Clinical Pharmacology of Human Insulin

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Nowadays, human insulin is used daily by millions of diabetic patients. The biological effect of human insulin is comparable to that of porcine insulin. However, after subcutaneous injection, pharmacological and clinical studies showed pharmacokinetic and pharmacodynamic differences between human and animal insulins. Human insulin tends to have faster absorption and shorter duration of action compared with animal insulin. These differences are more pronounced and can be of clinical relevance with intermediate- and long-acting insulin preparations. Optimal metabolic control can be achieved with either human or highly purified animal insulin preparations, provided appropriate insulin replacement strategies are used.

The development of manufacturing techniques for human insulin has made it possible to treat IDDM patients with a hormone that has an amino acid sequence identical to endogenous insulin. After characterization of the biological activity of human insulin in vitro and in animal studies, a series of efficacy and safety trials with human insulin in humans was performed (1,2). In the first years, several studies compared the potency of human insulin and animal insulin preparations with regard to their pharmacological properties. Later, such studies were performed to compare human insulin preparations manufactured using different methods (3,4).

It is surprising how much of the literature on human insulin, including proceedings of commercially sponsored symposia as well as papers and reports published in books and supplements to well-known journals, was printed 10 years ago, all non-peer-reviewed, compared with the number of original papers published on human insulin that have passed a peer-review system. This is disturbing, because pharmacological differences between human insulin and animal insulin might have practical implications for the daily therapy of millions of patients.

In this paper, we will review the properties of human insulin preparations available today for clinical practice. Furthermore, we will describe the pharmacological differences between human insulin and highly purified (monocomponent) insulin preparations of animal origin. We attempt to give a balanced overview of the results of all studies, comparing various pharmacological aspects of human insulin and animal insulin. As a result, it was necessary to quote papers that were not peer-reviewed.

A major emphasis of this review is the presentation of the time-action profiles of the most widely used human insulin preparations. A mere discussion of differences between human insulin and animal insulins would be somewhat out of date, because, in many countries, human insulin is already used by most patients.

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

STRUCTURE, PRODUCTION, PURITY, AND POTENCY OF HUMAN INSULIN

Structure

The structure of animal insulin has minor but potentially important differences from human insulin: Porcine insulin differs by one amino acid (alanine instead of threonine at the carboxy-terminal of the B-chain, i.e., position B30), and beef insulin differs by two additional alterations of the sequence of the A-chain (threonine and isoleucine on positions A8 and A10 are alanine and valine). Thus, there is nearly a complete homology between human insulin and porcine insulin in the amino acid sequence.

None of the differences between human insulin and animal insulins is thought to be at sites crucial to the binding or action of insulin. Therefore, it could be expected that the receptor binding and cellular interactions of human insulin would not differ significantly from those of pork or beef insulin (2). The amino acid on position B30 is near one of the parts of the insulin molecule thought to be involved in the self-association of two insulin molecules into dimers. Thus, the self-association tendency could be different between human insulin and porcine insulin (5).

The physicochemical properties of human, pork, and beef insulins differ somewhat because of their different amino acid sequence. Threonine adds

one extra hydroxyl group to the human insulin molecule. This increases its hydrophilic properties and decreases the lipophilic properties, as compared with that of porcine insulin. Thus, the solubility of human insulin in aqueous solutions is higher than that of porcine insulin.

Production

One way to mass produce human insulin was to exchange alanine in position B30 of porcine insulin with threonine, using an enzymatic-chemical method (semi-synthetic technique) (6). During the last decades, biosynthetic production of human insulin was made possible through advances in genetic engineering, especially in recombinant DNA technology (7,8). Methods used to produce human insulin have changed considerably during the last decade. At the end of the 1980s, the semi-synthetic production of human insulin was essentially stopped and replaced by biosynthetic production. In the beginning of the biosynthetic production of human insulin, the A and B chains were produced separately and had to be combined. At present, biosynthetic human insulin is produced with a perfect three-dimensional structure; that is, all foldings and disulfide bridges of the insulin precursor produced by the bacteria or yeast cells are identical to endogenous insulin. The correct spherical structure is important for the insulin-insulin receptor interaction, and hence for the biological action of insulin. Porcine insulin has a slightly different three-dimensional structure when compared with human insulin (9).

