OCCURENCE OF ADVERSE EVENTS DUE TO CONTINUOUS GLUCOSE MONITORING

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Aims: Continuous glucose monitoring (CGM) using transcutaneous sensors is becoming a sophisticated method to control and regulate glucose metabolism. The transcutaneous sensor of the CGM system (CGMSTM Medtronic Minimed, Northridge, CA, USA) is chosen to measure glucose concentration in interstitial fluid up to three days after insertion even though its function remains stable for a longer period. The question arises, which factors really limit the period of sensor insertion without unnecessary risk. The aim of this study was to assess any adverse events occurring in the course of 9 days after the sensor insertion.

Methods: In a group of 22 healthy volunteers aged 21.8 ± 1.30 y (mean $\pm$ SE) a total of 26 sensors was inserted subcutaneously in gluteal or lumbar region for 9 days. Before insertion the site was sprayed with an antiseptic (Cutasept F, Bode Chemie, Hamburg, Germany). Local adverse reactions and disturbances in general condition were examined.

Results: In the course of 184 sensor-days, there were only minor local adverse events: hypersensitivity, itching, pain, redness, burning, subcutaneous hemorrhage. Additionally, sleep disturbances, attention deficits, problems related to the CGMS monitor, to adhesive tape and/or sensor were found. None of these resulted in sensor withdrawal. In 12 volunteers (55 %) no complications were observed. The sensor function measured according to electrical signals (ISIG) failed (always on day 1–2) in 4 cases (16 %).

Conclusions: The present FDA approved 3-day insertion period for Medtronic transcutaneous sensor does not seem to limit its use and appears to be worth a careful revision.

INTRODUCTION

Continuous glucose monitoring (CGM) of glucose concentration in interstitial fluid is becoming a sophisticated method to control and regulate glucose metabolism^{1,2}. Since the beginning of the third millenium, CGMSTM, Medtronic Minimed, Northridge, CA, USA³ and STS system, Dexcom, San Diego, CA, USA^{4,5}, have made CGM, available for thousands of persons with diabetes. The transcutaneous CGMSTM sensor is labeled to measure the glucose concentration in interstitial fluid for up to three days after insertion even though it remains stable for a longer period^{5–11}. On the other hand, the potential risks of adverse events due to longer insertion time should be taken into consideration. As historically, this limitation was born from previous notions that devices inserted transcutaneously might cause dermal complications mostly infections. That is why, the aim of this study was to assess any adverse events which occur in the observational period of 9 days after the sensor insertion.

METHODS

Subjects

Twenty two healthy caucasians aged 21.8 ± 1.30 y (mean $\pm$ SE), BMI 23.4 ± 0.59 kg/m² (mean $\pm$ SE), 7 men, 15 women, entered and completed the study. The investigations were carried out from January to February 2007 in five sequential groups.

Insertion procedure

Twenty six sensors in the original package were stored since delivery in a cool place (5–8 °C). Fifteen minutes before insertion the sensor was taken from the refrigerator and allowed to reach room temperature. The insertion site was sprayed three times in one-min intervals with an antiseptic solution (Cutasept F, Bode Chemie, Hamburg, Germany), twice swabbed, and finally allowed to air-dry alone. Sen-Serter (Medtronic-Minimed, Northridge, CA, USA) was used to insert the sensor into subcutaneous tissue of gluteal or lumbar region (Fig. 1)

Adhesive tape (Tegaderm, 3M, Health Care, Neuss, Germany, and Transmitter Adhesive Patch, Medtronic MiniMed, Northridge, CA, USA) was used to keep the sensor attached to the skin. The sensors remained in the subcutaneous tissue for up to 9 days (Fig. 2).

Fig. 1. Insertion of sensor

Fig. 2. Inserted sensor with connecting cable and monitor CGMS

The follow-up process

The sensor function was estimated according to the value of ISIG (Input Signal for Glucose) and by the number of glucose readings in the glucose monitor. The optimum number of readings (288/24 h) confirmed the uninterrupted function of the sensor. Every volunteer was trained in handling the CGMS and instructed how to investigate his/her fingerprick blood samples by means of the Advance glucometer system¹² every 12 hours in order to calibrate CGMS. In accordance to the study protocol the sensor was removed on day 9.

Finally, the sensor insertion sites were inspected for signs of adverse events (infection, allergy, and/or other irritation), and photographs were taken.

