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# Effect of a Long-Term Acarbose Therapy on the Metabolic Control of Sulphonylurea-Treated Diabetic Patients

Dear Sir,

The blood glucose lowering effect of acarbose, an alpha-glucosidase inhibitor, has been adequately documented by short term studies [1–4]. However, a lack of effectiveness with longer term administration of acarbose in patients with Type 2 (non-insulin-dependent) diabetes has been reported [5].

In contrast to these findings, we would like to report our own results. After a 3-month prior period on sulphonylureas alone, 24 sulphonylurea-treated Type 2 diabetics (aged 53–79 years, Broca-index > 1,1, mean post-prandial blood glucose > 11 mmol/l, urinary glucose > 5 g/24 h) received in addition acarbose 300 mg/day or placebo for 6 months. Afterwards, all patients continued with sulphonylureas alone for a further 3 months.

During administration of acarbose, we saw a significant lowering of the post-prandial blood glucose values ($10.9 \pm 2.4$ compared with $16.0 \pm 3.6$ mmol/l, mean ± SD, $p < 0.001$), of mean daily blood glucose levels ($8.6 \pm 1.7$ compared with $12.3 \pm 2.8$ mmol/l; $p < 0.001$), of 24 h urinary glucose excretion ($2 \pm 0.4$ compared with $13 \pm 6$ g/24 h; $p < 0.005$) and $HbA_{1a-c}$ values ($9.1 \pm 0.4$ compared with $12.4 \pm 0.6\%$; $p < 0.005$).

Other laboratory determinations (fasting blood glucose, serum insulin, blood lipids, electrolytes, liver and kidney function) did not show any significant alterations during the entire study period. There was no change in body weight.

When acarbose was discontinued, the parameters specified above rose significantly again within 4 weeks (post-prandial blood glucose values: $14.9 \pm 3.2$ mmol/l; mean daily blood glucose levels: $12.7 \pm 2.3$ mmol/l; 24 h urinary glucose excretion: $12 \pm 5$ g/24 h and $HbA_{1a-c}$ values: $13.1 \pm 0.4\%$).

In the placebo group, there was no significant alteration of the metabolic state during the entire 12 months. Side effects (flatulence and meteorism) subsided after about 4 weeks and did not recur again during the rest of the experimental period.

Our results show that additional administration of acarbose to sulphonylurea-treated diabetics leads to a persistent improvement of metabolic control over a long period.

Yours sincerely
G. Sachse, H. Laube, E. Mäser and K. Federlin

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# Subcutaneous Degradation of Insulin

Dear Sir,

I would like to add some cautionary comments regarding the confusion over the extent of insulin degradation at the subcutaneous injection site in experimental animals and man reported in this journal [1] and elsewhere.

Evidence for considerable subcutaneous insulin degradation has been provided in rat [2, 3] and pigs [4] and might partly explain the higher dose requirements when insulin is administered subcutaneously rather than intravenously or intramuscularly during attempts to maintain normoglycaemia in diabetic man [5–9]. Indeed, adipose tissue of rats contains proteases which degrade insulin, and Paulsen et al. [7] showed a high level of insulin degrading activity in a homogenate of the adipose tissue of a patient with severe resistance to subcutaneously administered insulin.

However, confusion has arisen over whether the protease inhibitor aprotinin (Trasylol) can protect against insulin degradation at the subcutaneous site. It has been reported that aprotinin increases the rate and absolute amount of insulin absorption from the subcutaneous tissue of non-diabetics [10] and reduces the subcutaneous insulin requirements in some insulin-resistant diabetics [9, 11, 12], while others have been unable to confirm these findings in a Type 1 (insulin-dependent) diabetic patient [8] or in Type 2 (non-insulin dependent) diabetic subjects [1]. However, the latter group did not report glycaemic changes and concluded that aprotinin had no ef-

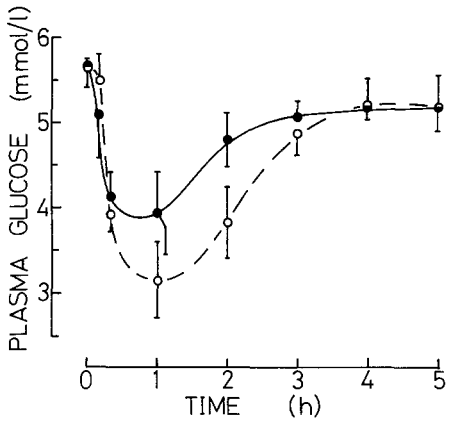


**Fig. 1.** Effect of subcutaneous injection of insulin (0.4 U/kg) alone (○—○) or with 300 KIU aprotinin in the injection solution (●—●) on the plasma glucose levels in male Wistar rats weighing 300–350 g. Aprotinin 300 KIU has been shown previously to enhance the biological response to peptide hormones injected subcutaneously into chicks [13]. Results are expressed as mean ± SEM in five animals

fect on the basis of plasma immunoreactive insulin levels, which do not necessarily reflect bioactive levels of insulin.

