Miscibility of human lente insulin with soluble insulin

Dear Sir,

Using the euglycaemic clamp technique in healthy subjects Heine et al. [1] have recently shown that, in contrast to human NPH insulin, human lente insulin delays the onset of action of soluble insulin when mixed in one syringe even when the mixture is injected within one minute. These results are unexpected in the light of previous investigations showing that the rapid hypoglycaemic effect of the soluble insulin component is preserved when porcine lente insulin is mixed with porcine soluble provided the preparations are injected immediately after mixing [2]. Here we report the results of two insulin absorption studies which confirm the findings by Heine et al. [1] and a clinical observation which is in accordance with the miscibility of porcine lente insulin with porcine soluble insulin.

We have investigated the miscibility of 10 U Monotard HM and 10 U Actrapid HM (both Novo, Copenhagen, Denmark) measuring plasma insulin, blood glucose, and C peptide concentrations following the subcutaneous injection of the insulins into the thighs of eight healthy young men using methods and experimental protocols as described previously [2]. All subjects took part in the following four experiments in random order: (a) separate injection of the two insulins into contralateral thighs; (b) injection of the same insulins in identical ratios immediately after mixing them in one syringe as a single portion; (c) injection of the same insulin mixture immediately after mixing in two equal portions into contralateral thighs; (d) injection of the same insulin mixture five minutes after mixing in one syringe. The results of the study are shown in the figure. There is a significant loss of the initial steep rise of plasma insulin levels and a decrease of the initial hypoglycaemic effect when the two insulins are mixed in one syringe even when administered immediately thereafter. There is, however, no difference in insulin absorption kinetics whether the insulin mixture is injected as a single portion or divided into two equal portions. In another eight subjects following a comparable study protocol the expected miscibility of the human NPH insulin preparation Protaphan (Novo, Copenhagen, Denmark) with Actrapid HM was documented (data not shown).

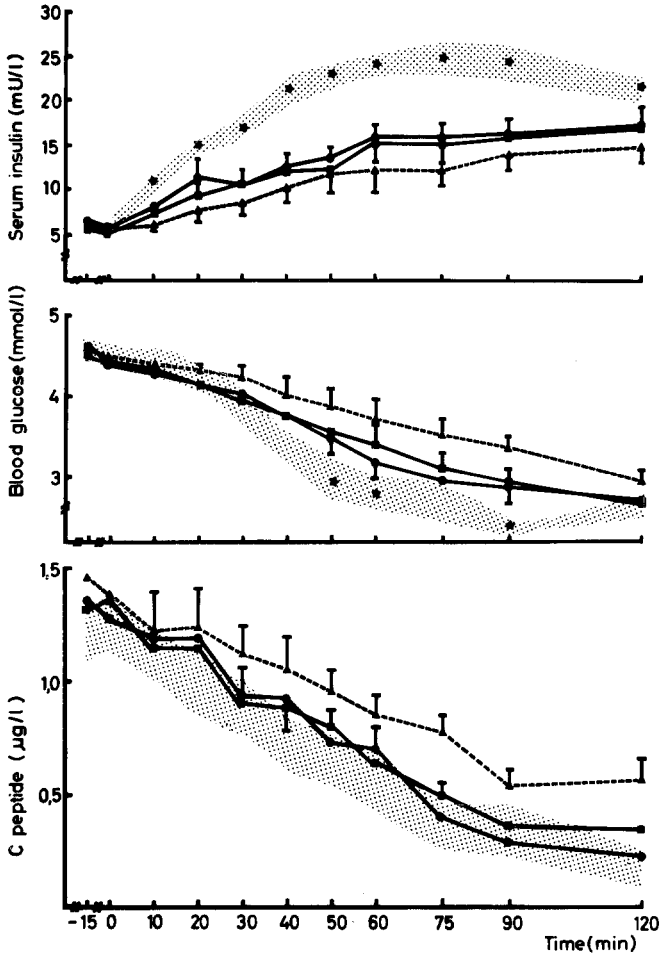

Fig. 1. Effect on circulating concentrations of insulin, glucose, and C peptide of subcutaneous injection of 10 U Monotard HM and 10 U Actrapid HM into thighs of eight non-diabetic men. Shaded area represents mean ± SEM of control tests (separate injection of the two insulins); ●—● injection of both insulins immediately after mixing as a single portion; ■—■ injection of both insulins immediately after mixing divided into two equal portions; ▲--▲ injection of both insulins five minutes after mixing as a single portion. Asterisks mark significant difference between experiments with immediate injection of the insulin mixture and control experiments

In a clinical study 76 unselected type 1 diabetic patients (age 27 ± 10 years, median duration of diabetes 8 years) were reexamined 14 ± 2 (mean ± SD) months after their participation in our teaching and treatment programme following a protocol previously described [3]. There was no difference between patients treated during the follow-up period with individually adjustable mixtures of porcine NPH (Insulatard) and porcine soluble insulin (Velosulin, both Nordisk, Copenhagen, Denmark; n = 31) and those treated with porcine lente (Monotard MC) and porcine soluble insulin (Actrapid MC, both Novo, Copenhagen, Denmark; n = 36) with respect to the total daily insulin dose (0.72 ± 0.19 U/kg/day and 0.68 ± 0.23 U/kg/day respectively), the proportion of soluble insulin thereof (32 ± 15% and 36 ± 14% respectively), improvement of HbA_{1c} (from 9.9 ± 1.8% to 9.5 ± 1.7% and from 10.4 ± 1.4% to 9.2 ± 1.7% respectively) nor with respect to the incidence of severe hypoglycaemic episodes during follow-up or any other parameter of relevance as described previously [3], thus supporting the equal clinical efficacy of porcine NPH and porcine lente insulin when mixed with soluble insulin.

These data confirm (1) that, in contrast to human NPH insulin, human lente insulin cannot be mixed with soluble insulin in one syringe without loosing the rapid hypoglycaemic effect of the soluble insulin component, and (2) porcine lente insulin can be mixed with soluble insulin when injected immediately after mixing. However, the reasons for the apparent differences in the miscibility of human and porcine insulins remain obscure.

Yours sincerely,
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References

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