Diabetes, coronary heart disease and sulphonylureas — not the final word

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Coronary heart disease incidence is increased two- to three-fold in patients with type II diabetes mellitus and remains the major burden of morbidity and mortality. Case fatality is significantly greater even in the thrombolytic era and in the longer term diabetes is associated with a poor prognosis with increased reinfarction, left ventricular failure and fatal arrhythmias.

The general poor outcome for diabetic patients following acute myocardial infarction argues strongly for preventive measures. It is clear that the major risk factors for coronary heart disease, cigarette smoking, blood pressure and serum cholesterol play an important role in the diabetic population. An obvious potential diabetes-specific risk factor is hyperglycaemia. However, an early prospective study which examined the effects of glycaemic control with various agents on coronary heart disease was stopped prematurely because of apparent excess cardiovascular mortality in the group receiving the sulphonylurea, tolbutamide[1]. This study was much criticized for methodological reasons and sulphonylureas remained a mainstay of treatment of type II diabetes particularly in Europe.

With the discovery of the ATP-sensitive potassium channels (K\textsubscript{ATP}) in the heart and the evaluation of their role in ischaemic heart disease questions have again been raised about the potential for adverse effects of sulphonylureas[2]. The principal targets of these compounds are K\textsubscript{ATP} channels which play a major role in controlling membrane potential in the pancreatic beta cell. Inhibition of these channels by sulphonylureas leads to depolarization of the beta cell in a similar way to glucose; the resulting calcium influx stimulates exocytosis of insulin-containing secretory granules. It is clear that K\textsubscript{ATP} channels are present in high density in other tissues such as muscle, including smooth and cardiac muscle and neurones. Their role in these tissues is less clearly defined but it is probable that they open in response to reduced ATP concentrations during ischaemia. In addition they are important in determining vascular smooth muscle tone.

K\textsubscript{ATP} channels have been strongly implicated in ischaemic preconditioning; this refers to the phenomenon that a brief period of ischaemia may render less severe a subsequent, more prolonged episode. The sulphonylurea glibenclamide has been shown to block both ischaemic and pharmacological preconditioning in various animal species and tissues including human cardiac muscle. In humans therapeutic concentrations of glibenclamide inhibit diazoxide (a K\textsubscript{ATP} opener) induced vasodilatation in human forearm inferring an in vivo action of the drug. In addition, ischaemic pre-conditioning during coronary angioplasty is inhibited by glibenclamide. These observations have prompted reviews seeking to clarify the possible clinical consequences of K\textsubscript{ATP} channel blockade by sulphonylureas[2,3].

Klamann et al.[4] have provided important and reassuring evidence that glibenclamide treatment does not affect in-hospital mortality of type II diabetic patients following acute myocardial infarction. Over a 6.5 year period (January 1991 to June 1997) all patients admitted with acute myocardial infarction were evaluated retrospectively and divided into four groups; non-diabetics, type II diabetics newly diagnosed on admission, type II diabetics taking glibenclamide and type II diabetics not taking sulphonylureas. Of 607 patients identified less than 1% were excluded because of lack of information on the diabetic state. Eight patients with type I diabetes were excluded. Mortality, creatinine kinase levels, atrial and ventricular arrhythmias and patient characteristics including possible confounding factors were recorded. Diabetic patients had a higher in-hospital mortality but there was no difference between type II diabetics treated with or without glibenclamide. In addition and consistent with previous reports the authors report a tendency towards lower creatine kinase increments in known diabetics regardless of the type of treatment. This possibly relates to the more diffuse coronary atherosclerosis in diabetics with less myocardium dependent on the occluded vessel. This study leaves open the possibility that more sulphonylurea-treated diabetic patients die before hospital admission. This is an important caveat as almost a half of all patients with acute myocardial infarction do not reach hospital and this figure may be even higher in the diabetic population.

Can these apparent conflicting findings be reconciled? On the one hand, important evidence of potentially adverse effects on K\textsubscript{ATP} channel activity in the myocardium and vasculature and on the other, no demonstrable effect on in-hospital mortality and
infarct size and no apparent adverse effect on the development of coronary heart disease. One possibility is that the potential adverse effect of sulphonylureas on pre-conditioning is counterbalanced by potential antiarrhythmic effects\[2,3\]. During ischaemia significant shortening of the action potential duration following K⁺ efflux through K_ATP channels could paradoxically be pro- or antiarrhythmogenic. Decrease in intracellular calcium secondary to reduced influx associated with shortening of the action potential would be expected to reduce the risk of arrhythmias due to calcium-dependent delayed depolarization. In contrast, arrhythmias due to re-entry mechanisms could be increased secondary to altered myocardial refractoriness. Therefore inhibition of K_ATP channels by sulphonylureas could on the one hand increase the risk of cell death and delayed afterdepolarization arrhythmias and on the other decrease re-entry arrhythmias. In several animal models of acute ischaemia, antiarrhythmic activity has been demonstrated with sulphonylureas with reduced episodes of ventricular tachycardia and fibrillation together with shortened duration. Antiarrhythmic action of sulphonylureas has also been demonstrated in patients during myocardial ischaemia\[2,3\].

