



ronment, there is more of a difference between capillary and interstitial glucose in times of rapid fluctuations in blood glucose. Patients may well experience hypoglycaemic symptoms before the monitor has registered them. Medtronic released another CGMS version in 2004 - the "Guardian Telemetered glucose Monitoring System", which included alarms which could alert patients to impending hypo or hyperglycaemia. The subsequent "Guardian RT CGMS" added a real time glucose data display, and the latest model - the "Guardian Real Time CGMS" includes a modified monitor and radiofrequency transmitter. It can be integrated with the Minimed Paradigm insulin pump. The real time glucose devices by definition do not adjust for the lag between interstitial and capillary glucose (presenting just the ambient glucose interstitial concentration) which may delay the diagnosis of hypoglycaemia. Alarms on the recent models which are linked with trend arrows do go some way to addressing this. There are seven different CGM devices with FDA approval in the United States (including the "GlucoWatch, G2 Biographer", "GlucoDay", Menarini Diagnostics, "Pendra", Pendragon Medical and "STS", Dexcom), but only the Medtronic devices are currently available in Australia or New Zealand.

### Safety of CGM

The Medtronic CGMS and Dexcom STS devices are very well tolerated by subjects. The inserted needles allows potential infection, but sterile insertion techniques mean that the rate of irritation and infection is low (0-3% in studies). There is usually minimal discomfort associated with

wearing these monitors, but some subjects find them inconvenient (especially in the shower!). In our study of pregnant women with diabetes, 44/48 women assessed the Medtronic CGMS as 'very easy to use or 'easy to use'. The level of inconvenience was rated as 'minimal' or 'minor' in 81% of subjects (3). In contrast, the "GlucoWatch" has been withdrawn from the market because of a high rate of skin burns.

### The Accuracy of CGM

The critical question regarding the usefulness of glucose monitoring devices is, how accurate is it? There have been many studies investigating Minimed CGMS. Gross et al (4) studied 135 adults with type 1 diabetes and compared the CGMS values with meter results, and found a good correlation ( $r=0.91$ ) between these values. Other investigators have found similar results. Tansey studied 200 children in the outpatient setting and found a mean relative absolute difference of the Guardian CGMS to meter values of 12% (5).

However, CGMS does appear to be less accurate in the hypoglycaemic range, and over-diagnose hypoglycaemia. Bodes' study of 71 patients with Type 1 diabetes found that the Guardian CGMS produced 46% false hypoglycaemia alerts, and read on average 12.8mg/dl below the concurrent glucometer readings (6). Metzger studied nine subjects with well controlled diabetes and two non-diabetic controls with two concurrent CGMS monitors (7). Despite an overall correlation of 0.84 between the two monitors, the concordance was not ideal - with >70% of values displaying >10% difference. The CGMS

device may be less accurate in patients who are well controlled and have less glucose excursions, as it relies on linear regression to calibrate.

### Clinical studies using CGM

#### Non-pregnant population

CGMS has been extensively studied in non-pregnant diabetic patients where it has demonstrated clinical usefulness, and has been able to enhance decision making by detecting previously unrecognised post prandial hyperglycaemia and nocturnal hyper and hypoglycaemia. It is worth noting, however, the limited benefit seen in improvement in HBA1c in clinical studies. Four randomised studies with over 200 subjects between them showed no or minimal improvement in HBA1c in subjects using CGMS vs fingerprick monitoring. A recent study, using the real time Guardian RT in 156 subjects, did find a significant reduction of 0.6% in those using the glucose monitor (8).

