ELSEVIER

Biosensors & Bioelectronics 16 (2001) 621–629

BIOSENSORS & BIOELECTRONICS

www.elsevier.com/locate/bios

Clinical evaluation of the GlucoWatch® biographer: a continual, non-invasive glucose monitor for patients with diabetes☆

M.J. Tierney [a,*], J.A. Tamada [a], R.O. Potts [a], L. Jovanovic [b], S. Garg [c], Cygnus Research Team [a]

[a] *Cygnus, Inc., 400 Penobscot Drive, Redwood City, CA 94063, USA*
[b] *Sansum Medical Research Institute, 2219 Bath Street, Santa Barbara, CA 93105, USA*
[c] *Barbara Davis Center for Childhood Diseases, University of Colorado Health Sciences Center, 4200 East 9th Ave, Box B140, Denver, CO 80262, USA*

Received 16 May 2000; received in revised form 16 November 2000; accepted 28 November 2000

Abstract

A device providing frequent, automatic, and non-invasive glucose measurements for persons with diabetes has been developed: the GlucoWatch® biographer. This device extracts glucose through intact skin via reverse iontophoresis where it is detected by an amperometric biosensor. The biographer can provide glucose readings every 20 min for 12 h. The performance of this device was evaluated in two large clinical studies in a controlled clinical environment ($n = 231$), and the home environment ($n = 124$). Accuracy of the biographer was evaluated by comparing the automatic biographer readings to serial finger-stick blood glucose (BG) measurements. Biographer performance was comparable in both environments. Mean difference between biographer and finger-stick measurements was -0.01 and 0.26 mmol l^{-1} for the clinical and home environments, respectively. The mean absolute value of the relative difference was 1.06 and 1.18 mmol l^{-1} for the same studies. Correlation coefficient (r) between biographer and finger-stick measurements was 0.85 and 0.80 for the two studies. In both studies, over 94% of the biographer readings were in the clinically acceptable A + B region of the Clarke Error Grid. A slight positive bias is observed for the biographer readings at low BG levels. Biographer accuracy is relatively constant over all rates of BG changes, except when BG decreases more than 10 mmol l^{-1} h^{-1}, which occurred for only 0.2% of points in the home environment study. Biographer precision, as measured by CV%, is approx. 10%. Skin irritation, characterized by erythema and edema, was either non-existent or mild in $>90\%$ of subjects and resolved in virtually all subjects without treatment in several days.

Keywords: Glucose monitor; Diabetes; GlucoWatch® biographer

1. Introduction

Intensive management of blood glucose levels has been shown to reduce the incidence of long-term complications in both type 1 and type 2 diabetes (The Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998). These intensive glycemic control regimens require multiple daily blood glucose tests to adjust insulin dosage. One drawback of tight glucose control for many diabetic patients, however, is an increased rate of hypoglycemic incidents. A glucose monitoring system that would provide a convenient and automatic method to make frequent glucose measurements as well as provide hypo- and hyperglycemic alarms would greatly facilitate intensive glucose control regimens. Additionally, the discomfort and inconvenience of finger-stick methods reduce the number of measurements many diabetic patients perform, making non-invasive measurements very desirable (Ginsberg, 1992).

A device providing these capabilities has been developed: the GlucoWatch® biographer (Cygnus, Inc., Redwood City, CA). This device utilizes a novel sampling technique—reverse iontophoresis—to extract glucose through the skin where it is detected by an amperomet-

☆ Finalist for the Biosensors and Bioelectronics award

* Corresponding author. Tel.: +1-650-599-2571; fax: +1-650-369-5318.

E-mail address: tierney@cygn.com (M.J. Tierney).

0956-5663/01/$ - see front matter
PII: S0956-5663(01)00189-0

ric biosensor. The biographer is a small, wrist-watch device containing both sampling and detection means, electronic circuitry, and a digital display (Fig. 1).

Feasibility studies of the performance of the GlucoWatch® biographer primarily in controlled, clinical environments have demonstrated high accuracy and precision (Garg et al., 1999; Tamada et al., 1999). This report describes the evaluation of the performance of the GlucoWatch biographer in two large clinical trials: a controlled clinical environment, and the home environment. This paper describes the operating principles of the device, and reviews the results of these clinical trials.