Purity

To ascertain a low immunogenicity of human insulin preparations, impurities had to be avoided. The semi-synthetic human insulin production could take advantage of the well-established production and purification methods for porcine insulin, which was used as the original substrate. Possible contaminations with proinsulinlike or glucagonlike substances, pancreatic polypeptide, somatostatin, and vasoactive intestinal peptides were avoided by using monocomponent porcine insulin. Contamination by enzymes or waste products, as a result of the enzymatic-chemical exchange of one amino acid during the secondary production step, also could be avoided (10). In contrast, the insulin production methods that use recombinant DNA technology have a higher propensity for contamination of the insulin product with various bacterial or yeast cell polypeptides. The first biosynthetic human insulin production using bacteria had more obstacles in achieving purity, attributable to the fact that the A-and B-chains had to be extracted separately, and the two chains had to be combined with an intact insulin molecule. Thus, proteins and other substances of bacterial origin, as well as waste products of the insulin recombination, had to be eliminated. Later, purification methods were developed to obtain insulin preparations free of any potentially harmful contamination by *Escherichia coli*-derived peptides (11–13). Antibodies to such peptides could not be detected in 10 patients treated with human insulin for 6 mo (12). Some of the problems of the recombinant DNA technique were circumvented when it became possible to produce homologous proinsulin by *E. coli* (13). Thus, only the C-peptide-like sequence had to be cleaved to achieve human insulin. Human insulin produced biosynthetically from yeast cells with a different insulin precursor (not identical to human proinsulin) was even easier to clear from impurities because the precursor is secreted into the medium, and after cleavage of C-peptide, the intact molecule can be obtained (14,15). Because of the sophisticated purification techniques, it can be assumed that advanced human insulin preparations are pure and free of any significant contamination (16). In regular insulin preparations, insulin molecules self-associate to dimers and large oligomers. In addition, a small amount of covalently aggregated dimers and other insulin-transformation products is formed in commercial insulin. These transformation products prevail in the blood of insulin-treated diabetic patients because they have a slower metabolic clearance relative to insulin monomers (17–19). Human insulin was reported as more susceptible to the production of such products than beef insulin (19). These transformation products are claimed to be highly immunogenic. In addition, degradation of the injected insulin occurs in the subcutaneous depot, resulting in degradation products that also might have immunogenic activity (20).

It has to be emphasized that even with a hormone identical to the human insulin, there are still major differences compared with the naturally occurring hormone. The route of insulin administration is different, and the insulin preparations contain additives like antiseptics, stabilizers, and, with NPH-insulins (Isophane), xenomorphous proteins like protamine.

Potency

In the first study that reports the effects of short-acting human insulin produced by recombinant DNA technology in healthy men, the plasma glucose decrement after subcutaneous injection of human insulin was similar to that of highly purified porcine insulin (21,22). The potency of semi-synthetic human insulin or biosynthetic human insulin also was reported to be similar to that of animal insulin after intravenous insulin infusion at various doses or after subcutaneous injection in diabetic patients (2).

In the rabbit hypoglycemia bioassay, used to estimate insulin strength, porcine and human insulin also had a similar potency (11,23). However, in this model, human insulin showed a more rapid onset and a shorter duration of action, along with a lower potency, compared with bovine insulin (23). Most investigators came to the conclusion that there is no difference in the biological potency of human insulin and animal

insulins (1,2). However, this seems to apply only for the intravenous route and not for subcutaneously injected insulin. Differences in the absorption properties of human insulin and animal insulins, and the results of clinical studies (see below), led to the suggestion that the daily dose of insulin should be reduced by 10 to 25% when switching from animal insulin to human insulin (24). Such a dosage reduction may be needed especially in those patients previously treated with bovine insulin or with mixed animal insulins.

The *British Pharmacopoeia; Codex medicamentarius* and the *Pharmacopeia of the United States* permit deviations from the declared concentration of commercial insulins of ± 5 and ± 10%, respectively. Thus, it cannot be excluded that some of the differences in the reported potencies could be attributable to variations in insulin dose.

