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Diabetologia

Letters to the Editor

Re: Hypoglycaemia (un)awareness: human vs animal insulin

Dear Sir,

In his editorial [1] Professor Michael Berger attempts to "disprove the suggestions made by A. Teuscher and W. G. Berger as to a difference in biological potency and hypoglycaemia awareness between porcine and human insulin preparations" [2].

First, it must be rectified that A. Teuscher and W. G. Berger in their paper do not make any statement on the biological potency of animal vs human insulin. M. Berger's studies are therefore scrutinized only as to their ability to disprove their observation of a reduced awareness in Type 1 (insulin-dependent) diabetic patients transferred from animal to human insulin. However, M. Berger's data relate only in one of the studies to awareness of hypoglycaemia; all other studies deal with the frequency of hypoglycaemia.

The study groups are heterogeneous. They include 7 healthy volunteers and 12 insulin pump patients in cross-over trials; 94 insulin pump patients, and a similar number of conventionally treated Type 1 and Type 2 (non-insulin-dependent) diabetic patients whose charts were, "for the purpose of this report", retrospectively analysed. Only the study with the 7 healthy volunteers was designed to assess hypoglycaemic symptoms. In this randomised cross-over trial 7 males were exposed to subcutaneous injections of porcine and human insulins. A score from 0 (no symptoms) to 3 (severe symptoms) for 7 hypoglycaemia-associated symptoms (sweating, trembling, sensation of heat, stomachache, visual symptoms, headache, hunger) was used. The mean score showed a distinct difference between Actrapid HM (mean + SD 4.1 + 0.7) and Actrapid MC (7.1 + 1.2). Although stated differently in the text, this difference is very suggestive for a decreased awareness under the human preparation. Unfortunately, the p-value cannot be calculated from M. Berger's data because the standard deviation of the individual differences is not given.

In this trial epinephrine levels were also measured; no significant differences were found. Comparable trials of similar size showed either no difference or a decreased response when the human preparation was given [3, 4]. These trials were performed in a number of volunteers ranging from 5 to 12 individuals. Of course, the risk of failing to demonstrate a difference when there really is one (statistical type II error) is considerable in small trials. However, we are not aware of one trial which would show the opposite effect, namely a decreased response to porcine insulin. M. Berger's other studies relate to hypoglycaemia frequency. If unawareness of hypoglycaemia is present, a decrease in the frequency of hypoglycaemia as recognised by the patients is to be expected. On the other hand, an increase in the frequency of more severe hypoglycaemia requiring help from family or colleagues is to be expected.

The incidence of severe hypoglycaemia associated with loss of consciousness was retrospectively determined in a population of 94 insulin pump treated diabetic patients (average treatment period 22 months for each preparation), in three groups of conventionally treated Type 1 diabetic patients (n = 76-130, 14 months), and in 42 (porcine) and 33 (human) insulin-treated Type 2 diabetic patients (24 months). M. Berger did not find a higher incidence of severe hypoglycaemia when the patients were transferred to human insulin. Of course, as the nature of the data is retrospective, a number of other factors might have influenced the results of this analysis. The difference between 0.159 episodes per patient year under porcine insulin and 0.095 episodes per patient year under human insulin might thus be due to information on exposure bias, lack of experience of health care team and patients in the beginning of the CSII era, unsuitable pumps at that time, varying criteria in the assessment of "severe hypoglycaemia", incomplete records, and overrepresentation of patients who responded well to CSII treatment in later years. Similar arguments apply to the data of the conventionally treated Type 1 and elderly insulin-treated Type 2 diabetic patients.

Also, severe hypoglycaemia is a rare event. Studies aiming to detect a significant difference in the occurrence of severe hypoglycaemia must be of considerable size; e.g. in order to detect a doubling of the risk of severe hypoglycaemia when assuming 5% (1%, 10%) of unexposed patients having at least one episode per year, approximately 1160 (6200, 540) patients, 580 (3100, 270) in each group would have to be followed up for 1 year [5]. In order to detect smaller effects which in this case are relevant, even bigger studies are needed. Therefore, in addition to the fact that M. Berger's studies are retrospective, and therefore subject to numerous biases, the sample size is insufficient and the probability of a type II error large. The case: control approach is in this context a more feasible alternative.

