Efficacy of short term continuous subcutaneous insulin lispro versus continuous intravenous regular insulin in poorly controlled, hospitalized, type 2 diabetic patients

S Boullu-Sanchis, F Ortega, G Chabrier, MS Busch, C Uhl, M Pinget, N Jeandidier

SUMMARY
Intravenous insulin infusion (IVII) is rapidly effective in improving glycaemia in uncontrolled hospitalized diabetic patients. This significantly improves their morbidity and mortality. Intravenous insulin infusion may lead to IV infusion complications and is a heavy burden for caregivers.

Aim: The aim of our work was to compare the efficacy of IV regular insulin versus lispro Continuous Subcutaneous Insulin Infusion (CSII), in improving glycaemia in patients hospitalized for uncontrolled type 2 diabetes, the efficacy being assessed on the average blood glucose level observed.

Methods: The study was designed as a prospective randomized study. Thirty-three type 2 diabetic patients, hospitalized for uncontrolled diabetes by their usual practitioner were included. After acceptance, patients were randomly assigned to lispro CSII (group 1, n=20) or IVII regular insulin (group 2, n=13) for 5 days. Ten capillary blood glucose/day were performed. Pre-meal blood glucose targets were 4.4-6.6 mmol/l. Mann Whitney, Wilcoxon and Fischer exact tests were used.

Results: BG levels decreased significantly (-3.4±0.55 mmol/l in group 1 and -3.60±0.55 mmol/l in group 2, P<0.01) during the first 12 hours. Mean daily blood glucose at day 5 was statistically improved in both groups compared to day 1 (P<0.05 Wilcoxon) and comparable between the 2 groups. No severe hypoglycaemia was reported. No catheter complications occurred in group 1, 7 occurred in group 2.

Conclusion: CSII and IVII infusion were comparable in rapidly improving hyperglycaemia in uncontrolled type 2 diabetic patients. CSII, being more convenient, could be preferred in medical and surgical settings.

Key-words: Subcutaneous lispro · Insulin infusion · Uncontrolled type 2 diabetes · Hospital diabetes management.

Résumé
La perfusion d’insuline intraveineuse (IVII) normalise rapidement la glycémie des diabétiques hospitalisés, ce qui améliore significativement leur morbi-mortalité. L’IVII peut entraîner les complications classiques de la voie IV et une charge de travail importante.

Objectif : Le but de cette étude était de comparer l’efficacité de IVII à celle de la perfusion sous cutanée (CSII) d’analogue rapide par pompe portable, en comparant les moyennes glycémiques obtenues dans une étude prospective, randomisée.

Méthodes : Trente trois diabétiques de type 2, hospitalisés pour déséquilibre glycémique, ont été randomisés dans 2 groupes et traités par lispro par CSII (groupe 1, n = 20) ou insuline rapide par IVII (groupe 2, n = 13) pendant 5 jours. Dix glycémies capillaires quotidiennes étaient réalisées. L’objectif glycémique était de 4,4 – 6,6 mmol/l avant chaque repas. L’analyse statistique a utilisé les tests Fischer exact, Mann Whitney et Wilcoxon.

Résultats : Une diminution significative de la glycémie était observée durant les 12 premières heures de traitement (groupe 1: -3,4±0,55 mmol/l et groupe 2: -3,60±0,55 mmol/l, P < 0,01). La glycémie moyenne du 5e jour était améliorée dans chaque groupe par rapport à celle du 1er jour (P < 0,05 Wilcoxon). Aucune hypoglycémie sévère n’est survenue. Le groupe 1 n’a pas présenté de complications liées au cathéter alors que 7 sont survenues dans le groupe 2.

Conclusion : CSII et IVII ont montré une efficacité comparable dans l’obtention d’une amélioration rapide de l’hyperglycémie. CSII est plus pratique et pourrait être préférée en hospitalisation dans les situations qui nécessitent une normalisation rapide de l’hyperglycémie.