2. Materials and methods

2.1. The GlucoWatch® biographer

The GlucoWatch® biographer is a wrist-watch device comprising all the necessary electrical circuitry to operate the iontophoresis and biosensor functions. A microprocessor is used to control the operation of the device as well as to convert the sensor signals into glucose readings. The electronic circuitry includes two independent potentiostat circuits to operate the amperometric biosensors (described below) and a galvanostat circuit for the iontophoresis function. The biographer also contains data storage memory, a liquid-crystal display, and a serial port for communication with a PC. Temperature and skin conductivity sensors detect skin temperature fluctuations and perspiration, respectively. The disposable portion of the device, the AutoSensor, fits into the skin-side of the biographer and comprises two identical sets of biosensor and iontophoresis electrodes, and two hydrogel disks. The biosensor working electrodes consist of a screen-printed layer of Pt/C composite ink. The reference and counter electrodes are made from screen printed Ag and Ag/AgCl layers. The biosensor counter electrode also functions as the iontophoresis electrode. The AutoSensor is shown in Fig. 2. Hydrogel discs serve as the biosensor electrolyte as well as the reservoirs into which the glucose is collected. The glucose oxidase enzyme (GOx) is dissolved into these hydrogel discs at a concentration sufficient to eliminate enzyme kinetics limitations on the biosensor signal.

Three separate technologies are incorporated into the design of the GlucoWatch® biographer: glucose sample extraction through reverse iontophoresis, glucose sample measurement by amperometric biosensor, and data verification and conversion leading to display of the glucose reading.

2.2. Reverse iontophoresis

The main function of human skin, and the non-viable stratum corneum portion of the epidermis in particular, is as a barrier membrane to the outside environment. Various means have been developed to breach this barrier to deliver drugs transdermally. One method, iontophoresis, utilizes electrical current to deliver charged drug compounds through the skin. It was realized that electrolyte ions in the body, such as Na^+,

Fig. 1. Photograph of the GlucoWatch® biographer.

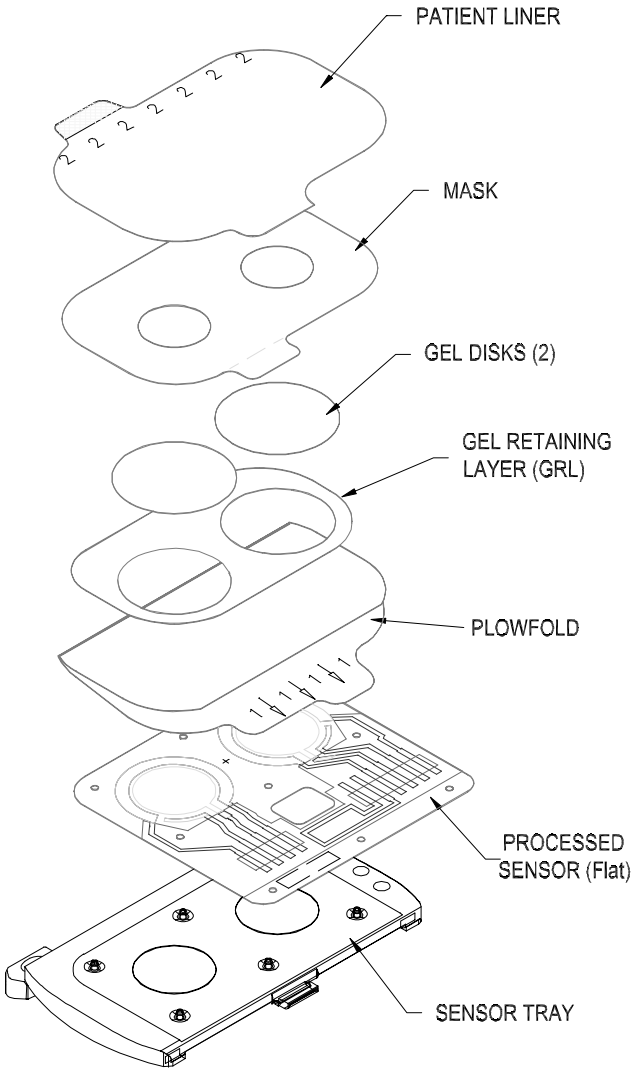

Fig. 2. GlucoWatch® biographer electrode assembly.

rather than charged drug molecules, can act as the charge carriers for this current. Thus, substances from within the body can be extracted outward through the skin as well. This process has been termed 'reverse iontophoresis' (Rao et al., 1993). Because the skin has a net negative charge at physiological pH, an electro-osmotic flow also occurs upon passage of iontophoretic current. Neutral molecules, such as glucose, are extracted through the skin via this electro-osmotic flow to the iontophoretic cathode along with Na^+ ions, the major carriers of the iontophoretic current. It has been demonstrated that the amount of glucose collected via reverse iontophoresis correlates with blood glucose with an average lag time of 20 min (Tamada et al., 1995). The amount of glucose extracted during one 3-min iontophoresis cycle is estimated to be 50–500 picomol.