HUMAN INSULIN PREPARATIONS

Shortly after its introduction human insulin became available in short-, intermediate-, and long-acting formulations. In principle, these formulations are identical to their porcine or bovine counterparts with respect to the content of auxiliary substances. Because most brands with animal insulins are still available, clinicians and patients are faced with a plethora of different insulin preparations. Even professionals find it difficult to keep track of the insulin preparations available in different countries, because various names may be used for the same insulin with different compositions and concentrations. Some of the insulin preparations marketed are of questionable usefulness, for example, mixtures of short- and intermediate-acting human insulin in 10% steps ranging from 10%:90% to 50%:50%. However, this comment should not be misinterpreted as a suggestion to withdraw animal insulin preparations from the market altogether. Some manufacturers of insulin have tried to withdraw animal insulins from the market (and some have actually done so). This is understandable from a commercial point of view (standardization of production). However, because human insulin has no clear clinical benefit, animal insulins should stay available.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF HUMAN INSULIN PREPARATIONS

Methods used to study the pharmacological properties of insulin preparations

In many studies investigating insulin absorption (pharmacokinetic studies) and/or insulin action (pharmacodynamic studies), inappropriate methods, different doses, and sites of administration have been used. This makes the comparison of the results difficult. In some studies, the diabetic patients investigated had been previously treated with animal insulins. As a result, these patients might have had insulin antibodies, which might have influenced the pharmacological properties of exogenous insulin preparations. In fact, the variable dissociation rates of insulin from circulating antibodies are likely to contribute to the high variability in the bioavailability of any insulin preparation.

In principle, the pharmacokinetic properties of insulin preparations could be studied using the direct method (i.e., measurement of serum insulin concentration) or an indirect method (i.e., injection of radiolabeled insulin and registration of the disappearance from the subcutaneous tissue). The problems and pitfalls that limit the use of the indirect method have been discussed in detail elsewhere (25).

Pharmacodynamic properties can be studied by following the blood glucose-lowering effect of a subcutaneous insulin injection over time. This test of insulin activity results in a stimulation of the counterregulatory response caused by hypoglycemia. The effect of the counterregulatory hormones tends to increase blood glucose, thereby leading to an underestimation of the response to the injected insulin. Thus, relevant pharmacodynamic differences can only be detected if doses or activities of the insulins investigated are substantially different. To avoid hypoglycemic episodes, blood glucose can be kept constant by an intravenous glucose infusion targeted to maintain blood glucose at normoglycemic values (euglycemic glucose clamps). Because the glucose requirement is proportional to the biological activity of insulin, it provides a direct measure of potency, at least with regard to glucose metabolism. Endogenous insulin secretion in healthy volunteer subjects can be suppressed by a low-dose intravenous insulin infusion. In our opinion, the euglycemic glucose clamp technique is the best method currently available to study pharmacodynamic properties of various insulin preparations. Moreover, pharmacokinetic properties can be studied simultaneously (2,26,27)

A recent survey of the literature showed that time-action profiles of many insulin preparations are not well-defined because different methods, patient-selection criteria, insulin doses, methods of insulin administration, insulin concentrations, and injection sites are used (28). This survey also highlights the large differences in the reported pharmacological properties of the same insulin preparations caused by the method used. For example, in the 22 studies analyzed, the onset of action after subcutaneous injection of human regular insulin ranged from 0.08–0.5 h, with peak action from 0.75–4 h, and duration of action from 4–12 h.

The direct comparison of pharmacokinetic and pharmacodynamic results obtained with the same group of volunteer subjects showed a considerable difference between the insulin concentration-time profile and the glucose infusion rate-time profile. Thus, an increase in serum insulin concentration does not result in an instantaneous increase in glucose metabolism (Fig. 1).

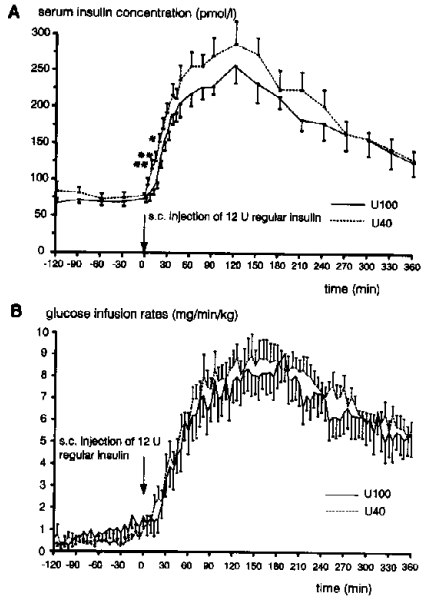

Figure 1—A: *Serum insulin concentrations during an 8-h euglycemic glucose clamp in 8 normal subjects. A subcutaneous injection of 12 U of regular human insulin was given at time 0, with a U40 formulation (mean + SE) on one day and a U100 formulation (mean − SE) on another day. Asterisks mark significantly different serum insulin concentrations.* *, $P < 0.05$; **, $P < 0.02$; *paired Student's t test) (55);* B: *Glucose infusion rates on the U40- (mean + SE) and on the U100- (mean − SE) insulin injection day.*

This phenomenon becomes more clear in view of more recent studies about the importance of the endothelial barrier on insulin transport across the capillary wall (29,30). A long series of events is interposed between the appearance of insulin in blood and changes in glucose metabolism. Thus, the time-dependent characteristics used to describe the pharmacological characteristics of insulin preparations have to be different for its kinetic and dynamic properties.

