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Autopsy and pump data

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Sudden Death due to Diabetic Ketoacidosis Following Power Failure of an Insulin Pump: Autopsy and Pump Data.

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Keywords

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None.

Informed consent
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Sudden Death due to Diabetic Ketoacidosis Following Power Failure of an Insulin Pump: Autopsy and Pump Data

Abstract

**Purpose.** To report a case in which autopsy findings and data from an insulin pump illustrate the course up to the death of a 31-year-old man with a history of type 1 diabetes mellitus who was found dead in his apartment with his insulin pump disassembled and placed in another room.

**Methods.** Autopsy findings including histological, toxicological and biochemical examination are presented. Postmortem download of data from the insulin pump gave the history of the pump, which included blood glucose, insulin bolus, carbohydrate intake and the time course in the days to death, and the pump settings were recorded. For this case report, police reports on the death as well as hospital records were also reviewed.

**Results.** At the patch for the insulin pump, nothing abnormal was found. Biochemical analysis showed glucose of 35 mmol/L in vitreous humor fluid indicating antemortem hyperglycemia, and ketone bodies in the blood of 11.0 mmol/L indicating ketoacidosis. Acute pulmonary hemostasis, chronic fat accumulation in the liver and acute fat accumulation in the kidneys were histological detected. There were no signs of late diabetic complications such as nephropathy or cardiovascular disease in the tissues. Insulin pump data showed that after three alarms, a power failure of the pump occurred leading to discontinuing insulin delivery, and about 48 hours before the deceased was found dead, his body was depleted of insulin.

**Conclusion.** The cause of death is believed to be diabetic ketoacidosis due to completely lack of insulin because of power failure of the insulin pump, which therefore has been a decisive factor in the cascade of events that led to death. The case is, to our knowledge, the first to illustrate a death caused by diabetic ketoacidosis which is supported by autopsy findings and by data of an insulin pump up to the time of power failure. It is a strong example of usefulness of postmortem download of data from insulin pumps to help determine the cause of death among diabetics. Forensic pathologists should therefore review data and history of the pump systematically.

**Keywords**

Diabetic ketoacidosis, sudden death, insulin pump, type 1 diabetes mellitus, continuous subcutaneous insulin infusion, hyperglycemia.

1. Introduction

Diabetic ketoacidosis (DKA) is a serious, life-threatening complication of diabetes and can occur in any type of diabetes. However, it is most frequently occurring in type 1 diabetes mellitus, which is a chronic autoimmune disease that manifests in hyperglycemia due to decreased or lack of insulin secretion caused by an autoimmune destruction of insulin-producing beta cells in the pancreas [1, 2]. Hyperglycemia increases the risk of developing sequelae but may also be of importance in the acute stage where DKA may develop.

**Diabetic Ketoacidosis**

With absolute insulin deficiency, as can be seen in untreated or undiagnosed type 1 diabetes, the body does not have access to energy via glucose, so it oxidizes free fatty acids to ketone bodies (beta-hydroxybutyrate and acetoacetate) resulting in ketoacidosis [1, 3, 4]. In DKA, the body attempts to compensate for the metabolic acidosis by hyperventilation, so carbon dioxide is vented and pH thus maintained. If the body is unable to do this, carbon dioxide will accumulate and the pH drops rapidly and can cause death [3, 4]. Symptoms of hyperglycemia (e.g. polyuria, dehydration, weight loss) may be present for several days but the development of metabolic changes at DKA typically occurs within 24 hours where the symptoms can be expanded with nausea and vomiting (>50%), fatigue, change in consciousness and ultimate coma and death. However, DKA may develop in less than 12 hours [3].

