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TECHNOLOGY REPORT

GlucoMen Day Continuous Glucose Monitoring System: A Screening for Enzymatic and Electrochemical Interferents

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Abstract

Background:

While most of the common drugs with the potential to interfere with continuous glucose monitoring (CGM) systems are accessible over the counter and can be assumed by CGM patients without medical supervision, many other chemicals are frequently used to treat critically ill patients. Continuous glucose monitoring reading accuracy may also be compromised in patients characterized by abnormally high concentrations of physiological interferents. In this article, 22 species selected from endogenous and exogenous chemicals were screened as possible interferents of GlucoMen®Day (GMD), the new microdialysis-based CGM system from A. Menarini Diagnostics.

Method:

Interference testing was performed according to the EP7-A2 guideline (Clinical and Laboratory Standards Institute 2005). Interference was evaluated at two levels of glucose, with each interferent additionally tested at two concentrations. Furthermore, two configurations of the GMD disposable sensor kit—one designed for subcutaneous application, the other for direct intravascular CGM—were challenged with interferent-spiked serum and blood samples, respectively.

Results:

With the exception of dopamine (however, at very high, nonphysiological concentrations), no interference was observed for all the tested substances. Interestingly, none of the common electrochemical interferents (including ascorbic acid, acetaminophen, and salicylic acid, which represent the major specificity issue for the competing CGM systems) significantly affected the system's output.

Conclusions:

These results provide clear insights into the advantages offered by the use of a microdialysis-based CGM system that additionally relies on the detection of hydrogen peroxide at low operating potential. GlucoMen Day may become the CGM system of choice for those patients who require either regular administration of drugs or their glycemia to be tightly controlled in the intensive care unit or similar environments.

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Abbreviations: (CGM) continuous glucose monitoring, (CLSI) Clinical and Laboratory Standards Institute, (GMD) GlucoMen Day, (GOx) glucose oxidase, (ICU) intensive care unit, (SMBG) self-monitoring of blood glucose

Keywords: critical care, GlucoMen Day, glucose, interferents, intravascular continuous glucose monitoring, microdialysis

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Introduction

There is a rapidly growing consensus within the scientific community on the diagnostic advantages offered by continuous glucose monitoring (CGM) systems in view of their ability to provide complete glucose patterns and supply rate and trend information that can help minimize the risks associated with diabetes.[1] The heart of all CGM systems currently available on the market are glucose biosensors, which invariably rely on electrochemical transduction principles (**Table 1**).

The combination of sophisticated sensor designs and innovative surface chemistries[2–4] has led to an outstanding improvement in CGM system performance. However, compounds other than the target, especially in complex matrixes such as interstitial fluid or circulating whole blood, may still affect the response of the biosensor, falsely elevating or lowering the corresponding glucose reading. These chemicals include nonglucose sugars and electrochemically active physiological compounds.

Table 1.
Overview of the Technical Characteristics of All Commercially Available Continuous Glucose Monitoring Systems[2–4]