Short-acting preparations

Pharmacological studies. Pharmacokinetic properties of short-acting human insulin individually assessed by decline of radioactivity of subcutaneously injected ^{125}I-labeled insulin showed a similar insulin absorption process of human and porcine insulin (31,32). However, in another study with the same method, human insulin was more rapidly absorbed than porcine insulin (33). Administration of human or porcine insulin by intravenous bolus in healthy volunteer subjects and IDDM patients showed that both insulins have similar biological activities (34). In studies with intravenous infusion of human or porcine insulin, plasma insulin concentrations and metabolic effects were comparable and strictly dose dependent (35–37). Combining intravenous insulin infusion with the euglycemic clamp technique showed that the pharmacodynamic properties of semi-synthetic human insulin and porcine insulin were indistinguishable in normal individuals as well as in diabetic patients (26,38–40).

The appearance of human insulin in plasma after subcutaneous injection was more rapid than after a similar dose of porcine insulin (32,33,41–43). However, no dose-dependent changes in pharmacokinetic parameters could be demonstrated after a subcutaneous insulin injection measuring blood glucose decline (21,44).

Measurement of the time-action profile of short-acting human insulin after its subcutaneous injection by the glucose clamp technique showed a more rapid onset of action and an earlier peak action than after injection of porcine insulin in healthy volunteer subjects as well as in IDDM patients (42).

In summary, in 11 of 16 studies analyzed, the authors concluded that human insulin was absorbed slightly faster from the subcutaneous injection site, independent of its semi-synthetic or biosynthetic origin (3,22,32,33,41–43,45–48). No difference in insulin absorption kinetics was seen in five studies (31,44,49–51). The mechanism of the faster absorption of human insulin in comparison to pork-regular insulin might be explained by the greater hydrophilicity of the human insulin molecule (9). X-ray studies of the tertiary structures of human and porcine insulin show differences only at the B30 region, where changes in the water attraction are located. Another explanation for the faster absorption of human insulin was the influence that the amino acid in position B30 has on the strength by which the dimers are held together within the hexamer (5). The changed solvent structure in the B28-B30 region and alterations in the intermolecular contacts have a weakening effect on the hexamer stability, resulting in a greater tendency to dissociate with decreasing concentration of insulin (5,9).

Clinical studies. In double-blind crossover studies in type I diabetic patients, treated either conventionally or with subcutaneous insulin infusion, blood glucose control, insulin requirement, and number of hypoglycemic episodes were not substantially different between human insulin and porcine insulin (46,52,53). However, in one double-blind study in 21 diabetic children who were in poor metabolic control, significantly higher HbA_1 values were reported during the treatment period with human insulin, compared with that with porcine insulin (15.7 ± 2.3 vs. 14.2 ± 2.3%; $P < 0.01$) (54).

Time-action profile and influence of insulin concentrations. Studies of short-acting human insulin in different concentrations (U40 vs. U100; Actrapid HM, Novo/Nordisk, Bagsvaerd, Denmark) found the onset of action occurred within 15–30 min, and peak action was observed 150–180 min after subcutaneous injection of 12 U (Fig. 1*B*) (55). No significant differences were observed in the glucose infusion rates needed to keep blood glucose constant after injection of insulin, with either U40 or U100 concentrations. However, serum insulin concentrations showed small but significant differences shortly after injection (Fig. 1*A*): Serum insulin concentrations were significantly higher 10–20 min after injection of the U40 formulation in comparison with the U100 formulation.

However, glucose infusion rates during this time were not significantly different. In this experiment, 6 h after injection of a moderate dose of "short-acting" insulin, still more than 50% of maximal glucose infusion rates were needed to keep blood glucose concentration constant. Therefore, compared with the endogenous insulin response to a meal, onset of action and peak action occurred considerably later. In addition, duration of action was longer, requiring consumption of a snack 2–3 h after insulin injection to prevent hypoglycemia. Moreover, it has to be emphasized that considerable deviations from the described time-action profile can occur depending on the subject's insulin sensitivity (i.e., in diabetic patients, depending on the degree of metabolic control or depending on the insulin doses used).