A literature review by Palmiere et al. [5] concludes that determination of vitreous glucose, beta-hydroxybutyrate in the blood and glycated hemoglobin in the blood are standard analyzes that can easily identify DKA in both diagnosed and non-diagnosed diabetics. Various studies agree on the following ranges for beta-hydroxybutyrate in the blood: <0.5 mmol/L (<5.2 mg/dL) is normal; 0.5-2.5 mmol/L (5.2-26.0 mg/dL) is increased; >2.5 mmol/L (>26.0 mg/dL) is pathological. There are several researchers who have performed postmortem studies of ketone bodies in the blood, and beta-hydroxybutyrate is the most reliable postmortem indicator of ketoacidosis and its severity [5, 6].
Vitreous glucose is preferentially used in postmortem biochemistry, as serum glucose decreases to a far greater extent after death due to autolysis and/or microbial metabolism. Moreover, vitreous humor is well protected from contamination due to its isolated location in the eye cavity [6-8]. To our knowledge, there is no internationally established range for the normal value of glucose in vitreous humor, but several researchers have investigated when vitreous glucose is considered elevated, and a cut-off value of between 10 and 13 mmol/L is reported [5, 6]. A study by Coe [9] reviewed over 6,000 cases and never found vitreous glucose concentrations above 11.1 mmol/L except in diabetics. Therefore, it is concluded that roughly all vitreous glucose values below 10 mmol/L are within the normal range.

Insulin Pumps

In insulin pump therapy, only fast-acting insulin is administered to imitate normal, physiological insulin secretion throughout the day. The insulin is given as a basal rate (continuous dose throughout the day), that can be adjusted to vary over the course of the day, and as a variable bolus dose administered to meals and correction of blood glucose and which the patient initiates via the pump [10, 11]. Compared to conventional insulin therapy with multiple daily injections (MDI), it has been shown that insulin pump therapy provides improved metabolic control in diabetics [12, 13], but as the pump only provides fast-acting insulin, a stop in this delivery may be fatal, as the body rapidly runs out of insulin, and thus the risk of developing DKA is potentially great.

The literature has previously reported cases with DKA as the cause of death due to, for example, intake of drugs [14, 15] or undetected diabetes mellitus [16, 17]. A single case report has described a death due to DKA in a type 1 diabetic with insulin pump, where the deceased had not replaced an empty ampoule of insulin [18]. In addition, a case has been described using the possibility of looking at data from an insulin pump and a continuous glucose monitoring system that showed the progress of blood glucose to death caused by hypoglycemia [19].

The present case is, to our knowledge, the first to illustrate a death caused by DKA which – in addition to autopsy findings and legal chemistry – is supported by the data and history of the insulin pump up to the time of power failure and, hence, discontinuation of insulin delivery.

2. Case presentation

Case history

A 31-year-old Caucasian male with a history of type 1 diabetes mellitus treated with an insulin pump was found dead in his apartment around noon on a Tuesday in September 2017. He lay on the couch and a bowl of vomit stood on the coffee table. There were no signs of fighting or drinking. A patch for the insulin pump was found on the abdominal wall but no tube or pump connected. However, this was found in the bedroom and thus not in the same room where the deceased was found.

The deceased had telephone contact with his mother the night before (Monday), where he sounded “strange”, but stated himself as well-being. Another relative reported that the deceased had more seizures recent months and these often occurred a few days after drinking alcohol. On Saturday night, 50-55 hours before he was found dead, he had been out drinking. According to hospital files, he started insulin pump therapy in January the same year and he had been advised regarding hyperglycemia and precautions for ketoacidosis. About two weeks before the death, he was verbally informed by a nurse that in case of pump failure, 8 IU of NovoRapid (Insulin aspart) should be given via insulin pen every three hours. The latest HbA1c, taken 6 months prior to his death, was 63 mmol/mol (estimated blood glucose of 10 mmol/L (180.2 mg/dL)).

Autopsy findings

At autopsy, performed same day the deceased was found, no lesions were observed except for fracture of sternum due to resuscitation attempts. There were possible fatty liver and severe acute blood and fluid accumulation in the lungs. CRP was measured at 14 mg/L in blood. The deceased’s height was 186 cm, and his weight was 98 kg (body mass index (BMI) 28.6).

When inspecting the patch for the insulin pump, no unusual findings were observed such as a bent catheter or other causes of inhibited passage of insulin into the body.