Mots-clés : Insuline lispro · Perfusion d’insuline sous cutanée · Diabétiques de type 2 déséquilibrés · Prise en charge hospitalière du diabète.
Continuous insulin infusion in hospital

Intravenous insulin infusion (IVII) using regular insulin is currently used in hospitalized patients to rapidly control hyperglycaemia. It has shown its efficacy in improving morbidity and mortality in hospitalized patients [1-4]. IVII is rapidly effective [5] but induces a reduction in patient's mobility, requires a dedicated running line, and may lead to other classical complications of intravenous infusion (IV) [6-9]; it is, thus, often restricted to intensive care unit (ICU) patients. Continuous Subcutaneous Insulin Infusion (CSII) doesn’t alter patient’s mobility and is an “easier to manage” technique. CSII using regular insulin was shown to be less efficient than the IV route [1] but CSII using rapid acting analogs has shown a better efficacy than using regular insulin in ambulatory patients [10] and was as effective as IVII in moderate ketoacidosis [11].

The aim of our study was to compare CSII using lispro and IV regular insulin, in their efficacy to rapidly improve glucose control in type 2 diabetic patients hospitalized for uncontrolled diabetes.

Efficacy was assessed on the average level of blood glucose in each group and on the time required to obtain near normal glycaemia.

Subjects and methods

Subjects

Patients were type 2 diabetic patients, hospitalized by their practitioner in the Diabetology Department for sustained uncontrolled diabetes. Selection criteria were: age >35 years at the time of diabetes diagnosis, C peptide >2.0 ng/ml, HbA1c >8.5% (N: 4-6%), BMI <40 kg/m2, creatinine clearance >70 ml/min at inclusion. Exclusion criteria were severe acute illness, ketonuria, and a contra indication to a rapid blood glucose level improvement such as unstable retinopathy.

All subjects provided written informed consent in accordance with the French Guidelines for the protection of human subjects (Loi Hurriet). Patient’s characteristics are summarized in table I.

Material: External H-tron infusion devices (Disetronic Medical SystemsGmbH, Sulzbach Switzerland) using specific 300 U Disetronic cartridges filled with lispro analog (Humalog® 100 U/ml, Lilly, USA) and intravenous infusion devices (IVID) as B-D Pilote A (Beckton Dickinson Infusion Systems, France) with regular insulin (Umuline® 100 U/ml, Lilly, USA) were used respectively in group 1 and in group 2.

The same capillary blood glucose (CBG) meters (One Touch Ultra, Lifescan Johnson & Johnson Company, USA) were used in all patients.

Study design

After signing informed consent, patients were included in the prospective observational study, randomized by drawing to either group 1 (CSII and Lispro, n=20) or group 2 (IV Infusion of regular Insulin, n=13) and treated during 5 full days.

A physical examination was performed including weight and height. Fasting blood glucose (BG), C peptide, triglycerides and creatinine levels were assessed prior to insulin therapy (day 1) and at day 5 for fasting BG and C peptide. A diabetic diet consisting of 50% carbohydrate (200 g), 35% fat and 15% protein was provided for all subjects during the 5 days. After reception of all data, patient charts were controlled and patients who met exclusion criteria (such as too low C peptide) were secondarily excluded.

Blood glucose assessment

The nursing staff performed ten capillary blood glucose (CBG) per day: 7 AM, 12 AM, 4 PM, 7 PM, 10 PM, 1 AM, 4 AM and ½ hours after each meal. Blood glucose goals ranged from 4.4 to 6.6 mmol/l pre-meal and <9.9 mmol/l post-meal.

At fasting baseline and day 5, blood samples were drawn for glucose and C peptide determination. Their plasma concentrations were assayed immediately. HbA1c was assessed using an HPLC technique.

Insulin administration

A pump continuously administered a IV solution of 0.4 ml of regular insulin diluted in 39.6 ml of saline 9g/l (corresponding to a concentration of 1 UI per 1 ml). Basal schedules and a bolus before each meal were prescribed, CSII was delivered using the same schedule. The subcutaneous infusion site was changed every 3 days in group 1 and the cartridge was changed as needed.

Statistics

The BMDP statistical software (Inc. Los Angeles, USA) was used for data analysis. All data are presented as

<table>
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<th>Table I Subject’s clinical and biological characteristics.</th>
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<td>Type of treatment (oral drug / oral drug and insulin)</td>
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<td>Duration of diabetes (years)</td>
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* Mann Whitney test has been used
# Fischer exact test has been used.
Mean ± SEM unless otherwise stated. Mann Whitney, Wilcoxon and Fischer exact tests were used. Statistical significance was defined for P values < to 0.05.