	Abbott Freestyle Navigator	DexCom SEVEN PLUS	Medtronic MiniMed Guardian REAL-Time	A. Menarini Diagnostics GlucoDay S	A. Menarini Diagnostics GMD
Detection	Amperometric (3-electrode system)	Amperometric (2-electrode system)	Amperometric (3-electrode system)	Amperometric (2-electrode system)	Amperometric (2-electrode system)
Working electrode	Carbon	Pt wire	Pt (plated on plastic)	Pt wire	Carbon (printed)
Reference electrode	Ag/AgCl	Ag/AgCl	Ag/AgCl (printed)	Ag/AgCl	Ag/AgCl (printed)
Counter electrode	Carbon	—	Pt (plated on plastic)	—	—
Mediator	Os-redox hydrogel	—	—	—	Prussian blue
System generation	Second (redox mediated)	First (H_2O_2 oxidation)	First (H_2O_2 oxidation)	First (H_2O_2 oxidation)	First (H_2O_2 reduction)
Operating potential versus Ag/AgCl	40 mV	500–700 mV	700 mV	620 mV	-20 mV
Enzyme	GOx (cross-linked Wired Enzyme™)	GOx (cross linked)	GOx	GOx (cross linked)	GOx (cross linked)
Flux modulating membrane	Cationic (vinyl pyridine-styrene copolymer)	Neutral (polyurethane/ polyethylene glycol copolymer)[a]	Neutral (polyurethane/ polyurea/polyethylene glycol/polysiloxane copolymer)[a]	Anionic (cellulose acetate/ polycarbonate)	Anionic (NAFION)
Oxygen dependence	Negligible	Moderate++	Moderate++	Moderate+	Moderate+
Microdialysis probe material	—	—	—	Regenerated cellulose	Polyethersulfone/polyvinyl pyrrolidone (subcutaneous probe); polyamide (intravascular probe)
Range of linear response	20–500 mg/dl	40–400 mg/dl	40–400 mg/dl	20–600 mg/dl	5–400 mg/dl
Insertion depth and angle	5 mm, 90°	12 mm, 45°	12 mm, 45°	~3–5 mm, ~0°	~3–5 mm, ~20°
Run-in time	10 h	2 h	2 h	2 h	2 h
Sensor lifetime	5 days (120 h)	7 days (166 h)	3 days (72 h)	2 days (48 h)	>4 days (100 h)
Data update frequency	1/min	1/5 min	1/5 min	1/3 min	1/min
Calibration frequency	After 10, 12, 24, 72 h	After 2 h; every 12 h thereafter	After 2, 6, 12 h; every 12 h thereafter	After 2 h; every 12 h thereafter	After 2 and 10 h; every 24 h thereafter

[a] Information obtained from patent literature; it may be inaccurate.

Commonly prescribed diabetes medications, antioxidants, and drugs represent additional species against which the specificity of the CGM device should be carefully tested. Investigations on the interfering effect of therapeutic agents is also expected to grow in importance as the use of CGM systems in surgical and intensive care units (ICUs)[5–7] will become more and more frequent, well beyond the original intended use of these devices.

GlucoMen®Day (GMD) is the second-generation CGM system developed by A. Menarini Diagnostics (Florence, Italy). This device, which integrates a novel Prussian blue-based, glucose oxidase (GOx)-modified glucose biosensor[8,9] with microdialytic technology,[10,11] relies on the use of disposable sensor kits that are currently available in two configurations. The first one, well established, uses a tiny coaxial microdialysis probe for continuous and minimally invasive sampling of glucose from the interstitial fluid.[12] The second prototype configuration uses a Luer Lock modified microdialysis probe (MicroEye®, Probe Scientific, UK) compatible with standard venous catheters. Hence, the resulting CGM device could be used straightforwardly in intensive care or surgical units, where direct intravascular monitoring of glucose is often seen as an urgent need.

As part of the analytical characterizations of the device, this article reports the results of the screening for possible interferents of the GMD system. The study was performed according to the EP7-A2 guideline issued by the Clinical and Laboratory Standards Institute (CLSI).[13] The results shown in this paper will provide clear insights into the advantages offered by a microdialysis-based CGM system, operating at low electrochemical potential, for continuously monitoring patients either under drug treatment or characterized by abnormally high concentrations of physiological interferents.

Materials and Methods

GlucoMen Day Disposable Sensor Kits

A detailed description of the GMD system (which consists of a disposable sensor kit, a recorder, and a control unit; **Figure 1A**) has been published previously.[12] The tests described in this article involved the use of both simplified disposable sensor kits (i.e., with no microdialysis probes integrated into the systems' fluidics) and kits equipped with either one or the other probe. The coaxial microdialysis probe for interstitial fluid use (**Figure 1B**) is a polyethersulfone/polyvinylpyrrolidone copolymer with an external diameter of 814 μm and a cutoff of 6 kDa. When perfused at 2.5 μl/min, the device responds to an instantaneous change in glucose concentration in approximately 2 min (signal update frequency = 1/min), with a typical *in vivo* recovery for glucose of (10 ± 4)%. Under the same conditions, the double lumen microdialysis probe for intravascular application (**Figure 1C**; in polyamide, 500 × 700 μm external diameter, and 9 kDa cut-off) exhibits a typical *ex vivo* recovery of (13 ± 2)%. Both disposable sensor kits were designed to ensure accurate tracking of *in vivo* glycemic excursions in the 5–400 mg/dl (0.3–22.2 mM) range.

