Technical risks with subcutaneous insulin infusion

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SUMMARY
The popularity of continuous subcutaneous insulin infusion (CSII), as a way for achieving long term strict glycaemic control in diabetic patients, has increased over the last ten years. Most reports on technical faults, often leading to metabolic emergencies, mainly ketoacidosis, have been published in the 1980s. Obstruction of infusion set and infection of infusion site are the most frequent events. Insulin precipitation or aggregation is thought to be one of the precipitating factors. Few data are available about failures of the pump itself. We report our experience of pump malfunctions recorded between 2001 and 2004 in 376 pumps used by patients treated with CSII therapy in Brittany. Recent studies indicate a decrease of metabolic complication frequency during CSII. This suggests technical improvements and/or a greater experience of physicians in selecting and educating patients. We report instructions for monitoring insulin pump therapy that should be included in a formal educational program for pump users. Clinical studies using newly available devices should reassess technical risks associated with CSII.

Key-words: Insulin pumps · Technical failures · Ketoacidosis · Education.

RÉSUMÉ
Le traitement ambulatoire par pompe à insuline sous cutanée connaît un essor considérable depuis une dizaine d’années en raison de l’amélioration métabolique qu’il peut apporter chez certains patients diabétiques. Le risque de survenue d’incidents techniques, pouvant entraîner des décompensations métaboliques aiguës, principalement des acidocétoses, a surtout été étudié dans le courant des années 1980. Les obstructions de cathéter et les infections du site de perfusion, probablement favorisées par une agrégation ou une précipitation de l’insuline, sont les incidents techniques les plus fréquemment rapportés. Plus rarement, des données ont été publiées sur les incidents relatifs à la pompe elle-même et nous rapportons notre expérience régionale concernant les pannes survenues entre 2001 et 2004 sur un parc de 376 pompes. Les études les plus récentes indiquent une diminution de l’incidence des complications métaboliques aigües au cours du traitement par pompe à insuline, suggérant une meilleure maîtrise de cette technique. Il pourrait s’agir d’une plus grande expérience des prescripteurs dans la sélection et l’éducation des patients. Nous rappelons les consignes spécifiques de surveillance et de sécurité qui doivent être impérativement transmises aux futurs utilisateurs d’une pompe à insuline. Des innovations techniques ont également pu diminuer la fréquence des incidents mais il apparaît nécessaire de réaliser des études cliniques utilisant les nouveaux matériaux pour réévaluer les risques techniques de cette thérapeutique.

Mots-clés : Pompe à insuline · Incidents techniques · Acidocétose · Éducation.

Guilhem I, Leguerrier AM, Lecordier F, Poirier JY, Maugendre D††. Technical risks with subcutaneous insulin infusion
Diabetes Metab 2006;32:279-284

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Received: January 10th, 2006; accepted: March 14th, 2006.
Introduction

Continuous subcutaneous insulin infusion (CSII) was introduced in the late 1970s as a way of achieving strict glycaemic control in type 1 diabetic patients. The initial excitement over this new technology waned within a few years due to increasing doubts about insulin pump safety and efficacy [1]. However, interest in the role of CSII in improving metabolic control was renewed after 1993 when the Diabetes Control and Complications Trial was published [2,3].

Among the potential complications of CSII use (e.g. diabetic ketoacidosis, hypoglycemia, pump or catheter malfunctions and site infections), the risk of diabetic ketoacidosis (DKA) is still a matter of debate. In early studies, CSII use was associated with an overall increased frequency of DKA and infusion system malfunction was reported as a major cause of DKA [4-7]. However, the increased risk of DKA was not confirmed in studies published after 1993, as discussed in recent reviews on insulin pump therapy [1,2]. Accordingly, the majority of studies reporting on technical difficulties with CSII were published before 1990, suggesting that improvements in this technology and/or in patient and physician vigilance have lowered this risk.

The present review will focus on the technical problems associated with CSII and their metabolic complications, highlighting the need of an adequate education program to prevent these risks.

Technical problems with CSII

Although pump failures are not rare events, most infusion system failures involve the infusion set components and the subcutaneous infusion site [5].

