MEASUREMENT OF ACCIDENTAL URINARY INSULIN LOSS FROM A DISLOCATED INTRAPERITONEAL INSULIN CATHETER

W.N. KÜHN-VELTEN (1, 2), H. GENESIUS (1), K. J. WIEFELS (1)

SUMMARY - We report the case of a type-2 diabetic woman who received continuous intraperitoneal insulin infusion and developed deterioration of metabolic control by accidental insulin loss into urine (54 U per day) as a consequence of catheter migration which probably resulted in bladder wall injury. Due to iodine allergy of this patient, an analyte addition procedure for insulin quantification in urine had to be applied to allow proof of insulin loss from the catheter tip before as well as reversal to zero insulin excretion after implantation of a new intraperitoneal port and a shorter catheter. The lost fraction of insulin accounted nearly completely for the difference between pre- and postoperatively required insulin doses (146 versus 88 U per day).

Key-words: diabetes mellitus, continuous intraperitoneal insulin infusion, insulin analysis, analyte addition procedure.

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Continuous intraperitoneal insulin infusion has developed as an attractive alternative option in the treatment of patients with diabetes mellitus, in particular those exhibiting delayed absorption of subcutaneously applied insulin [1-3]. There are two alternatives for system assembly, namely complete implantation versus external pump coupled to an intraperitoneal port [1]. This insulin application route has certain advantages as it realizes a more physiological simulation as compared to subcutaneous delivery, and since coupling of implantable pumps to intraperitoneal insulin delivery is, on the average, associated with lower morbidity and a higher survival than coupling to intravenous catheters [4]. Irrespective of assembly mode, frequent complications of intraperitoneal systems include catheter breaking and migration, catheter obstruction due to macrophage chemotaxis or local tissue-omentum reaction, formation of insulin aggregates, as well as subcutaneous or deeper infections; abdominal location of the catheter also affects the efficiency of insulin infusion [4-9]. Duodenum and cecum erosion have been reported as unusual but severe complications of intraperitoneal insulin delivery from an external pump [10-11].

Here we report, for the first time, on a novel complication in the course of the intraperitoneal insulin infusion scheme in a type-2 diabetic patient with subcutaneous insulin resistance, namely deterioration of metabolic control by accidental insulin loss into urine due to catheter dislocation probably resulting in bladder wall injury.

CASE REPORT

In the 68-year old woman (154 cm, 48.0 kg, BMI = 20.2 kg/m²), type-2 diabetes mellitus was first diagnosed in 1992, and conventional insulin therapy started in 1995 with satisfactory outcome following a myocardial infarction. Since the patient developed an extreme subcutaneous insulin resistance during the year 2000 with required insulin doses frequently exceeding 1000 U per day and blood glucose concentrations still remaining at around 25 mmol/l, an intraperitoneal port (DiaPort, 18 cm catheter length, MiniMed model 506 (Sylmar, CA, USA) as the external pump) for continuous intraperitoneal insulin infusion (CIPII) was implanted in November 2000. As a result, insulin doses (Hoechst Insuman Insufat 100) could be drastically reduced, the daily rate amounting to 59 U with a mean blood glucose concentration over 24 hr of 11.2 mmol/l on discharge.

By the end of June 2001, the patient was readmitted to the Diabetes Clinic because of constant hyperglycemia and increasing insulin demand (Table I). On admission, the patient complained of pain in the right hypogastrium. There were no signs of acute inflammation (C-reactive protein 6.2 mg/l), the insulin pump was correctly functioning as established on the basis of technical examination, and the catheter was flushable. However, computer tomography clearly demonstrated a distinctive impression of the right-lateral urinary bladder wall in direct contact with the catheter tip. Though the exact position of the tip could not be determined due to the limited resolution of the method, it was presumed that the catheter might have injured or even perforated the bladder wall with the consequence of accidental urinary loss of a fraction of the infused insulin. It was therefore mandatory to elaborate an alternative method in order to verify this working hypothesis and, eventually, to determine that fraction (see below).

