Sulfonylureas and ischaemic preconditioning

A double-blind, placebo-controlled evaluation of glimepiride and glibenclamide

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Aims Glimepiride is a new sulfonylurea for diabetes treatment which is supposed to impact less on extra-pancreatic ATP-dependent K^+ channels than the conventional drug glibenclamide. This study was performed to evaluate whether this results in a better maintenance of ATP-dependent K^+ channel mediated ischaemic myocardial preconditioning.

Methods and Results In a double-blind placebo-controlled study the period of total coronary occlusion during balloon angioplasty of high grade coronary artery stenoses was used as a model to compare the effects of both drugs. Quantification of myocardial ischaemia was achieved by recording the intracoronary ECG and the time to the occurrence of angina during vessel occlusion. All patients underwent three dilatations. The first dilatation (dilatation 1) served to determine the severity of ischaemia during vessel occlusion. During dilatation 2, baseline values were recorded. Thereafter, glimepiride (15 patients: 1·162 mg), glibenclamide (15 patients: 2·54 mg) or placebo (15 patients) were intravenously administered over 12 min. Dilatation 3 started 10 min after the beginning of the drug administration.

Mean ST segment shifts in the placebo group decreased by 35% (dilatation 2: 0·23; dilatation 3: 0·15 mV; CI −0·55 to 0·00 mV; $P=0·049$). A similar reduction also occurred in the glimepiride group, in which repetitive balloon occlusion led to a 34% reduction (dilatation 2: 0·35; dilatation 3: 0·23 mV; CI −0·21 to −0·02 mV; $P=0·01$). There was little influence however, on mean ST segment shifts in the glibenclamide group (dilatation 2 and dilatation 3: 0·24 mV; CI −0·10 to 0·25 mV; $P=0·34$). Accordingly, time to angina during balloon occlusion slightly increased (by 30%) in the placebo group (dilatation 2: 37 s; dilatation 3: 48 s; CI 0·0 to 15·0 s; $P=0·16$); increased by 13% in the glimepiride group (dilatation 2: 40 s; dilatation 3: 45 s; CI 0·0 to 14·0 s; $P=0·023$); and remained unchanged in the glibenclamide group (dilatation 2 and dilatation 3: 30 s; CI −7·5 to 7·5 s; $P=0·67$).

Conclusion These results show that glimepiride maintains myocardial preconditioning, while glibenclamide might be able to prevent it.
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Key Words: Glimepiride, glibenclamide, ischaemic preconditioning, percutaneous transluminal coronary angioplasty.

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Introduction

Glimepiride is a new generation sulfonylurea for the treatment of diabetes and is supposed to have several benefits over conventional substances such as gliben-clamide. The benefits include rapid onset and longer duration of action, lower insulin level and reduced cardiovascular side effects[1]. The latter observation might be caused by a specific effect on pancreatic ATP-dependent K^+ channels. Cardiac potassium channels, which play a key role in myocardial ischaemia and arrhythmias, may be less involved. This is of particular interest because the safety of this group of drugs with respect to cardiovascular mortality, has been under discussion since the publication of the UGDP results in 1970[2].

As with all sulfonylureas, glimepiride closes the ATP-dependent K^+ channels of the pancreatic beta cells, permitting calcium ion inflow which in consequence triggers insulin secretion. Since these channels are also found in the myocardium, sulfonylureas exhibit several cardiovascular effects, such as prevention of shortening of the action potential during circumscribed myocardial ischaemia. This effect might be responsible for the antiarrhythmic effects of glibenclamide[3–5]. Furthermore, opening of these channels during ischaemia reduces inflow of calcium ions into vascular smooth muscle cells, resulting in vasodilatation that combats hypoxia or ischaemia[6]. Finally, blockade of these channels may worsen post-ischaemic wall function, probably by preventing ischaemic preconditioning[7–10].

The present study was performed to evaluate whether the new generation sulfonylurea glimepiride has a lower impact on ischaemic preconditioning than the conventional drug glibenclamide. Balloon inflation during percutaneous transluminal coronary angioplasty (PTCA) with recording of the intracoronary ECG was used as a sensitive and reliable marker for the development of myocardial ischaemia[10–13].

