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Comparison of Two Twice-Daily Insulin Regimens: Ultralente/Soluble and Soluble/Isophane

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Summary. The relative efficacy of two twice-daily insulin regimens using highly purified insulins, once daily Ultratard with twice daily Actrapid (ultralente/soluble) and twice daily Actrapid with twice daily Retard (soluble/isophane), has been studied in 12 diabetics in a cross-over study. Control was optimised as an out-patient, and assessed by in-patient 24 hour profiles. Similar day-time glucose control was achieved, but the mean overnight plasma glucose concentrations were more steady on ultralente/soluble (0100, 0300, 0500, 0700, 0800 h values 5.6, 5.3, 5.8, 7.8, 10.4 mmol/l) than on soluble/isophane (4.3, 3.4, 5.2, 7.5, 12.2 mmol/l). The minimum overnight plasma glucose concentrations were lower ($p < 0.05$) on soluble/isophane (mean 2.8 mmol/l) than on ultralente/soluble (mean 4.8 mmol/l), associated with higher ($p < 0.05$) nocturnal free plasma insulin levels after the evening soluble/isophane injection. The plasma glucose rise between 0700 and 0800 h was greater ($p < 0.05$) on soluble/isophane than on ultralente/soluble. The morning insulin injection should probably be taken immediately on rising, to prevent the pre-breakfast plasma glucose rise. The ultralente/soluble combination gave similar day-time plasma glucose control to soluble/isophane with less nocturnal hypoglycaemia.

Key words: Insulin therapy, hypoglycaemia, plasma insulin, diabetes control.

There is increasing evidence that improved blood glucose control might prevent the long-term complications of diabetes [1]. Once daily injections of insulin fail to provide an insulin "pulse" to cover the evening meal [2, 3]. A frequently used twice-daily regimen is a combination of soluble and isophane injections [4–7] with the morning soluble and isophane injections aiming to cover breakfast and lunch respectively, and the evening injections for the evening meal and the night respectively. An alternative insulin regimen is a constant basal insulin supplement with a long-acting ultralente insulin in order to provide normal basal plasma glucose concentrations, with additional twice-daily soluble insulin, before breakfast and before the evening meal, to cover meals [8]. To study the relative efficacy of the two insulin regimens, we have undertaken a cross-over study in insulin-requiring diabetics.

Patients and Methods

Fifteen insulin-dependent (Type 1) diabetic patients gave informed consent for the study, but subsequently three were unable to comply with the 24 h studies. All patients had presented before age 45 years, and had no measurable plasma C-peptide (< 0.06 nmol/l after meals). Their mean age was 41 years (range 21–65 years) and mean ideal body weight 108% (range 95–128%).

Ten patients had been treated with a soluble and isophane insulin regimen, and were initially studied on that regimen using the highly purified insulins Novo Actrapid MC and Nordisk Retard. Two were on other insulin regimens and were initially transferred to an ultralente and soluble insulin regimen, using the purified insulins Novo Ultratard MC and Actrapid MC respectively. The distribution of carbohydrates was adjusted according to the insulin regimens [8]. Patients took a series of blood samples four times per day at home (before breakfast, lunch, evening meal and before bed) using an Autolet [9], with blood samples taken into potassium fluoride vacuum collector bottles for laboratory blood glucose measurement [10]. The insulin doses or diet were altered after discussion with a doctor, aiming for < 7 mmol/l blood glucose. The patients were admitted for a 24 h study starting at 1730 h, with venous blood samples taken from an indwelling Teflon cannula. The patients were given their normal diet and insulin and remained ambulant, but took less exercise than normal.