We have tested a variety of protease inhibitors in an attempt to reduce degradation of peptide hormones at the subcutaneous injection site. Aprotinin and E-aminocaproic acid were found most effective in chicks in enhancing the hypercalcaemic response to subcutaneous injection of parathyroid hormone and its 1–34 amino terminal fragment (hPTH 1–34) [13]. Also, by radioimmunoassay and bioassay respectively, it was confirmed that aprotinin raised circulating levels of parathyroid hormone and of another peptide hormone, calcitonin, when injected subcutaneously. On the basis of these findings, E-aminocaproic acid has been included in the diluent of hPTH 1–34 injected subcutaneously in a multi-centre clinical trial for the treatment of involutional osteoporosis [14]. However, in a parallel study in mature greyhounds [15] addition of E-aminocaproic acid did not increase the hypercalcaemic response (3.1 mmol/l) to subcutaneous injection of hPTH 1–34, 24 nmol. Therefore, the formulation of species-specific protease inhibitors may be required.

Caution must be exercised regarding the effectiveness in diabetic man of protease inhibitors screened in animal models. Although Hoare and Offord [16] have shown that aprotinin protects against degradation of insulin by isolated rat peri-renal adipose tissue, we have been unable to show that aprotinin increases the hypoglycaemic response when mixed with the subcutaneous injection of insulin in the same species (Fig. 1), even though partial inactivation of insulin seems to occur [2].

As there are great differences in the rate of absorption of insulin within and between patients [17], partly no doubt, because of variability in subcutaneous blood flow [18, 19], differences between species in histological structure of the subcutaneous tissues [2] and, as shown here, differences in proteolytic degradation of insulin between (and perhaps within) species, we must be careful not to extrapolate results obtained in one sub-population of man to another, and even more so from results in experimental animals to the diabetic subject.

Yours sincerely
R. W. Stevenson

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# Glycosylated Haemoglobin and Reticulocyte Count in Diabetes

Dear Sir,

It has been suggested that, in poorly controlled diabetes, the increase in the level of glycosylated haemoglobin, because of its greater oxygen affinity, may lead to polycythaemia [1]. This hypothesis is supported by the results of Graham et al. [2], who found a weak but significant correlation between the glycosylated haemoglobin level and red blood cell count in adult diabetic subjects and of Kawahara and Ditzel [3], who found increased haematocrit, haemoglobin and 2,3-DPG concentration in diabetic children.

However, Bodansky et al. [4] and Lev-Ran [5] question whether the hypoxic effect of glycosylated haemoglobin in diabetes is sufficient to induce polycythaemia.

We have measured the red cell counts, haematocrit and reticulocyte, haemoglobin and glycosylated haemoglobin ($HbA_1$) levels in 80 diabetic outpatients (40 males, 40 females, mean age (± SEM) 36 ± 2.8 years). All the subjects were non-smokers and none suffered from cardiac, pulmonary or haematological disease. $HbA_1$ levels did not differ significantly according to whether the patients were treated with diet alone, hypoglycaemic drugs or insulin. Their results were compared with those of a control group of 100 subjects (50 males, 50 females, mean age 38 ± 3 years, all non-smokers). The reticulocyte count and $HbA_1$ levels were significantly higher in the diabetic subjects compared with those of the control subjects (both $p < 0.001$). No significant differences were found in the other parameters.

The reticulocyte count was significantly correlated with the $HbA_1$ level in the diabetic subjects, independently of sex ($r = 0.68$, $p < 0.001$). Ten diabetic subjects (five males, five females, $HbA_1$ 5.8–16%) were re-studied 1 month later. Their reticulocyte count and $HbA_1$ level showed parallel variations (basal: $r = 0.68$, $p < 0.05$; 1 month later: $r = 0.91$, $p < 0.001$).

Our results suggest that the increase in glycosylated haemoglobin found in diabetic patients may cause sufficient chronic hypoxia to stimulate erythropoietin production and thus lead to an elevation in the reticulocyte count.

Yours sincerely
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**Table 1.** $HbA_1$, reticulocyte count, total haemoglobin, haematocrit and red blood cell count in diabetic and healthy subjects

| | Diabetic patients ($n = 80$) | Healthy subjects ($n = 100$) |
|---|---|---|
| $HbA_1$ (%) | 9.3 ± 0.4 | 6.4 ± 0.1[a] |
| Reticulocyte count (%) | 9.34 ± 0.8 | 6.37 ± 0.3[a] |
| Total haemoglobin (g/dl) | 14.1 ± 0.6 | 13.9 ± 0.4 |
| Haematocrit (%) | 41.3 ± 0.8 | 39.1 ± 0.9 |
| Red blood cell × $10^{12}$/l | 4.5 ± 0.2 | 4.42 ± 0.3 |

Results are expressed as mean ± SEM
[a] $p < 0.001$ diabetic versus healthy subjects

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