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Capillary glucose meter accuracy and sources of error in the ambulatory setting

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Abstract

Hand-held glucose meters are used throughout the health system by both patients with diabetes and also by health care practitioners. Glucose meter technology is constantly evolving. The current generation of meters and strips are quick to use and require a very small volume of blood. This review aims to describe meters currently available in New Zealand, for use in the ambulatory setting. It also aims to discuss the limits of meter performance and provide technical information that is relevant to the clinician, using locally available data. Commoner causes and consequences of end-user (patient and health professional) error are illustrated using clinical case examples. No meter offers definite advantages over other meters in all clinical situations, rather meters should be chosen because they fit the needs of individual patients and because the provider is able to offer appropriate educational and quality assurance backup to the meter user. A broad understanding of the advantages and disadvantages of the subsidised meter systems available in New Zealand will help the health practitioner decide when it is in the best interests of their patients to change or update meter technology.

Glucose results derived from hand-held meters are used by patients and their health care team to make therapeutic decisions such as insulin dosing. Incorrect glucose values may result in both acute and also long-term therapeutic consequences. It is therefore essential that results are as accurate and precise as possible.

Meter technology has shown incremental improvements since the introduction of the first commercially available hand-held meters in 1970s, including improvements in ease of use, technical performance and affordability.[1-3] Capillary glucose testing is an international multi-billion dollar industry.[2] In New Zealand reimbursement of test strips for the 12 months to June 2009 was $19 million, accounting for 40% of PHARMAC's entire diabetes 'spend'. The number of meters available has expanded, both in New Zealand as well as internationally.[1,2]

Currently in New Zealand, six different meters are available for use with PHARMAC funded strips (see Table 1). It is therefore timely to describe current meter technology from a clinical perspective, highlighting some of the limits of meter performance. This review focuses on technical issues that impact on clinical interpretation of meter results in the ambulatory setting. It does not aim to be a comprehensive technical discussion. Although there are additional meter systems available in New Zealand with unsubsidised strips such as the Glucocard, which is used in many hospital inpatient settings, the focus of this review is meters with subsidised strips.

Table 1. Meters with subsidised test strips

System	Accu-Chek Performa	CareSens II	CareSens POP	FreeStyle Lite	On Call Advanced	Optium Xceed
						
Manufacturer	Roche Diagnostics	i-Sens Corp	i-Sens Corp	Abbott Diabetes Care	Acon Laboratories	Abbott Diabetes Care
Test Strip	Accu-Chek Performa	CareSens (includes lancets)	CareSens (includes lancets)	FreeStyle Lite	On Call Advanced (includes lancets)	Optium
Coding	Automatic via code chip	Manual input	Manual input	Not needed	Automatic via code chip	Automatic via code chip
Test Time	5 seconds	5 seconds	5 seconds	5 seconds	5 seconds	5 seconds
Sample volume	0.6 µL	0.5 µL	0.5 µL	0.3 µL	0.8 µL	0.6 µL
Operation Temperature	6º–44ºC	10º–40ºC	10º–40ºC	4º–40ºC	5º–45ºC	10º–50ºC

The clinical impact of recent improvements in hand held blood glucose meter systems

Recent developments in meter technology have improved this testing system's ease of use and analytical robustness.[1-3] Test strips now require 8µL or less of blood (see Table 1).

Using a low blood volume system has the following advantages: It allows most patients to get a successful sample each time they undertake lancing. It allows a shallower finger lancing depth, thus patients should experience less pain.[2] In addition, the need to squeeze fingers for blood letting, a practice that may lead to a change in the effective composition of the blood test sample and a false glucose value, is reduced. Strip technology utilises a capillary filling system with a fill indicator or fill time detector to ensure that the assay does not start until sufficient blood sample is provided to the strip. This minimises the risk of obtaining a 'false low' result caused by insufficient sample volume.[3]

A development that has been appreciated by patients residing in colder areas of New Zealand, is the wider functional temperature range of meter and strip systems.[3] Historically, low winter temperatures and cold houses made it difficult for patients to obtain accurate results. A temperature sensor is now present either in the meter or in the strips. This allows correction of the glucose value for ambient temperature across a wide temperature range. Inadvertent patient use of time expired meter test strips, which often contain 'spoiled' analytical reagents, was a common source of error with older systems. This error has been minimised but not eliminated in some meter and strip systems. One example of how this is achieved, is by determining the expiry date of the strip batch from the calibration chip and pre-setting the meter software to 'disallow' strip use after the batch's expiry date.

One meter system, the Optium Xceed, can be dual calibrated to measure both glucose and also capillary ketones (beta hydroxybutryrate), allowing patients to treat mild ketoacidosis at home.

