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First application of a transcutaneous optical single-port glucose monitoring device in patients with type 1 diabetes mellitus

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ABSTRACT

The combination of continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion can be used to improve the treatment of patients with diabetes. The aim of this study was to advance an existing preclinical single-port system for clinical application by integrating the sensors of a phosphorescence based CGM system into a standard insulin infusion set. The extracorporeal optical phase fluorimeter was miniaturised and is now comparable with commercial CGM systems regarding size, weight and wear comfort. Sensor chemistry was adapted to improve the adhesion of the sensor elements on the insulin infusion set. In-vitro tests showed a linear correlation of $R^2 = 0.998$ between sensor values and reference glucose values in the range of 0-300 mg/dl. Electrical and cytotoxicity tests showed no negative impact on human health. Two single-port devices were tested in each of 12 patients with type 1 diabetes mellitus in a clinical set-up for 12 h. Without additional data processing, the overall median absolute relative difference (median ARD) was 22.5%. For some of the used devices the median ARD was even well below 10%. The present results show that individual glucose sensors performance of the single-port system is comparable with commercial CGM systems but further improvements are needed. The new system offers a high extent of safety and usability by combining insulin infusion and continuous glucose measurement in a single-port system which could become a central element in an artificial pancreas for an improved treatment of patients with type 1 diabetes mellitus.

1. Introduction

In type 1 diabetes mellitus (T1DM) the insulin-producing beta cells are destroyed due to an autoimmune reaction (Todd, 2010). Although type 1 diabetes can be diagnosed at any age, it is one of the most common chronic childhood diseases. Peaks in presentation occur between 5 and 7 years of age and at or near puberty (Atkinson et al., 2014). Renal insufficiency, cardiovascular disease and retinopathy are some of the major long term complications related to a lack of adequate glucose control (Pandey et al., 2015). To avoid these complications patients with T1DM require a exogenous supply of insulin to maintain their blood glucose level in the physiological range which is best monitored by the use of continuous glucose monitoring (CGM) systems (Gifford, 2013). The use of CGM systems has been shown to result in improved diabetes therapy by optimising overall glucose levels and reducing the number of hypoglycaemic events (Garg, 2016). Combining continuous subcutaneous insulin infusion (CSII) with CGM can further improve the treatment of T1DM by e.g. reducing the burden of care and enhancing quality of life (Ang et al., 2015; Rodbard, 2016).

Currently, commercially available systems which combine CGM and CSII consist of two separate devices directly attached to the body: a continuous glucose sensor and an insulin infusion set. These two devices are inserted into the subcutaneous adipose tissue (SAT) at a certain distance from each other. Each insertion causes a trauma which may trigger a complex inflammatory response (Gifford, 2013). Besides the pain during insertion, each insertion site also bears the risk of infection which can be minimised by using single-port systems. Single-port systems only use one insertion site to apply both the continuous glucose sensor and the insulin infusion set. Insulin is delivered directly at the site of glucose measurement but does not influence glucose values (Hajnsek et al., 2014; Lindpointner et al., 2010; Tschaikner et al.,

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2015). Single-port systems are currently being tested in clinical studies but are not yet commercially available (Regittnig et al., 2013; Tschaikner et al., 2015).

Commercially available CGM systems are usually based on amperometric detection of glucose (Kropff and DeVries, 2016) but these electrochemical sensors can be affected by active agents (e.g. acetaminophen, ascorbate, acetylsalicylic acid etc.) that interfere with glucose measurements (Basu et al., 2016; Garg, 2016; Pasic et al., 2006). Optical glucose sensors on the other hand, especially those based on oxygen sensors as transducing element, are not influenced by electrochemically active agents (Ben Mohammadi et al., 2014; Dutt-Ballerstadt et al., 2014; Mortellaro and DeHennis, 2014; Müller et al., 2013; Nacht et al., 2014) which makes them ideal candidates to measuring critical parameters such as glucose in medicated patients.

Based on the concept of an optical single-port system which has been tested in-vitro and preclinically (Hajnsek et al., 2014; Nacht et al., 2014) we aimed to demonstrate the usability and feasibility of this system in patients with T1DM. The used single-port system gives the possibility to simultaneously measure glucose without interferences from other active agents and delivers insulin at the same site with a lower risk of infections. Therefore, it has the great potential to become the central element of an artificial pancreas system (Rumpler et al., 2016). The aim of this study was the further development of the preclinically used single-port system toward the first-in-man study with a focus on the accuracy and reliability of the CGM function of the system.

2. Material and methods

2.1. Materials

Both phosphorescence oxygen indicators, platinum(II)-6-aza-13,20,27-triphenyltetra(*tert*-butylbenzo)-porphyrin (tbutPtNTBP) and platinum(II)-meso-tetra(4-fluorophenyl)tetrabenzoporphyrin (PtTPTBPF) were synthesised as previously described (Nacht et al., 2014).