An Adverse Event (AE) is defined as any untoward medical occurrence in a research subject treated with a medical device during a study or post-study follow-up period, regardless of causality assessment. This includes adverse clinical or laboratory findings, intercurrent illness, or an exacerbation or progression of a disease/condition present at baseline. In our study, all adverse events, regardless of causality and relationship to sensor use or study procedures, were reported during the period of time of sensor use. Following the completion of sensor use and all study procedures, only adverse events with a possible rela-

Fig. 3. Local minor subcutaneous hemorrhage

tionship to sensor use or study procedures were reported. The intensity of adverse events is generally rated on a three-point scale: (1) mild, (2) moderate, and (3) severe. The term severe is a subjective measure of intensity: thus a severe adverse event is not necessarily serious.

At the end of the study each person filled out a questionnaire focused on sleep disturbances, attention deficits, technical problems related to CGMS monitor, discomfort related to sensor, discomfort related to adhesive tape, local hypersensitivity, local itching, local pain, local redness, local burning, and/or local subcutaneous hemorrhage.

End points

There were four end points indicating the sensor withdrawal:

1. serious adverse event related to sensor
2. end of the sensor function
3. decision of the tested person
4. end of the study (day 9)

Helsinki approval

The procedure followed was in accordance with the Helsinki Declaration of 1975 as revised in 1983, and agreed by the local ethics committee.

RESULTS

The outcomes of all 22 participants using a total of 26 sensors for 184 sensor-days (i.e. 8,4 sensor-days per participant) were evaluated.

In this study, all AE were mild. No influence on sensor function or precision/accuracy of glucose values was found. There was no AE resulting in sensor removal. The most frequent adverse events were: discomfort related to adhesive tape and itching. See Table 1 for details.

Small local hemorrhage (Fig. 3) did not result in sensor removal.

Disturbed sensor function documented by irreversible ISIG decrease (below 10 nA) was found in 4 of 26 sensors and resulted in sensor removal. These 4 sensor failures appeared in the course of the first or second day after the sensor insertion.

Table 1. Frequency of adverse events in 22 persons (100 %) using transcutaneous sensors CGM

Adverse events	Number of test persons	Percentage %
Sleep disturbances	2	9
Attention deficit	1	5
Technical problems related to monitor	5	23
Discomfort related to sensor	4	18
Discomfort related to adhesive tape	6	27
Local AE		
Hypersensitivity	4	18
Itching	3	14
Redness and/or pain and/or burning and/or hypersensitivity and/or itching	3	14
Minor subcutaneous hemorrhage	1	5
No local AE	11	50

Two of 22 volunteers refused to continue the study which resulted in 2 sensor removals. One volunteer lost one sensor accidentally.

There were 19 of 26 sensors withdrawn at the end of the observational period on day 9 in accordance to the study design.

DISCUSSION

The use of CGM has become a hot topic in the present diabetology^{13–21}. The Food and Drug Association (FDA), USA, approved the use of Medtronic transcutaneous sensors for three days only. However, this limitation seems to be rather empirical than evidence based. Therefore, this pilot practice oriented study is focused on the occurrence of adverse events due to prolonged insertion of transcutaneous sensors.

The microbial safety of transcutaneous procedures (subcutaneous and intramuscular injections, insertion of subcutaneous catheters for continuous insulin infusion by means of insulin pump, intravenous or intraarterial catheters etc.) is a key point in medical care. At the Faculty of Medicine, Palacký University, Olomouc, Czech Republic, attention was paid to the practical use of recent methods of insulin administration²². Thorough investigations of potential hazards due to re-use of disposable needles have been done in persons with type 1 diabetes mellitus²³. This study was performed with healthy persons with encouraging outcomes. The question arises whether these results may be generalized for persons with diabetes. To date, the transcutaneous sensor of the CGMS was used for 9 days or even longer to control the effectiveness of CSII in persons with type 1 diabetes²⁴ or to determine the glycaemic index of various foods^{25, 26}. No serious adverse

events were seen which is compatible with the observations of other groups^{5, 6}.

We may conclude that subjects using the CGMS are at low risk for developing a local skin infection at the site of the sensor insertion. That is why the following indications for sensor removal may be recommended: (1) disturbed sensor function (2) serious AE or (3) the wish of the tested person. The present FDA approved 3-day insertion period for Medtronic transcutaneous sensors appears to be worth a careful revision.

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