Methods

Patients

Forty-five patients (15 from each treatment group) with stable coronary heart disease undergoing elective uncomplicated transluminal coronary angioplasty were investigated. The inclusion criteria were age between 20 and 70 years; no history of diabetes; fasting blood glucose below $6 \cdot 6$ mmol . l^{-1} (120 mg . dl^{-1}); at least one coronary artery stenosis higher or equal to 70% diameter stenosis; written informed consent for participation in the study, which was approved by the Ethics Committee of the University Hospital Frankfurt/Main and the participating institutions. Exclusion criteria were myocardial infarction during the last 4 weeks; severely impaired myocardial function (ejection fraction <35%); presumed high risk angioplasty; ECG changes that could interfere with the interpretation of the ST segment; impaired hepatic or renal function; progressive fatal disease; pregnancy or breastfeeding; childbearing potential; mental disorder.

Design

This was a multicentre (three centres), observer-blind, randomized placebo-controlled three parallel group study comparing the effects of glimepiride, glibenclamide and placebo on tolerance of ischaemia. Each treatment group consisted of 15 patients. Baseline characteristics are depicted in Table 1. Beta-blockers and calcium antagonist therapy were equally distributed within the three groups. These substances were withdrawn 24 to 72 h prior to the investigation according to

their half-life time to avoid the influence on myocardial ischaemia. Nitrates and diuretics were withheld on the day of the study. No patient received digitalis. No patient received K_{ATP} channel openers or antiarrhythmic therapy. Drug therapy did not differ between the three groups.

Percutaneous transluminal coronary angioplasty (PTCA) was performed by standard techniques using the femoral approach[11–13]. After administration of 200 IU heparin . kg^{-1} body weight and intubation of the coronary vessel, baseline angiography was performed to visualize the target lesion. After crossing the lesion with the guidewire, the balloon catheter was placed within the lesion. The balloon was inflated between 30 and 120 s until ischaemic signs in the ECG or symptoms occurred. Throughout the whole investigation, the balloon and the guidewire were left in position and were not moved since stable conditions were essential for subsequent measurements.

All patients underwent three dilatations. The first dilatation (dilatation 1) served to determine whether the patient was an appropriate candidate for the study. Only those with an ST segment shift of at least $0 \cdot 3$ mV in the intracoronary ECG were included in the following investigation. The balloon was released either at the occurence of severe angina, ST segment shift $>0 \cdot 6$ mV or after 120 s of inflation. Duration of PTCA averaged 86 s and did not differ between the three study groups (Table 1). The procedure itself was not analysed further since the introduction of the guidewire and the manipulation of placing the balloon catheter in a high grade stenosis would not cause a reproducible myocardial ischaemia.

Dilatation 1 was followed by a 5 min recovery period in which angina vanished and the ECG normalized. No patient showed persistent ischaemia. The study itself was carried out using two balloon dilatations: (dilatation 2 and dilatation 3). Both interventions were performed with balloon pressures and time intervals identical to those used in dilatation 1. Dilatation 2 served as a baseline examination before drug administration. After normalization of clinical and electrocardiographic signs of ischaemia patients were randomized to one of three treatments: glimepiride (15 patients: 1 mg infused intravenously within 3 min, followed by 18 μg . min^{-1} given for 9 min dissolved in aqua pro injection [target concentration 300 ng . ml^{-1}]); glibenclamide sodium salt (15 patients: 2 mg intravenously over 3 min, followed by 60 μg . min^{-1} for 9 min dissolved in aqua pro injection [target concentration 400 ng . ml^{-1}]); or placebo (15 patients: physiological saline ; 3 min bolus, followed by a 9 min short infusion). Dilatation 3 was initiated 10 min after the start of the study drug administration. The doses of the drugs were selected to achieve therapeutic drug concentrations in the blood and similar lowering of blood glucose levels (equivalent to 4 mg glimepiride and 10 mg glibenclamide, orally).

