antagonist of the verapamil type.

Parallel findings were obtained for CO. Administration of esmolol and tedisamil led to a significant reduction of CO in some measurements, whereas gallopamil demonstrated a neutral behavior. Here, the effects of esmolol were slightly superior to those of tedisamil.

In addition to its negative chronotropic effects, the negative inotropic effects of esmolol also contribute to a reduction in CO, as can be seen by the fall in right ventricular ejection fraction. Considering, in contrast, mean PC pressures as indirect parameters of left ventricular function, esmolol produced almost no effect, which is indicative of a generally moderate negative inotropic effect. Tedisamil, on the other hand, led to an increase in mean PC pressures, while gallopamil resulted in a more favorable decrease in this parameter, in particular during exercise. According to the study of Thormann *et al.*,⁵⁵ the inotropic loss caused by tedisamil is of no clinical relevance. Correspondingly, our study reported no relevant changes in right ventricular ejection fraction after tedisamil, so that a pronounced cardiodepressive effect appears improbable.

Esmolol and, to a lesser degree, gallopamil led to a slight reduction in systolic blood pressures, while the values increased only insignificantly after tedisamil at rest. Diastolic blood pressures were not significantly influenced by either drug.

Of the three drugs tested, esmolol induced the most distinct increase in vascular resistances, followed by tedisamil for SVR at rest. Gallopamil, on the other hand, was found to provoke only insignificant variations. As vascular resistances were calculated values, and taking the formulae applied into account, the results obtained are mainly attributable to a decrease in CO rather than to a vasoconstrictive effect. The

behavior of mean pulmonary artery and systemic pressures confirm this postulation. Another assumption would be that tedisamil produced an increase in tone through a direct influence on the K⁺ channels of muscle tissue cells with subsequent increase in the cytoplasmatic calcium content. This hypothesis is indirectly supported by the vasorelaxant activity of K⁺ channel openers.^{7, 56, 57}

Despite partly distinct alterations in catecholamine plasma levels, esmolol and gallopamil did not produce any significant effects. A decrease in norepinephrine and epinephrine plasma levels could be observed after tedisamil, which is indicative of the anti-ischemic efficacy of tedisamil, but not of esmolol and gallopamil. The cause of these favorable effects of tedisamil on myocardial oxygen demand and myocardial perfusion has not been fully clarified yet.⁵⁵ A possible explanation may be that the improved balance in myocardial oxygen supply and demand during exercise might result in a reduction of ischemia-related catecholamine release.^{58, 59} This mechanism of action has already been postulated for alinidin by Löllgen *et al.*⁶⁰ Grohs *et al.*⁹ have suggested that, in addition to its direct effects on the sinus node, tedisamil might produce an indirect rate-reducing effect as a result of the decrease in plasma catecholamines.

The main focus of the study was now the comparison of the anti-ischemic net effects resulting from the hemodynamic and neurohumoral properties of the three drugs. At the doses applied, gallopamil proved to have the least antianginal potency. Neither rate–pressure product nor myocardial oxygen consumption was significantly improved after administration of gallopamil. The general constancy of the rate–pressure product is in keeping with the results of earlier studies.^{43, 61} Myocardial ischemia was, nevertheless, decreased significantly, which is conclusively proven by the reduction in ST-segment depression by 34% during maximum exercise as well as by a reduction in pulmonary artery lactate content by 12% at rest and 17% at peak exercise. The latter finding is also indicative of an improved balance in myocardial oxygen supply and demand of skeletal muscles attributable to peripheral vasodilation. Most important, however, appears to be the improved supply to ischemic myocardial zones, since otherwise the dichotomy between rate–pressure product and MVO₂ on the one hand and ST-segment depression on the other hand could not be explained. This conclusion was supported in studies by Eichstädt *et al.* and Gutmann and Eichstädt,^{48, 49} and by Eichstädt *et al.*²¹ using longitudinal thallium scintigraphy in patients with angiographically proven CAD. In these patients, who received intravenous and/or oral gallopamil therapy, a significant increase in the perfusion of ischemic myocardial zones could be confirmed. The same authors were also able to show that perfusion in unimpaired areas increased to a much lesser extent, so that the underlying mechanism appears to be a redistribution in the sense of a “reverse steal” phenomenon.⁴⁸

As was explicitly proven in the present study, the anti-ischemic effects of tedisamil and esmolol, which were confirmed by the distinct decrease in all indirect myocardial parameters of oxygen consumption, are based mainly on a reduction in heart rate. As a result, there is not only an im-

provement in diastolic myocardial perfusion and, subsequently, perfusion of subendocardial areas,⁶² but also a coronary autoregulatory improvement in endo-/epicardial perfusion conditions^{51, 63, 64} with redistribution of blood flow in favor of ischemic zones.^{18–64} In addition, myocardial oxygen consumption is decreased when the heart has to work less.¹¹

Conclusion

If the present results are extrapolated to the respective substance groups, the following indications will result:

The use of beta blockers should be preferred in the treatment of exercise-induced myocardial ischemia,⁶⁵ because they succeed in limiting effectively the increases in heart rate, blood pressure, and contractility caused by sympathetic stimulation, warranting at the same time an improved exercise tolerance. Problems may arise when coronary constriction occurs, as has been seen with some beta blockers, which, in the presence of vasospastic angina or dynamic stenoses could aggravate ischemia.⁶⁵ The use of this substance group is further limited in bradycardiac arrhythmias and left heart insufficiency.

Calcium antagonists decrease myocardial oxygen demand via a reduction in ventricular afterload and abolish coronary vasospasms through vascular relaxation; they improve collateral blood flow and produce a redistribution of blood flow.⁶⁵ In addition, calcium antagonists of the verapamil type decrease both oxygen demand and consumption via heart rate reduction and negative inotropy. These properties are a disadvantage in patients with heart failure and bradycardiac arrhythmias. Calcium antagonists are characteristically predestined in the treatment of vasospastic angina, exercise-independent anginal attacks, or myocardial ischemia with concomitant ventricular impairment.⁶⁶

As both beta blockers and calcium antagonists have a specific mode of action and, correspondingly, respective limitations, the potassium-channel blocker tedisamil should be a welcome addition to the therapeutic armamentarium of anti-ischemic substances. Because of its selective bradycardiac properties⁶ without clinically relevant ventricular impairment or greater side effects, tedisamil can be safely applied in the treatment of exercise-induced myocardial ischemia. If larger studies are able to support this trend, tedisamil could well be a therapeutic alternative to nitrates and calcium antagonists of the nifedipine type in cases with left ventricular impairment.

Further studies must determine the future of potassium-channel blockers and, in particular, of tedisamil regarding their place in the management of coronary artery disease.

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