2.3. Amperometric biosensor

Measurement of such a small amount of glucose requires a specifically designed biosensor (Tierney et al., 1999). The biosensor in the GlucoWatch® biographer utilizes direct detection of H_2O_2 generated by the glucose oxidase-catalyzed reaction:

$$\text{glucose} + O_2 \xrightarrow{\text{GOx}} \text{gluconic acid} + H_2O_2$$

on the electrocatalytic surface of the Pt-graphite working electrode. Peroxide-based chemistry is optimum for this application for many of the same reasons that it has been superceded by, for example, mediated chemistries in other applications. Oxygen deficiency, a potential problem for glucose sensing in blood or tissue, is not a limitation to the sensing reaction because of the low concentration of extracted glucose. Another advantage of transdermal sampling is the elimination or reduction of interfering species which commonly cause problems with peroxide-based sensing chemistries. Most importantly, this chemistry is compatible with iontophoresis sampling, as it utilizes no soluble components that could be delivered into the skin to cause toxicity problems, and it is ideally suited for periodic sensor operation.

The 50–500 picomol of glucose extracted during each sampling cycle corresponds to a concentration of 2.5–25 μM in each hydrogel pad. Although accurately quantifying this amount of glucose initially seems daunting, the amount of analyte reaching the sensor surface is comparable to many implantable sensors (Zhang et al., 1994; Cambiaso et al., 1996). The membranes which limit glucose diffusion, confer permselectivity and improve biocompatibility in such sensors attenuate the effective measured concentration of glucose. In the GlucoWatch® biographer, the skin itself serves as the permselective membrane, eliminating the need for any additional layers. The skin and the reverse iontophoresis process limit transport of glucose to the sensor, eliminating oxygen deficiency problems. Both size-exclusion and charge-exclusion permselectivity is achieved as well. The barrier properties of the skin effectively filter out compounds of molecular weight much greater than 500 daltons. Measuring glucose only at the iontophoretic cathode while interfering species such as uric and ascorbic acid migrate to the iontophoretic anode confers charge selectivity on the system. Therefore, while the sample delivered to the sensor may have a low glucose concentration, it is devoid of many of the species that interfere with the glucose measurement. Operating the biosensor at 0.42 V versus Ag/AgCl, a relatively low potential for H_2O_2 detection, further improves selectivity towards glucose over co-extracted species, such as tyrosine and tryptophan, which are electroactive at higher potentials. Operating at this low potential, with its subsequent slow electrode kinetics, is made possible by integrating the signal over a 7-min period.

2.4. Data verification and conversion

To produce a glucose measurement, a number of steps take place, shown schematically in Fig. 3. First, an iontophoresis current of 0.3 mA is delivered for 3 min to collect glucose at the iontophoretic cathode. During this time, the concentration of H_2O_2 produced by the glucose/GOx reaction increases in the hydrogel at the cathode. Next, the biosensors are biased at 0.42 V versus Ag/AgCl, and the biosensor current at the iontophoretic cathode is integrated for 7 min during which the concentration of H_2O_2 in the gel is depleted to near zero. This collect-and-purge scheme effectively increases the sensitivity of the system by pre-concentrating the analyte, while reducing noise by the time-integration inherent in collecting glucose over 3 min. The polarity of the iontophoresis current is then reversed and the process is repeated. The integrated currents of the two biosensors are summed and input to a signal processing algorithm (Kurnik et al., 1999). A one-point calibration of the system, after 3 h elapsed time, is provided by a single finger-stick blood glucose measurement. This calibration accounts for variability in the skin permeability to glucose as well as biosensor sensitivity. Thereafter, the calibration factor is used by the signal processing algorithm to provide a glucose measurement every 20 min for 12 h. Because the biosensors are worn on the wrist, they are subject to environmental conditions (temperature fluctuations, mechanical shocks, etc.) that could adversely affect the sensor signal. Before the glucose reading is calculated, the raw biosensor data is first compared against criteria determined a priori to ensure data integrity. Parameters checked include low or rapidly changing temperature, the presence of excess perspiration, excess noise in the data, or sensor connection faults. If the presence of any of these parameters is detected, the glucose reading is skipped to ensure the accuracy of the glucose measurements.

2.5. Clinical study designs

The performance of the GlucoWatch® biographer was evaluated in two separate clinical trials: a controlled clinic setting and the home environment. Table 1

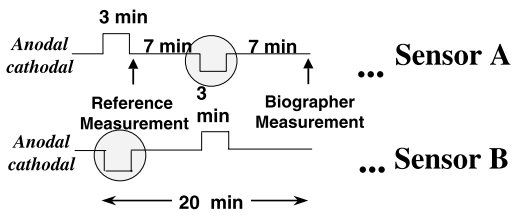

Fig. 3. Diagram of the GlucoWatch® biographer iontophoresis and biosensor duty cycles. Glucose is collected at each respective sensor during the circled iontophoresis cycles.