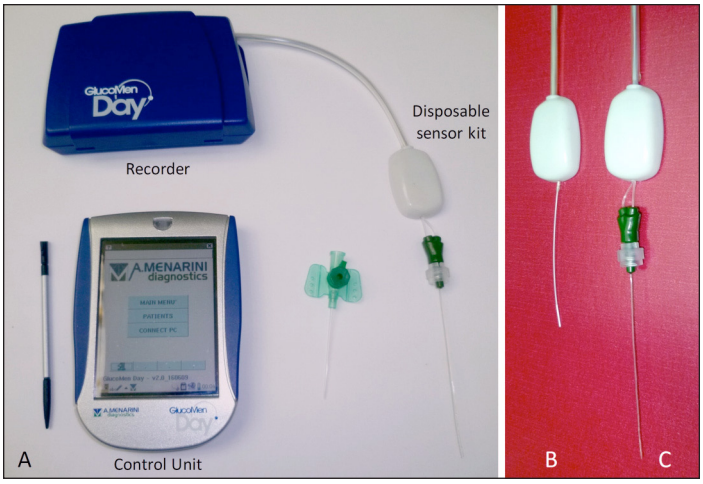

Figure 1. The **(A)** GMD system and disposable sensor kits for **(B)** interstitial fluid and **(C)** intravascular application.

Test Solutions

The EP7-A2 guideline indicates 80 and 120 mg/dl, respectively, as the low and high recommended test levels for glucose. Although unrepresentative of conditions of hypoglycemia and hyperglycemia, the two glucose levels used for screening potential interferents of the GMD system were selected accordingly. Glucose test levels 1 (8 mg/dl, 0.44 mM) and 2 (12 mg/dl, 0.67 mM) were prepared using the GMD "perfusion solution"[12] with an additional 0.1% v/v of Kathon®CG as the microbial preservative. The well-characterized *in vivo* performance of the interstitial fluid probe (the glucose recovery of which is approximately 10%) was taken into account when defining 8 and 12 mg/dl as the actual concentrations of the two glucose test levels. These values, apparently very low, indeed reflected what the probe would recover and bring to the biosensor having subcutaneous concentrations of glucose 10 times higher. Standard solutions of each interferent were prepared by adding two different concentrations of a given compound to both glucose standard solution levels 1 and 2.

A synthetic serum sample (i.e., a control solution employed by clinical chemistry analyzers) was additionally used as a model matrix with which to challenge the performance of the disposable sensor kit designed for interstitial fluid applications. Besides glucose (116 mg/dl, 6.44 mM) such a serum also contained a range of chemicals (uric acid, 0.34 mM; urea, 7.5 mM; triglycerides, 1.1 mM) at their nearly normal physiological levels. Selected interferents were further spiked into the serum in order to obtain in such a matrix the same high test levels previously prepared in glucosated buffers.

Similarly, interferent-spiked venous blood samples were used to assess the performance of the disposable sensor kits designed for intravascular applications. Several blood samples from healthy volunteers were first pooled in order to obtain a homogeneous matrix (in terms of composition and hematocrit) for all interferent-spiked samples. Such blood was then added with 2.5 mg/ml of sodium fluoride as the glycolysis inhibitor, split into subaliquots, and spiked with the interferents. All the resulting samples showed a 36% hematocrit and a plasma-equivalent glucose concentration of 142 mg/dl (7.88 mM), as assessed by means of a YSI 2300 STAT PLUS analyzer.