The study was well tolerated by all patients. No major complications (myocardial infarction, large

Table 1 Clinical, anatomical, chemical and haemodynamic findings in the three groups of patients

Treatment group	Placebo	Glimepiride	Glibenclamide	P	
Age (years)	57 ± 8	58 ± 11	57 ± 8	0·89	
Sex, patients					
male	15	13	12	0·25	
female	0	2	3		
Target lesion					
LAD	5	6	9		
LCX	5	4	2		
RCA	5	5	4	0·55	
Severity of stenosis (% lumen reduction)					
before PTCA	85 ± 8	86 ± 9	85 ± 9		
after PTCA	29 ± 12	24 ± 12	28 ± 11		
Median change	− 50	− 59	− 50		
Duration of balloon occlusion per PTCA(s)	84 ± 27	86 ± 31	87 ± 30	0·92	
Blood glucose levels (mmol . l^{-1})				10min;	15 min
before	5·4 ± 1·05	5·2 ± 0·99	5·5 ± 1·1	(a) 0·025	0·02
10 min	5·5 ± 0·99	4·9 ± 0·89	5·4 ± 0·94	(b) 0·60	0·049
15 min	5·4 ± 0·94	4·7 ± 0·78	5·0 ± 0·83	(c) 0·17	0·94
P baseline/10 min	0·42	0·02	1·0		
P baseline/15 min	0·73	0·0006	0·01		
Insulin level (U)					
before	15·3 ± 2·8	16·6 ± 4·5	15·2 ± 4·7	(a) 0·31	0·007
10 min	15·3 ± 3·1	18·2 ± 5·5	38·1 ± 22	(b) 0·0001	0·0001
12 min	14·5 ± 3·1	18·7 ± 5·8	48·1 ± 27·5	(c) 0·0001	0·0001
P baseline/10 min	0·91	0·23	0·0001		
P baseline/12 min	0·09	0·04	0·0001		
Drug concentration at 10 min (ng . ml^{-1} serum)					
10 min of infusion		371 ± 80	391 ± 114		
12 min of infusion		485 ± 104	475 ± 107		
Heart rate at dilatation 2 (beats . min^{-1})	66 ± 7	72 ± 15	67 ± 12	0·90	
Blood pressure at dilation 2 (mmHg)					
Systolic	142 ± 29	146 ± 30	134 ± 22	0·13	
Diastolic	82 ± 15	88 ± 21	79 ± 12	0·17	

LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; RCA=right coronary artery; PTCA: percutaneous transluminal coronary angioplasty; Dilatation 2=dilatation before drug administration.
(a) comparison of changes within placebo vs within glimepiride.
(b) comparison of changes within placebo vs within glibenclamide.
(c) comparison of changes within glimepiride vs within glibenclamide.

dissections, emergency bypass operation, severe bleedings, severe hypoglycaemia) occurred. The primary method of measurement for the study was the intracoronary ECG, derived from the tip of the guidewire acting as an electrode, recording the ECG directly from the myocardial area supplied by the vessel to be dilated. The ST segment shift was measured 80 ms after the J-point. ECG recordings were started 30 s before each dilatation and were obtained every 15 s during balloon inflation. After deflation, recordings were obtained every 15 s for another 60 s and a final tracing was taken after 3 min. At the same time, heart rate and arterial blood pressure were recorded.

Blood samples of glucose levels and drug concentrations were taken from the cardiac catheter before drug administration, at the start of dilatation 3 (10 min after start of the drug) and 3 min after the end of dilatation 3; insulin samples before drug administration, 10 and 12 min after the start of drug administration. Blood glucose was determined using a Reflolux® II M (Boehringer Mannheim, Germany) and Haemo-Glucotest® 20-800 R test strips. Drug concentrations were measured at the end of patient inclusion by Hoechst, Germany, from serum stored at − 20 °C. The detection limit of glimepiride was 5 ng . ml^{-1} and 3 ng . ml^{-1} for glibenclamide, respectively. Table 1 shows the actual values.

Data analysis

The primary variable was the mean ST segment shift (mV) during dilatation. The mean for each patient was calculated as the area under the curve relative to the starting point (the value immediately before dilatation) divided by the length of the interval over which the patient was dilated. The secondary variables were the maximum ST segment shift, and the time to onset of angina pain during dilatation. No quantification of the severity of angina was done.

