For debate . . .

Do angiotensin converting enzyme inhibitors represent a progress in hypertension care in diabetes mellitus?

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Introduction. The excess mortality of Type 1 (insulin-dependent) diabetes mellitus is mainly due to the development of diabetic nephropathy with proteinuria and hypertension as its leading clinical features. Only quite recently, it has been recognized that the prognosis of diabetic nephropathy, including its mortality, depends largely on the degree of hypertension control [1, 2]. In Type 2 (non-insulin-dependent) diabetes mellitus, excess mortality is due to cardiovascular disease and hypertension plays a leading role as a risk factor in this context [3]. Although, specific intervention studies on hypertension in Type 2 diabetes are not available, treatment of hypertension is strongly recommended in both types of diabetes [4]. Apart from these facts [1–4], the obvious current vogue of interest in hypertension in diabetic patients has been triggered by the introduction and marketing of new antihypertensive agents, such as angiotensin converting enzyme inhibitors. Actually, it has been postulated that these new antihypertensive drugs represent a major progress in the hypertension care of diabetic patients. In the following, we challenge this view by analysing the evidence for suggested advantages of the new drugs over conventional antihypertensive agents, such as thiazide diuretics and β -blockers.

Do angiotensin converting enzyme inhibitors exert a specific nephroprotection?

In Type 1 (insulin-dependent) diabetes, preservation of glomerular function due to lowering of intraglomerular pressure independent of the systemic blood pressure

lowering effect has been suggested as a specific action of angiotensin converting enzyme inhibitors (ACEIs) [5]. However, this hypothesis still remains controversial in animal studies [6–8] and its relevance for human diabetic patients is uncertain [9, 10]. Several studies on the effects of ACEIs in Type 1 diabetic patients have claimed to address this issue. In order to document a specific nephroprotection by ACEIs in patients with diabetic nephropathy, an improvement of prognosis, i.e. a retardation of the loss of renal function, over and above the effect of the reduction of systemic blood pressure, by the drug needs to be proven. This would require a randomized prospective study in patients with diabetic nephropathy comparing the effects of ACEIs *and other antihypertensive agents* on the course of renal function; under both models of treatment comparable degrees of blood pressure control would have to be maintained throughout the study. To date, no such study has been performed. In contrast, various reports available in the literature are based upon uncontrolled studies, with conflicting results [11, 12].

In one retrospective analysis [13], captopril treatment turned out to be equally or, if anything, less effective in retarding the decline of glomerular filtration rate: $5.8 \text{ ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$ on captopril vs $4.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$ on conventional treatment. Furthermore, it has been claimed that ACEIs may even be beneficial in normotensive diabetic patients by reducing albuminuria [14, 15]. However, these studies have also included patients with blood pressure readings above 140/90 mmHg – values which are not normotensive according to definitions of the World Health Organisation and International Society of Hypertension [16]. It is of note that a similar beneficial effect on albuminuria in “normotensive” Type 1 diabetic patients has been reported for the β -blocker metoprolol [17]. Thus, to date observed beneficial effects on renal function cannot be attributed to a specific nephroprotective effect of ACEIs, but are rather due to the reduction of systemic blood pressure as such.

The section “For debate . . .” is open to contributions dealing with issues of a particularly debatable nature in diabetology. Contributions are published either standing by themselves or accompanied by invited comments. Other comments from the readership may be published as Letters to the Editor. Manuscripts intended for publication in this section of the journal are accepted at the discretion of the Editor-in-Chief and may be subject to a referee procedure.

Do ACEIs improve glucose tolerance?

It has been suggested that ACEIs may improve insulin sensitivity and, hence, glucose tolerance by yet unknown mechanisms [18]. To substantiate such a hypothesis, adequate long-term evaluations of glucose metabolism during ACEI therapy have to be awaited. Since blood pressure lowering by other means [19] may be associated with increasing insulin sensitivity, such studies would have to be carried out including appropriate control groups. In the meantime, available evidence in Type 1 and Type 2 diabetic patients treated with ACEIs does not indicate any clinically significant change in glucose metabolism attributable to the ACEI medication [14, 15, 20].

Do ACEIs have fewer side effects than conventional antihypertensive drugs?

It has been suggested that ACEI therapy is associated with a better quality of life due to a reduced incidence of side effects when compared to conventional antihypertensive agents. Much of this suggestion stems from a prospective controlled trial in non-diabetic hypertensive men comparing captopril, methyldopa and propranolol [21]. However, methyldopa and propranolol are not recommended as first line drugs in diabetic patients [4]. Later studies in non-diabetic patients showed that the overall frequency of side effects of ACEIs was not significantly different when compared to the cardioselective β -blocker atenolol [22] or a combination of triamterene and hydrochlorothiazide [23].