Table 1
Summary of the designs of the two clinical studies

Study name	Clinic environment	Home environment
Environment	Controlled clinical environment	Home
Duration	1 day	5 days (Wed. to Sun.)
Biographers worn per day	2	1
Comparative BG device	HemoCue analyzer[a]	One touch profile[b]
Frequency of comparative BG measurements	2 per hour	1 per hour

[a] HemoCue® (Aktiebolaget Leo, Helsingborg, Sweden).
[b] One Touch® Profile® (Johnson & Johnson, New Brunswic, NJ).

summarizes the designs of the two studies. Each study took place at six clinical sites, geographically distributed in the United States. All subjects wore the biographer for 15-h sessions (3-h warm-up and 12 h of measurements). In the clinic setting, subject movement was limited and clinical staff applied and calibrated the biographers. In the home environment study subjects were trained to assemble, apply, and calibrate the biographer themselves, and were instructed to follow their usual daily routines as they wore the biographer over the course of 5 days. All biographer readings were masked from the subjects and investigators during the study period. Biographer readings were compared to fingerstick blood glucose measurements taken once or twice per hour, depending on the study protocol (Table 1). In the clinic study, insulin dosing was adjusted by the investigator during the study to induce mildly hypoglycemic and hyperglycemic levels (targeted between 2.22 and 25 mmol l^{-1}). All dose adjustments for insulin were done using the fingerstick BG measurements. Subjects in all studies signed informed consent forms required by the clinical sites' institutional review boards.

The demographic distribution of the subjects in the two studies was similar. The mean ($\pm$ SD) age of the subjects was 48.2 ± 15.0 and 46.5 ± 11.7 years of age for the clinical environment and the home environment studies, respectively, and there were roughly equal numbers of males and females in both studies. Caucasians made up 71.9% and 79.8% of the subjects and African–Americans 10.4 and 8.9% of the subjects in the two studies. Approximately two-thirds of the subjects (65.5 and 59.7%) had type 1 diabetes, and the mean ($\pm$ SD) duration of diabetes was 16.6 ± 9.8 and 16.9 ± 10.2 years for the two studies, respectively.

2.6. Data analysis

The data from each biographer were downloaded via a serial interface to a personal computer. Finger-stick

BG measurements, demographic information, and other data were recorded from case report forms. To calculate measures of accuracy, the data were compiled to generate paired biographer/finger-stick BG values.

The complex nature of the GlucoWatch® biographer data requires a number of statistical measures to characterize its performance. Difference statistics calculated include mean difference (MD, mean of the differences between biographer and finger-stick BG measurements) and its standard deviation (SD), mean relative difference (MRD, mean of the relative differences), and mean absolute relative difference (MARD, mean of the absolute value of the relative differences). The pooled correlation coefficient between the biographer readings and the finger-stick BG measurements is also calculated. Deming linear regression is used to calculate slope and intercept for the relationship between the biographer readings and blood glucose values. Deming linear regression takes into account error in the independent variable, i.e. the BG measurements (Deming, 1943). Root-mean square error (RMSE) is calculated between the biographer reading and the value predicted by the Deming regression. The Clarke Error Grid Analysis (EGA) superimposes regions of differing therapeutic utility onto the correlation plot (Clarke et al., 1987). MD, MRD, and Deming slope are measures of bias, or systematic error, in the biographer measurement. Scatter, or random error, in the biographer measurements is indicated by MARD, SD, RMSE, and the correlation coefficient. The EGA provides a measure of the overall clinical utility of the readings.

3. Results

Fig. 4a–f show example profiles of the biographer and comparative fingerstick BG measurements for 6 subjects in the home environment study, representing the range in observed biographer performance. These plots show close tracking of the biographer results with finger-stick values over the 12-h study. Sometimes, individual statistics do not accurately represent the degree of tracking. For example, when glucose levels are low and relatively unchanging, the correlation will be low, yet the tracking will be quite acceptable clinically (Fig. 4d, subject 60742). Similarly, the MARD will be large since the denominator (BG) is small.

The correlation coefficient (r) between biographer readings and BG measurements was 0.85 and 0.80 in the clinical environment and home environment studies, respectively (Table 2). The Deming slopes were near unity, the intercepts near zero, and the RMSE was 2.24 and 2.42 mmol l^{-1} in the two studies. The distribution of points in the clinically acceptable (A + B) regions of the EGA was over 94% in both studies, with no more than 0.1% in the E region. This distribution is similar to that reported for conventional fingerstick BG monitors (Clarke et al., 1987; Kilpatrick et al., 1994), albeit in those studies the fraction of points in the A region was greater. The high percentage of points in the clinically relevant (A + B) region confirms the clinical usefulness of the biographer measurements.