All the employed chemicals were of analytical grade and obtained from Sigma-Aldrich.

Procedures

While the initial screening with buffer solutions was performed at room temperature [(23 ± 2) °C], the tests involving the use of interferent-spiked serum and blood samples were performed at (35 ± 1)°C, i.e., the temperature that is most commonly experienced by the biosensor during *in vivo* tests.

Interference Testing in Buffer Solutions

All interferent-spiked samples were initially screened using simplified disposable sensor kits that did not integrate the microdialysis probe into the system's fluidics. The samples were thus flowed through the tubing of the kits directly into the biosensor flow cells. Following the EP7-A2 guideline, two different concentrations of each individual interferent (low and high), at two different glucose levels, were tested. Typically, the high test level was either the recommended test concentration of a drug or its high therapeutic dose, within (or higher than) the reference concentration range of an endogenous compound (**Table 2**).

For nonglucose sugars (most of which are not listed in the CLSI document), the high test levels were in the ranges often screened for conventional self-monitoring of blood glucose (SMBG) meters.

Interference testing was performed by alternating into the biosensor flow cell a given glucosated buffer (either interferent-free or interferent-spiked) and the perfusion solution, regularly at 20 min intervals. The background-corrected signals corresponding to glucose levels 1 and 2 (with no interferent added) and those relative to all the possible glucose/interferent combinations were used to calculate the %bias values (i.e., the relative difference of the signals obtained for the interferent-spiked glucose samples and the unspiked ones).

The chemicals were classified as potential interferents and underwent further testing when inducing a %bias > ±10%.

Interference Testing in Complex Matrixes

The effect of those substances inducing non-negligible biases when directly flowed into the biosensor flow cell was further investigated using the industrialized disposable sensor kits, thus introducing the microdialytic sampling process into the analytical procedure. On the one hand, the kits for interstitial fluid use were challenged with serum samples spiked with high concentrations of each suspect interferent. On the other hand, the kits for intravascular application were tested using venous blood samples similarly spiked with high concentrations of interferents. Testing was performed by alternating the microdialysis probes between the glucosated samples (serum or blood, either unspiked or interferent-spiked) and the perfusion solution (regularly at 20–30 min intervals). The %bias values were calculated as previously described.

Results

The microdialytic sampling process commonly results in a substantial dilution of both analyte and interferents. However, because no %recovery data were available for the 22 tested chemicals, the initial screening for interference was performed by flowing the interferent-spiked sample solutions directly into the biosensor flow cell. Excluding *a priori* any mediation from the microdialytic process (e.g., dilution, electrostatic repulsion, or size exclusion), this approach allowed the evaluation of the possible effect of each chemical directly on the glucose biosensor. It is additionally worth noting

Table 2.
Chemicals Screened as Possible Interferents of the GlucoMen Day System: Therapeutic, Reference, and Recommended Test Concentrations and Low and High Tested Levels

	Interferent	Molecular weight, Da	Therapeutic or Reference concentration, µM	Recommended test concentration, µM	Test levels in buffer		Test levels in serum or blood, µM
					Low, µM	High, µM	
Exogenous chemicals	Acetaminophen	151.20	66–200 (>1324)[a]	1324	132	1323	1323
	Ascorbic acid	176.12	23–114	342	23	114	342
	Dopamine	153.18	1.96	5.87	144	849	849
	Ibuprofen–Na^+	228.27	48.5–340 (2425)[a]	2425	49	2425	—
	Salicylic acid	138.12	720–2170 (2900)[a]	4340	145	3620	4344
	Tetracycline	444.44	4.5– 11.3	34	4.5	11.3	—
	Tolazamide	311.40	—	—	48	482	—
	Tolbutamide	270.35	200–400	2370	160	2370	—
Endogenous chemicals	Bilirubin	584.66	5–21	342[b]	1.7	342	—
	Cholesterol	386.65	2950–5200	13,000[b]	900	1800	12,932
	Creatinine	113.12	53–115	442[b]	133	442	—
	Glutathione	307.32	790–1050	3000[b]	5	65	1055
	Urea	60.06	1100–14,300	42,900[b]	3000	7000	—
	Uric Acid	168.11	150–476	1400[b]	200	500	1408
Nonglucose sugars	Fructose	180.16	56–333	1000[b]	416	3330	—
	Galactose	180.16	<280	840[b]	555	3330	—
	Lactose	342.30	—	—	88	876	—
	Maltose	342.30	—	—	1461	13,146	13,146
	Mannose	180.16	—	—	28	722	—
	Sorbitol	182.17	—	—	384	1702	—
	Xylitol	152.15	—	—	0.7	13.1	—
	Xylose	150.13	—	—	1332	19,983	19,983