Histological, biochemistry and toxicological examination

In addition to acute pulmonary hemostasis and chronic fat accumulation in the liver, the microscopic examination of the tissue showed fatty vacuoles in the epithelial cells of the renal tubules (Armanni-Ebstein lesions) which are strongly associated with DKA [7], and the pancreas was characterized by severe autolysis. Remaining tissues,
such as brain, pituitary gland and heart, were normal in the microscopic examination. A postmortem CT performed before the autopsy confirmed the findings in liver and lungs and furthermore showed brain edema.

The vitreous humor fluid showed a very high glucose level of 35 mmol/L (630.6 mg/dL). Electrolytes were as follows (mmol/L): sodium 109, potassium > 25 (impregnable high), calcium 1.26 and chloride 89. The toxicological report was negative for alcohol in the blood and demonstrated elevated beta-hydroxybutyrate of 11.0 mmol/L (114.5 mg/dL). The latter indicates a deadly level of ketone bodies in the blood.

**Insulin pump data**

**Settings**

Data from the insulin pump was downloaded and it was noted that there was insulin left in the ampoule of the pump. The active insulin time (the time interval from the insulin is administered until it is exhausted and out of the body) was four hours. See Box 1 for insulin pump settings.

**Box 1. Settings of the insulin pump**

- Basal program 1, total 24.3 IU/day:
  - From midnight: 1.10 IU/hour
  - From 5 a.m.: 1.80 IU/hour
  - From 9 a.m.: 0.75 IU/hour
  - From 5 p.m.: 0.80 IU/hour
- Active insulin time: 4 hours.
- Maximum basal: 2 IU/hour, maximum bolus 20 IU.
- Bolus Wizard is activated.
- Carb ratio: 10 g/IU 24 hours a day
- Insulin sensitivity: 2 mmol/L per IU 24 hours a day
- Reminders: Low Reservoir.
Fig. 1. Insulin pump history of the days up to pump failure showing blood glucose measurements (mmol/L), basal rate, bolus administrations and carbohydrate intake.
**Pump history**

The pattern for Saturday was not different from other days and, therefore, resembled an ordinary day for the deceased when it came to diabetes (Fig. 1). Saturday evening, the pump showed the first low battery alert and announced the battery should be replaced soon. Early Sunday morning, another alarm was triggered, which again pointed out battery replacement. Specifying this alarm, showed that the battery should be replaced to ensure insulin delivery. Thirty-one minutes later, a third alarm appeared indicating that the battery should be replaced right now and that the insulin delivery had stopped. Eleven minutes after this, power failure of the pump was announced and the pump history ends (Table 1).

**Table 1. Pump alarms and notifications of Saturday and Sunday with time, measured blood glucose, intake of carbs, administered insulin bolus and activities.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose (mmol/L)</th>
<th>Carbs (g)</th>
<th>Bolus (IU)</th>
<th>Pump info/-alert</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saturday</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:15 a.m.</td>
<td>5.3</td>
<td>85</td>
<td>8.1</td>
<td>Basal 0.7 IU/hour</td>
</tr>
<tr>
<td>10:19 a.m.</td>
<td>-</td>
<td>-</td>
<td>8.1</td>
<td>Basal 0.7 IU/hour</td>
</tr>
<tr>
<td>01:43 p.m.</td>
<td>10.2</td>
<td>-</td>
<td>-</td>
<td>Basal 0.7 IU/hour</td>
</tr>
<tr>
<td>01:57 p.m.</td>
<td>11.4</td>
<td>50</td>
<td>6.5</td>
<td>Basal 0.7 IU/hour</td>
</tr>
<tr>
<td>02:30 p.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Basal stopped/interrupted</td>
</tr>
<tr>
<td>05:51 p.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Basal resumed</td>
</tr>
<tr>
<td>06:29 p.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Basal stopped/interrupted</td>
</tr>
<tr>
<td>06:32 p.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Fill of tubing, 6.023 IU delivered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fill of cannula, 0.675 IU delivered</td>
</tr>
<tr>
<td>06:33 p.m.</td>
<td>8.3</td>
<td>50</td>
<td>5.6</td>
<td>Basal resumed</td>
</tr>
<tr>
<td>09:40 p.m.</td>
<td>15.8</td>
<td>61</td>
<td>9.6</td>
<td>Basal 0.7 IU/hour</td>
</tr>
<tr>
<td>09:41 p.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Low battery, pump</td>
</tr>
<tr>
<td><strong>Sunday</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>07:12 a.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Replace battery</td>
</tr>
<tr>
<td>07:43 a.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Replace battery now</td>
</tr>
<tr>
<td>07:54 a.m.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Pump error</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Power failure</td>
</tr>
</tbody>
</table>