For both studies, MD was less than 0.28 mmol l^{-1} and MARD ranged from 19.0 to 21.3%. The small values for MD and MRD and a Deming slope near unity indicate that the overall bias in the biographer measurements was small. The values for SD, MARD, RMSE, and correlation coefficient show a clinically acceptable amount of noise in the data sets, as well as similar scatter in the home environment as in the controlled clinical environment. The ability of the data screening routines to ensure data integrity is shown by the similar performance between the two studies. The uncontrolled home environment (greater range of motion, temperature variations, etc) caused each biographer to screen, on average, an additional two readings to maintain a high level of performance (a mean of 26 biographer readings per 12-h use in the home environment compared to 28 in the clinic environment study).

A mixed model analysis of variance (ANOVA) was used to estimate the statistical significance of clinical site, study day, and AutoSensor lot on the per-biogra-pher MD, SD, MRD, MARD, Deming linear regression, and correlation coefficient. The effects of the demographic variables of age, ethnicity, gender, type of diabetes, duration of diabetes, and body mass index were assessed using the same ANOVA. Although some individual parameters showed statistically significant

Table 2
Accuracy measures for the two clinical studies

	Clinic environment	Home environment
No. of subjects	231	124
No. of biographer uses	406	420
No. of paired points	6909	2996
Avg. glucose readings per use	28	26
Difference statistics		
MD (mmol l^{-1})	−0.01	0.26
SD (mmol l^{-1})	2.31	2.40
MRD (%)	3.7	7.0
MARD (%)	19.0	21.3
Regression		
Deming		
Slope	0.93	0.95
Intercept (mmol l^{-1})	0.66	0.70
RMSE (mmol l^{-1})	2.24	2.36
Linear		
Correlation	0.85	0.80
Error grid analysis		
Pts in Zones A+B (%)	95.3	94.2
Pts in Zone E (%)	0.0	0.1