#### Pregnant population

Yogev et al (9) conducted one of the first larger trials of the CGMS in pregnant women with Type 1 diabetes. Thirty four women underwent a CGMS study. Their CGMS results were analysed separately to their glucose diaries by a blinded experienced physician. The CGMS revealed multiple episodes of hyper and hypoglycaemia which were not detected by intermittent meter glucose levels. The insulin regimen of the patients was altered in 70% of the subjects, based on the CGMS results. Chen et al went on to study 47 Israeli and 10 American pregnant women

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with GDM, both diet and insulin treated, in the third trimester. In the Israeli women, they found a mean of  $131 \pm 31$  minutes per day of unrecognised hyperglycaemia ( $>140\text{mg/dl}$  or  $7.8\text{mmol/l}$ ) in the insulin treated group and  $94 \pm 23$  minutes per day in the diet group. Thirty one nocturnal hypoglycaemic events ( $>30$  minutes with glucose  $<50\text{mg/dl}$ ) were recorded in 14 of the insulin treated Israeli women and 8 of the 10 American women also had overnight hypoglycaemia. In 76% of the Israeli women and all of the American women, the CGMS study altered management decisions which had been based on fingerprick glucose monitoring. We also conducted a study of CGMS in the community setting -68 CGMS traces were obtained in 55 pregnant women - 37 with gestational diabetes, 10 with Type 2 and 8 with Type 1 diabetes (3). 42/68 (62%) of traces were assessed as providing additional information which altered clinical management decisions. The CGMS traces were most useful in patients with Type 1 diabetes, who are prone to more significant glucose excursions. Although intermittent fingerprick glucose estimation can certainly demonstrate post prandial hyperglycaemia, it appears from these clinical studies that CGMS can detect some hyperglycaemia that is missed with intermittent monitoring. Possible explanations for this include that postprandial hyperglycaemia may also extend for longer than can be demonstrated by a single fingerprick level, and that the CGMS removes the potential for error in the patients timing and method of glucose estimation.

The detection of unrecognised hypoglycaemia is another specific advantage of CGMS. Maternal hypoglycaemia is a common occurrence in pre-existing diabetes in pregnancy, occurring up to 15 times more often than in the non-pregnant state in the intensive management arm of the Diabetes Control and Complications Trial. Hypoglycaemia is potentially damaging to mother and fetus, with animal studies showing that hypoglycaemia in the first trimester can be teratogenic. Human data is limited, and observational studies have failed to link the incidence of hypoglycaemia with congenital malformations, but logic would suggest that hypoglycaemia is best avoided in developing brains. The more advanced continuous

glucose monitors which have hypoglycaemic alarms and trend alarms and enable patients to check their glucose with a meter value will also help to address the issue of poorer accuracy of the monitors in the hypoglycaemic range.

Another advantage of the continuous glucose monitors is the extra information and feedback it provides to the subjects. Pregnant women with diabetes tend to be highly motivated to improve their glucose levels, and the 24 hour profiles can be informative and useful for the subjects themselves. In our community based CGM study 43/48 subjects (90%) reported that their understanding of how they could control blood glucose was either 'clearly better' or 'better' after using the CGMS (as opposed to 'the same', 'worse' and 'clearly worse') (3).

As yet, there is no data in pregnant women showing an improvement in HBA1c with the use of CGM. There is of course also no data showing improved obstetric endpoints with CGM use, which would require very large subject numbers to be adequately powered.

#### Future role

CGM devices are also already being used to study new treatments and insulin regimes, because of their unique 72 hour glucose profile.

Pregnancy represents a unique chance for clinicians to study in detail the effects of glucose excursions on clinical end points. CGM may enhance our ability to identify the effects of hypo and hyperglycaemia on the developing fetus, by recording in new detail the extent of glucose excursions. Kersson (10) has already used the CGM to show that hyperglycaemic in the second trimester was linked to early large for gestational age babies in women with Type 1 diabetes. It may help us to tease out the role of hyperglycaemia amongst other contributors to macrosomia, placental dysfunction and other adverse events. In time, continuous glucose monitors may help to improve obstetric outcomes in pregnant diabetic women and their offspring.

#### Conclusion

CGM is a promising tool which has shown

some, but limited benefit in improving glycaemic control in women with diabetes in pregnancy. When used judiciously, with knowledge of its limitations, it is a useful adjunct for the clinician and patient who are striving to optimise glycaemic control in pregnancy. It shows promise as a research and clinical tool in the future, as technological advances improve its accuracy and features.