The homogeneity of the various baseline values was assessed using an analysis of variance with a treatment effect. Haemodynamic, clinical and chemical baseline values are presented as mean ± standard deviation.

Comparison of primary and secondary variables within and between the treatment groups are described using non-parametric methods and corresponding 95% confidence intervals (CI). All related values are therefore reported as medians. The level of significance was 0·05.

Results

All three groups were comparable with respect to age, sex, severity of stenosis, type of vessels affected, duration of balloon occlusion, baseline heart rate, blood pressure, basal glucose and insulin level (Table 1).

Analysis within groups (Comparison dilatation 2, dilatation 3)

Table 2 presents the individual data of the mean and maximum ST segment shift for the 45 patients, Figs 1 and 2 the percent mean and the maximum ST segment shifts at dilatation 2 and dilatation 3 for each of the treatment groups. Baseline values (dilatation 2) were similar in all three groups. In the glimepiride group, repetitive balloon occlusion led to a reduction in the mean ST segment shift from 0·35 mV to 0·23 mV (-34%; median decrease: 0·12; CI 0·02 to 0·21; $P=0·01$), while the maximum ST segment shift decreased by 33% from 0·6 to 0·4 mV (median decrease: 0·1 mV; CI 0·0 to 0·2 mV; $P=0·02$). The time to the onset of angina increased by 13% (Fig. 3; median increase: 7·5 s; CI 0·0 to 14·0 s; $P=0·023$).

There was minimal influence by glibenclamide on mean and maximum ST segment shifts: 0·24 mV and 0·4 mV, respectively, at both dilatation 2 and dilatation 3. The time of onset of angina (both values 30 s; median reduction: 1·5 s; CI $-7·5$ to 7·5 s; $P=0·67$) was similar during both dilatation 2 and dilatation 3.

The mean ST segment shift in the placebo group decreased by 35% (from a median value of 0·23 mV during dilatation 2 to 0·15 mV during dilatation 3; median decrease: 0·1 mV; CI 0·0 to 0·55 mV; $P=0·049$). The maximum ST segment shift decreased by 40% from 0·5 to 0·3 mV (median decrease: 0·2 mV; CI 0·0 to 0·7 mV; $P=0·009$). There was an increase of 30% in the time to occurrence of angina during balloon inflation (37 vs 48 s; median increase: 1·5 s; CI 0·0 to 15·0 s; $P=0·16$).

Between-group comparison (based on the change from dilatation 2 to dilatation 3)

Glimepiride showed a decrease in the mean ST segment shift from dilatation 2 to dilatation 3 similar to those observed in the placebo group (median difference for 'glimepiride–placebo': $-0·01$ mV; CI $-0·16$ to 0·15 mV; $P=0·87$). Glibenclamide showed a tendency towards a more prominent ST depression than placebo and glimepiride ('glibenclamide–placebo': median

difference: 0·04 mV; CI $-0·07$ to 0·46 mV; $P=0·34$; 'glimepiride–glibenclamide' median difference: $-0·09$ mV; CI $-0·23$ to 0·03 mV; $P=0·17$).

Maximum ST segment shift showed similar trends in the glimepiride and placebo groups ('glimepiride–placebo' median difference: 0·10 mV; CI $-0·10$ to 0·30 mV; $P=0·51$). The decrease in the glibenclamide group was less than that in the placebo group ('glibenclamide–placebo' median difference: 0·10 mV; CI 0·0 to 0·9 mV; $P=0·15$). The glimepiride group had a slightly larger reduction in the maximum ST segment shift than the glibenclamide group ('glimepiride–glibenclamide' median difference: $-0·10$ mV; CI $-0·20$ to 0·10 mV; $P=0·28$).