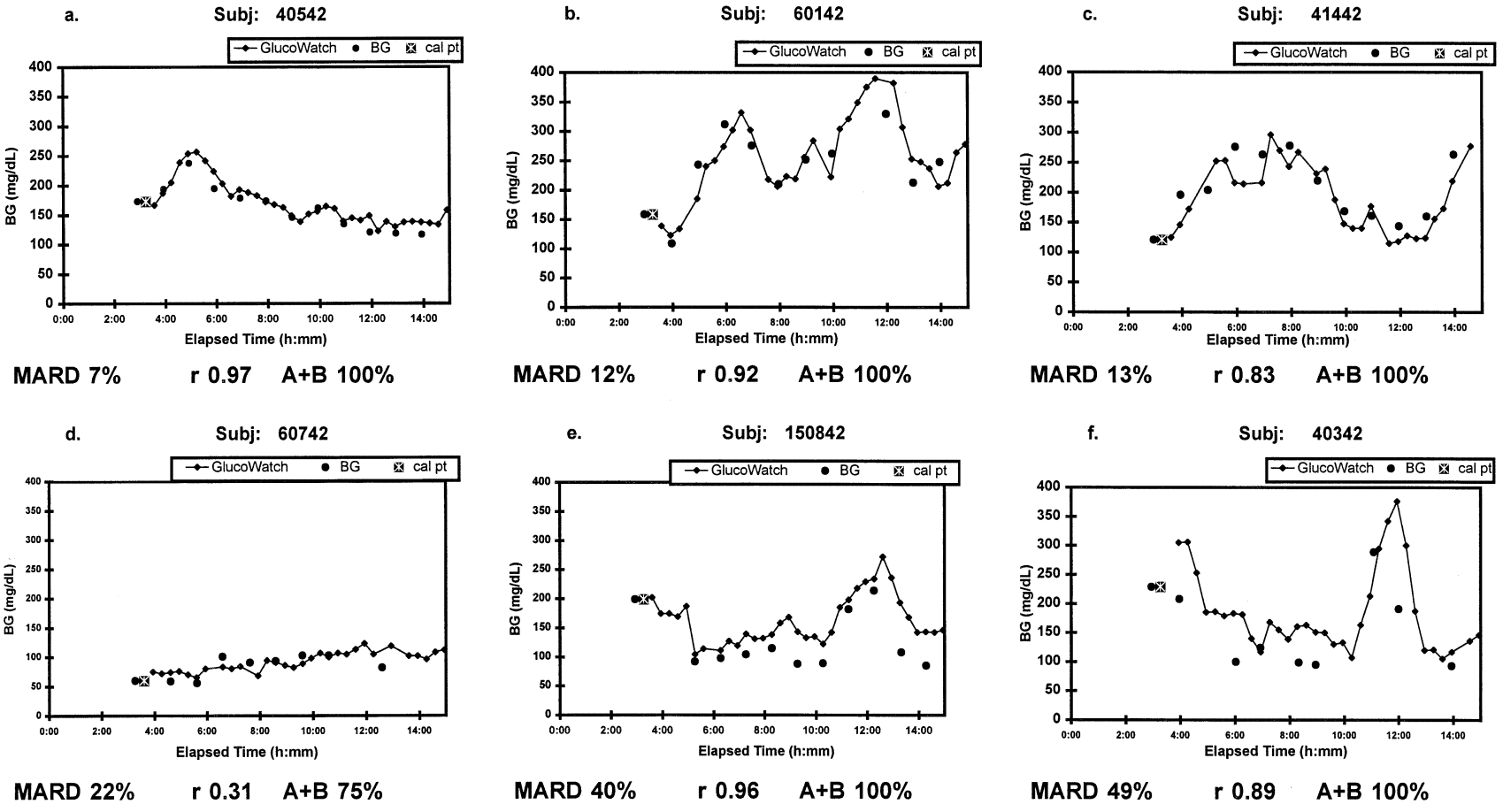

Fig. 4. Example blood glucose profiles from the biographer and comparative blood glucose measurements from the home environment study.

Table 3
Effect of blood glucose range on biographer accuracy

Glucose range (mmol l^{-1})		Clinic environment	Home environment		
MD (mmol l^{-1})	Full range	−0.01	0.26		
	⩽ = 5.56	1.13	1.19		
	5.56–10	0.23	0.36		
	10–13.33	−0.20	0.09		
	>13.33	−0.97	−0.94		
SD (mmol l^{-1})	Full range	2.31	2.40		
	⩽ = 5.56	1.50	1.47		
	5.56–10	1.86	1.85		
	10–13.33	2.56	2.78		
	>13.33	2.76	3.41		
MRD (%)	Full range	3.7	7.0		
	⩽ = 5.56	28.2	29.4		
	5.56–10	3.4	5.2		
	10–13.33	−1.6	0.9		
	>13.33	−5.9	-5.5		
MARD (%)	Full range	19.0	21.3		
	⩽ = 5.56	33.0	34.3		
	5.56–10	17.8	18.4		
	10–13.33	17.1	19.0		
	>13.33	14.3	18.0	Total	
No. of points	Full range	6909	2996	9905	100%
	⩽ = 5.56	972	540	1512	15%
	5.56–10	2832	1323	4155	42%
	10–13.33	1595	702	2297	23%
	>13.33	1510	431	1941	20%

differences ($P < 0.05$), the majority of these differences were small and of no consistent direction in the two studies. Therefore, the differences were judged not to be clinically meaningful.

To assess the biographer accuracy in different BG ranges, MD, MRD, and MARD are calculated for all the paired points in ranges corresponding to hypoglycemia (finger-stick blood value $\leqslant 5.56$ mmol l^{-1}), euglycemia (5.56–10 mmol l^{-1}), hyperglycemia (10–13.33 mmol l^{-1}), and extreme hyperglycemia (> 13.33 mmol l^{-1}) for both studies (Table 3). A slight positive bias at low glucose levels and a slight negative bias at high glucose levels are observed. This effect has been shown to be significantly reduced when the biographer readings are compared to a laboratory analyzer, indicating that part of the bias originates in the finger-stick meters used as the comparative measure in this study (Tierney et al., 2000).

The effect of the rate and direction of blood glucose changes on two accuracy measures (relative difference and absolute relative difference) was analyzed. The rate of change of blood glucose with time (dBG/dt) was calculated from the finger-stick blood glucose measurements. The rates of change were divided into eight regions (Table 4). Throughout most of the range, from -6.67 to $+10$ mmol l^{-1} h^{-1}, there was a slight trend for MRD to go from positive to negative as the rate of change of blood glucose goes from negative to positive. Thus, at decreasing blood glucose levels, the biographer read higher values than the finger-stick measurement and at increasing blood glucose levels, the biographer read lower than the finger-stick measurement. This effect is caused by the inherent time-averaging that occurs during the GlucoWatch® biographer measurement. For very rapidly decreasing blood glucose levels, more than -6.67 mmol l^{-1} h^{-1}, the MRD exceeded 23% in the clinic environment study, indicating that the biographer read high in those cases. The MARD was relatively unaffected by the rate or direction of blood glucose changes except for very rapidly decreasing blood glucose levels (more than -6.67 mmol l^{-1} h^{-1}) where the MARD was higher compared to other ranges, exceeding 27%. The incidence of very rapidly decreasing blood glucose was rare, with only 81 points (1.2%) with dBG/dt $\leqslant 10$ mmol l^{-1} h^{-1}, and 180 points (2.6%) with dBG/dt between -6.67 and -10 mmol l^{-1} h^{-1} in the clinic environment study, a protocol which intentionally induced mild hypoglycemia. The home environment study, which would be expected to reflect actual use, had a much lower incidence of rapidly decreasing blood glucose: only 6 points (0.2%) with dBG/dt $\leqslant 10$ mmol l^{-1} h^{-1}, and 39 points (1.4%) with dBG/dt between -6.67 and -10 mmol l^{-1} h^{-1}.