Results

Thirty-seven type 2 diabetic patients agreed to participate to the study and were randomized. Four patients (2 in each group) were secondarily excluded; due to the reception after inclusion of an HbA1c level lower than 8.5% or a C peptide level lower than 2 ng/ml. One patient was mistakenly enrolled due to a calculation error in his BMI and was excluded after his chart was checked. Thirty-three patients (n=20 in group 1 and n=13 in group 2) were actually included and completed the study.

The average morning fasting plasma BG of day 1, were comparable in group 1 and 2; respectively 10.8 ± 0.8 vs 11.2 ± 0.7 mmol/l, (NS, Mann Whitney) and decreased significantly at day 5, in the 2 groups (7.0 ± 0.4 vs 6.6 ± 0.3 mmol/l, Wilcoxon, P<0.05). The average CBG before initiation of insulin treatment were comparable between the 2 groups (9.1 ± 0.7 in group 1 vs 9.4 ± 0.6 mmol/l in group 2, NS, Mann Whitney) and decreased in a comparable way (figure 1) during the first 12 hours (-3.4 ± 0.55 mmol/l in group 1 vs -3.60 ± 0.55 mmol/l in group 2; Wilcoxon, P<0.01).

The mean daily CBG for day 1 and for day 5 were first calculated, using the pre and postprandial glucose assessments (10 tests) and secondarily using the 3 pre-prandial tests (figure 2), showing a significant and comparable decrease of the mean CBG levels in the 2 groups.

The percents of the pre-prandial CBG in the target range during the 5 days of treatment were comparable in the 2 groups (42.0 ± 3.1% vs 43.9 ± 3.2%, NS, Fischer exact test). The percent of the post-prandial CBG in the target range during the 5 days of treatment was better in group 2 (47.5% ± 3.5% vs 66.8 ± 3.1%, P<0.05, Fischer exact test). The Daily Standard Deviation of BG, a validated glucose stabil-
Continuous insulin infusion in hospital

ity parameter, was lower in group 2 than in group 1 at day 1 (3.24±0.27 and 2.53±0.22 mmol/l, P<0.05, Mann Whitney) but improved significantly from day 1 to day 5 to a comparable value in both groups (2.36±0.16 in group 1 and 2.09±0.22 mmol/l in group 2; NS, Mann Whitney). The weight remained stable during the 5 days: -0.2±0.2 kg in group 1 and -0.4±0.5 kg in group 2.

Plasma C peptide mean values were comparable at day 1 and decreased significantly from day 1 (2.52±0.20 ng/ml group 1; 2.64±0.30 ng/ml group 2) to day 5 (1.24±0.22 ng/ml group 1; 1.33±0.16 ng/ml group 2; Wilcoxon, P<0.05). Daily insulin requirements were lower in group 1 than in group 2 and stabilized more rapidly in group 1 (figure 3).

No severe hypoglycaemia, as defined by the DCCT, was reported. The number of hypoglycaemic episodes (BG<3.3 mmol/l) per day of treatment and per patient tended to be higher in group 1 (0.06 in group 1 vs 0.015 in group 2, P>0.05, Wilcoxon).

No local complications such as local cutaneous infection, catheter leakage or blockage occurred in group 1, while in group 2 IV catheters had to be changed 7 times in 6 patients due to either IV catheter obstructions (5 cases) leading to transient BG increase or inflammatory and local inflammations (2 cases) (P < 0.01; Fischer exact test).

Discussion

Our data show that in hospitalized for uncontrolled diabetes patients; CSII has comparable efficacy compared to IVII in rapidly (12 hours) controlling blood glucose for the 5 next days.

Good glucose control in hospital during acute illness or surgery has been proven to improve morbidity and mortality [1-4, 6]. It has been proven cost effective in some pathologies; after cardiac surgery, the decrease in deep sternal wound infection saved 21 000 $ for 1 499 treated patients [12]. The best target blood glucose is difficult to determine in hospitalized patients. In most of the studies, glycaemia <8.3 mmol/l or even close to normal is necessary to obtain a statistical improvement in morbidity or mortality in different situations [2]; the level of benefit being directly linked to the level of glycaemia and not to the insulin dose [13]. This blood glucose range of 8.3 mmol/l has been reached in our study, in 12 hours, in the 2 groups of patients. The algorithms used in the study were comparable to the recent recommendations [1]. This protocol (Appendix) was derived from the Mirouze studies on IV insulin delivery and Skyler algorithms for subcutaneous insulin adaptation [14-16]. Correction doses were added when necessary to modify scheduled insulin. When correction doses were frequently required, or when the glycaemia increased with the scheduled insulin, doses were increased the following day to accommodate for increasing needs.