Failures of infusion sets

Various types of infusion set defects have been reported: infusion set obstruction, leakage from the infusion site while the needle is placed in the subcutaneous tissue or if the cannula is dislodged, leakage at the infusion set connection (between the syringe and the infusion tubing) or leakage at the infusion tubing (between the syringe connection and the injection site) [5,8].

In a 1-year prospective study including 127 patients, Mecklenburg et al. recorded the types and frequencies of catheter defects [5]. Of the 127 patients, 103 (81%) experienced a total of 886 infusion set failures. The most common malfunction was due to an obstruction of the infusion tubing. This is in agreement with the study of Peden et al. who have shown that insulin delivery failures due to blockage of the indwelling needle were the most common cause of acute severe loss of glycaemic control during a follow-up of 1 880 patient-months [4]. It was suggested that the occlusion of the indwelling needle may be due to insulin precipitation [4,5].

The second most common type of infusion set malfunction is leakage from the infusion site. Pickup reported 3.4 episodes/patient in an 8-month study [8] and Mecklenburg 262 episodes in 1 428 patients-months [5]. Mecklenburg et al. hypothesized that leakage from the infusion site may be related to the formation of a relatively impermeable sheath around the subcutaneous needle. In this study, only 31% of patients experienced such leakage. These patients could either display a special cutaneous response to the insulin set infusion or differently manage CSII therapy, since frequent switching of injection sites might reduce the occurrence of this adverse event.

Leakage at the infusion set connection or in the infusion tubing are the least frequently reported malfunctions [5]. In a more recent 6 month-study, Hirsch et al. did not observe any catheter leakage. This could be attributed to the small number of patients in this study (n=10) or to improvements in catheters [7].

Patients should be aware that the pump alarm system usually does not detect leakage. Moreover, in more than 85% of occlusion events, the metabolic deterioration occurs before the activation of high pressure alarms [7,9]. Failure of infusion sets is often associated with transient loss of metabolic control and is a major cause of DKA [4-7]. It is also associated with deterioration in chronic metabolic control [10]. Although improvements have been made with pump alarm system and catheters, patients should suspect an infusion set malfunction when unexplained hyperglycaemia occurs.

Infection and inflammation of the infusion site

It is the most frequent complication associated with CSII and a major reason for discontinuation of this treatment [1]. Moreover, this complication can be serious since an infected infusion site has been implicated in the development of a toxic shock syndrome and a case of bacterial endocarditis, the latter leading to death [11,12].

Erythema, subcutaneous nodules or abscesses, requiring antibiotic treatment and/or surgical drainage, have been reported [13]. Staphylococcus aureus and Staphylococcus epidermidis are often involved [11,14]. Additionally, cases of contact dermatitis attributed to the component of the infusion sets and tape have been described [1].

Due to the lack of standardization of data, frequency of infected or inflamed infusion sites varies widely in the literature, from 0.06 to 12 events per patient per year [3].

Mecklenburg et al. reported an experience with 161 patients (2 978 patient-months) before and after the onset of pump therapy. No patients had infections at the insulin injection site before the onset of pump therapy whereas after pump usage, 29% of them had a total of...
109 infected infusion sites, corresponding to a frequency of one event in every 27 patients-months [11]. 54% of patients with infections had more than one episode, and there was a significantly increased risk of experiencing a second infection once a first infection occurred. Clearly, the indwelling cutaneous needle used during pump therapy predisposes to infection at the insulin injection site. However, the fact that cutaneous infections occur only in one third of patients and recur in some of them, indicates several additional contributing factors. It was suggested that patients who are nasal carriers of Staphylococcus aureus may be at higher risk [11]. The use of diluted insulin (before 1990) may be another risk factor, possibly due to tissue disruption favoured by a higher flow rate or to a less efficient antibacterial effect of diluted insulin preparations [11].

Giving appropriate instructions to patients before CSII use is crucial to prevent cutaneous complications. Chanteleau stressed that since patients were advised to use topical disinfectant prior to insertion of the needle, the rate of serious infections has declined in their centre [6]. However, the risk of acute cutaneous complication increases with the indwelling time of the catheter needles, mainly when exceeding 48 h [14]. Finally, patients with poor metabolic control may be at higher risk [6].

**Insulin precipitation or aggregation**

The type of insulin preparation has been reported as one of several possible factors influencing the occurrence of both obstruction of the infusion tubing and infection of infusion sites during CSII [15,16].