Clinical implications. Rapid initial delivery of insulin plays a crucial role in the control of meal-related glycemic excursions. Thus, the more rapid onset of action of human insulin might have an advantage over short-acting animal insulins. It was shown in two studies that subcutaneously injected human insulin was superior to porcine insulin in the control of meal-related glycemic excursions in IDDM patients (48,56). In another study with IDDM patients, no differences in postprandial glycemic excursions could be demonstrated (51). The preprandial glucose levels were elevated in this study (>13.5 mM), and, therefore, prandial glycemic increases were small, ranging from 0–4.4 mM. In this context, the slightly faster absorption of human insulin did not result in clinically important differences.

Obviously, the pharmacodynamic characteristics of human short-acting human insulin are far from ideal. In other words, the time-action profile of these preparations differs considerably from the prandial insulin requirements. Development of short-acting insulin analogues with a significantly faster onset of action might help to improve prandial control (5,57,58).

Intermediate-acting preparations (NPH and lente)

Pharmacological studies. Intermediate-acting human insulin preparations injected subcutaneously showed variable results in pharmacological studies when compared with their animal insulin counterparts. No differences in the decline of blood glucose concentrations after injection of biosynthetic human insulin or porcine insulin could be observed in the first pharmacodynamic study with NPH insulins (44). However, NPH insulins with human insulin showed a more rapid onset and shorter duration of action than corresponding animal insulins in a series of later pharmacological studies (4,27,41,59,60). In contrast to these results, the disappearance rates of ^{125}I-labeled human or porcine NPH insulin preparations were not significantly different when given to diabetic patients (32,61).

The differences in the pharmacological properties were attributed to the more hydrophilic properties of human insulin and to differences in the interaction of human insulin and animal insulin with protamine (41). Also, formulation differences, such as the nature and quantity of the protamine in the formulas used were implied.

Direct comparison of semi-synthetic and biosynthetic human NPH insulin after injection in healthy volunteer subjects showed a similar maximal hypoglycemic effect within 3–5 h after administration (4). Thereafter, with semi-synthetic NPH insulin, plasma glucose remained significantly lower than with biosynthetic NPH insulin. These results suggested that the biosynthetic human NPH insulin had a less potent glucose-lowering effect and a relatively shorter duration of action compared with semi-synthetic NPH insulin.

Comparison of human protamine-sodium insulin with human NPH insulin in normal subjects during a euglycemic clamp showed a slightly earlier peak in plasma insulin concentrations with the protamine sodium insulin and a longer duration of action with the NPH insulin (62). In a disappearance study in diabetic patients, human NPH insulin showed a decline of radioactivity similar to the Monotard (Monotard MC, Novo/Nordisk) (61). A semi-synthetic human insulin preparation (Monotard HM, Novo/Nordisk) showed similar disappearance rates compared with a porcine lente preparation in 11 IDDM patients (31). In accordance with this, no significant differences were found in serum insulin concentrations between human and porcine Monotard in short-term studies with healthy volunteer subjects (41,46).

Clinical studies. In the first clinical trial with diabetic patients, significantly higher blood glucose levels were observed with human insulin before the morning and evening injection compared with the levels when treated with animal insulin. This was attributed to a more rapid absorption of the human NPH insulin (63). In a 15-mo double-blind crossover study, Home et al. (64) found a small but significant difference in the metabolic control between human and porcine insulin in 96 insulin-treated diabetic patients. The fasting blood glucose concentration and HbA_1 were significantly higher with human insulin than with porcine insulin (11.1 vs. 9.3 mM and 11.7 vs. 11.1%, respectively). A short-term double-blind crossover study in 8 IDDM patients, comparing human with porcine lente insulin, resulted in no differences in blood glucose control (31).