[a] Toxic level.
[b] Common pathological value.

that, in view of the strong imbalance between glucose and interferent concentrations (either 8 or 12 mg/dl for glucose versus the actual CLSI recommended test levels for each interferent), the test conditions described in this article are probably the most severe reported in the literature.

Given the lack of specific recommendations on acceptance criteria to be applied for interference testing, most of the SMBG meters manufacturers adopt either ±10% or ±15% bias as the level above which the effect of a given chemical is considered as significant. By analogy, a ±10% bias criterion along with the evidence for a clear dose-dependent effect[14] was used in the present study for classifying a substance as an interferent of the GMD system.

The results of the screening tests with buffer solutions are reported in **Table 3**. Notably, at low interferent concentrations, none of the tested compounds induced a bias exceeding ±4% of the signal observed for the interferent-free glucose solutions. Interestingly, even under the worst case conditions (i.e., glycemic level 1 and high interferent concentrations), only dopamine, glutathione, xylose, and maltose induced non-negligible biases (-37%, +20%, +10%, and +8%, respectively).

Table 3.
%Bias for the 22 Screened Chemicals[a]

		Low interferent concentration		High interferent concentration	
		Glycemic level 1 (low)	Glycemic level 2 (high)	Glycemic level 1 (low)	Glycemic level 2 (high)
Exogenous chemicals	Acetaminophen	-4	-3	-4	-3
	Ascorbic acid	-4	-3	-7	-5
	Dopamine	-5	-3	-37	-15
	Ibuprofen	1	0.5	2	2
	Salicylic acid	-2	-1	0.5	0.5
	Tetracycline	-1	-1	0.5	0.5
	Tolazamide	2	2	6	2
	Tolbutamide	-1	-1	-1	-1
Endogenous chemicals	Bilirubin	0	0	3	2
	Cholesterol	2	1	7	5
	Creatinine	-1	1	0	0
	Glutathione	-3	-2	20	16
	Urea	-0.5	-0.5	-1	-1
	Uric acid	-3	-2	-4	-3
Nonglucose sugars	Fructose	-3	-2	-2	-1
	Galactose	0.5	0.5	2	1
	Lactose	-1	-0.5	0	0
	Maltose	2	1	8	4
	Mannose	-1	-1	4	3
	Sorbitol	0	0	0.5	0.5
	Xylitol	0	0	0	0
	Xylose	2	2	10	5

[a] Values are the average of three measurements performed using three different simplified disposable sensor kits (mean relative standard deviation = 6%). Test concentrations as reported in **Table 2**.

In order to evaluate whether these chemicals would still represent an issue under real operating conditions of the CGM device, their effect was reassessed by introducing the microdialytic sampling process into the analytical procedure and using more complex matrixes (serum and blood, respectively) for spiking each individual interferent. Ascorbic acid and cholesterol (which exhibited borderline behavior) along with salicylic acid, glutathione, and uric acid were additionally retested at higher concentrations in order to further challenge the system (**Table 2**).

Confirming the beneficial effect of microdialytic sampling, none of the tested compounds, with the exception of dopamine and (inconsistently) glutathione, induced a bias > ±10% (**Figures 2** to **4**).