IVII using regular insulin is considered as the gold standard for poorly controlled hospitalized patients. In attempting to meet the illness related fluctuations in insulin requirements and to later return to lower doses, IVII gives good flexibility [3]. IV is preferred to subcutaneous insulin
infusion in recommendations, based on the rapidly changing insulin requirements, impaired perfusion of subcutaneous sites in ICU patients (blood pressure variations, vasoconstriction, severe edema) require pressor supports and use of total parenteral nutrition; stacking of the insulin effect causing protracted hypoglycaemia. These recommendations [1,3] are still based on CSII using regular insulin results and not rapid analogs, probably explaining the inadequate slow subcutaneous insulin kinetics unable to respond to the very rapid changes of insulin requirements. The kinetics of rapid analogs may allow rapid rate changes and avoid insulin stacking. A study has recently demonstrated the efficacy of subcutaneous insulin infusion in moderate ketoacidosis [9] and in controlling severely insulin resistant patients [17]. As well, IVII or CSII have been both shown to rapidly improve poorly controlled type 2 diabetic patients, allowing a rapid change of treatment or even a return to oral agents [18,19].

We excluded all severely ill patients from our study, an eventual CSII lack of efficacy would have been a risk for such patients. As well we excluded patients with a C peptide lower than 2 ng/ml in order to exclude type 1 patients whose insulin resistance would had been different from the majority of patients and patients with renal insufficiency to avoid insulin dose disparity or insulin kinetics modification.

Our study confirms the higher frequency of local complication of IV infusion compared to CSII. Complications due to IV infusion are well known. In patients with peripheral catheters, 3 types of complications occur frequently: phlebitis (19.7%), catheter related infections (6.9%) and obstructions of the catheter (6%) [7,8]. Infusion pumps were at three times more at risk of infections and phlebitis unless the infusate is prepared centrally in sterile pumps were at three times more at risk of infections and obstructions of the catheter. Complications linked to bed confinement such as venous thrombosis may be avoided.

CSII external pumps are now more user friendly, users benefit from different features such as preprogrammed bolus size or alarms facilitating the external pump handling and management. The choice of a single type of pump, a precise protocol, a nursing staff trained in collaboration with the department of diabetology will make CSII feasible in some medical facilities where diabetes is frequent and where hyperglycaemia has been proven to be an important feature for morbi-mortality such as cardiology, neurovascular or cardiac surgery departments – this is considered in different recommendations [1].

Metabolic control evolution was very similar in the 2 groups regarding capillary blood glucose during the first 12 hours, mean blood glucose and Daily Standard Deviation. The near normalization of CBG levels is obtained in about 12 hours in the 2 groups, the rapid efficacy of IV insulin infusion had already been shown [5]. The comparison between the 2 curves is interesting. Group 1 CBG were slightly higher during the first hours but the 2 curves got identical after about 9 hours. The statistical test didn’t show any statistical significance even for the post prandial values, this is probably due to the small number of patients. The differences between mean CBG were constantly less than 2 mmol/l. It is thus difficult to evaluate the clinical impact of such minor discrepancies for such a short time.

The percent of the post-prandial BG in the target range during the 5 days of treatment was significantly better in group 2, the mean post prandial BG were 10.39±0.27 mmol/l in group 1 vs 9.02±033 mmol/l in group 2, these values are relatively close from a clinical point of view. No dramatic excursions in group 1 were observed, as shown by the mean post prandial BG values, SEM and by the Daily Standard Deviation. No post prandial BG data have been found in the literature concerning morbi-mortality studies, a target range is thus difficult to define.