Table 4
Effect of rate of change of blood glucose on biographer accuracy

Rate of change (mmol l^{-1} h^{-1})		Clinic environment	Home environment		
MRD (%)	All points	3.7	7.0		
	[⩽ = −10]	36.0	10.4		
	[−10 to −6.67]	23.0	22.5		
	[−6.67 to −3.33]	10.5	19.2		
	[−3.33 to 0]	5.9	10.5		
	[0 to 3.33]	0.2	3.0		
	[3.33 to 6.67]	−4.8	−6.3		
	[6.67 to 10]	−6.7	−11.3		
	[>10]	−6.5	−16.1		
MARD (%)	All points	19.0	21.3		
	[⩽ = −10]	39.9	13.8		
	[−10 to −6.67]	27.6	31.8		
	[−6.67 to −3.33]	23.0	25.7		
	[−3.33 to 0]	19.5	22.3		
	[0 to 3.33]	17.7	18.9		
	[3.33 to 6.67]	15.4	19.3		
	[6.67 to 10]	12.3	16.7		
	[>10]	13.6	22.1	Total	
No. of points	All points	6883	2800	9683	100%
	[⩽ = −10]	81	6	87	1%
	[−10 to −6.67]	180	39	219	2%
	[−6.67 to −3.33]	786	254	1,040	11%
	[−3.33 to 0]	2672	1275	3947	41%
	[0 to 3.33]	2082	898	2980	31%
	[3.33 to 6.67]	748	268	1016	10%
	[6.67 to 10]	214	52	266	3%
	[>10]	120	8	128	1%

Table 5
Biographer precision estimates

Glucose range (mmol l^{-1})	CV (%)	SD (mmol l^{-1})
⩽ = 5.56	10.3	0.48
5.56–10	8.1	0.63
10–13.33	7.4	0.85
>13.33	6.3	1.03
Number of subjects	160	
Number of paired points	3531	

The precision of the biographer was assessed by comparing the paired readings from two synchronized biographers worn simultaneously and calibrated with the same finger-stick blood glucose value in the clinic environment study. The precision, as measured by coefficient of variation, improved slightly with finger-stick BG range (Table 5). No clinically significant difference in precision is observed over the different glucose ranges.

Dermatology assessments, performed following all studies for all biographer application areas, were evaluated using a modified Draize skin scoring system in which erythema and edema were scored separately on a scale from 0 to 4 (Draize et al., 1944). Either no or mild skin irritation was present in virtually all subjects. Edema and erythema scores of 0 or 1 (none to mild) postremoval were reported for the vast majority of biographer applications (83.4 and 84.9%, respectively). Intense erythema (score of 4) was observed in one case (0.09%); strong edema (score of 3) was observed in 13 cases (1.2%). Irritation resolved without treatment after several days in virtually all subjects.

4. Conclusions

We conclude that the GlucoWatch® biographer provides frequent, non-invasive measurements of glucose (up to 3 per hour) over a 12-h period with high accuracy and precision. No consistent difference in performance is seen whether the biographer is worn in either a controlled clinical environment or an uncontrolled home environment. The accuracy of the biographer measurement, based on MD, MRD, slope and intercept, is similar to that of existing, single point SMBG meters (Kilpatrick et al., 1994; Brunner et al., 1998; Louie et al., 2000). However, the scatter of the data, as measured by MARD, SD, and RMSE, is somewhat higher for the biographer than for home

meters. This slightly higher scatter is due in part to the fact that the biographer and the comparative finger-stick meter measure not only different samples, but different types of samples (interstitial fluid vs blood), while literature reports typically compare finger-stick meter and laboratory standard method measurements of the same blood sample. In addition, by reviewing a number of sequential readings, the user will be able to utilize the continual nature of the glucose measurements provided by the biographer to mitigate the somewhat higher scatter in the data. The clinical utility, as described by the distribution of points on the Clarke Error Grid, is similar to that reported for conventional finger-stick BG monitors (Clarke et al., 1987; Kilpatrick et al., 1994). It is believed that the GlucoWatch® biographer will facilitate both acute and long-term diabetes management and assist patients with diabetes, together with their health care team, to achieve better glycemic control without increasing the frequency of hypoglycemic episodes, and thus delay the onset of the complications of diabetes.

