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Editorial

Human insulin: much ado about hypoglycaemia (un)awareness

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Summary. The biological effects, hypoglycaemic symptoms, endocrine counterregulatory responses and glucose recovery following the injection of purified porcine and human insulin preparations were compared in a number of controlled clinical investigations and prospective clinical trials. In these studies involving healthy volunteers, Type 1 (insulin-dependent) diabetic patients on continuous subcutaneous insulin infusion or intensified conventional insulin therapy and insulin treated Type 2 (non-insulin-dependent) diabetic patients, no differences with regard to biological effects, counterregulatory responses, hypoglycaemic awareness or the long-term incidence of severe hypoglycaemia between porcine and human insulin preparations were identified. These data fail to confirm any specific risk of severe hypoglycaemia attributable to the use of human insulin preparations in the treatment of patients with diabetes mellitus.

Key words: Diabetes mellitus, human insulin, hypoglycaemia.

In the early eighties, human insulin preparations were introduced into clinical medicine after a series of efficacy and safety trials had been performed with most satisfactory outcomes [1, 2]. Since then, more than a million diabetic patients have been started on, or switched over to, treatments with human insulin preparations worldwide. In fact, in some countries the majority of all insulin-dependent diabetic patients are being treated with human insulins; and in some others the marketing of heterologous insulin preparations has been discontinued altogether. However, in a recent report [3] it was suggested that human insulin therapy might be associated with the development of unawareness of hypoglycaemia based on three case reports and retrospective interviews of a selected group of Type 1 diabetic patients 1 to 48 months after they had been transferred from heterologous to human insulin preparations. In contrast to this hypothesis, we report evidence from a series of controlled, prospective studies demonstrating identical biological effects of both human and purified porcine insulins in healthy and diabetic man.

Studies in healthy volunteers

Studies in human volunteers have demonstrated a slightly, but, at least in most studies, significantly faster absorption of subcutaneously injected human regular insulin when compared with respective porcine insulin preparations [1, 2]. A shorter action profile has been reported for human NPH insulin preparations when compared with respective porcine and bovine insulins [1, 2, 4]. In addition, admixtures of human regular and lente-type insulins within one syringe result in a rapid loss of fast-acting insulin [5] – a phenomenon which appears to have more clinical relevance for human than for porcine insulin preparations [6]. In some studies, differences between human and porcine regular insulins were reported with regard to various counterregulatory endocrine responses (namely adrenaline, growth hormone and cortisol) following their intravenous administration [1, 7, 8]. However, these observations could not be confirmed in subsequent studies on the effects of intravenously injected human versus porcine insulin in normal man [9–11]: no difference between homologous and heterologous insulin preparations was observed at dosages above 0.075 U/kg body weight for any one of the endocrine responses tested, such as ACTH, prolactin, growth hormone, cortisol, adrenaline, noradrenaline, renine and C-peptide. Recently, we have reported a randomised controlled double-blind study in seven healthy males [age 28 ± 2 (mean $\pm$ SD) years, body mass index 21.7 ± 0.6 kg/m^2] comparing the metabolic and hormonal effects of 0.15 U/kg body weight *subcutaneously* injected into the paraumbilical region for human biosynthetic insulin (Humulin, Eli Lilly, Indianapolis, Ind, USA), semisyn-

Table 1. Effects of 0.15 U/kg regular human biosynthetic (BHI), human semisynthetic (SSH) and purified porcine (PI) insulins injected subcutaneously in seven healthy males

