IMPROVED BLOOD GLUCOSE VARIABILITY, HBA1C, INSUMAN INFUSAT® AND LESS INSULIN REQUIREMENT IN IDDM PATIENTS USING INSULIN LISPRO IN CSII. THE SWEDISH MULTICENTER LISPRO INSULIN STUDY

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SUMMARY - The aim of the study was to compare lispro (LP) and Insuman® (I) insulin in continuous subcutaneous insulin infusion (CSII) therapy with respect to blood glucose control as expressed by the standard deviation of blood glucose (SDBG) and HbA1c, and to monitor the well-being (WBQ) and treatment satisfaction (DTSQ) parameters during such treatment. Forty-one IDDM patients who had used CSII for at least 6 months participated in an open-label, randomized, cross-over, multicenter study for 4 months (2 months LP and 2 months I or vice versa). Boluses with LP were given 5 min before each meal and with I 30 min before each meal. During LP administration compared with I, the SDBG of all blood glucose values (3.6 mmol/l vs. 3.9 mmol/l, \( p = 0.012 \)) was significantly lower, as well as the SDBG of the postprandial blood glucose values (3.6 mmol/l vs. 4.0 mmol/l, \( p = 0.006 \)). The HbA1c was significantly lower during LP administration (7.4% vs. 7.6%, \( p = 0.047 \)). The incidence of hypoglycemic events per 30 days (capillary blood glucose < 3.0 mmol/l and/or symptoms) did not significantly differ between LP and I (9.7 vs. 8.0 per month, \( p = 0.23 \)). The total amount of daily insulin was slightly but significantly lower with LP than with I (38.0 IU vs. 40.3 IU, \( p = 0.047 \)). There was no treatment effects of LP compared to I concerning WBQ and DTSQ. It is concluded that in CSII therapy LP is superior to I with respect to the stability of blood glucose control, a lower HbA1c, a less insulin requirement without increasing the frequency of hypoglycemia.

Key-words: IDDM, lispro insulin, CSII, blood glucose stability, WBQ, DTSQ.

RÉSUMÉ - Amélioration de la variabilité glyémique, de l'HbA1c et réduction des besoins insuliniens chez des patients diabétiques insulino-dépendants traités par Lispro par pompe externe ambulatoire.

L'étude suédoise lispro multicentrique.

L'objectif de l'étude était de comparer la lispro (LP) et l'Insuman (I) lors de l'administration continue sous-cutanée d'insuline (CSII) pour leurs effets sur le contrôle glyémique, jugé par la déviation standard de la glycémie (SDBG) et par l'HbA1c, et d'évaluer les paramètres de bien-être (WBQ) et de satisfaction du traitement (DTSQ) sous ce régime. Quarante et un patients diabétiques de type 1 traités depuis au moins 6 mois par CSII ont pris part à cette étude ouverte, randomisée, en cross-over, multicentrique, durant 4 mois (2 mois LP et 2 mois I ou vice versa). Les bolus de LP étaient administrés 5 min avant chaque repas et ceux de I 30 min avant chaque repas. Lors de l'administration de LP, par comparaison avec I, la SDBG de toutes les valeurs glycémiennes (3,6 mmol/l vs 3,9 mmol/l, \( p = 0.012 \)) était significativement réduite, de même que la SDBG des valeurs post-prandiales (3,6 mmol/l vs 4,0 mmol/l, \( p = 0.006 \)). L'HbA1c était significativement plus basse lors du traitement LP (7,4 % vs 7,6 %, \( p = 0.047 \)). L'incidence des événements hypoglycémiques sur 30 jours (glycémie capillaire < 3,0 mmol/l et/ou symptômes) n'était pas significativement diffé- rente entre LP et I (9,7 vs 8,0 par mois, \( p = 0.23 \)). La quantité totale d'insuline délivrée était légèrement mais significativement plus basse avec LP qu'avec I (38,0 UI vs 40,3 UI, \( p = 0.004 \)). Il n'y avait pas d'influence du traitement sur les paramètres WBQ et DTSQ. En conclusion, l'insuline LP pour le traitement par CSII est supérieure à l'insuline I en terme de stabilité du contrôle glyémique, permettant une réduction de l'HbA1c et des besoins insuliniens sans augmenter la fréquence des hypoglycémies.