There was a slightly greater increase in the time to onset of angina from dilatation 2 to dilatation 3 in the glimepiride than in the placebo group ('glimepiride–placebo' median difference: 3·5 s; CI $-4·0$ to 13·0 s; $P=0·32$). The glibenclamide group showed a decrease in the time to onset of angina compared to both the glimepride ('glimepiride–glibenclamide' median difference: 10·0 s; CI 0·0 to 15·0 s; $P=0·039$) and placebo ('glibenclamide–placebo' median difference: $-3·0$ s; CI -15 to 0·0 s; $P=0·15$) groups.

Insulin concentrations increased slightly after 10 min of glimepiride infusion. Substantial increases were measured in the glibenclamide group and negligible decreases were observed in the placebo group. Similar trends were observed after 12 min of infusion. Patients in the glimepiride and glibenclamide groups showed larger decreases in their blood glucose levels after 10 and 15 min of infusion than the placebo group. After 10 min of infusion, the glimepiride group had shown a greater decrease in blood glucose levels than the glibenclamide group, although after 15 min of infusion the groups exhibited similar results. Taken together, the changes in blood glucose were judged to be clinically irrelevant.

Discussion

The observation that brief, single or recurrent episodes of myocardial ischaemia and reperfusion limit the size of myocardial infarction after subsequent complete vascular occlusion has led to the concept of 'ischaemic preconditioning'[14]. Until now the clinical role of preconditioning in humans has been unclear[15]. Deutsch and co-workers focusing on this issue analysed clinical, electrocardiographic and haemodynamic data of 12 patients undergoing transluminal coronary angioplasty[16]. There were fewer signs of ischaemia during the second period of coronary occlusion, supporting the concept of ischaemic preconditioning. These data were subsequently confirmed by others[9,17]. Interestingly, results from the TIMI IV study revealed that previous angina confers a beneficial effect on in-hospital outcome after acute myocardial infarction, a finding compatible with ischaemic preconditioning[18]. However, this was questioned later by Marber *et al.*[19] who pointed out

Table 2   Mean ST segment shift as area-under-the-curve and maximum ST segment shift for the three groups of patients

Patient No.	Mean ST segment shift		Maximum ST segment shift	
	Dilatation 2 (baseline)	Dilatation 3 (end-point)	Dilatation 2 (baseline)	Dilatation 3 (end-point)
Glimepiride				
1	0·50000	0·13333	0·8	0·4
2	0·85238	0·99167	1·2	1·4
3	0·61667	0·23333	0·8	0·6
4	0·22500	0·13333	0·4	0·3
5	0·20000	0·18750	0·5	0·4
6	0·25000	0·30000	0·4	0·4
7	0·08125	0·03125	0·1	0·1
8	0·31250	0·16250	0·5	0·3
9	0·62500	0·45000	0·8	0·6
10	0·11250	0·09583	0·3	0·3
11	0·35000	0·41875	0·6	0·6
12	3·16875	2·99375	3·9	4·0
13	1·09375	0·81875	1·8	1·4
14	1·58125	1·33125	2·1	1·9
15	0·22500	0·10625	0·4	0·3
Glibenclamide				
16	0·70000	0·55833	1·4	0·9
17	0·98750	0·65000	1·6	1·2
18	0·34444	0·28333	0·6	0·6
19	0·11667	0·80286	0·3	1·6
20	0·70625	0·65000	0·8	0·8
21	0·04286	0·15714	0·1	0·2
22	0·27500	0·23750	0·4	0·3
23	0·19375	0·14375	0·3	0·2
24	0·16250	0·20000	0·4	0·4
25	0·22500	0·08750	0·4	0·2
26	0·44375	0·28125	0·7	0·6
27	0·13750	0·16250	0·3	0·3
28	0·33750	1·97500	2·0	3·6
29	0·23750	0·20625	0·4	0·4
30	0·18125	0·08125	0·3	0·2
Placebo				
31	0·68333	0·15000	1·4	0·4
32	0·40000	0·33333	1·1	0·8
33	0·11250	0·28750	0·3	0·4
34	3·17500	0·51429	4·8	1·3
35	0·18389	0·13333	0·4	0·3
36	0·05833	0·07500	0·1	0·1
37	0·05000	0·05000	0·1	0·1
38	0·11429	0·02857	0·2	0·2
39	0·11250	0·05000	0·3	0·2
40	0·41250	0·40000	0·7	0·6
41	1·13750	1·21250	1·8	1·9
42	1·68125	0·57431	2·3	0·9
43	0·58750	0·16875	0·8	0·3
44	0·07857	0·11250	0·4	0·2
45	0·23125	0·04375	0·5	0·1

that in animal studies preconditioning effects may not last longer than 120 min. The existence of a 'second window' with delayed protection is under discussion.