Thus, the use of human NPH insulin instead of animal NPH insulin could be a disadvantage. This finding was tested by another 6-mo double-blind, crossover study in 22 IDDM patients, which resulted in similar 24-h blood glucose profiles, fasting blood glucose levels, HbA_{1c} levels, number of hypoglycemic events, and insulin-dose requirements when using semi-synthetic human NPH insulin and porcine NPH insulin (65). The authors discuss the possibility that it might be of clinical importance whether semi-synthetic or

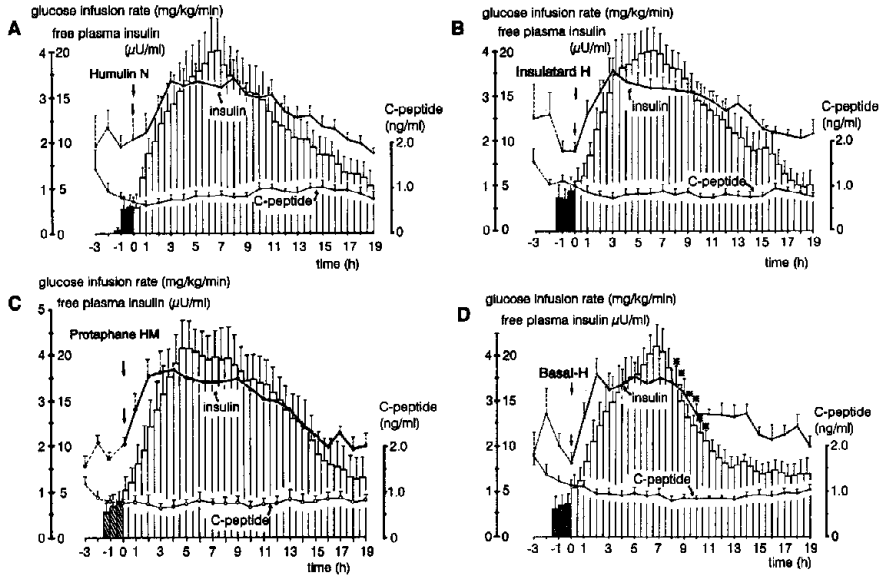

Figure 2—*Glucose infusion rates (□), plasma free insulin (– – –), and C-peptide (———) concentrations after subcutaneous injection of 12 U of 4 different human NPH insulin formulations (biosynthetic origin: Humulin N [A], Lilly, Indianapolis, IN; semi-synthetic origin: Insulatard H [B] and protaphane HM [C], Novo/Nordisk; Basal H-Insulin [D], Hoechst AG, Frankfurt/Main, Germany; all U40) at time 0 during 19-h euglycemic glucose clamps in 6 normal subjects. (▨), Basal glucose infusion rate, expressed as means + SD. *, Significantly different glucose infusion rates of Basal-H human insulin as compared with the other NPH insulins (P < 0.05; ANOVA and Student's t test [67]).*

biosynthetic human NPH insulin preparations are used.

Time-action profile. Human NPH insulins were absorbed at a faster rate than human zinc insulins (lente insulin) in an euglycemic clamp study over 8 h with healthy volunteer subjects. The result was an increased metabolic effect within the first 4 h after injection (66). Thus, early after injection, the metabolic effects of human NPH and human zinc insulin preparations are different from each other.

The time-action profiles of four widely used human NPH insulin preparations were investigated in healthy subjects using the euglycemic clamp technique (Fig. 2) (67). The overall time-action profiles were interchangeable. The onset of action (defined as half-maximal action) of all NPH insulins tested was within 2.5–3 h, with peak action after 5–7 h, and duration of action (defined as >25% of maximal action) between 13–16 h. This study showed that there are no clinically important differences in the duration of action of human NPH insulins from different insulin manufacturers.

Clinical implications. The more rapid absorption and shorter duration of action of intermediate-acting human insulin preparations have clinical implications. Injecting human NPH insulin before dinner instead of at bedtime might impair metabolic control during the night. Higher fasting blood glucose concentrations in the morning, attributable to a waning of insulin action, have been observed in diabetic patients using human NPH insulins compared with porcine NPH insulins (54,63).

Use of NPH insulin and long-acting insulin preparations. The problem of elevated fasting blood glucose concentrations when human NPH insulin was used as the evening injection led to trials in which the evening injection was moved to bedtime, or long-acting human insulin preparations (Ultratard HM) were used. Fasting blood glucose concentrations were significantly lower when the evening dose of human NPH insulin was given at bedtime instead of at dinner (7.5 ± 1.1 vs. 10.0 ± 1.6 mM; $P < 0.02$) (68). Human ultralente insulin injected at bedtime, with its longer duration of action, resulted in lower fasting blood glucose concentrations compared with human NPH insulin (69,70).

In a crossover, randomized double-blind trial of 82 IDDM patients, the use of human lente (Monotard HM, Novo/Nordisk) or NPH insulin, given twice daily in combination with regular human insulin, resulted in comparable metabolic control (71). With both regimens, the major problem was elevated blood glucose concentrations before breakfast (NPH insulin versus lente insulin: 8.8 ± 0.5 vs. 9.0 ± 0.5 mM, NS). Thus, the use of human lente insulin instead of NPH insulin does not appear to result in better metabolic control during the night.