Beta-cell and cardiac muscle K_ATP channels both possess a pore-forming subunit designated Kir 6.2, but different sulphonylurea receptor subunits. Two genes encoding sulphonylurea receptors have been cloned designated SUR1 and SUR2A. SUR1 is a regulatory subunit for beta-cell K_ATP channels and SUR2A for cardiac muscle channels. Gribble et al\[5\] have studied binding characteristics of sulphonylureas using cloned beta-cell (Kir 6.2/SUR1) and cardiac (Kir 6.2/SUR2A) K_ATP channels expressed in Xenopus oocytes. The first generation sulphonylurea, tolbutamide and the second generation glibenclamide were more efficient inhibitors of beta-cell than cardiac K_ATP channels. Tolbutamide inhibited beta-cell but not cardiac K_ATP channels with high affinity. Glibenclamide inhibited both beta-cell and cardiac K_ATP channels with high affinity, but the effect on the cardiac channel was largely abolished by physiological concentrations of intracellular MgADP, suggesting that the drug was unlikely to be active in vivo. However the authors could not exclude the possibility that other cytosolic molecules could influence glibenclamide/cardiac K_ATP channel interactions and that under some circumstances glibenclamide and related drugs might block cardiac channels. They suggest that drugs which interact only with SUR1 receptors would be the best sulphonylurea treatment for type II diabetes\[5\].

Thus, in vitro studies suggest that tolbutamide is unlikely to interact with cardiac muscle K_ATP channels and this was the drug used in the UGDP study which raised concerns over cardiovascular disease\[4\]. Of interest, some other clinical studies did not support potential adverse cardiovascular effects with this drug or indeed glibenclamide\[2,3\]. Recently a sulphonylurea, glimepiride, which appears to be devoid of vascular K_ATP channel binding properties in animal models has been introduced into clinical practice. Klepzig et al\[6\] compared the effects of glibenclamide and glimepiride on ischaemic preconditioning during angioplasty of high grade coronary artery stenoses in patients with stable coronary heart disease. Myocardial ischaemia was quantified by intracoronary ECG and time to occurrence of angina during vessel occlusion. The authors concluded that glimepiride maintained myocardial preconditioning in this model while glibenclamide could prevent it\[6\].

It is clear that the relevance of sulphonylurea cardiovascular system interactions remains to be resolved fully with current conflicting experimental and clinical findings. The introduction of more specific compounds opens the possibility for large scale, controlled clinical trials with hard clinical end points in order once and for all to end the dilemma. Nonetheless there is no doubt that the findings of Klamann et al\[4\] will provide further reassurance for clinicians using sulphonylureas. However, in diabetic patients with acute myocardial infarction there is no doubt about appropriate therapy; oral agents should be discontinued and insulin therapy commenced. The DIGAMI study has clearly shown that an insulin-glucose infusion followed by at least three months of a multi-dose insulin regime significantly improves long-term prognosis. This benefit was particularly evident in patients who had no previous insulin therapy\[7\].

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References

Should we transfer patients with acute myocardial infarction to a tertiary care hospital for primary angioplasty?

See page 823 for the article to which this Editorial refers

The advantages and disadvantages of primary angioplasty and pharmacological reperfusion are well-known. A meta-analysis of all randomized studies has shown a significant reduction in the incidence of death and reinfarction at 30 days, favouring primary angioplasty. Since most hospitals throughout the world do not have catheterization facilities or are not able to provide a 24-hour service, the obvious question arises whether one should routinely transfer patients with ST-segment elevation acute coronary syndromes to a tertiary care hospital for intervention. This question was addressed in the PRAGUE (Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis) study in this issue.

In the PRAGUE study, 300 patients were randomized to in-hospital fibrinolysis with streptokinase, transfer to a tertiary care hospital with the same fibrinolytic regimen given during transport, or transfer to the hospital for primary angioplasty/stenting but without pre-treatment with streptokinase. The primary end-point of the study, the composite of death, reinfarction and stroke at 30 days, was observed in 8% of the patients randomized to primary angioplasty/stenting, in 15% of the patients randomized to the combined therapy and in 23% of the patients who were treated in the community hospitals (P<0.02 vs primary angioplasty). From these results the authors conclude that patients presenting with ST-segment elevations or new bundle branch block should get primary coronary angioplasty/stenting even if these procedures require transfer to a tertiary care hospital provided that the coronary interventions can be performed within 90 min.

Is this far-reaching recommendation acceptable to the cardiological community? The answer is no. Although the PRAGUE investigators should be congratulated for having successfully completed a very difficult study, at least from a logistical point of view, scrutinizing the results of the study indicates that the populations and treatments studied and the corresponding outcomes are not representative of what is generally being observed nowadays. First, the number of patients studied is small and selected from a much larger population of 1588 patients presenting with ST-segment elevations or bundle branch block to community hospitals. It is not totally clear why so many patients were excluded. The mortality, reinfarction and stroke rates observed in the fibrinolysis-alone arm of this study population are twice that observed with the same fibrinolytic in much larger trials. Also, in the other two arms of the study these end-points were more frequently observed than in most recent trials. Secondly, the use of streptokinase as the fibrinolytic agent has put the pharmacological reperfusion-alone and combination arms at a disadvantage when compared with up-to-date mechanical reperfusion (angioplasty with stenting in 79% of the patients!). Although streptokinase is still the most frequently prescribed fibrinolytic, better agents are available. Although these agents are more expensive, cost constraints cannot be used as an argument here since fibrinolysis was compared with much more expensive treatment strategies. Thirdly, in spite of relatively short distances and investigators trying to keep the transfer time as short as possible, the delay between admission to the community hospital and the first balloon inflation at the tertiary care hospital was more than 90 min on average. These delays are likely to be much longer in the real world, outside the setting of a clinical trial.

The worst outcome with pre-intervention fibrinolysis as compared with primary angioplasty/stenting in...