HYPOGLYCEMIA

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In a Parisian diabetic clinic the incidence of hypoglycemia was found to be at least once a month in 58% of insulin treated diabetic patients[1]. In a one year prospective study from Nottingham 9% of 1229 insulin-treated patients needed hospital treatment for severe hypoglycemia[2]. During the study 204 episodes of severe hypoglycemia occurred in 130 insulin treated patients (9%), 3 sulfonylurea treated patients and in one patient with insulinoma. Among the insulin treated patients 96 were seen once, 18 were seen twice, and 16 patients were seen on three or more occasions in the hospital. The reason for the hypoglycemic attacks could not be found in 37%, but hypoglycemia due to variation in insulin absorption may be included in this group. Thus, the intraindividual day-to-day varation for the rate of insulin absorption is 25% on the average. Therefore, periods with increased insulin absorption and a blood glucose level close to normal may cause increased risk of hypoglycemia. 30% of the hypoglycemic episodes were due to missed or delayed meals, 14% followed a recent increase in insulin dose, 6% had hypoglycemia in connection with exercise, 6% in connection with alcohol intake, and in 3% of the cases the patients had lost their warning of hypoglycemia. The mean insulin dose in patients admitted twice or more was 1.2 IU per kilogram per day as against 0.9 IU/ kg/day for those admitted once. Both were significantly higher than that of an aged matched clinic population without episodes of hypoglycemia. From Denmark we know that a normal weight type I diabetic without residual beta-cell function gets approximately 0.6 IU per kilo per 24 hours, when treated with highly purified insulin preparations. In recent years many efforts have been exercised to obtain strict metabolic control in insulin treated diabetics. In the largest study : The diabetes control and complication trial (DCCT) intensified treatment with pen or pump is compared with standard treatment with one or two daily injections of insulin[3]. The group treated intensively had blood glucose concentrations close to normal concomitant with haemoglobin Ale close to normal and significantly lower than that of the control group. During the first year of the study severe hypoglycemic reactions were found in 26% of the intensively treated patients as compared to 10% in the control group[3]. Also the number of events were approximately 3 times as high in the strict control group than in the control group[3]. It is therefore evident that an intensified insulin treatment with near normalization of the blood glucose level increases the risk of severe hypoglycemic reactions.

In another study it was shown that the correlation between number of blood glucose concentrations below 3 mmol/1 and the median blood glucose concentration during 24 hours did not differ between conventional treatment and pump-treatment (CSII)[4]. The lower the average blood glucose concentration during 24 hours the more frequent occurence of blood glucose concentrations below 3 mmol/l[4].

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Whereas the distribution of blood glucose concentrations below 3 mmol/1 in CSII treated patients were equally divided over 24 hours, the conventionally treated patients had peak occurrence of hypoglycemia at 11 o'clock a.m. This might be caused by the fact that insulin levels decline overnight on conventional therapy (but not on CSII) resulting in fasting hyperglycemia. The attempt to treat this with a high morning dose of insulin in turn leads to relative hyperinsulinemia and hypoglycemia before lunch. Hypoglycemia before lunch also emphasizes the importance of a mid-morning snack to avoid hypoglycemia.

Another time point with great risk of hypoglycemia is 2 to 3 a.m. during night time. At this time the insulin sensitivity has increased and a concurrent lack of caloric intake during night time make the insulin requirement very low[5] However, due to the absorption kinetic, the absorption of intermediate acting insulin injected before supper may be maximal at this time of the night thus causing risk of hypoglycemia. It has previously been shown that if the blood glucose concentration at bed-time (11 p.m.) is below 6 mmol/1 in patients receiving twice daily insulin, 80% of the patients will have nocturnal hypoglycemia (blood glucose below 3 mmol/1)[6] None of the 17 examined patients woke up during this nightly hypoglycemia. In some of these patients nocturnal hypoglycemia may be avoided by postponing the injection of intermediate acting insulin from supper to 10-11 p.m.

The hypoglycemic attack is followed by a period with increasing glucose concentrations called the glucose recovery or counterregulation. To identify factors of importance for glucose recovery a total number of 31 patients were examined during and after insulin induced hypoglycemia[7]. Thereafter the 10 patients with the slowest recovery were compared with the 10 patients with the fastest recovery[7]. No difference in responses of plasma glucagon, plasma norepinephrine and cortisol between the two groups was found. The patients having the slowest recovery had a significantly increased epinephrine response whereas the response of growth hormone was significantly impaired glucose recovery also had the highest amount of insulin binding antibodies and free insulin concentrations compared with the group with the fast recovery[7]. Thus it seems that insulin binding antibodies may act as a depot of circulating insulin and may be associated with slow recovery after insulin induced hypoglycemia emphasizing the importance of insulin for glucose recovery after hypoglycemia.

The influence of duration of diabetes on glucose recovery after hypoglycemia can be summarized as follows : After short duration of diabetes (few months) the patients have a normal glucose recovery with a normal glucagon and epinephrine response to hypoglycemia. During the next five years duration of diabetes the glucose recovery is slightly impaired despite increased epinephrine response to hypoglycemia, probably due to the increased stress, whereas the glucagon response is significantly impaired[8]. After long duration of diabetes the glucose recovery is severely impaired with an almost absent response of glucagon and epinephrine to hypoglycemia.[8] It therefore seems that glucagon is the most important counterregulatory hormone. This was also found in a study by Cryer and co-workers, who showed that in the presence of glucagon, growth hormone and epinephrine deficiency did not cause impaired glucose recovery after hypoglycemia[9] During glucagon deficiency epinephrine partly compensates

for the impaired glucagon response, making epinephrine the second most important glucose counterregulatory hormone[9].

In conclusion, a defective counterregulation in type I diabetes may be caused by hyperinsulinemia, which is related to the absorption characteristics of the different types of insulin and to the occurence of insulin binding antibodies, and by impaired secretion of counterregulatory hormones. Among the latter, defective glucose counterregulation is most pronounced with combined deficiencies of glucagon and epinephrine, glucagon being the most important whereas cortisol and growth hormone seem of minor importance[8].

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