In the above study (and others quoted), the diabetic patients mixed the regular insulin with the lente insulin immediately before the injection. It is well known that this procedure results in modifications of the time-action profile of regular insulin (see below).

Long-acting human insulin preparations

Ultralente insulin preparations made with bovine or porcine insulin have a different pharmacokinetic profile from those made with human insulin (72,73). It is known that human zinc insulin crystals bind water more avidly than pork insulin crystals. It may be that this causes a faster dissociation of those zinc insulin complexes (2,9). Thus, a better solubility of the crystals of the human insulin ultralente preparations compared with

those of bovine insulin could possibly explain the faster absorption (74).

Pharmacological studies. The ultralente formulation with bovine insulin does not show a peak action. Its long duration of action lasts up to 32 h (72,73,75). In contrast, the human ultralente insulin preparations show a peak of action after 8.5 h (73). In one study, the duration of action of human ultralente was reported to be no shorter than that of bovine ultralente (73).

Hildebrandt et al. (74) reported that human ultralente had a substantially faster absorption than bovine ultralente, when comparing the disappearance rates of ^{125}I-labeled insulin preparations at different doses in IDDM patients. The faster absorption of human ultralente compared with bovine was confirmed in healthy volunteer subjects by measuring blood glucose decline after injection (72).

A comparison between a human insulin zinc suspension (Humulin Zn, Lilly), which was entirely crystalline in its formulation (like ultralente), and the intermediate-acting porcine lente insulin zinc suspension (Monotard MC, Novo/Nordisk; 30% amorphous and 70% crystalline formulation) showed no differences in the duration of hypoglycemic action in a single-dose crossover study in 10 healthy men (76).

Clinical studies. Ultratard HM was studied in a double-blind crossover study in 18 insulin-treated IDDM and NIDDM patients and found to be as effective as bovine ultralente in controlling basal plasma glucose with once-daily morning injections (77). The authors concluded that Ultratard HM is suitable for meeting basal insulin requirements in diabetic patients. In this study, there was no indication that Ultratard HM has a faster absorption from subcutaneous tissue than bovine ultralente.

Time-action profile. The variable results of the pharmacological and clinical studies do not provide a definite answer to the clinically important question of whether the duration of action of human ultralente falls between that of intermediate-acting and long-acting insulin, or whether it is similar to that of long-acting insulin.

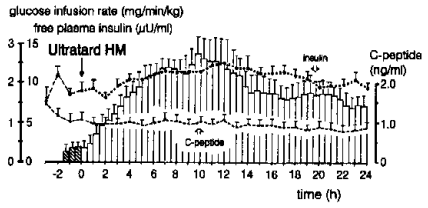

Figure 3—*Glucose infusion rates (□), plasma free insulin (– – –), and C-peptide (———) concentrations after subcutaneous injection of 12 U of a human lente insulin formulation (Ultratard HM) at time 0 during 24-h euglycemic glucose clamps in 7 normal subjects. (▨), Basal glucose infusion rates; means + SD (78).*

A study of the time-action profile of Ultratard HM using the euglycemic clamp technique (injection of 12 U in healthy subjects) revealed that peak action (reached after 10 h) was two-thirds that of a NPH insulin (Fig. 3, in comparison to Fig. 2*c*) (78). With both insulins, after 20 hours free plasma insulin concentrations had returned to basal values and glucose infusion rates indicated that the metabolic effect had nearly returned to basal values. Thus, the duration of action of human ultralente is not considerably longer than that of NPH insulin.

Clinical implications. Thus, once-daily injections of Ultratard HM in the given dose (12 U) will not provide sufficient basal insulinemia during the whole day. Twice-daily injections of human ultralente insulin are necessary to achieve basal insulin requirements.

Clinical trials showed that such an insulin regimen resulted in lower fasting blood glucose concentrations than twice-daily injections of human lente insulin (79,80). If only once-daily injection of human ultralente was used, injection in the morning resulted in a higher fasting blood glucose concentration than injection at bedtime (81,82). In a study of IDDM patients that used a multiple-injection regimen to compare human isophane insulin with human ultralente at bedtime, blood glucose at 0800 was significantly lower with isophane insulin than with the ultralente preparation (10.2 ± 1.2 vs. 14.3 ± 1.3 mM); although the dose of the bedtime ultralente insulin injection (0.35 U · kg^{-1} · day^{-1}) was significantly higher than the dose of isophane insulin (0.25 U · kg · day^{-1}; $P < 0.005$) (83).