Glucose oxidase from *Aspergillus niger* (200 U/mg), polystyrene (PS) (average Mw 250 kD), ethylcelullose (EC) (48.0–49.5% ethoxyl basis), albumin fraction V from bovine serum (BSA), catalase from bovine liver (2000–5000 U/mg), D-(+)-glucose ≥ 99.5%, glutaraldehyde solution (GA) (Grade II, 25% in H_2O) and sodium sulphite (Na_2SO_3) ≥ 98%, potassium phosphate monobasic (KH_2PO_4) ≥ 99%, sodium phosphate dibasic (Na_2HPO_4) ≥ 99% and sodium chloride (NaCl) ≥ 99% were purchased from Sigma-Aldrich (St. Louis, MO, USA), HydroMed D4 from AdvanSource Biomaterials Corp (Wilmington, MA, USA) and the silicon primer MED-160 from NuSil Technology (Carpinteria, CA, USA). The solvents toluene and ethanol (EtOH) from VWR International (Radnor, PA, USA) and hydrogen peroxide (30%) from Carl Roth (Carl Roth GmbH, Karlsruhe, Germany). Human Plasma (K2 EDTA) was purchased by SERALAB.

The polyethylenterephalat foil (Mylars® A) was obtained from Dr. D. Müller GmbH (Ahlhorn, Germany), Contact™ Detach (G29/8 mm) insulin infusion sets from Unomedical a/s (Lejre, Denmark), Sterican® cannula (0.5 × 60 mm, 23 G) from VWR International and OPSITE FLEXIGRID® wound dressing film (6.0 × 7.0 cm) from Smith&Nephew (London, UK). Nitrogen gas (≥ 99.999%) was delivered from Linde Gas GmbH (Stadl-Paura, Austria). The artificial skin was purchased from Manuel Höpfer und Anja Mankel GbR (Herdecke, Germany).

A notebook HP Pavilion X2 10-K080NG from Hewlett-Packard (Palo Alto, CA, USA) was used to log the raw data and set the measuring variables.

2.2. Sensing principle of the single-port system

Our single-port system consists of two different units: a sensor unit and an optical read-out unit. A schematic diagram of this concept is illustrated in Fig. 1. Two phosphorescence based sensors, a glucose sensor and a reference oxygen sensor, are coated onto the cannula of a Contact™ Detach insulin infusion set (Unomedical a/s, Lejre, Denmark) forming the sensor unit. This allows delivering insulin and measuring the glucose concentration at the

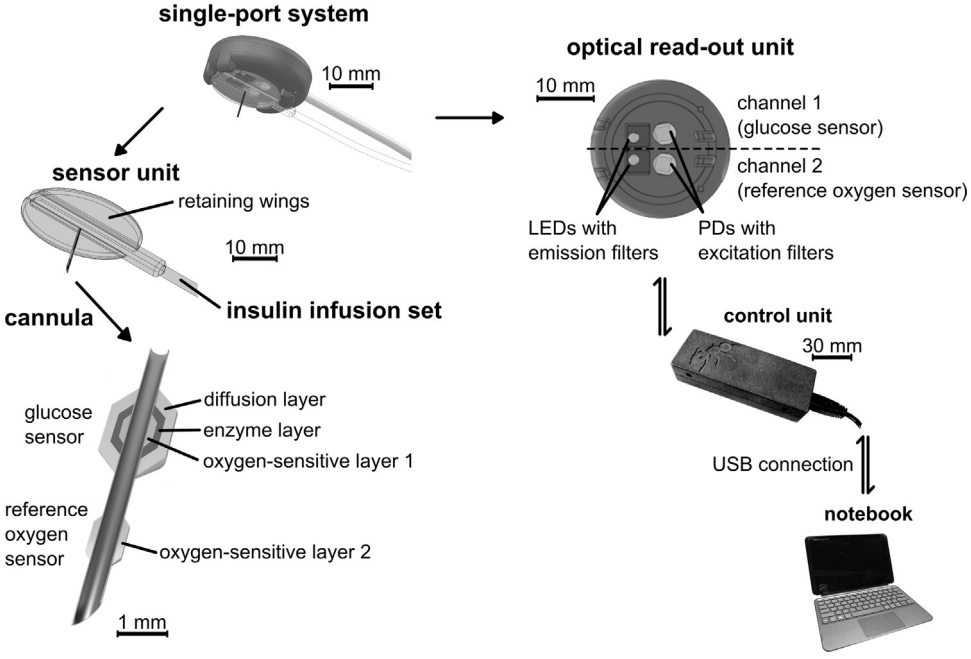

Fig. 1. Schematic diagram of the single-port system. It consists of two units: The sensor unit and the optical read-out unit. The sensor unit comprises two phosphorescence based sensors coated onto the cannula of the insulin infusion set. The optical read-out unit is a miniaturised two channel phase fluorimeter which can be attached to the sensor unit. The optical read-out unit is connected via a thin, flexible cable to the control unit, where the signal is processed. To log the raw data and set the measuring parameters, the control unit is USB connected to a notebook.

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