It has been shown that phosphate-buffered insulin was associated with less infusion site inflammation and infusion set occlusion than unbuffered insulin and, therefore buffered insulin is preferred [9,10,15].

Insulin concentration is another factor influencing insulin aggregation. Hirsch et al. [7] examined occlusion rate with two different concentrations of insulin. They showed that occlusion occurred more frequently with the U-100 compared with the U-40. These authors hypothesized that, rather than the flow rate per se, the increased time duration of insulin in the syringe and catheter may promote increased insulin aggregation.

More recently, cannula occlusion has been reported with use of short-acting insulin analogs [17] whereas in vitro studies [16] and randomised prospective trials have failed to demonstrate any difference in catheter occlusion between short-acting insulin analogs and regular insulin [18]. Interruption of insulin analog infusion leads to greater and more rapid metabolic deterioration than an interruption of regular insulin infusion. However, insulin analogs have been shown to correct this metabolic deterioration more rapidly [19]. Nevertheless, due to their pharmacokinetic advantages, short-acting insulin analogs are now extensively used in CSII [1].

Although the use of buffered insulin has decreased the frequency of occlusion, pump users continue to experience unexplained hyperglycaemia that is corrected by catheter change, suggesting that insulin precipitation or aggregation remains an unsolved problem in CSII.

**Malfunctions of the insulin pump**

Various malfunctions of CSII systems have been described, including pump breakdown, pump runaway, battery or drive mechanism failure, corrosion in battery or other components, memory loss, inability to start pump out of an electrical “lock” position and alarm malfunctions [5,20]. Most studies reporting pump malfunctions have been published in the late 1980s and next to no data are available with the new generation devices.

In the study of Mecklenburg et al. [5], 25% of patients detected a total of 41 episodes of pump fault; the most common was drive mechanism failure, accounting for 29% of the events.

Between April 2001 and October 2004, we studied pump malfunctions occurring in 376 new insulin pumps used in ambulatory treatment with CSII. Cumulative follow-up was 410 pump-years. We recorded all the defects that were observed by patients and confirmed by our team. Failures of infusion sets were excluded. A malfunction occurred in 94 pumps (23 malfunctions per 100 pump-years), after 0.1 to 36 months of functioning. The median pump failure time was 28 months (figure 1). Complete
Breakdown of the pump was the most common event, accounting for 46% of cases; in 29% of events, a mechanical defect occurred and the manufacturer recommended replacement of the pump; in 14% of events, repeated alarms required replacement; the remaining 12% of events were due to a minor defect. Over-delivery of insulin by pump runaway was not observed. Patients switched to multiple insulin injections if necessary. Pumps were sent back to the manufacturer; one was normal, 8 were repaired and 85 were replaced. Information about the cause of malfunctions was given by the manufacturers in only 13 cases.

Our data showed that in spite of advancements in CSII technology, insulin pump malfunctions remain frequent events.

### Acute metabolic complications related to technical defects of CSII

#### Ketoacidosis

This is the second most frequent acute complication associated with the use of insulin pumps. The lack of a subcutaneous depot of long acting insulin may predispose to ketoacidosis. Consequently, ketoacidosis can develop very quickly during an intercurrent illness or a technical failure of the infusion system [4,21]. Moreover, it has been shown that the mean serum potassium concentration on presentation to hospital with ketoacidosis was significantly higher in patients treated with CSII as compared with those treated with insulin injections [21]. Severe hyperkalaemia with CSII can be serious as episodes of cardiac arrest have been reported [4,12,21].

Early studies indicated a high rate of DKA with CSII [4,11], but the frequency of DKA decreased in the late 1990s, presumably due to an increase in patient vigilance, physician experience with CSII and technical improvements [2]. However, the specific DKA risk of CSII related to a potential technical or mechanical failure remains [21]. Infusion system failures are especially problematical when they occur at night as patients can be deprived of insulin for many hours while asleep.

Several studies reported that malfunction of the infusion system or inflamed infusion sites were the precipitating factors in approximately 40% of episodes of acute uncontrolled diabetes [4,6]; whereas in other studies, about 70% of episodes were precipitated by intercurrent illness [11,21].