C peptide reduction was comparable in the 2 groups. Plasma C peptide decreased between day 1 and day 5 significantly in the 2 groups, by 48.6±5.3% in group 1 and 52.±8.7% in group 2. C peptide reduction is probably due in part to the near normalization of glycaemia (insulin secretion stops when glycaemia reaches 4.4 mmol/l). The second reason may be the improvement of insulin sensitivity linked to improved gluco toxicity and free fatty acid levels. Since we had only 2 C peptide assessments at day 1 and day 5, it is difficult to determine the impact of glycaemia near normalization in the 12 first hours and of insulin resistance improvement from 12 hours to day 5.

Insulin doses were lower in group 1 on day 1 and remained lower during the five days. Since the CBG levels
were comparable in the 2 groups, the lower insulin doses in group 1 actually showed a better efficacy of analog subcutaneous insulin and not an underestimate of the doses to be administered. The fact that insulin doses in group 1 tended to increase less than in group 2 for comparable glucose levels during the five days confirmed that the needs in insulin were actually less in group 1. This cannot be explained by the population characteristics since group 1 patients tended to have a higher HbA1c, BMI and triglycerides levels. The study of Umpierrez comparing subcutaneous lispro infusion and IV insulin infusion during moderate ketoacidosis also showed that lower doses of analogs were necessary to obtain comparable glycaemic control without any explanation.[11]. This is not a negative point since decrease in morbidity has been shown to be correlated with glucose and triglycerides control and not with insulin doses [20].

All patients had been hospitalized for sustained uncontrolled diabetes, as proven by their glycaemia and HbA1c at admission. The causes for the diabetes deterioration were investigated during hospitalization. Five asymptomatic urinary infections were the only reported sepsis. Seven oral agent failures were diagnosed. Other causes were considered as poor therapeutic or dietary compliance.

Our study has some limitations. We were not able to include the 60 patients that we planned to enroll during the one-year inclusion duration. Our randomization protocol explains the different number of patients in each group. Prior to the study, 60 cards numbered from 1 to 60 were prepared, and a card was drawn for each patient enrolled. Each number was randomly assigned to a treatment, medical staff being unaware of this assignment before drawing the card. Unable to include the total 60 planned patients; we didn’t obtain the same number of patients in each group. Nevertheless, the patient characteristics remained comparable except for higher HbA1c and triglycerides in group 1. Patients in this group had worse diabetes control and were probably more insulin resistant; this was not considered as a severe study limitation since we proved that despite higher HbA1c and triglycerides, group 1 results, in term of glucose control and insulin dose, were comparable to group 2 results, confirming the good efficacy of CSII.

Mild hypoglycaemic episodes were more frequent and post-prandial glycaemia were slightly higher in group 1, our subcutaneous algorithms were comparable to IV in the study, but subcutaneous boluses were slightly lower due to our fear of hypoglycaemia and our lack of experience. In fact subcutaneous analog has slower kinetics and could be adapted with less precaution.

Conclusion

This study showed that the efficacy of IV and subcutaneous infusion was comparable in rapidly controlling hyperglycaemia in type 2 diabetic patients. Intravenous insulin is underutilized in hospital settings due to institutional obstacles such as its restriction to intensive care units. The results of this study suggest using CSII and rapid analogs as an alternative to IVII to rapidly improve blood glucose levels in poorly controlled, non-critically ill, hospitalized type 2 diabetic patients.

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References

Appendix

Capillary blood glucose determination

Capillary blood glucose determinations were performed at the beginning of each basal rate period or meal period and the glucose level was used to determine the next period insulin dose and to eventually compensate for the programmed dose. Programmed doses were assessed every day, based on the glycaemic evolution during a period and prescribed for a glycaemia of 5.5 mmol/l. The “good” dose being the dose allowing the glycaemia to remain stable.

Nurses were to follow the compensatory protocol if the glycaemia was not in the target range they were asked to adapt the dose on a compensatory basis, on real time capillary blood glucose. The blood glucose target defined in the study was 4.4 to 6.6 mmol/l.

Intravenous insulin infusion protocol

IV regular insulin, diluted in saline 9°/9° (40 UI of insulin in 40 ml of saline 9°/9°), was administered continuously using an infusion pump. The insulin doses infused were distributed between basal rates during inter prandial periods and bolus during meal periods of 90 minutes.