Treatment with a once-daily injection of human ultralente over a period of 6 mo resulted in a significant improvement in metabolic control (a drop in HbA_{1c} from 13.2 to 10.6%) in 22 NIDDM patients with secondary sulfonylurea failure (84). However, there were frequent episodes of hypoglycemia. In the same study, 10 patients who were receiving once-daily injections of a bovine lente insulin preparation showed a similar improvement in metabolic control (from 13.1 to 11.2%), but the frequency of hypoglycemic episodes was significantly lower. In this study, the pharmacodynamic properties of human ultralente in comparison with the more flat action profile of bovine lente insulin are clearly unsuitable as a single-daily injection in NIDDM patients when aiming at improved metabolic control.

In contrast to the comment we made regarding the shorter duration of action of human NPH insulins, no clinical disadvantage could be seen with the shorter duration of action of human ultralente compared with its bovine counterpart. For example, we do not recommend use of bovine ultralente to our patients because of the prolonged duration of action, which potentially could cause an overlapping interaction between the metabolic activity of the insulin of the current injection and that of the previous day. This unpredictable accumulation of insulin action can result in prolonged and severe hypoglycemias. Moreover, the patient cannot adapt the dose to changing insulin needs, for example, when exercise is planned. Thus,

the shorter duration of action of human ultralente appears to be an advantage and not a disadvantage in clinical practice.

Miscibility. One problem of Ultratard (and other human lente insulin preparations) is that it cannot be premixed with short-acting insulins in one syringe without a considerable change in the time-action profile (i.e., a retardation of the onset of action of the short-acting insulin). This effect is pronounced even when the mixed human lente insulin preparations are injected immediately after being drawn into the syringe (25,85–88). This delay is caused by a binding of the added regular insulin to zinc, present in excess in the ultralente (and lente) insulins, which results in an amorphous precipitation of zinc insulin. Mixing of human regular and NPH insulin does not result in blunting of the action of the soluble component, regardless of whether it is readily mixed or premixed (3,89).

Another problem with ultralente insulin preparations is the high variability of its insulin bioavailability after injection, a phenomenon well known to the clinician. However, data showing this variability are only available for bovine ultralente (75,90), and, to our knowledge, no formal investigations of this aspect have been published for Ultratard.

EFFECT OF HUMAN INSULIN ON INTERMEDIARY METABOLITES AND LIPID METABOLISM—

In vitro studies with insulin receptors from human lymphocytes, as well as measurements of lipid metabolism in rat adipocytes and hepatocytes, showed that the biological actions of biosynthetic human insulin and porcine insulin were identical (91,92). Injection of 0.075 U/kg of either human insulin or porcine insulin by intravenous bolus were reported to result in differences in intermediate metabolites and counterregulatory hormones (93). However, no statistical analysis was given and the reported differences appear to be small. Effects on intermediary metabolite concentrations (blood lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate) were similar after subcutaneous injection of human insulin, porcine, and bovine insulin (49,50), or during euglycemic clamp studies with intravenous infusion of human insulin or porcine insulin (26,38, 39,94).

Although, the initial studies showed differences in hepatic action between human insulin and porcine insulin (21), this was not confirmed in later turnover studies. Suppression of hepatic glucose production and stimulation of peripheral glucose utilization were basically identical with human insulin and porcine regular insulin (94)

CONCLUSIONS— Human insulin preparations of both biosynthetic and semi-synthetic origin have similar, but not identical, pharmacological properties when compared with purified porcine insulin. Pharmacodynamic differences between human insulin and animal insulin preparations in clinical pharmacology are small with short-acting insulin preparations, considerable with NPH insulins, and substantial concerning long-acting insulin preparations. Development and introduction of human insulin has not revolutionized insulin treatment of IDDM patients. Obviously, the change from animal to human insulin per se does not improve metabolic control.

The choice of insulins with appropriate pharmacological characteristics, purity, and origin of the insulin preparations are important prerequisites for optimal therapy. A successful insulin regimen must consider insulin replacement strategies that are appropriate for the patient's lifestyle and individual treatment goals (95–97). And, most important, the patients must receive instruction on the time-action profiles of the insulins they use, and information on how to adapt the doses to achieve good metabolic control while avoiding hypoglycemic episodes.

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