When the above data from the insulin pump and information from the police report are merged, a timeline can be set for various events in the last few days of the deceased (Fig. 2).
Fig. 2. Timeline of events in the last days of the deceased before he was found dead.
3. Discussion
The history of the insulin pump showed that dysfunction was not due to a mechanical malfunction, such as a bended catheter or hose, or other obstruction of the insulin supply, but that the battery ran out of power after three alarms, of which the first alarm was approximately ten hours prior to power failure.

It is known that high glucose and/or high ketone bodies in the blood can be caused by conditions other than DKA, including alcohol excess, sepsis, malnutrition, hypo-/hyperthermia and acute death. However, most of the causes only have an elevated value on one of the parameters, and if both glucose and ketone bodies are elevated, as they may be in malnutrition or hypothermia, it is not at all at the same level as in DKA [16]. In the case of ketoacidosis due to malnutrition, analyses may show normal or low glucose levels [7, 20], and in cases where both glucose and ketone bodies are elevated, these levels are much lower than in DKA [16]. The same is true of hypothermia, and often there is no significant hyperglycemia [16, 20] in the present case, the deceased was not malnourished (BMI 28.6), was not known with an alcohol abuse, had not been found in cold environments, and by examination of the tissue of his heart and vessels, there was no evidence of disease. The very high levels of ketone bodies in the blood (11 mmol/L) and of the vitreous glucose (35 mmol/L) indicate DKA rather than hypothermia or malnutrition. In alcoholic ketoacidosis, glucose levels are normal or low [7, 18], and at sudden death due to e.g. ischemic heart disease, cerebrovascular disease or thromboembolism, there is elevated glucose levels but no elevated ketone bodies [20]. Although not specific of DKA, but very indicative, the detected Armanni-Ebstein lesions, hepatic steatosis and brain edema strongly support DKA as the cause of death [7].

**Time aspect of developing a ketoacidosis**

The time it takes to develop a life-threatening acidification of the blood can be individual and depend on several factors. In the event of an insulin pump stop, a pump user will have a shortage of insulin in the body within a few hours as both basal and bolus administrations is given as fast-acting insulin. Therefore, ketoacidosis can develop very quickly (<24 hours) [3]. It is thus not very unlikely that DKA may occur overnight if a pump stop occurs in the evening. In the case of conventional insulin therapy with MDI of fast-acting insulin, the diabetic also administers a basal dose of slow-acting insulin. Thus, in this form of treatment, there will always be a depot of insulin in the body throughout the day if administration of fast-acting insulin stops [10]. Therefore, DKA may develop faster in pump users at the discontinuation of fast-acting insulin compared with diabetics treated with MDI. Theoretically, insulin pump therapy can thus be associated with greater risk of DKA, but the conclusions of various publications differ regarding this increased risk [21, 22]. However, most publications agree that there is no increased risk and a recent study has even shown that insulin pump therapy is associated with a lower risk of DKA compared to MDI [12].

In the current case, the pump settings showed an active insulin time of four hours, and as insulin delivery stopped around 8 a.m., the body’s insulin deposit should have been emptied around noon the same day. The night before he was found dead, his mother talked with him on the phone. As far as we know, the phone call was the last time anyone heard from the deceased, and thus the time when he was certainly still alive. The exact time of the conversation is not known – we only know that it took place in the evening. Subsequently the mother indicated that the deceased had sounded "strange". This may be time-related to the fact that he may already had developed a slightly impaired consciousness due to ketoacidosis. The deceased was found dead around forty-eight hours after his body no longer had any insulin and it is therefore somewhere in this time interval that the ketoacidosis is developed, but exactly how fast this has happened is hard to say since the deceased had been dead somewhere between 0-21 hours before being found. The only thing we can conclude for sure is that the ketoacidosis has been developed and caused death in under 48 hours.