Mots-clés : diabète de type 1, insuline lispro, traitement par pompe à insuline, stabilité glyémique, qualité de vie.
The intensive treatment of diabetes to lower the HbA1c reduces the risk of long-term complications in IDDM patients [1, 2]. The goal of intensive treatment is near normoglycemia and hence continuous subcutaneous insulin infusion (CSII) is an effective instrument when combined with regular home blood glucose monitoring [3].

CSII permits IDDM patients to follow flexible lifestyle, giving them also the capability to easily correct blood glucose values by alterations in infusion rates to meet swings in these values. Owing to its pharmacokinetic properties, lispro insulin (LP) produces comfort for the patient with respect to the timing of insulin injections and meals. These advantages are related to the more rapid onset and shorter duration of action of a LP bolus [4]. Taken together, LP appears to improve treatment satisfaction [5] and metabolic control when used in multiple, daily-Insuman Infusat® injection regimens (MDI) [6]. Owing to its pharmacokinetic properties, LP should offer advantages over conventional short-acting insulins when delivered by continuous infusion, as it has also been suggested in earlier studies [7-10]. The aim of the present investigation was to ascertain whether LP yields less fluctuating blood glucose values than regular insulin when used in CSII and to determine its effect on HbA1c insulin requirement, subjective well-being and treatment satisfaction after a treatment period of two months.

MATERIAL AND METHODS

Patients — A total of 41 adults (19 females) with IDDM between the ages of 20 and 58 years from four Swedish centers were included in this open, randomized, cross-over trial. All these patients were treated by Swedish centers were included in this open, randomi-

Experimental record — After a run-in period of 2-4 weeks, during which Insuman Infusat® ( Hoechst Marion Roussel, Germany) (I) was used by all subjects, the patients were randomly assigned to receive either LP (Humalog®, Eli Lilly, USA) or I with a cross-over after 2 months, giving a total study period of 18-20 weeks. In this open study the patients were instructed to take each meal bolus with LP 5 min before the meal and with I 30 min before the meal. They were also instructed to insert the cannula in the paraumbilical region, and to change the infusion site with an interval depending on whether they used a metal needle (3 days) or a soft needle (7 days). The patients had their normal meals and were expected to maintain their ordinary life-style activities. Each patient was asked to register insulin dosage, all episodes of hypoglycemia and ketosis in a patient study diary. A hypoglycemic episode was defined as a blood glucose value of Insuman Infusat® <3.0 mmol/l and/or subjective signs of hypoglycemia. Ketosis was measured semiquantitatively in urine, using the Ketostix® method and each patient was instructed to check for ketones when blood glucose was >12 mmol/l.

Throughout the study, the patients attended an outpatient clinic at monthly intervals and during the first month in each treatment period, they also had telephone contacts on a weekly basis. At the end of each treatment period, blood glucose variability (SDBG), HbA1c, daily insulin consumption and the patients’ well-being and treatment satisfaction were estimated.

Each patient’s blood glucose variability was calculated as the standard deviation (SD) of the blood glucose measurements (SDBG), according to Moberg et al. [11] during the last month of each treatment period, when approximately 70 blood glucose values were generated by each patient.

The well-being scales, designed by Bradley [12, 13] and earlier translated into Swedish [14], were intended to measure well-being (WBQ, depressed mood 6 items, anxiety 6 items, energy 4 items and various aspects of positive well-being 6 items) and treatment satisfaction (DTSQ, 6 items about various aspects of positive well-being 6 items and treatment satisfaction 6 items). The well-being scales, designed by Bradley et al. [12, 13] and earlier translated into Swedish [14], were intended to measure well-being (WBQ, depressed mood 6 items, anxiety 6 items, energy 4 items and various aspects of positive well-being 6 items) and treatment satisfaction (DTSQ, 6 items about various aspects of positive well-being 6 items) and treatment satisfaction (DTSQ, 6 items about various aspects of positive well-being 6 items) and treatment satisfaction (DTSQ, 6 items about various aspects of positive well-being 6 items).
aspects of the treatment and two items about the perceived frequency of hyper- or hypoglycemia).