	Blood glucose		Glucagon		Adrenaline		Growth hormone	
	CONCmin (mmol/l)	$T_{CONCmin}$ (min)	CONCmax (pg/ml)	$T_{CONCmax}$ (min)	CONCmax (pg/ml)	$T_{CONCmax}$ (min)	CONCmax (ng/ml)	$T_{CONCmax}$ (min)
BHI	2.1 (0.2)	62 (4)	207 (19)	111 (14)	426 (67)	100 (15)	19.9 (5.7)	118 (17)
SSH	2.1 (0.2)	64 (4)	242 (31)	109 (13)	428 (28)	120 (18)	14.9 (2.8)	126 (16)
PI	2.1 (0.2)	65 (4)	216 (25)	122 (15)	398 (52)	118 (17)	17.6 (3.0)	145 (12)
	Noradrenaline		Prolactin		Cortisol		Potassium	
	CONCmax (pg/ml)	$T_{CONCmax}$ (min)	CONCmax (ng/ml)	$T_{CONCmax}$ (min)	CONCmax (ng/ml)	$T_{CONCmax}$ (min)	CONCmin (mmol/l)	$T_{CONCmin}$ (min)
BHI	330 (35)	96 (16)	11.4 (3.2)	115 (18)	14.7 (0.3)	114 (13)	3.2 (0.1)	100 (10)
SSH	327 (24)	90 (16)	13.8 (2.7)	154 (12)	15.5 (1.3)	120 (16)	3.2 (0.1)	111 (6)
PI	289 (38)	124 (21)	13.3 (2.4)	146 (12)	16.7 (1.1)	150 (15)	3.2 (0.1)	120 (13)

CONCmin = nadir concentration, CONCmax = maximal concentration, $T_{CONCmin}$, $T_{CONCmax}$ = time between insulin injection and CONCmin and CONCmax, respectively; values are means (SEM); none of the differences are statistically significant

thetic human insulin (Actrapid HM, Novo Industri, Copenhagen, Denmark) and highly purified porcine insulin (Actrapid MC, Novo) [12]: none of the endocrine responses showed any significant difference between the three insulin preparations tested, whether these responses were evaluated as maximum responses $CONC_{max}$, as the time span between insulin administration and the maximal response $T_{CONCmax}$ (Table 1) or as the area under the concentration-time-curve over a period of 120 min (data not shown). In addition, the subjects were asked to assess their subjective symptoms using a 4-point scoring system (from 0 = no symptom to 3 = severe symptom) for the following seven potential hypoglycaemia-associated symptoms: sensation of heat, sweating, stomachache, hunger, trembling, visual symptoms, headache. For none of the respective symptoms nor for the added symptom score (mean ± SD for Humulin 5.6 ± 1.1, Actrapid HM 4.1 ± 0.7, Actrapid MC 7.1 ± 1.2) was there any significant difference between the three insulin preparations tested.

Studies in Type 1 diabetic patients on continuous subcutaneous insulin infusion

In a study carried out in 1981, i.e. before the general introduction of human insulin preparations, we evaluated the efficacy and safety of human semisynthetic insulin versus purified porcine insulin as used during continuous subcutaneous insulin infusion (CSII) in 12 near-normoglycaemic, C-peptide negative Type 1 diabetic patients (age 26 ± 2, duration of diabetes 12 ± 2 years) in a double-blind cross-over trial [13]. Over the two experimental periods of 3 weeks each, there were no differences between human and porcine insulin preparations with regard to mean daily blood glucose levels, glycosylated haemoglobin values, insulin requirements and the incidence of mild hypoglycaemic reactions, while no case of severe hypoglycaemia occurred throughout the study. Furthermore, we asked the patients to assess the potency of the insulin preparation which they were currently using by responding once weekly to a standardised questionnaire. The unequivocal result of this double-blind procedure was that the patients were unable to identify any difference between human and porcine insulin preparations.