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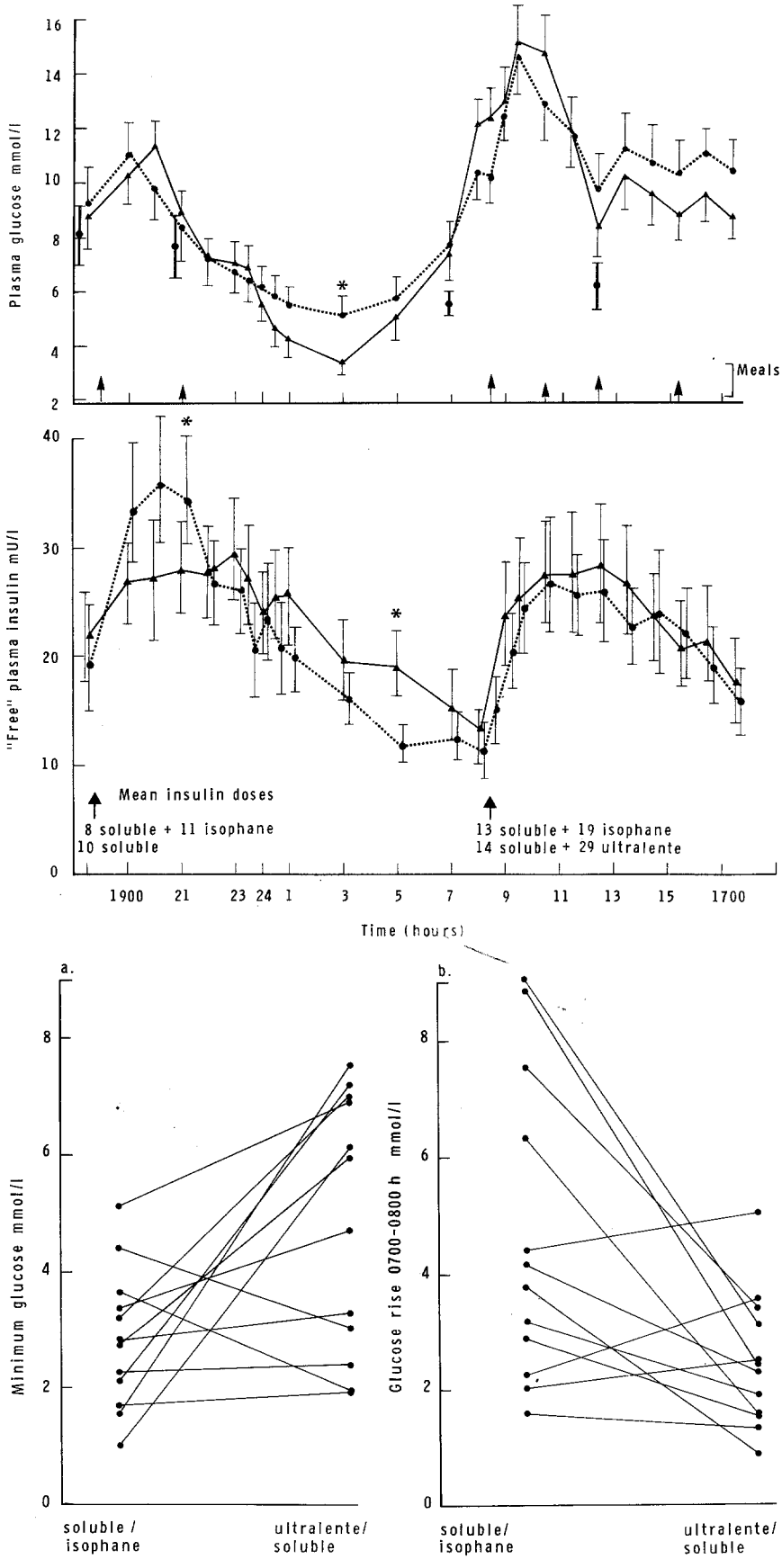

Fig. 1. Plasma glucose and plasma insulin concentrations during 24 h in-patient assessments on two insulin regimens in 12 subjects (mean ± SEM). ●·····● ultralente/soluble; ▲——▲ soluble/isophane; * $p < 0.05$ between regimens. Isolated points ● represent mean ± SEM capillary blood glucose at home in day-time series one week after the final in-patient study

Fig. 2. a Lower minimum nocturnal plasma glucose concentration on soluble/isophane than ultralente/soluble ($p < 0.05$ Wilcoxon). **b** Greater plasma glucose rise between 0700 and 0800 h, before the morning insulin injection, on soluble/isophane than on ultralente/soluble ($p < 0.01$ Wilcoxon)

The patients were then changed to the alternative regimen, with the ultralente dose initially chosen to equal two-thirds of the total daily isophane dose. Control was again optimised under out-patient supervision using the same criteria, before a further 24 h study. In four patients the 24 h study was repeated because unrepresentative nocturnal plasma glucose concentrations had been found in the first study (all > 20 mmol/l), whereas the home fasting blood glucose values had been < 7 mmol/l before and one week after the initial study.