The ATP-dependent K^+ channels seem to play a key role in preconditioning[7–10,20]. The channels open when the intracellular ATP concentration falls below 1 mM[21]. This causes cell membrane hyperpolarization, a shortening of the action potential[22] and a reduced inflow of calcium ions into the cell[7]. As a consequence, ATP utilization [23] and contractility of the muscle decrease leading to conservation of energy. Accordingly, blockade of these channels could abolish energy conserving effects.

Glibenclamide selectively blocks the opening of ATP-dependent K^+ channels and thereby may prevent ischaemic preconditioning. Thus, experiments in rabbits[24] and dogs[25] showed that the limitation of infarct size caused by ischaemic preconditioning could be prohibited by application of this drug. Tomai *et al*.[9] performed a study in man using a protocol very similar
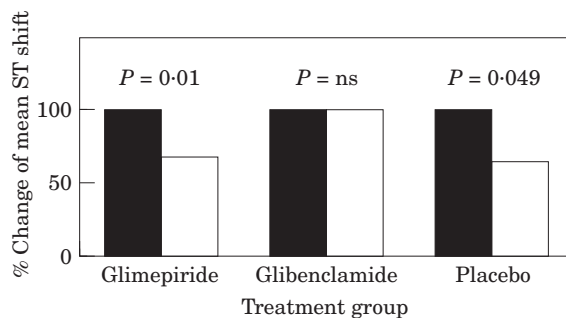
Figure 1   **Glimepiride and placebo show typical effects of ischaemic preconditioning, i.e. reduction of mean ST segment depression after repetitive balloon occlusion. However, preconditioning was abolished by glibenclamide. ■=dilatation 2; □=dilatation 3.**
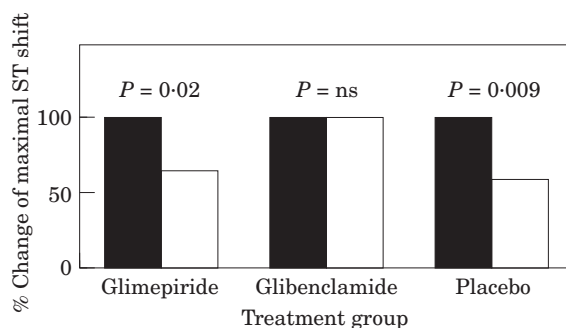

Figure 2   **Maximum ST segment depression is reduced after repetitive balloon occlusion of the coronary vessel during glimepiride and placebo application. However, no change occurred during glibenclamide–administration. ■=dilatation 2; □=dilatation 3.**
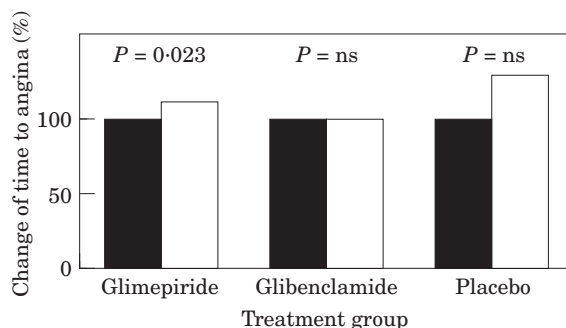

Figure 3   **Repetitive balloon occlusion led to a prolongation of the time to angina during glimepiride and although not significant ($P=0.16$), during placebo administration. No change could be observed with glibenclamide. ■= dilatation 2; □=dilatation 3.**

to our study. Pretreatment with glibenclamide was found to completely abolish ischaemic preconditioning. This result is confirmed by our data which showed that ST depression and time to the occurrence of angina remained unchanged in the corresponding group of patients, whereas a clear effect could be seen in the placebo group.