The study by A. Teuscher and W. G. Berger intended to inform physicians that decreased awareness of hypoglycaemia in 66 out of 176 patients transferred to human insulin was a potentially important clinical problem [2]. The change of symptoms was a major feature as summarised in Table 1. Randomised double-blind trials with carefully constructed questionnaires and case: control studies of se-

Table 1. Features of hypoglycaemia under animal vs human insulin as experienced by some patients transferred for the first time from animal to human insulin [1]

	Animal insulin	Human insulin
Awareness	Usually by patient	Often by others
Onset	Less abrupt	More abrupt
Ability to react	Maintained	Impaired
Symptoms	Well-defined	Ill-defined
Hunger-feeling	Pronounced	Vague
Sweating	Earlier	Later
Pronounced fatigue	Infrequent	Frequent
Recovery time	Shorter	Longer

vere hypoglycaemia aiming to determine the relative risk associated with human insulin will help to clarify this question. The data presented by M. Berger, however, are not suitable to contribute to this clarification. We, on the other hand, strongly agree with one of his earlier statements, namely that "the present vogue for human insulin is not matched by comparable benefits in clinical practice" [6]. We just would like to add that human insulin might even be associated with important disadvantages in a number of insulin-dependent diabetic patients.
Yours sincerely,

M. Egger, A. Teuscher and W. G. Berger

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Hypoglycaemia in newly diagnosed diabetic children and adolescents - comparison between human and porcine insulin

Dear Sir,

We wish to add to Dr. Berger's editorial conclusion [1] that human insulin preparations do not cause more hypoglycaemia than porcine insulin. We have recently analysed in a double blind study 30 newly diagnosed juvenile Type 1 (insulin-dependent) diabetic patients with a mean age of 11.7 ± 3.4 years who were followed closely for 2 years. Fourteen patients were treated with human insulin (2 daily insulin injections of mixed human Monotard and Actrapid (Novo, Denmark) and 16 patients with a highly purified porcine preparation (Monotard and Actrapid MC, Novo, Denmark). The patients were followed by our multidisciplinary team and performed self blood glucose monitoring, a mean of 3 times per day during the whole period. Detailed history and laboratory examinations were performed at diagnosis, at 1 month and subsequently every 3 months [2]. Chemical hypoglycaemia was defined as blood glucose levels of 2.76 mmol/l or less. The monthly incidence of chemical hypoglycaemic episodes is shown in Table 1.

It is evident that there was no difference in the number of hypoglycaemic episodes in both groups of patients. Nor did we find differences in the mean periodic blood glucose values, as estimated from the 53,000 self blood glucose estimations performed by the 30 juvenile patients over 2 years. During the first year, one patient receiving porcine insulin, had 2 episodes of symptomatic hypoglycaemia at night, one with convulsions. Blood glucose during one of the episodes was 1.88 mmol/l. This same patient had during the second year an additional 4 episodes of symptomatic hypoglycaemia, all before dawn, 3 of them with questionable loss of consciousness. In one of them blood glucose was 2.76 mmol on the same morning. Another patient also receiving porcine insulin had 8 episodes of symptomatic hypoglycaemia, all during the second year. Most hypoglycaemic episodes occurred before dawn. Blood glucose measured during one of the events was 1.60-2.54 mmol/l, with no convulsions.

The above observation confirms our previous study that a comprehensive therapeutic approach by a multidisciplinary team [3] induces a high degree of compliance on the part of the patient. In conclusion, this close follow-up demonstrated no difference between human and porcine insulin in regard to hypoglycaemic episodes, as well as diabetes control during the first 24 months of the disease [2].

Yours sincerely,
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Variability of the first phase insulin response to intravenous glucose

Dear Sir,

The very interesting study recently published on these pages by Smith et al. [1] conceptualized a component of B-cell function that has recently and not so recently attracted a good deal of attention [2]. The so-called early phase insulin response of a rapid intravenous

Table 1. Newly diagnosed Type 1 (insulin-dependent) diabetes mellitus - number of hypoglycaemic episodes per patient (blood glucose < 2.76 mmol/l) per month during the first 2 years - human vs porcine insulin treatment (mean ± SD)

Months	1	2-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24
Human Insulin (n=14)	0.7 ±1.5	1.7 ±1.5	1.0 ±1.5	0.8 ±1.3	0.9 ±1.9	0.8 ±1.0	1.2 ±2.5	1.3 ±1.3	1.9 ±2.2
Porcine Insulin (n=16)	1.1 ±2.2	3.1 ±5.0	2.1 ±3.5	1.7 ±2.3	0.9 ±1.2	1.3 ±1.2	1.2 ±1.4	2.1 ±2.3	2.5 ±2.9