Acknowledgements

The authors wish to acknowledge the members of the Cygnus Research Team without whom this work would not have been possible: Neil Ackerman, Qiang Chen, Tom Conn, Shashi Desai, Tim Dunn, Steve Fermi, Yalia Jayalakshmi, Ronald Kurnik, Tim Lake, Matt Lesho, Margarita Lopatin, Sam Morley, Norman Parris, Ken Pitzer, Rahila Rabia, Michael Reidy, Pravin Soni, Chris Uhegbu, Michelle Van Wyhe, Prema Vijayakumar, Charles Wei, Steve Williams, and Christine Wu.

References

Brunner, G.A., Ellmerer, M., Sendlhofer, G., et al., 1998. Validation of home blood glucose meters with respect to clinical and analytical approaches. Diab. Care 21 (4), 585–590.

Cambiaso, A., Delfino, L., Grattarola, M., Verreschi, G., Ashworth, D., Maines, A., et al., 1996. Modelling and simulation of a diffusion limited glucose biosensor. Sens. Act. B. 33, 203–207.

Clarke, W.L., Cox, D., Gonder-Frederick, L.A., Carter, W., Pohl, S.L., 1987. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diab. Care 10 (5), 622–628.

Deming, W.E., 1943. Statistical Adjustment of Data. Wiley, New York.

The Diabetes Control and Complications Trial Research Group, 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New Engl. J. Med. 329 (4), 977–986.

Draize, J.H., Woodard, G., Calvery, H.O., 1944. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Ther. 83, 377–390.

Garg, S.K., Potts, R.O., Ackerman, N.R., Fermi, S.J., Tamada, J.A., Chase, H.P., 1999. Correlation of fingerstick blood glucose measurements with GlucoWatch biographer glucose results in young subjects with type 1 diabetes. Diab. Care 22, 1708–1714.

Ginsberg, B.H., 1992. An overview of minimally invasive technologies. Clin. Chem. 38, 1596–1600.

Kilpatrick, E.S., McLeod, M.J., Rumley, A.G., Small, M., 1994. A ward comparison between the One Touch II and Glucometer II blood glucose meters. Diab. Med. 11, 214–217.

Kurnik, R.T., Oliver, J.J., Waterhouse, S.R., Dunn, T., Jayalakshmi, Y., Lesho, M., et al., 1999. Application of the mixtures of experts algorithm for signal processing in a noninvasive glucose monitoring system. Sens. Act. B. 60, 1–8.

Louie, R.F., Tang, Z., Sutton, D.V., et al., 2000. Point-of-care glucose testing. Effects of critical care variables, influence of reference instruments, and a modular glucose meter design. Arch. Pathol. Lab. Med. 124, 257–266.

Rao, G., Glikfeld, P., Guy, R.H., 1993. Reverse iontophoresis: development of a noninvasive approach for glucose monitoring. Pharm. Res. 10, 1751–1755.

Tamada, J.A., Bohannon, N.J.V., Potts, R.O., 1995. Measurement of glucose in diabetic subjects using noninvasive transdermal extraction. Nat. Med. 1 (11), 1198–1201.

Tamada, J.A., Garg, S., Jovanovic, L., Pitzer, K.R., Fermi, S., Potts, R.O., et al., 1999. Noninvasive glucose monitoring: comprehensive clinical results. J. Am. Med. Ass. 282 (19), 1839–1844.

Tierney, M.J., Jayalakshmi, Y., Parris, N.A., Reidy, M.P., Uhegbu, C., Vijayakumar, P., 1999. Design of a biosensor for continual, transdermal glucose monitoring. Clin. Chem. 45 (9), 1681–1683.

Tierney, M.J., Tamada, J.A., Potts, R.O., et al., 2000. The GlucoWatch biographer: a frequent, automatic, and noninvasive glucose monitor. Ann. Med. 32, 632–641.

UK Prospective Diabetes Study Group, 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet 352, 837–853.

Zhang, Y., Hu, Y., Wilson, G.W., Moatti-Sirat, D., Poitout, V., Reach, G., 1994. Elimination of the acetaminophen interference in an implantable glucose sensor. Anal. Chem. 66, 1183–1188.