Whatever the precipitating factor, DKA during CSII is rapid in onset and pump users have to be instructed to react promptly to technical problems or unexplained hyperglycaemia. An adequate education program about DKA risk prevention should be provided.

#### Hypoglycaemia

Severe hypoglycaemia is an unusual complication with CSII therapy. Furthermore, the risk of severe hypoglycaemic events may be reduced by CSII as compared with intensive insulin injection regimens [1-3].

Severe hypoglycaemia occurs very infrequently with pump malfunctions. In our study, no pump runaway was observed. While few case reports on over-delivery of insulin by insulin pumps have been described this event is exceedingly rare [1,5]. However, in case of severe hypoglycaemia, the disadvantage of CSII is to continue insulin delivery, thereby maintaining severe hypoglycaemia.

### Prevention and treatment of technical and metabolic complications of CSII

Most studies reporting on CSII treatment-related complications stressed that CSII risks can be minimized when the physician is more experienced and when appropriate instructions are given to the patient [1,2]. Pickup et al. emphasize the need to limit the availability of CSII for use of specialist centres and selected patients [2].

An adequate education program should include the following issues:

#### Blood glucose monitoring

To minimize the risk of DKA and to allow early recognition of hypoglycaemia, patients should monitor 4-5 times a day (before meals, at bedtime, and when necessary, at 3 AM).

#### Technical aspects

Frequent switching of injection sites may reduce the occurrence of obstruction and leakage from the infusion site.

Cannula dislodgement can be improved by additional taping of the cannula.

Battery failure and empty syringe are common causes of interruption of insulin delivery. Patients should know the corresponding alarms and they should always have spares available.

When a pump dysfunction is suspected, patients should inject insulin with pen. They must always have insulin pens available to switch to multiple insulin injections if necessary.

During outpatient visits, physicians should ask patients about any technical difficulties. They must examined the pump and check the pump memory, especially looking for previous alarms.

#### Prevention of cutaneous complications

Cutaneous complications during CSII can be successfully prevented by appropriate antiseptic preparation of the skin [14], including usual body hygiene, handwashing before insertion of needles, topical disinfection of needle insertion sites, sterile covering of the needle, needle change every 48-72 h and no catheter reuse [14]. Moreover, in case of an inflamed infusion site, the needle should be promptly removed.
If the patient is allergic to tape, hypoallergenic tape or other skin protective agents may be necessary.

Management of hypoglycaemia

Frequent self-monitoring of blood glucose may help to avoid hypoglycaemia. Patients and family members should be instructed about the causes, symptoms, prevention and treatment of hypoglycaemia, including the use of glucagon. After severe or unexplained hypoglycaemia, patients should check basal infusion rates and bolus doses previously infused as over-delivery of insulin is often due to programming error.

To avoid maintenance of severe hypoglycaemia by the open-loop device, we encourage patients, especially those living alone, to programme the safety alarm which will stop the pump if it has not been manipulated for more than 12 hours. In addition, family members of pump users should stop or remove the pump when severe hypoglycaemia occurs.

Management of hyperglycaemia/prevention of DKA

The patient must be instructed that urine ketones or ketonemia should be checked if unexplained hyperglycaemia occurs. If ketones are present, the infusion set and site should be changed immediately. Short-acting insulin analogs should be given by pen every 2 hours, until ketones disappear.

In the event of ill health, monitoring of blood glucose must be intensive to adjust the insulin infusion rate. A professional healthcare “24 hours on-call” service should be available to assist pump users in management of such events.

 Interruption of the pump

This interruption should not exceed 2 hours to avoid metabolic deterioration [22]. Moreover, it has been shown that a local depot of insulin by a bolus injection should be given to patients whose pump has been deliberately stopped [19].

Conclusion

CSII has proven to be effective in optimizing glycaemic control in selected diabetic patients. Consequently, CSII is now widely used in clinical practice. However, technical risks of this therapy should not be underestimated. We underline the importance of patient selection, education and follow-up. A professional 24 hour on-call service and frequent out-patient visits for technical reassessment are required. Finally, there is a need for evaluating newly available devices and for establishing procedures for testing insulin pumps.

Acknowledgments – We thank Christine Kelly for helpful comments during the preparation of the manuscript.

References