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

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**I**ntravenous insulin infusion (IVII) using regular insulin is currently used in hospitalized patients to rapidly control hyperglycemia. It has shown its efficacy in improving morbidity and mortality in hospitalized patients (1, 2, 3, 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, 7, 8, 9); it is, thus, often restricted to intensive care unit (ICU) patients. Continuous Subcutaneous Insulin Infusion (CSII) does not 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 hospitalized for uncontrolled diabetes type 2 diabetic patients. Efficacy was assessed on the average level of blood glucose in each group and on the time required to obtain near normal glycemia.

## 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 / m<sup>2</sup>, 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 1.

### Material

External H-tron infusion devices (Disetronic Medical Systems GmbH, 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.

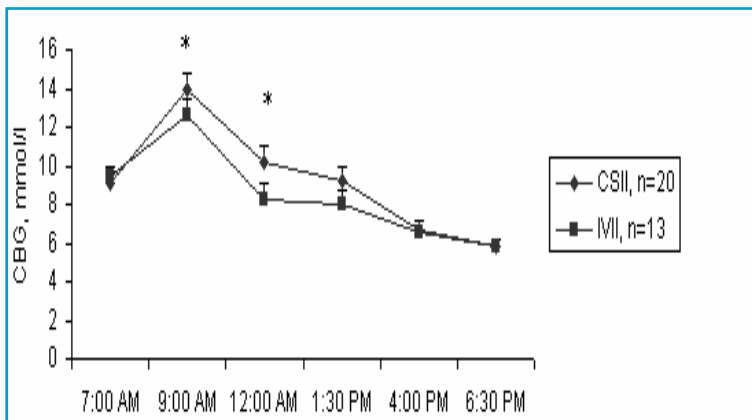
### Study design

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 (200g), 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, 6.30 PM, 4 PM, 11 PM, 1 AM, 4 AM and 90 mins after each meal. Blood glucose goals ranged from 4.4 to 6.6 mmol/l pre-meal and < 9.9 mmol/l post-meal.



**Figure 1:** Comparison of the evolution of capillary blood glucose (CBG) during the first 12 hours of insulin infusion.

\* Mann Whitney,  $P > 0.05$

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 administered continuously a solution of 0.4 ml of IV regular insulin diluted in 39.6 ml of saline 9‰ (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 cartridge was changed as needed.

### Statistics

The BMDP statistical software (Inc. Los Angeles, USA) was used for data analysis. All data is presented as Mean  $\pm$  SEM unless otherwise stated. Mann Whitney, Wilcoxon and Fischer exact tests were used. Statistical significance was defined for  $P$  values  $< 0.05$ .

### Results

Thirty-seven type 2 diabetic patients, agreed to participate to the study and were randomized. Four patients (2 in each group) were secondary excluded; due to the reception after inclusion of a 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  $11.2 \pm 0.7$  mmol/l, (NS, Mann Whitney)

and decreased significantly at day 5, in the 2 groups ( $7.0 \pm 0.4$  vs  $6.6 \pm 0.3$  mmol/l, Wilcoxon,  $P < 0.05$ ). The average CBG before initiation of insulin treatment were comparable between the 2 groups ( $9.1 \pm 0.7$  in group1 vs  $9.4 \pm 0.6$  mmol / l in group 2, NS, Mann Whitney) and decreased in a comparable way (figure 1) during the first 12 hours ( $-3.4 \pm 0.55$  mmol/l in group1 vs  $-3.60 \pm 0.55$  mmol/l in group2; 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 ( $42.0 \pm 3.1\%$  vs  $43.9 \pm 3.2\%$ , 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 ( $47.5\% \pm 3.5\%$  vs  $66.8 \pm 3.1\%$ ,  $P < 0.05$ , Fischer exact test). The Daily Standard Deviation of BG, a validated glucose stability parameter, was lower in group 2 than in group 1 at day 1 ( $3.24 \pm 0.27$  and  $2.53 \pm 0.22$  mmol/l,  $P < 0.05$ , Mann Whitney) but improved significantly from day 1 to day 5 to a comparable value in both groups ( $2.36 \pm 0.16$  in group1 and  $2.09 \pm 0.22$  mmol/l in group2; NS, Mann Whitney). The weight remained stable during the 5 days:  $-0.2 \pm 0.2$  kg in group 1 and  $-0.4 \pm 0.5$  kg in group 2.