Plasma samples were stored at −20 °C before assay. Plasma glucose was measured with glucose oxidase (Boehringer kit, GOD-perid), plasma C-peptide by charcoal phase separation [11] (precision, ± 1 SD, ± 0.02 nmol/l) using M1230 antiserum and labelled C-peptide kindly provided by Dr. Lise Heding. Plasma "free" insulin was assessed after polyethylene glycol precipitation [12] (precision, ± 1 SD, ± 1.0 mU/l). Plasma cortisol was measured by competitive protein binding assay [13]. Statistical methods used include Student's paired t-test, least-square linear correlation, and the Wilcoxon matched-pairs test.

Results

"Optimised" blood glucose control was obtained on soluble/isophane and on ultralente/soluble regimens after mean out-patient supervision periods of 8 months (mean 10 series of blood glucose measurements) and 9 months (mean 11 series) respectively. The mean (± SEM) values in the last three series were similar on the two regimens (mean before breakfast, lunch, evening meal and bed, 8.3 ± 1.0, 6.9 ± 0.4, 7.5 ± 0.8, 6.9 ± 0.8 mmol/l on soluble/isophane and 8.2 ± 0.8, 6.9 ± 0.7, 8.6 ± 0.8, 7.7 ± 1.0 mmol/l on ultralente/soluble respectively). On the two regimens, the mean daily dose of ultralente insulin (29 units) was similar to the two combined isophane insulin doses (30 units). The mean 24 h plasma glucose profiles on the study day on the two regimens in the 12 patients are shown in Figure 1. The plasma glucose concentrations during the day were similar. However, the minimum overnight plasma glucose concentrations were significantly lower on soluble/isophane (2.8 ± 1.2 mmol/l, mean ± 1 SD) than on ultralente/soluble (4.8 ± 2.2 mmol/l, $p = < 0.05$) (Fig. 2). There was a significantly greater rise ($p < 0.05$) of the plasma glucose between 0700 and 0800 h on the soluble/isophane compared with the ultralente/soluble regimen (Fig. 2), which did not correlate significantly with either a low minimum plasma glucose concentration or nocturnal plasma cortisol concentrations. There was thus no evidence for a "Somogyi" effect.

Discussion

The day-time control on the two regimens was similar. The main difference between the regimens was the greater nocturnal biochemical hypoglycaemia with soluble/isophane. Isophane has a shorter time course than ultralente, and on soluble/isophane near-normal pre-breakfast plasma glucose concentrations were achieved at the expense of higher nocturnal free plasma insulin levels and nocturnal hypoglycaemia. Subsequently the greater increase in plasma glucose from 0700 to 0800 h may be due to a decrease in insulin supply from the evening isophane injection [14], and the more steady plasma insulin levels from ultralente insulin may be advantageous. A similar, but less marked plasma glucose rise also occurs with a constant intravenous insulin infusion [15], and studies with a closed-loop insulin delivery system show that from 0600 to 0900 h diabetics require twice the previous basal insulin supply to maintain normal plasma glucose concentrations [16]. The pre-breakfast glucose rise might be aggravated by a regimen in which the plasma insulin levels are falling at the same time [14], and the evening isophane injection can be given later before bed [14, 17] to counteract its limited length of action. Equally in some patients the ultralente insulin might with advantage be given with the short-acting injection before the pre-evening meal rather than in the morning. The day-time could then be covered with a combination of short- and medium-acting insulins before breakfast [8], or by three subcutaneous insulin injections, possibly through a subcutaneously implanted needle [7].

The lesser activity during the in-patient study is one explanation for the higher day-time plasma glucose concentrations than with the home blood glucose measurements. An additional explanation is that during the in-patient study the insulin injection was delayed 1 h after the patients arose, and during this time the plasma glucose increased markedly, with little further increase following breakfast or lunch. At home most patients took their insulin immediately on rising, and the home pre-breakfast plasma glucose values were more similar to the in-patient profile 0700 than to the 0800 h values. Thus, it is probably important for patients to take their morning injection immediately on rising, to counteract the pre-breakfast increase in plasma glucose concentrations.

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