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Clinical aspects on glucose-lowering therapies in type 2 diabetes

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ABSTRACT

Type 2 diabetes is a progressive disease with deterioration of glycaemic control over time in association with loss of endogenous insulin secretion. As a consequence of this, sulphonylureas (SU), which exert their mode of action by stimulating the pancreatic β -cells, are expected to be less effective with longer duration of diabetes. Thus SU is often withdrawn when insulin is started and SU is less frequently added to insulin and metformin in patients not reaching glycaemic goals. The aim of the work presented in this thesis was to investigate different aspects on the use of SU in patients with diabetes exceeding more than 5-10 years.

In **Study I** glycaemic control and β -cell function were monitored during a period of SU withdrawal in 25 patients, median diabetes duration 19 (8-29) years and on combined SU + insulin for more than five years. In 80% glycaemic control deteriorated after SU withdrawal. Diabetes duration was positively correlated to the increase in fasting plasma glucose, i.e. in this group of patients a longer diabetes duration indicated more benefit of SU.

In **Study II** changes in HbA_{1c} and β -cell function, assessed as C-peptide/glucose ratio, were observed at two time points, ten years apart, in patients who had attended the Diabetes Day Care Centre in 1997/1998. Of 462 patients, 171 attended the follow-up visit ten years later. Possible relations between SU treatment and changes in β -cell function were studied. HbA_{1c} and β -cell function decreased but long-term use of SU was not associated with a more pronounced decline in β -cell function. It was concluded that these observations did not support the concept that SU is harmful to the β -cell.

Study III was performed to test whether SU still can be effective after more than ten years of diabetes. This randomized, placebo-controlled, double-blind, cross-over study included 43 patients, median diabetes duration 16 (10-30) years, with on-going metformin and insulin therapy. During two treatment periods of 12 weeks, separated by a washout period of six weeks, patients were given placebo/glimepiride in a randomized order as add-on therapy. No changes in baseline therapy were made except for insulin reduction if needed. HbA_{1c} and changes in insulin requirement were primary outcomes. With glimepiride, HbA_{1c} decreased from 7.0% to 6.4% (63-56 mmol/mol) while no change was observed during the placebo period. The insulin dose was reduced in 23 patients (median change 29%) with glimepiride addition. No severe hypoglycaemia occurred but 22 patients reported 124 minor hypoglycaemias, 74% of them occurring during the glimepiride period. Nocturnal glycaemia was monitored with CGMS at the end of each treatment period. In 15 patients on glimepiride episodes of glucose < 3.1 mmol/l were observed; and in six patients when placebo was added. It was concluded that addition of glimepiride to insulin + metformin therapy can lower HbA_{1c} and reduce insulin requirement despite a long duration of diabetes.

In **Study IV** the accuracy of nocturnal CGMS monitoring was assessed after 48 and 72 hours in 14 patients on combined oral and insulin therapy. The study was conducted in the early era of CGMS and the sensor was the first model on the market. Nocturnal reference P-glucose values were assessed seven times and compared to sensor readings. In a Clark Error Grid model 100% of values were within zones A+B after 48 hours while only 44 % were in zone A and 7% in the unacceptable zone D after 72 hours. With the sensor used in the study the accuracy of CGMS thus deteriorated over time.

Conclusion: The decline in β -cell function over times varies considerably between patients. Sulphonylureas are effective when combined with insulin and metformin in many patients with long-standing type 2 diabetes; and long-term treatment with SU is not associated with a pronounced decline in β -cell function.