Our study extends the knowledge to the cardiac effects of a newer oral sulfonylurea for diabetes treatment. Glimepiride lowers blood glucose at lower insulin levels than glibenclamide[1,26]. The mechanism is unclear. Possible explanations are a different membrane environment of the sulfonylurea receptor, different receptor proteins[27], stronger extrapancreatic effects or increased insulin sensitivity. Whether the reduced blocking effect on the cardiac ATP-dependent K^+ channel, as observed in our study, is also due to different kinetic binding parameters cannot be answered. However, it appears that the new drug has less effects on K^+ channel-mediated myocardial preconditioning than the old substance at equipotent effects on blood glucose. We cannot rule out that differences in plasma insulin levels may have an influence on our results. This question should be addressed in a further study investigating patients with elevated insulin levels.

We also cannot completely rule out that the differences between glimepiride and glibenclamide are independent of the blockade of the ATP-dependent K^+ channels. It has been shown that high doses of intra-coronarily infused glibenclamide decrease coronary blood flow[28]. However, our study was performed with usual therapeutic serum concentrations of the drugs that are reached by oral administration of 4 mg glimepiride and 10 mg glibenclamide, respectively. Another possibility would be that glibenclamide but not glimepiride prevents the recruitment of coronary collaterals. Thus, differences in myocardial ischaemia during balloon occlusion would not be a consequence of different mechanisms of action on the potassium channels but simply reflect differences in blood supply. However, this seems improbable for several reasons. It has been shown that glibenclamide prevents preconditioning independent of effects on collateral flow in dogs[25]. These results were confirmed in pigs[29] which have no collateral blood flow. Studies of Auchampach and co-workers[7] revealed that pretreatment with aprikalim, an ATP-dependent potassium channel opener, resulted in a marked improvement of ischaemic and reperfused myocardium; this effect could be antagonized by the blockade of the channels using glibenclamide. The ability of aprikalim and glibenclamide to alter post-ischaemic wall function occurred independently of differences in systemic haemodynamics, area at risk and coronary blood flow during occlusion as measured by radioactive microspheres[7]. Furthermore, Deutsch and co-workers showed in man that reduction of myocardial ischaemia during repeated coronary occlusions was associated with an unchanged coronary wedge pressure[16].

It is well known that glibenclamide has direct effects on myocardial ischaemia. Two studies showed that intravenous or intracoronary application of the drug attenuate acute ischaemic ST T wave changes[30,31]. However it must be emphasized, that doses administered were about 5- to 10- fold higher than in our investigation and that these authors observed a reduction of acute ischaemia whereas in the model of ischaemic preconditioning glibenclamide maintains myocardial ischaemia.

Finally, it may be argued that differences in insulin levels might influence myocardial perfusion. The results of our study confirmed that insulin levels during glibenclamide administration were higher than during glimepiride infusion. High insulin levels, however, are associated with decreased contraction of vascular smooth muscle cells[32] and thus should lead to the opposite result, an improvement of myocardial perfusion.

Direct comparison between the two drugs revealed that glimepiride had trends towards fewer cardiovascular side effects than glibenclamide. However, the size of the study population was primarily designed to compare the effect of the two drugs with placebo. Direct comparison of the two drugs requires much larger patient groups. In conclusion, the results of our study reveal evidence that the new sulfonylurea glimepiride maintains ischaemic preconditioning, while it appears that the old substance, glibenclamide, prevents preconditioning. Nevertheless, it remains to be established whether this difference between glimepiride and glibenclamide with regard to their influence on ischaemic preconditioning pays in clinical practice. Possible beneficial effects on ischaemic preconditioning might be outbalanced by the potentially proarrhythmic effect of shortening of the action potential during myocardial ischaemia[33]. However, as the plateau phase of the action potential shortens the opening probability of the voltage gated calcium channels decreases. This might contribute to a reduction of myocardial ischaemia. Furthermore, recently published data indicate that ischaemic preconditioning itself decreases QT dispersion in the surface ECG thus leading to a reduction of arrhythmias[34]. Thus, large scale clinical trials are needed to clarify the potential benefit of drugs like glimepiride.

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