The corresponding dose-response tests confirmed that only dopamine concentrations > 600 μM and glutathione concentrations > 900 μM changed the biosensor output by more than ±10% (data not shown).

The minor differences in the %bias values that emerge by comparing **Figures 2** and **3** were ascribed to the differences in chemical composition, active length and cutoff existing between the subcutaneous and the intravascular probe, and/or differences in the samples' matrixes.

Discussion

According to Food and Drug Administration recommendations, subcutaneous CGM systems are

intended for use as adjunctive devices to complement, not replace, the information obtained from standard SMBG meters. Even though it is clearly indicated that therapy decisions should exclusively be based on blood glucometers results, reliable and accurate continuous glucose readings would undoubtedly represent information of much higher value for both the diabetes patient and the clinician. Similar considerations also apply to critically ill patients from intensive care or surgical units, where the information provided by a CGM device could help the nursing staff in the titration of insulin therapy while minimizing the efforts for frequent but discontinuous blood sampling and the number of analyses for glucose to be performed at the central laboratory.

The clinical accuracy of the GMD system in its interstitial fluid configuration has been evaluated.[12] In order to get further insights into the analytical performance of the device, this laboratory study assessed the possible interfering effect of 22 species, selected in view of their possible presence in either blood or interstitial fluid and their potential to interfere with the sensing process of GMD.

Sugars

While the effect of most of the nonglucose sugars was negligible (**Table 3**), maltose and xylose slightly increased the electrochemical signal (+8% and +10%, respectively), suggesting a minor cross reactivity of GOx with such species. It is, however, important to note that this issue only emerged at very high concentrations of both sugars, 13.1 and 20.0 mM, respectively. When normalizing the corresponding signals for the actual concentration of glucose in test levels 1 (0.44 mM) or 2 (0.67 mM), a relative activity of GOx toward maltose and xylose lower than 1% could be calculated, in line with literature values.

Endogenous Chemicals

Among endogenous chemicals, only cholesterol (+7%) and glutathione (+20%) were found to induce non-negligible biases (**Table 3**). In particular, the observed positive bias induced by glutathione was ascribed to the reported activity of Prussian blue toward thiol compounds.[15] It is, however, worth noting that, while intracellular levels of reduced glutathione are in the millimolar range, the extracellular concentrations of this antioxidant in all bodily fluids (including plasma) are reported not to exceed the low micromolar range.[16] Moreover, the dose-response tests performed using the industrialized disposable sensor kits (equipped with either one or the other microdialysis probe) confirmed that only glutathione concentrations > 900 μM significantly affected the biosensor's output. Interference from glutathione was thus considered as an unlikely event in both the subcutaneous and the intravascular application of the GMD device.

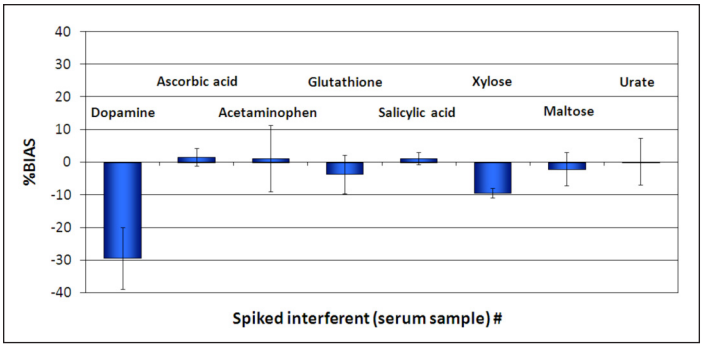

Figure 2. GlucoMen Day disposable sensor kits for interstitial fluid application: analysis of interferent-spiked serum samples (n = 3). Test concentrations as reported in **Table 2**.