Earlier in the year, the deceased experienced cramps, and had a tendency for these cramps after drinking larger amounts of alcohol. One theory may be that he had a prolonged seizure, where he was unable to adequately ventilate carbon dioxide and hence the development of the ketoacidosis accelerated.

**Importance of insulin pump data**

Sometimes, it can be complicated to determine whether DKA is the cause of death as macroscopic and microscopic findings that can be done, such as cerebral edema or Armanni-Ebstein lesions, are not specific to the diagnosis as these acute complications may also occur for other reasons. Biochemical analyzes of, for example, glucose in vitreous humor fluid and beta-hydroxybutyrate in the blood can supplement the postmortem examination and help to address the cause of death [5, 7, 18]. Reading the insulin pump’s data and history can provide additional information in the time before death, thus giving an indication of what triggered the DKA.

In this case, the pump ran out of power and thus did not provide insulin at all. If instead, the pump history had shown insulin doses all the way up to death, it would more indicate that there was, for example, a form of obstruction or kinking of the tube or the subcutaneous catheter, so that the insulin delivered did not enter the body at all. Another example of a pump history that may indicate death due to DKA could be that the pump user has skipped some insulin doses, e.g. due to alcohol intoxication.

**Unanswered questions**
Why the deceased did not respond to the three pump alarms remain uncertain. As he is out drinking when the first alarm sounds, one theory may be that he defers to do something about it, and early morning the day after – where the subsequent two alarms sound – he may have slept and therefore did not respond promptly. The insulin pump and associated hose were found in the bathroom, and the deceased lay in the living room. In the pump history, it has not been registered that the pump has been disconnected, which means that it has been removed after power failure. It is therefore quite likely that the deceased must have noticed that the pump was switched off, and one may wonder if the deceased had a blurred consciousness.

Another theory of why the deceased did not respond to power failure, could be that he simply did not realize the seriousness of the situation. Symptoms of DKA like vomiting, general malaise and fatigue can easily be confused with those seen by hangover, and the deceased may not have considered, he was developing ketoacidosis.

4. Conclusion

High vitreous glucose and elevated blood ketone bodies are indicative of DKA along with the fact that the deceased was diagnosed with diabetes. The history of the insulin pump showed completely disruption of insulin delivery due to power failure, and thus the history supports a basis for the development of ketoacidosis. In addition, the microscopic examinations also provided supportive findings in the form of Armanni-Ebstein lesions, brain edema and hepatic steatosis, which, however, are not specific to DKA, but are often seen in the condition. In conclusion, when autopsy results are seen in the light of the insulin pump’s data and history, it provides an overall picture that is highly compatible with DKA. Therefore, DKA is believed to be the cause of death due to lack of insulin because of power failure of the pump, and the manner of death is thought to be an accident.

The present case is a strong example of usefulness of postmortem download of data from insulin pumps together with the biochemical investigations to determine the cause of death among diabetics.

In cases where the deceased is an insulin pump user, forensic pathologists should therefore review data of the pump systematically – not only in unexplained cases where findings are negative, but also in cases where the findings give an immediate cause of death, as the course before entry of death can thus be better characterized and help confirm the cause of death.

Conflict of interest

The authors declare that they have no conflict of interest.

Patient consent

Consent has been obtained from the family of the deceased for publication of this article.

References


Sudden Death due to Diabetic Ketoacidosis Following Power Failure of an Insulin Pump: Autopsy and Pump Data

Highlights:
- Analysis showed high glucose in vitreous humor fluid and ketone bodies in the blood
- Pump data showed power failure leading to discontinuation of insulin delivery
- Results indicated that diabetic ketoacidosis was the cause of death
- Insulin pump data provided additional information of what triggered death
- The case is a strong example of usefulness of postmortem download of pump data