Over the subsequent years almost all of our CSII-treated patients have gradually been switched over to the use of human insulin preparations. The strategies and the outcome of our CSII treatment clinic have been described previously [14, 15] with overall incidence rates for severe hypoglycaemia of 0.13 per patient per year [16] and for ketoacidosis of 0.03 per patient per year [17]. For the purpose of this report, we have retrospectively analysed the records of all 94 CSII treated patients who have been under our continuous ambulatory care for more than 1 year. In this analysis, mean duration of CSII treatment for each of the 94 patients was 3.6 (range 1-6) years; altogether 344 patient years were evaluated. During this period of time, 22 patients developed 44 cases of severe hypoglycaemia as defined earlier [16] resulting in an incidence of 0.13 per patient per year. Twenty-eight of those severe hypoglycaemias occurred during 176 patient years on porcine insulin preparations and 16 during 168 patient years on human insulin preparations. Albeit the circumstances of CSII therapy at a time when predominantly porcine insulins were used, compared to the present time in which almost exclusively human insulins are used, are not strictly identical (e.g. types of insulin pumps used, experience of the health care team responsible for the therapy), these data strongly contradict a greater risk of human insulin preparations with regard to the development of severe hypoglycaemia for near-normoglycaemic patients with CSII therapy.

Studies in Type 1 diabetic patients with intensified conventional insulin therapy

Since 1978, all Type 1 diabetic patients referred to this department have been subjected to a 5-day in-patient diabetes treatment and teaching programme (DTTP), the details of which have been described [18, 19]. Out of the 500 patients presently admitted to the DTTP annually, approximately 100 patients are randomly selected each year for systematic follow-up evaluation for 1 to 2 years after the DTTP; during this time most of these patients are exclusively treated by their family physicians.

We have previously reported on the outcome of these prospective evaluations of the longterm quality of diabetes care [16, 18, 19]. In general, the scope of the DTTP has remained unchanged during the past 9 years. However, after 1983/84 the vast majority of patients have opted for preprandial injections of regular insulin before each meal and twice daily injections of NPH insulin preparations to cover basal insulin requirements [19]. Furthermore, since the spring 1985 human insulin preparations [Actrapid HM and Protaphan HM (Novo), Velasulin H and Insulatard H (Nordisk, Copenhagen, Denmark), Hoechst Regular and Hoechst Basal (Hoechst, Frankfurt, FRG) have been used exclusively.

For the purpose of this report, we have reanalysed the follow-up data as collected over several years in order to identify any potential alteration of the incidence of severe hypoglycaemia in association with the general introduction of human insulin preparations. Table 2 summarises the results of three follow-up studies carried out for randomly selected patients subjected to the DTTP in 1982 (when only porcine insulin preparations were used), 1983/84 (when only newly discovered diabetic patients or patients, who were already on homologous insulins on admission or patients with immunological side effects of heterologous insulin were treated with human insulin), and 1985/86 (when all patients were treated with human insulin preparations only). None of the described parameters of diabetes care in particular the incidence of severe hypoglycaemia showed any differences between the patients treated with purified porcine or human insulin preparations, respectively.

Studies in elderly insulin-treated Type 2 diabetic patients

Finally, we want to report on a follow-up study of 94 consecutively admitted Type 2 diabetic patients, aged more than 60 years, who had been admitted during 1984/85 to our diabetes ward for initiation or readjustment of insulin therapy after their previous sulfonylurea treatment had failed to remain effective. Complete reevaluation was performed on 75 patients 24 ± 7 months after the patients had been discharged from our department where they participated in a specific treatment and teaching programme adjusted to the particular needs of the elderly. As with Type 1 diabetic patients, after the spring of 1985 all newly referred patients were treated with human insulin preparations exclusively.

Out of the 94 patients 11 had died in the meantime (without any fatality due to acute metabolic decompensation) and 8 could not be re-examined for various reasons. For the remaining 75 patients age (mean ± SD) at follow-up was 68 ± 6 years, diabetes duration 15 ± 8 years, body mass index 27 ± 3 kg/m^2, daily insu-

Table 2. Follow-up of three groups of Type 1 (insulin-dependent) diabetic patients after their participation at the Düsseldorf diabetes treatment and teaching programme (DTTP)