As a further potential advantage of the new drugs it is assumed that ACEIs do not mask or prolong insulin-induced hypoglycaemia in Type 1 diabetic patients as (non-cardioselective) β -blocking agents might do [4]. But the risk of this potentially hazardous side effect can be kept at a minimum by using cardioselective β -blockers in low doses [24, 25]. Even at low levels of glycosylated haemoglobin, the incidence of severe hypoglycaemia does not appear to be increased under such therapy in our experience [26]. On the other hand, two astonishing cases of severe hypoglycaemia briefly after initiation of captopril therapy in chronically hyperglycaemic Type 2 diabetic patients on sulfonylurea plus biguanide medication have been reported [27].

In essential hypertension and in Type 2 diabetic patients, treatment with diuretics has been associated with a potassium-loss mediated impairment of glycaemic control [28, 29]. However, this problem can be minimized by a low-dose thiazide diuretic treatment in combination with a potassium sparing diuretic [28, 30]. The results of a recently published study comparing the influence of diuretics and ACEIs on glucose metabolism can not be attributed to a drug specific effect, since potassium balance – a major confounding factor in studies on insulin sensitivity – was not maintained in this study [29]. The use of cardioselective β -blockers has not led to a significant deterioration of glycaemic control in Type 2 diabetic patients [31]. Two recent publications have claimed adverse effects

of β -blocker therapy on glucose metabolism [32, 33]. However, the validity of both studies is questionable [34], since neither included appropriate control groups, rendering any causal relationship between antihypertensive treatment and impaired glucose tolerance highly speculative. Rather, the results of the studies were due to weight gain [32] and the particular genetic background [33] in the patients receiving β -blockers.

It has been suggested that ACEI treatment is superior to conventional antihypertensive agents with respect to changes in serum lipid profiles. Adverse effects of conventional antihypertensive agents on lipid metabolism have been repeatedly described; these effects may be transient, however. In fact, in non-diabetic hypertensive patients long-term therapy with thiazide diuretics or cardioselective β -blockers does not increase serum cholesterol concentrations in most of the trials [35–37]. No long-term studies are available for diabetic patients and no such studies exist for ACEIs.

On the other hand, severe and life-threatening side effects have been reported for ACEI therapy, such as severe hypotension, hyperkalaemia, deterioration of renal function, neutropenia, angio-oedema and urticaria. In addition, a rather large number of less serious and reversible side effects associated with ACEI treatment have been communicated, such as cough, rash and taste disturbance. Women of childbearing age must not take ACEIs unless they use effective contraception [38].

Finally, it should be remembered that conventional antihypertensive therapy may have desirable side effects, which could be of special relevance for diabetic patients. Thus, diuretics can lower excessive body sodium, which has been related to the pathophysiology of hypertension in diabetes [39], and long-term thiazide use may protect against osteoporosis and hip fractures in the elderly [40]. Betablockers are effective drugs in the primary and secondary prevention of coronary heart disease [37]. In this context it is of note, that the only documentation of an improvement of the prognosis of diabetic nephropathy and the mortality of these patients is based upon blood pressure lowering therapy with conventional antihypertensive agents [2].

A particular note is warranted concerning the antihypertensive therapy in Type 2 diabetic patients, the majority of whom are in the geriatric age range and have already developed atherosclerotic disease [3]. Special caution is warranted concerning ACEI treatment in Type 2 diabetic patients with renal insufficiency [41], severe chronic heart failure [42] advanced atherosclerosis [43], and specifically with renal artery stenosis – a frequent finding in hypertensive Type 2 diabetic patients [44]. In elderly multimorbid Type 2 diabetic patients, the potential benefit of antihypertensive drug treatment must be carefully balanced against the increasing risk of pharmacological therapy.

In summary, unless documented by adequate prospective and controlled trials the suggested decreased incidence of side effects and the improved quality of life during ACEI therapy compared to the treatment with conventional antihypertensive agents in diabetic patients must remain hypothetical.

Conclusions

Obviously, the introduction of new antihypertensive drugs, as promising they may ever be, will by itself not lead to an improvement of the overall quality of hypertension care in diabetic patients. Rather, the standards of hypertension care in unselected patient populations will depend (on the part of physicians) on systematic attempts to diagnose early and to initiate effective therapy, and (on the part of patients) on adherence to agreed therapeutic procedures [26].

In contrast to the tremendous interest in new pharmaceutical principles in antihypertensive therapy, surprisingly few attempts have been directed towards assessment and improvement of overall quality of hypertension care in diabetic patients. The few available data indicate very infrequent blood pressure measurements in diabetic patients both in general practitioners' offices and in diabetes centres [45, 46], and high percentages of patients with either untreated hypertension [47] or insufficient blood pressure control despite treatment [26, 46].

These problems are most unlikely to be solved by the mere introduction of ACEIs or any other new antihypertensive drug. One may even fear that the emphasis on promoting such new, still incompletely evaluated drugs may detract physicians and patients from the necessity to comply to tedious rules of long-term hypertension care using well established therapeutic principles. On the other hand, one might hope that the present most active marketing campaign for ACEIs will foster the interest for the real problems of hypertension care in diabetes. In this indirect way, the ACEIs may indeed contribute to the urgently needed improvement of hypertension care in diabetic patients.

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