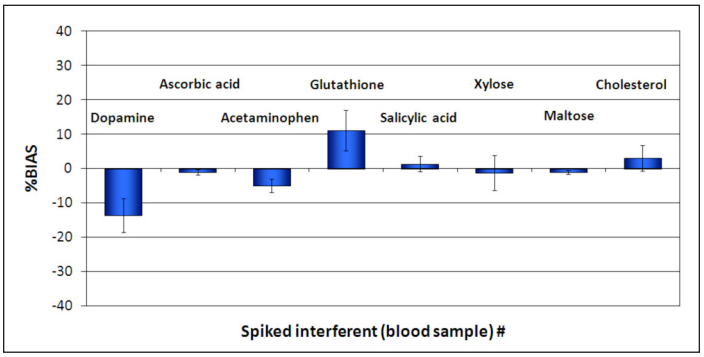

Figure 3. GlucoMen Day disposable sensor kits for intravascular application: analysis of interferent-spiked blood samples (n = 3). Test concentrations as reported in **Table 2**.

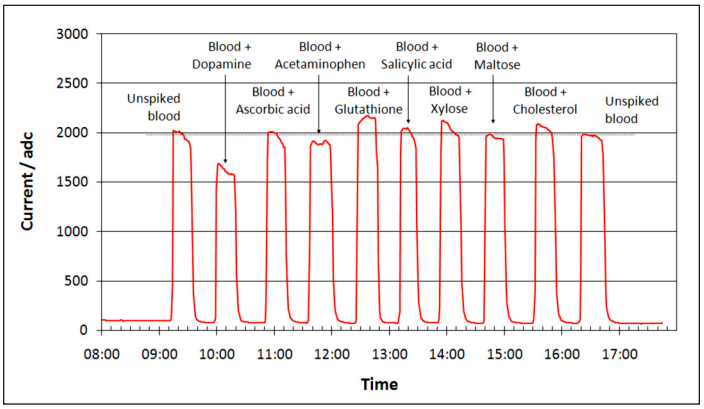

Figure 4. GlucoMen Day disposable sensor kits for intravascular application (analysis of interferent-spiked blood samples): raw current profile.

Often included in the lists of possible electrochemical interferents in view of its ease to be oxidized, uric acid had substantially no impact on the GMD signal (-4%).

Exogenous Chemicals

Among exogenous chemicals, dopamine induced the most significant bias on the CGM readings (-37%; **Table 3**). Such a relevant effect, observed at its high test level, was attributed to a direct redox reaction between dopamine and hydrogen peroxide, resulting in the solution-phase consumption of H_2O_2 and the consequent suppression of the electrochemical signal. The concentration of dopamine used for this test (849 μM or 13 mg/dl) was, however, well above the test concentration currently recommended by the EP7-A2 guideline (5.87 μM). The 13 mg/dl level (suggested by the previous issue of the guideline on interference testing[17]) is reported in the interference studies of most glucose tests strips and was, therefore, adopted in the present work for the sake of comparison with other well-established systems. Given that the steady-state plasma values measured in dopamine-treated critically ill patients are typically lower than 2 μM[18] and that the low tested level for this drug (144 μM) had only a negligible effect on the GMD signal (-5%), interference from dopamine was considered to be an unlikely event even in an ICU setting.

It is also particularly worth noting that none of the drugs or drugs derivatives that typically behave as electrochemical interferents for most blood glucose meters[14] and CGM systems had a significant impact on the GMD response (**Table 3**). Ascorbic acid, which is reported to have minor effects on both Freestyle Navigator (Abbott[3]) and Guardian REAL-Time (Medtronic Minimed[19]), induced a bias as low as -7% even at its high recommended test level. Acetaminophen, which is also reported to affect the response of Guardian REAL-Time[19] and may represent a major specificity issue for SEVEN PLUS (DexCom[20]), changed the GMD response by less than -4%. Being described as the main interferent for Freestyle Navigator,[21] the bias induced by salicylic acid was absolutely negligible (<1%).

