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Letters to the editor

Comments on subcutaneous glucose monitoring

Dear Sir,

The increasing experience with subcutaneous glucose monitoring warrants comment regarding the problems in applying this technique to human diabetic subjects.

Variations in blood glucose are followed closely by changes in the s. c. tissue glucose although a delay of about 10 min can be measured [1, 2], apparently caused by the distribution rate of change of the glucose diffusion equilibrium between the intravascular and intercellular spaces [3].

The estimation of the s. c. glucose concentration has been performed employing different methods which influenced the results. By using the wick method [4, 5], the s. c. glucose concentration represented almost 100 % of the running glycaemia of dogs [4] and of sheep [5]. In these studies the maximum indwelling time of a wick was 20 min for measurements to follow the pattern of tissue glucose after induced alterations. Implanting the wicks at interval of 20 min could increase the local blood flow and change the capillary barrier, thus overestimating the s. c. glucose concentration. By employing the filtrate collection and equilibration method, Schmidt et al. [3] obtained values between 44 and 46 % of the corresponding blood glucose. The ultrafiltration technique constantly removes glucose from the s. c. space causing drainage, thereby leading to underestimation of glucose concentration. Using the equilibration method in healthy volunteers, a decline of the glucose concentration to 46 % of the blood glucose in the hourly collected equilibration fluids of hollow fibres was observed. To estimate the tissue glucose concentration we developed a technique [6] which consists of recirculating phosphate saline in a microdialysis probe until the inner glucose concentration equals the outer concentration. We applied this method [6] in healthy volunteers ($n = 10$), recirculating phosphate buffer 44 times in the fasting state and 36 times during a hyperglycaemic clamp, obtaining values of 72 ± 6 % and 78 ± 6 % of the glycaemia, respectively.

An inhibition factor "Q" causes a drift in the sensor signal after 10–15 h [7]. Kerner et al. [8] showed that a low molecular weight substance present in the human plasma, s. c. extracellular fluid, and possibly in saliva and urine, inactivates or causes a dramatic drift in the sensor signal. In short-term measurements this inhibition factor cannot be detected [9]. The substance to be measured by the electrode does not play any role, i. e. hydrogen peroxide, oxygen, etc; the "Q" factor is always present (not present in rats).

Regarding calibration, methods based on "in vitro", "in vivo" and a combination of both have been performed unsuccessfully. A "one point in vitro, one point in vivo" calibration method [1, 2] is rather easy to accomplish but is not considered to be accurate because both the zero in vitro and the actual blood glucose value do not correspond to their respective subcutaneous values. A "two point in vivo" calibration, based on testing the sensor's response under two blood glucose levels and then applying a conversion linear function formula to adjust the signal [9] does not seem very promising because in practice it is improbable to obtain a blood glucose plateau in diabetic patients, except under experimental glucose clamps. A calibration method should be exact, practicable, accepted by the patients, and should be performed within a short period. Such a calibration method, which fulfils the properties mentioned, is still lacking.

The utilisation of needle sensors have shown no reliability on long-duration s. c. glucose monitoring; some of them do not even immediately react to glucose although they are constructed for such purposes [9]. Due to the fact that it is not possible to get a long-term response with this type of sensor, Pickup et al. [10] suggested the utilization of such sensors as short-term nocturnal hypoglycaemic alarm devices.

The microdialysis technique seems more promising for continuous monitoring of the s. c. glucose [1, 2]. By now long-term measurements lasting more than 1 day in vivo have been carried out opening new perspectives of monitoring and treating diabetic patients [2]. Only a very slight drift of the sensor signal occurs by the application of the technique [1, 2] compared with the implantable enzyme electrodes, which show a considerable drift immediately after implantation [8, 10].

Yours sincerely,

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Response from the authors

Dear Sir,
Remarks regarding the pessimistic view expressed by Sternberg et al. in their letter on the future of glucose sensing with an implanted microsensor appear appropriate.

1. The delay between changes in blood glucose and those in the signal produced by the glucose sensing system may depend strongly on the nature of the system (i.e. implanted glucose sensor vs microdialysis system, size of the implanted glucose sensor). In rats, a sharp increase in the current generated by a miniaturized sensor (0.4 mm diameter wire) implanted in the subcutaneous tissue was consistently observed within 5 min following an i.p. glucose load (see Figs. 2 and 5 in [1], not quoted in Sternberg's review, showing the results observed for sensors implanted over 3 or 10 days, respectively).

2. The nature of the "true" glucose concentration in extracellular fluid is a controversial issue nicely reviewed by Schmidt et al. [2]. It is clear that the value obtained depends partially on the method of measure (i.e. Wick technique, dialysis or ultrafiltration method), and, if an implanted glucose sensor is used, on the geometry of the sensor.

3. Clinical trials of a glucose monitoring system [3] (quoted as reference [9] by Sternberg et al.) were performed approximately 14 h after implantation. Thus, the fact that the sensitivity of this sensor was lower when assessed during implantation than when observed in vitro may be related to Pfeiffer factor Q. This low sensor sensitivity is not a novel observation, and nothing but a confirmation of what we have already observed in rats [1] and dogs [4]. We are currently investigating its significance.

4. The fact that the sensor's sensitivity is not identical in vivo and in vitro on one hand, and that the "true" glucose concentration in situ cannot be directly measured on the other hand, highlights the issue of calibration in the field of glucose sensing. We were sad (but not surprised) to learn that "the one point in vitro, one point in vivo calibration method [5, 6] is rather easy to accomplish but is not considered to be accurate because both the zero in vitro and the actual blood glucose value do not correspond to their respective subcutaneous values". By contrast, the two-point calibration method [1, 3, 7, 8] yields accurate estimation of blood glucose concentration and is now being used by others [9, 10], and this should encourage Sternberg and his colleagues to use it. Indeed a) there is no need to obtain a long plateau (such as that achieved by the clamp technique), if the delay between the change in blood glucose concentration and the response of the signal is short, as shown above. b) The method is not difficult to perform since only two blood glucose measurements are needed. c) It is difficult to imagine that patients using a continuous glucose monitoring system will not check at least twice that their system is working. We do agree, however, that efforts to make the method user-friendly are needed.

5. We previously published [1] the proof that the sensor we are currently evaluating in vivo in the animal and in man works for at least 10 days when implanted in the s.c. tissue of normal rats. Others consider the possibility of a permanently implanted device using the same type of sensors [11]. We therefore do not share the pessimistic view that "it is not possible to get a long term response with this type of sensor". Using a glucose sensor for the detection of nocturnal hypoglycaemia, as proposed by J. Pickup, may be viewed not as a drawback, but as an important progress in diabetes management, if one considers the recent results of the Diabetes Control and Complications Trial.

6. Finally, although it is understandable that Sternberg and his colleagues defend the future of microdialysis [5, 6], they should not be so pessimistic considering other strategies for glucose sensing such as the use of implanted microsensors [12]. They should instead meditate on the conclusion of the balanced editorial published by Pickup in a recent issue of the Lancet [13]: "Thus, despite the promise of microdialysis and near infrared spectroscopy, it would be premature to abandon research into implanted electrochemical sensing devices". According to Ambrose G. Bierce (1842–1914), "there is but one way to do nothing and diverse ways to do something".

Yours sincerely,
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