Four periods of basal rates were determined:
— 9h00 AM to 12h00 AM,
— 1h30 PM to 7h00 PM,
— 8h30 PM to 1h30 AM
— 1h30 AM to 7h30 AM.

Three, 90 minutes periods of meal bolus were determined:
— 7h30 AM to 9h00 AM,
— 12h00 AM to 1h30 PM
— 7h00 to 8h30 PM

Each bolus duration was divided in 3 periods: a first period of 20 minutes, a second period of 20 minutes and a third period of 50 minutes; a different dose of insulin being prescribed for each period (for example: 8 UI hour⁻¹ for 20 minutes then 10 UI hour⁻¹ for 20 minutes and 6 UI hour⁻¹ for 50 minutes).

The first day of infusion, insulin doses were based on the patient’s weight (Table I).

Correction doses were performed at the beginning of each period, when glycaemia was out of the target range. The corrected doses were adapted to the glycaemia observed at the beginning of each period, based on the following protocol.

**Basal rates:**

- Glycaemia <2.2 mmol/l, basal rate was lowered of 0.4 UI hour⁻¹
- 2.2 < glycaemia < 3.3 mmol/l, basal rate was lowered of 0.2 UI hour⁻¹
- 3.3 < glycaemia < 4.4 mmol/l, basal rate was lowered of 0.1 UI hour⁻¹
- 4.4 < glycaemia < 6.6 mmol/l basal rate was administered as scheduled prescription
- 6.6 < glycaemia < 8.2 mmol/l basal rate was increased of 0.1 UI hour⁻¹
- 8.2 < glycaemia < 11.0 mmol/l basal rate was increased of 0.2 UI hour⁻¹
- Glycaemia >11.0 mmol/l basal rate was increased of 0.3 UI hour⁻¹ and a bolus of 60 UI hour⁻¹ was performed during 4 minutes.

Table I.

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<th>Basal rates for patients &lt;80 kg</th>
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<td>9h00 AM to 12h00 AM: 0.8 UI hour⁻¹</td>
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<td>1h30 PM to 7h00 PM: 1.2 UI hour⁻¹</td>
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<td>8h30 PM to 1h30 AM: 1.0 UI hour⁻¹</td>
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<td>1h30 AM to 7h30 AM: 0.6 UI hour⁻¹</td>
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<th>Prandial bolus for patients &lt;80 kg</th>
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<td>8 UI hour⁻¹ for 20 minutes</td>
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<td>10 UI hour⁻¹ for 20 minutes</td>
<td>12 UI hour⁻¹ for 20 minutes</td>
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<tr>
<td>6 UI hour⁻¹ for 50 minutes</td>
<td>8 UI hour⁻¹ for 50 minutes</td>
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Prandial bolus:

– Glycaemia >11 mmol/l, bolus was increased of 2 UI for each of the 3 periods (20 minutes, 20 minutes and 50 minutes)
– Glycaemia >16.5 mmol/l, bolus was increased of 3 UI for each of the 3 periods (20 minutes, 20 minutes and 50 minutes)

When correction doses had been required, doses were modified the following day to accommodate for the changing needs.

Protocol of subcutaneous insulin infusion

Lispro analog insulin was used in specific cartridges for External H-tron infusion devices. The subcutaneous infusion site was changed every 3 days and cartridge was changed as needed. The insulin doses infused were distributed between basal rates during inter prandial periods and bolus performed just before meal, using the same schedule as in the IV protocol.

Four periods of basal schedule were determined:

– 7h30 AM to 12h00 AM
– 12h00 AM to 7h00 PM
– 7h00 PM to 1h30 AM
– 1h30 AM to 7h30 AM

Three bolus were performed at the time of each meal: 7h30 AM, 12h00 AM and 7h00 PM.

The first day of infusion, insulin doses were based on the patient’s weight (Table II).

Correction insulin doses were performed when glycaemia was out of the target range at the beginning of each period. The corrected doses were adapted to the glycaemia observed at the beginning of each period, based on the following protocol:

– Glycaemia > than 11.0 mmol/l: additional bolus of 2 UI
– Glycaemia > than 16.5 mmol/l: additional bolus of 3 UI

When correction doses had been required, doses were modified the following day to accommodate for the changing needs.

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<td><strong>Meal bolus</strong></td>
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