Glycated hemoglobin (as HbA1c) was determined by the Hitachi 917 Automatic Analyzer (Roche Diagnostics, Germany), using a reference range for healthy subjects of 4.0-5.5%. The total imprecision was = 4% CV both at HbA1c 4.5% and 10.5%.

Analytic and statistical methods — The power analysis suggested that forty-one patients were needed to detect a mean difference of 0.8 mmol/l of the total SDBG efficacy variable and of 0.5% of the corresponding HbA1c variable between the two treatment groups with a 0.05 level of significance and a 80% power, using a two-tailed test, based on normal distribution.

The data from 41 patients were included in the analyses, using an intent-to-treat methodology. The analyses were performed, using the value of the last month in each treatment period for each patient during each 2-month period of the cross-over study. The descriptive statistical results are given as means±SD. The two treatments were compared, applying a standard cross-over analysis with respect to within-subject changes. For approximately normally distributed data, the statistical inference was based on the t-distribution. Differences of means are presented, together with a 95% confidence interval. Well-being and treatment satisfaction were analyzed by analysis of variance (ANOVA) applied to a cross-over study with period and treatment group as interaction factors. Internal consistency for each scale was measured by Cronbach’s alpha [15]. Differences between LP and the reference group of type I patients were tested by Student’s t-test for unpaired observations. Probabilities below 0.05 were regarded as statistically significant.

RESULTS

All 41 patients completed the study. Blood glucose data for two patients were missing, owing to technical problems. No differences were observed in the preprandial blood glucose values and in the SDBG of preprandial values between the two different treatment periods (Table II). The mean of all blood glucose values, the mean of blood glucose 2 hr after dinner, the SD of all blood glucose values, the SDBG of blood glucose 2 hr after dinner and the total amount of daily insulin were significantly reduced by LP. HbA1c was significantly reduced by LP treatment, as compared to I. There was no significant difference in the number of hypoglycemic events or events of ketosis during LP vs. I. One episode of ketoacidosis due to pump failure occurred during treatment with LP.

The reliability estimates for depression, anxiety, energy, positive well-being, general well-being and treatment satisfaction indicated good reliability since all the scales satisfied the 0.60 reliability standard for group comparison [16]. No treatment effects were observed in the well-being scores for depression, anxiety, energy, positive well-being, general well-being or treatment satisfaction. When the well-being and treatment satisfaction parameters were compared for LP and a reference group of Type I diabetes patients, a significant improvement was found for depression, anxiety and general well-being (Table III).

| TABLE II. | Means of the last 4 weeks in each treatment period with lispro insulin (LP) and Insuman Infusatin® (I) respectively and mean (95% CI) differences between these periods with statistical significance (p). |
|-----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|           | LP              | I               | Difference between LP and I | 95% CI          | p               |
| SDBG of all blood glucose values (mmol/l) | 3.6             | 3.9             | -0.3            | 0.1 ; 0.5       | 0.012           |
| SDBG of preprandial values (mmol/l)     | 3.4             | 3.6             | -0.2            | -0.4 ; 0.3      | 0.86            |
| SDBG of postprandial values (mmol/l)   | 3.6             | 4.0             | -0.4            | 0.1 ; 0.7       | 0.006           |
| Mean glycemia (mmol/l)                  | 8.3             | 8.9             | -0.6            | 0.3 ; 1.0       | <0.001          |
| Preprandial glycemia (mmol/l)           | 8.5             | 8.4             | 0.1             | -0.4 ; 0.3      | 0.86            |
| Postprandial glycemia (mmol/l)          | 8.1             | 9.6             | -1.5            | 1.0 ; 2.0       | <0.001          |
| Hypoglycemic events (per 30 days)       | 9.7             | 8.0             | 1.7             | -5.1 ; 1.3      | 0.23            |
| HbA1c (ref.value 4.0-5.5 %)              | 7.4             | 7.6             | -0.2            | 0.0 ; 0.3       | 0.047           |
| Total amount of insulin IU/24h           | 38.0            | 40.3            | -2.3            | 0.8 ; 3.8       | 0.004           |
was performed in a postprandial situation. Melki assessed which were included in this calculation of the SD BG, adopted as their primary effect variable on CSII for three months, reported a similar lowering who compared LP and Actrapid t