Plasma C peptide mean values were comparable at day 1 and decreased significantly from day 1 ( $2.52 \pm 0.20$  ng/ml group 1;  $2.64 \pm 0.30$  ng/ml group 2) to day 5 ( $1.24 \pm 0.22$  ng/ml group 1;  $1.33 \pm 0.16$  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).

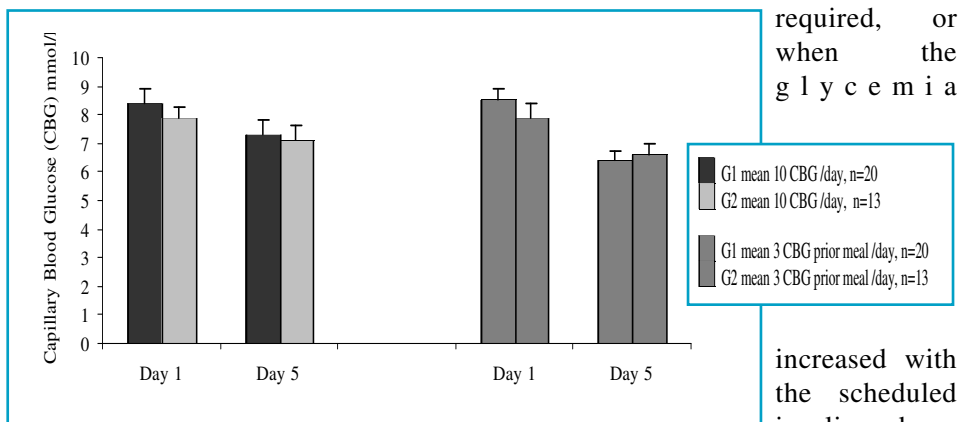
No severe hypoglycemia, as defined by the DCCT, was reported. The number of hypoglycemia (BG  $< 3.3$  mmol/l) per day of treatment and per patient tended to be higher in group1 ( $0.06$  in group1 vs  $0.015$  in group 2,  $P > 0.05$ , Wilcoxon).

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).



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**Figure 2:** Comparison of the evolution of the mean daily capillary blood glucose (CBG) at day 1 compared to day 5; considering first, the 10 CBG performed (pre and post meal) and second only the 3 pre meal CBG for each group (group 1 (G1) and group 2 (G2))

Mann Whitney test between the 2 groups: NS, \* Wilcoxon test:  $P < 0.05$

## Discussion

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

A good glucose control in hospital during acute illness or surgery has been proven to improve morbidity and mortality (1, 2, 3, 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 1499 treated patients (1). The best target blood glucose is difficult to determine in hospitalized patients. In most of the studies, a glycemia  $< 8.3$  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 glycemia and not to the insulin dose (14). 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 (15, 16, 17). Correction doses were added when necessary to modify scheduled insulin. When correction doses were frequently

needed.

IVII using regular insulin is considered as the gold standard for hospitalized poorly controlled patients. In attempting to meet the illness related fluctuations in insulin requirements and to later return to lower doses, IVII gives a 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) requirements for pressor supports and use of total parenteral nutrition; stacking of the insulin effect causing protracted hypoglycemia. These recommendations (1, 3) are still based on CSII using regular insulin results and not rapid analogs, probably explaining the inadequate slow subcutaneous insulin kinetic unable to respond to the very rapid changes of insulin requirements. The kinetic of rapid analog may allow rapid rates 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 (18). As well, IVII or CSII have been both described to rapidly improve poorly controlled type 2 diabetes patients, allowing a rapid change of treatment of even a return to oral agents (19, 20).

required, or when the glycemia

increased with the scheduled insulin, doses were increased the following day to accommodate for increasing