Year of participation at the DTTP	No. of patients recruited initially	No. of patients completely reevaluated	Period of follow-up (months)	Insulin preparations used	Age (years)	Diabetes duration (years)	Glycosylated haemoglobin (%)		Percentage (%) of patients with at least one severe hypoglycaemia per year	Incidence of severe hypoglycaemia (per patient, per year)
							initially	at follow-up		
1982	76	76	14 ± 2	Porcine insulins only	27 ± 10	9 ± 7	10.2 ± 1.6	9.4 ± 1.7[a]	11	0.22
1983/84	88	83	15 ± 2	Porcine (n = 50), human (n = 33)	29 ± 10	11 ± 6	8.4 ± 1.7	6.8 ± 1.5[b]	11[c]	0.13[c]
1985/86	130	119	13 ± 2	Human insulins only	27 ± 7	8 ± 7	10.7 ± 2.5	9.4 ± 2.0[a]	8	0.16

[a] Normal values of laboratory method below 7.8% of total haemoglobin; [b] normal value of laboratory method below 5.6% of total haemoglobin; [c] when the 50 patients on porcine insulins and the 33 patients on human insulins were analysed separately no significant differences for the frequency of severe hypoglycaemia were found; values are means ± SD

lin dose 0.60 ± 0.29 U/kg body weight and median duration of insulin therapy 4 years. Since their discharge from our diabetes ward, glycosylated haemoglobin values had fallen from 8.7 ± 1.9 to 7.3 ± 1.4% (Thiobarbiturate method, normal range 4.1–5.6% of total haemoglobin). In order to determine the potential impact of differences between homologous and heterologous insulin preparations, we have analysed the incidence of severe hypoglycaemia separately for those 42 patients treated at follow-up with porcine insulins [Mixtard and Insulatard (Nordisk, Gentofte, Denmark)] and those 33 patients treated with human insulin preparations [Mixtard H and Insulatard H (Nordisk, Gentofte, Denmark) or Actraphane HM and Protaphane HM (Novo) or Depot H and Basal H (Hoechst, Frankfurt, FRG)]. In both groups, four patients each had at least one severe hypoglycaemia during the 2 years of follow-up and incidence rates were 0.10 per patient per year during treatment with porcine and 0.08 per patient per year during treatment with human insulin preparations ($p > 0.1$).

Comments

The results of these controlled studies in healthy volunteers and CSII-treated Type 1 diabetic patients as well as the prospective analyses of follow-up data from CSII- and conventionally-treated Type 1 diabetic patients and insulin-treated Type 2 diabetic patients disprove the suggestions made by Teuscher and Berger [3] as to a difference in the biological potency and hypoglycaemia awareness between porcine and human insulin preparations. The apparent precipitation of severe hypoglycaemia following the transfer of porcine or porcine/bovine insulin-treated Type 1 diabetic patients [3] must be ascribed to a variety of different reasons. Thus, patients and physicians tend to intensify their efforts to strive for normoglycaemia in the context of *any* revision of insulin therapy. The use of larger proportions of regular insulin of the total insulin dosage as advocated in the context of intensified insulin treatment strategies [20, 21] can result in late hypoglycaemia in patients with circulating insulin antibodies resulting from previous treatment with bovine/porcine insulin preparations [20]. Subnormal or low-normal levels of glycaemia are bound to blunt counterregulatory endocrine responses and, hence, early (sympathoadrenal) hypoglycaemic symptoms [22], especially in patients whose glycosylated haemoglobin is lowered intentionally towards normal at the time when transfer from heterologous to homologous insulin preparations is being made. These and other circumstances related to treatment and patient education strategies [19] may have contributed to the precipitation of hypoglycaemia reported in anecdotal cases following the transfer of Type 1 diabetic patients from porcine/bovine to human insulin preparations. The evidence presented in this report should suffice to confirm identical biological potencies of purified and porcine human insulin preparations as evaluated under standardised conditions and thus provide reasurrance to those more than a million diabetic patients (and their physicians) having been transferred to human insulin preparations in recent years.

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