Notably, only one of the SDBG . Taken together, the SD BG of all blood glucose values but not preprandial values, as expressed by the lowers the variability of postprandial blood glucose during CSII. The present study demonstrates that LP cose values when delivered as a continuous infusion acting preparations in controlling pre-meal blood glu-

From a pharmacokinetic point of view, one may speculate whether such a point in the early cross-over study by Zinman et al. [7] and Schmauss et al. [8] while our patients used the same site for up to seven days. Therefore, one may speculate upon whether the different insulins and/or vials used were of importance with respect to the alterations in insulin requirements.

In our randomized, cross-over study comparing LP and I, we could not demonstrate a significant difference in the rate of hypoglycemic events, as defined by a blood glucose <3.0 mmol/l and/or subjective symptoms. In a further analysis of our material, motivated by the findings of Melki et al., we could not confirm their observations with respect to blood glucose values <2.0 mmol/l. Taken together, we consider our present findings concerning hypoglycemia to be very much in support of those of Melki et al.

Hypoglycemia was defined as a blood glucose <3.0 mmol/l in the early cross-over study by Zinman et al. and its rate was calculated over 30 days. The difference between LP and human regular insulin was not significant [7]. Schmauss et al. defined hypoglycemia as a blood glucose <3.5 mmol/l and/or symptoms of hypoglycemia in their randomised, cross-over study and no significant differences were registered over 30 days [8]. Furthermore, Renner et al. [10] in their large multicenter trial showed comparable results of the hypoglycemic frequency as Schmauss et al. [8]. To avoid confusion due to a carry-over effect, Melki et al. restricted the analysis of hypoglycemic events to the last 30 days of the first three-month treatment period. They did not find any significant difference with respect to blood glucose values <3.0 mmol/l while the

<table>
<thead>
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<th>CSII</th>
<th>(Non CSII treated)</th>
<th>Difference between LP and I (CSII) (p)</th>
<th>Difference between LP (CSII) and (non CSII) (p)</th>
<th>Possible range of scores</th>
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<td>LP n=41 I n=41 (IDDM) 1 n=153</td>
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<td>Depression</td>
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<td>3.0±2.7</td>
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<td>Energy</td>
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<td>8.6±1.8</td>
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<td>Positive well-being</td>
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<td>13.0±3.1</td>
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<td>General well-being</td>
<td>52.6±7.1</td>
<td>51.2±8.8</td>
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<td>Treatment satisfaction</td>
<td>29.8±6.7</td>
<td>28.8±5.2</td>
<td>29.0±5.6</td>
<td>0.343</td>
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TABLE III. Well-being and treatment satisfaction scores at the end of each 8-month period of treatment with lispro insulin (LP) and Insuman Infusat® (I). Results expressed as means±SD.

DISCUSSION

Current data indicate that, in comparison with human regular insulin, LP offers a possibility of improving postprandial glucose control in IDDM patients when used before main meals. From a pharmacokinetic point of view, one may speculate whether such a short-acting insulin analogue is superior to less short-acting preparations in controlling pre-meal blood glucose values when delivered as a continuous infusion during CSII. The present study demonstrates that LP lowers the variability of postprandial blood glucose values but not preprandial values, as expressed by the SD BG. Taken together, the SD BG of all blood glucose values were reduced significantly by LP, however. Notably, only one of the five daily blood glucose assessments which were included in this calculation was performed in a postprandial situation. Melki et al. who compared LP and Actrapid® in 39 IDDM patients on CSII for three months, reported a similar lowering of the SD BG, adopted as their primary effect variable [9]. Their calculation of the SD BG included seven values, of which three were postprandial determinations. They also reported a lowering of Hba1c by LP of approximately 0.5 % over three months, which seems to correspond well to the 0.2 % effect of LP over two months in our study [9]. The total daily insulin dose was approximately 2 units lower when LP was used in our study mainly attributed to a reduction of bolus doses. Notably, Melki et al. reported lower bolus doses but not total daily doses with LP [9]. We compared LP against regular insulin specially adapted for use in pumps. Zinman et al. [7], Schmauss et al. [8] and Renner et al. [10] who used regular insulins in comparison with LP in their CSII studies, did not find significant differences with respect to the daily insulin requirement.