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 have been different from the majority of patients and patients with renal insufficiency to avoid insulin doses disparity or insulin kinetic 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 conditions and not at ward level (1). In many institutions, IVII is definitely restricted to ICU since it deserves a "high alert status" as any IV medications. For IVII, insulin has to be diluted in physiologic saline, and the rates have to be changed manually; most of IV infusion pumps do not have any memory. These procedures may be at risk of sepsis, dilution errors, insulin mistakes (glargine for regular) and rates changes may be delayed or forgotten. Subcutaneous insulin may be used in pre-filled cartridges, avoiding insulin mistakes or septic manipulations. Scheduled rates, as well as compensatory rates duration, may be pre programmed pump being able to change rates automatically. This is easier for the caregivers and avoids mistakenly maintaining high bolus rates instead of switching to basal rates. We did not observe any of these mistakes using IV in our study but in diabetology departments, physicians and nursing staff are used to insulin prescription and manipulation. On the contrary, mishandling could be more frequent in general medical or surgical facilities and CSII could be a great help (1). In case of multiple IV medications, CSII avoids the use of a dedicated line or multiple IV punctures.

It allows patients to be kept ambulatory. The patient's comfort and mobility are improved and thus 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 one single type of pump, a precise protocol, a nursing staff trained in collaboration with the department of diabetology will make feasible CSII in some medical facilities where diabetes is frequent and where hyperglycemia 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).

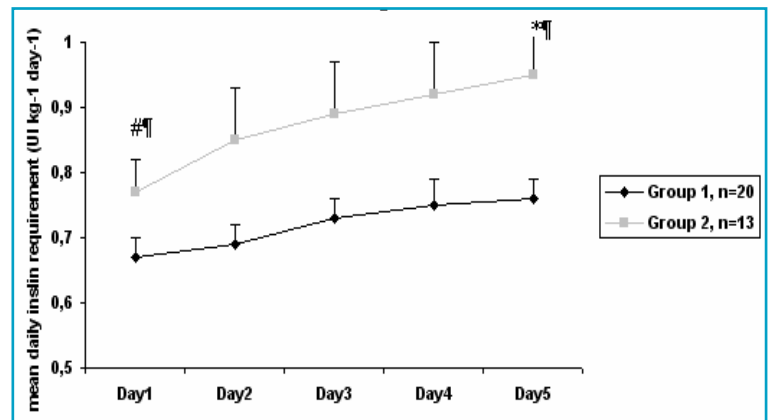
Metabolic control evolution was very similar in the 2 groups regarding capillary blood glucose during the first 12 hours, mean blood glucose and Daily Standard Deviation. The near normalization of CBG levels is obtained in about 12 hours in the 2 groups, the rapid efficacy of IV insulin infusion had 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 did not show any statistical significance even for the post prandial values, this is probably due to a 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 discrepancy 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 ± 0.33 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, of  $48.6 \pm 5.3\%$  in group 1 and of  $52.3 \pm 8.7\%$  in group 2. C peptide reduction is probably due in part to the near normalization of glycemia (insulin secretion stops when glycemia reaches 4.4 mmol/l). The second reason may be the improvement of insulin sensitivity linked to improved glucotoxicity and free fatty acids levels. Since we had only 2 C peptide assessments at day 1 and day 5, it is difficult to determine what is the impact of either glycemia near normalization in the 12 first hours and 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



**Figure 3:** Comparison of the evolution of the mean daily insulin requirements in the 2 groups for the 5 days  
Mann Whitney test: \*  $P < 0.05$ ; #  $P > 0.05$

obtain comparable glycemic 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 (12). All patients had been hospitalized for sustained uncontrolled diabetes, as proven by their glycemia 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 dietetic compliance.

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

## Conclusion

This study showed that the efficacy of IV and subcutaneous infusion was comparable in rapidly controlling hyperglycemia in type 2 diabetic patients. It is stated that intravenous insulin is underutilized in hospital settings due to institutional obstacles such as their restriction to intensive care units. The results

of this study would allow using CSII and rapid analog 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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