The substantial immunity of GMD to all the common electrochemical interferents was ascribed to the distinguishing features of its glucose biosensor. Indeed, systems such as SEVEN PLUS and Guardian REAL-Time (but also GlucoDay S) rely on the use of a platinum working electrode where the H_2O_2 generated by GOx is oxidized (**Table 1**). However, oxidation of H_2O_2 at platinum surfaces can only be achieved through the application of high potentials, which also cause a number of endogenous and exogenous species to be co-oxidized. Being either cationic (Freestyle Navigator) or neutral (SEVEN PLUS and Guardian REAL-Time), the flux-limiting membranes of the current generation of needle-type CGM systems cannot completely prevent the anionic interferents from reaching the electrode surface. Stopping acetaminophen is even more difficult since this molecule is uncharged and its exclusion cannot be based on electrostatic repulsion criteria.

In this perspective, the Prussian blue mediator of GMD allows the detection of H_2O_2 at very low potentials where hydrogen peroxide undergoes electrocatalytic reduction with substantially no interference from other electrochemically active chemicals. The polysulfonated (polyanionic) film of NAFION® in which GOx is entrapped additionally represents an active barrier that inherently limits access of all anionic interferents to the electrode surface.

As a microdialysis-based system, GMD obviously lacks the potential for miniaturization typical of needle-type CGM systems. However, the device features a number of favorable performance characteristics (besides accuracy) that may help mitigate such a competitive disadvantage.

First of all, GMD is inherently less exposed to interferences. Indeed, because of the microdialytic sampling process, the concentration of a specie in the dialysate that reaches the biosensor flow cell is significantly lower than the corresponding level in either the interstitial fluid or the blood stream. For any given material, cutoff and active length of the microdialysis probe, and applied flow rate, the extent of dilution will depend on the molecular weight, charge, and other physicochemical properties of each compound. The filtering capacity of the microdialysis probe also reduces the likelihood of molecules with fouling properties to reach the electrode surface, thus minimizing any change in the baseline current[22] over the course of monitoring.

With Freestyle Navigator being the only exception, the needle-type CGM systems also rely on the amount of oxygen dissolved into the interstitial fluid for their correct functioning.[2] However, in patients with particular hypoxic conditions or deficient vascularization at the implantation site, the amount of dissolved oxygen may be limiting for the enzymatic reaction to occur or may significantly fluctuate over time, with a dramatic impact on the accuracy.[22] On the contrary, the reaction occurring in the biosensor flow cell of GMD essentially depends

on the pO_2 level in the stream of perfusion solution,[10] which is nearly constant ([163 ± 13] mmHg) within the operating temperature of the device and is obviously independent on the physiopathologic state of the patient.

Interestingly, the buffering capacity of the perfusion solution also makes the response of the GMD biosensor insensitive to possible changes in pH of the biological matrix where glucose is collected.

Conclusions

In this article, 22 species selected from endogenous and exogenous chemicals were screened as possible interferents of GMD, the second-generation microdialysis-based CGM system from A. Menarini Diagnostics. These tests, which were performed according to the EP7-A2 guideline (CLSI), involved both the configurations of the GMD disposable sensor kit, designed for either subcutaneous or intravascular applications.

With the exception of dopamine (however, at concentrations much higher than those expected *in vivo*), no interference was observed for all the tested substances. Interestingly, none of the common electrochemical interferents (including those that represent the major specificity issue for the competing CGM systems) significantly affected the system's output, even at their higher recommended test level.

While confirming that the most common interfering drugs accessible over the counter are not an issue, the promising outcome of this interference study represents solid grounds for a deeper investigation of the performance on the GMD system within the challenging ICU setting, where many other chemicals, often at very high concentrations, are used to treat critically ill patients. The preliminary *in vitro* screening for interferents on compounds such as dobutamine, norepinephrine, midazolam, and propofol, commonly in use in ICUs, will continue accordingly.

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Disclosure:

Fausto Lucarelli, Francesco Valgimigli, and Cosimo Scuffi are full-time employees of A. Menarini Diagnostics.

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