The infusion site was changed with intervals of 24-48 hours to reduce the risk of skin reactions by Zinman et al. [7] and Schmauss et al. [8] while our patients used the same site for up to seven days. Therefore, one may speculate upon whether the different insulins and/or vials used were of importance with respect to the alterations in insulin requirements.

In our present data, we could not demonstrate a significant difference in the rate of hypoglycemic events, as defined by a blood glucose <3.0 mmol/l and/or subjective symptoms. In a further analysis of our material, motivated by the findings of Melki et al., we could not confirm their observations with respect to blood glucose values <2.0 mmol/l. Taken together, we consider our present findings concerning hypoglycemia to be very much in support of those of Melki et al. Hypoglycemia was defined as a blood glucose <3.0 mmol/l in the early cross-over study by Zinman et al. and its rate was calculated over 30 days. The difference between LP and human regular insulin was not significant [7]. Schmauss et al. defined hypoglycemia as a blood glucose <3.5 mmol/l and/or symptoms of hypoglycemia in their randomised, cross-over study and no significant differences were registered over 30 days [8]. Furthermore, Renner et al. [10] in their large multicenter trial showed comparable results of the hypoglycemic frequency as Schmauss et al. [8]. To avoid confusion due to a carry-over effect, Melki et al. restricted the analysis of hypoglycemic events to the last 30 days of the first three-month treatment period. They did not find any significant difference with respect to blood glucose values <3.0 mmol/l while the

1Results derived from the Swedish population study (14).
incidence of blood glucose values <2.0 mmol/l was significantly lower with LP [9].

CSII has been shown to improve well-being and treatment satisfaction as compared to MDI using regular insulin [17]. In IDDM patients on multiple daily insulin injections LP insulin has also been shown to improve treatment satisfaction and treatment flexibility [5]. In the study by Schmauss et al., LP did not improve the quality of life, as measured by questionnaires concerning health, distress, treatment satisfaction and treatment flexibility during CSII [8]. In the study by Renner et al. [10], a sufficient number of patients were measured by the DTSQ to detect differences between the LP and regular insulin. Unfortunately, in their analyses Renner et al., did not treat the two items of hyper- and hypoglycemia individually as recommended by Bradley et al. [12]. Therefore the interpretation of their results is difficult. In our hands, the same questionnaire did not yield significant differences between LP and ID when used by CSII patients.

For comparison, we included a reference group of IDDM patients of comparable age, duration of diabetes, HbA1c and BMI in our analysis [14]. This comparison revealed that LP patients had a significantly lower score for depression and anxiety and a higher score for general well-being compared to IDDM patients treated by a conventional treatment regime. This suggests that patients using CSII for a considerable time attain a high level of well-being and that improvements with respect to such parameters may be difficult to detect in a relatively small study group. Furthermore, it should be noted that patients scoring at a maximum at the baseline can do no better than give a maximum score again when confronted by the same questionnaire. For this reason, a new version of this questionnaire has been developed, the validity of which is currently being analysed elsewhere [18].

It is concluded that LP is safe in CSII therapy and that it is superior to Insumin® with respect to the stability of blood glucose control, as determined by the standard deviation of blood glucose values and that it improves glucose control as determined by HbA1c without increasing the frequency of hypoglycemia. Furthermore during CSII LP yields less insulin requirement. These findings confirm previous studies [7-10] on this issue.

Acknowledgments – This work was supported by grants from Eli Lilly (Sweden) AB, the Bert von Kanton Foundation, the Karolinska Institutet and the Swedish Medical Research Council Grant (No.19x-6589) and the Division of Internal Medicine, Danderyd Hospital Foundation for Nursing Research (No.176). We want to thank Martin Alenius and Anders Sjöberg for statistical assistance and statistical advice.


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