After the successful proof of insulin flowing off (see below), a new intraperitoneal port (DiaPort, 15 cm catheter length, MiniMed model 508 external pump) was surgically implanted since previous attempts to external catheter repositioning were unsuccessful. With the exception of a transitory wound infection

<table>
<thead>
<tr>
<th>Parameter /Time point (ref.: surgery)</th>
<th>3 days before</th>
<th>3 days after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood glucose during 24 hr (mmol/l)</td>
<td>14.0</td>
<td>15.3</td>
</tr>
<tr>
<td>Fasting serum insulin (mU/l)</td>
<td>22.4</td>
<td>76.9</td>
</tr>
<tr>
<td>Fasting serum C-peptide (µg/l)</td>
<td>8.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Insulin infusion (U/24hr) – basal rate</td>
<td>62.0</td>
<td>37.0</td>
</tr>
<tr>
<td>– on-demand</td>
<td>84.0</td>
<td>51.0</td>
</tr>
<tr>
<td>Estimated urinary insulin loss (U/24 hr)*</td>
<td>54 ± 12</td>
<td>1 ± 10</td>
</tr>
</tbody>
</table>

* Mean ± SD; see Figure 1 for details.
peak level of C-reactive protein: 51 mg/l) no further complications occurred. The patient was dismissed in metabolically satisfactory condition; a mean blood glucose concentration of 8.7 mmol/l during 24 hr was finally achieved with a daily insulin dose of 136 U.

**BIOLOGICAL ANALYSES**

In addition to the routine metabolic analyses (Table I), urine samples were collected 3 days before (1,200 ml /24 hr) and after catheter port replacement (1,400 ml /24 hr), respectively. The analytical method for insulin quantification was a microparticle-enzyme immunoassay (MEIA) running on an Abbott IMx system. It was established in concomitant experiments that the analyte was stable in frozen (−20°C) urine samples for at least five days. To overcome possible matrix effects and to achieve the necessary accuracy in low-level insulin quantifications, an analyte addition procedure was applied [12]. To 1 ml of diluted urine specimen (1: 1,000 with 9 g/l NaCl) or NaCl, 1 ml of diluted (from 1: 385,000 to 1: 4,150,000 with NaCl) Insuman Infusat 100 aliquots were added. When results were plotted against added insulin concentrations, slopes of the regression lines represent analyte recovery and abscissa intercepts represent analyte concentrations in unspiked samples irrespective of recovery and test signal height (Fig. 1). For the urinary insulin measurements, recoveries were constant (range 10.2 to 11.9%; average 11%), but corrected insulin concentrations in unspiked samples differed significantly (P < 0.0001) between pre- and postoperative samples where the former (P < 0.0001) but not the latter (0.20 < P < 0.50) were different from zero. In addition, the regression line for the postoperative urine sample did not differ from the insulin standard curve obtained with NaCl alone (Fig. 1). After
consideration of an average 11% recovery, the results indicate that the patient had lost about 45 U of insulin/\textit{h} corresponding to 54 U per day into the urine via the migrating catheter before replacement, and that this measure could explain the difference in insulin requirements and serum levels in relation to the post-operative state (Table I).

**DISCUSSION**

To our knowledge, this is the first report of insulin leakage from an intraperitoneal insulin infusion catheter into the urinary bladder. Since the usual radiocontrast imaging [9], which was also successfully applied to prove catheter perforation into the duodenum in a single case [10], could not be performed here due to contrast medium allergy, an alternative had to be developed in order to verify inappropriate insulin loss from the catheter tip and to determine therapeutic consequences.

The analyte addition procedure is one possible solution of the problem to quantify small amounts of an analyte in complex and variable matrices. It is, for instance, the method of choice for detection of trace elements by atomic absorption spectrometry; similar approaches include addition of an internal standard, which is chemically different from the analyte, or of the isotopically labelled analyte [12]. All these procedures have the capacity to exclude matrix effects and variable recoveries as confounding analytical variables and were therefore particularly appropriate for the case reported here. In the direct comparison of urine samples obtained before and after catheter replacement, the analyte addition procedure revealed indeed identical recoveries but different insulin concentrations in unspiked samples. Though insulin re- sorption kinetics was not investigated in detail, the approximate balance demonstrated that the amount lost was nearly equivalent to the difference between pre- and post-operatively infused insulin doses; this conclusion was supported by similar glucose concentrations found. Further post-operative improvement of glycemic control by 43% required an expected 55% higher insulin infusion rate.

This proven urinary excretion of considerable amounts of insulin was probably due to bladder wall injury as a result of intraperitoneal insulin catheter migration. Though the catheter was more flexible than that used in a previous case of duodenum perforation [10], it can not be excluded that this particular case of catheter dislocation could have been promoted by the guide catheter of the DiaPort system which is necessarily still more rigid than catheters of the completely implantable systems. It is suggested that such a complication should generally be taken into consideration in cases where catheter occlusion or breaking had been excluded as the cause of a sudden increase in insulin doses required with adequate metabolic responses missing.

**REFERENCES**


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