Understanding how the difference between venous and capillary samples impacts on meter performance

Finger stick test results are derived by converting an electrochemically generated signal to a glucose value by means of an algorithm. In New Zealand and most other countries, the current expectation from clinicians is that the algorithm is programmed so that a capillary whole blood glucose sample (i.e. finger stick result) will read as a laboratory venous plasma sample (i.e. a venesection result). Thus if a patient went to get a laboratory plasma venous glucose check and did a simultaneous capillary test with their meter, the expectation is that the two glucose results should read approximately the same. The comparison between a capillary finger stick test and a laboratory plasma venous glucose is not however straightforward, in part because two different types of samples are being used, which have some shared but also have some distinct physiological characteristics.[3-5]

Whole blood (e.g. a capillary sample) is composed predominantly of plasma and cells. In the laboratory, glucose is measured on a plasma sample i.e. a whole blood sample

is centrifuged, followed by removal of the cellular component of blood. Red cells have a lower water and glucose content than plasma. As a result of this, the glucose concentration of whole blood is about 11% less than the glucose concentration of plasma.[4] Historically, some meters available in New Zealand gave capillary results as a whole blood glucose equivalent. When these meter systems were updated, the algorithm was also updated to display results as venous plasma equivalent, rather than whole blood equivalent. For example, a whole blood glucose of 5.0mmol/L from an 'old' meter would equate to a plasma glucose of around 5.6mmol/L, using a 'new' meter. This change had the potential to cause confusion.

The current international recommendation, aimed to provide harmonised reporting and reduce confusion, is to report glucose results as plasma equivalent.[4] All meters currently available in New Zealand do this.

A second major difference between capillary and laboratory venous results, relates to the fact that the glucose value of a capillary sample is higher than for a corresponding venous sample, because glucose uptake by tissues as blood flows from the capillaries to the veins partially depletes the venous sample of glucose. Tissue uptake of glucose increases after food.[6] The glucose gradient between capillary and venous samples therefore shows a postprandial increase which may be as high as 20% total glucose concentration.[5,6]

In summary, because capillary and plasma glucose samples have several physiologically distinct characteristics, comparison between these two samples is not expected to correlate as closely as a comparison that uses the same type of blood sample, for example comparing the same venous sample using two different measurement techniques. Clinicians should anticipate a slight variation in glucose values between capillary and venous samples but at least 95% of capillary results should show an analytical variance of <20%, when compared to a laboratory result.[7,8]

Figures 1a and 1b illustrate this point, using results from the On Call Advanced meter (methodology is based on a previous study).[8] This meter and test strip system can measure venous as well as capillary whole blood i.e. a venous sample from the antecubital fossa can be applied directly to the test strip. Figure 1a compares a laboratory venous plasma glucose sample with a simultaneously collected capillary whole blood sample i.e. two distinct samples are used. Figure 1b compares the same venous sample, obtained from the antecubital fossa, using two different methods. Not surprisingly, visual inspection of results in Figure 1b (the same venous sample measured using two different methods) shows a closer correlation than those of 1a (separate venous and capillary samples, obtained from different anatomical sites).

Figure 1a. Comparison of venous plasma with capillary glucose (On Call Advanced)

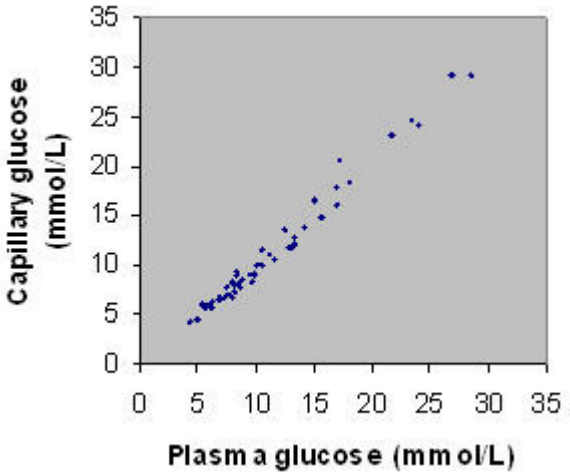
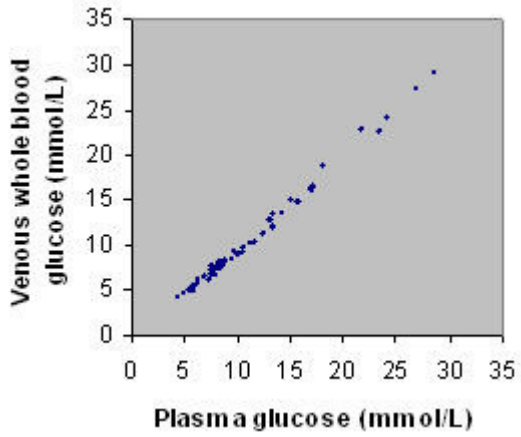


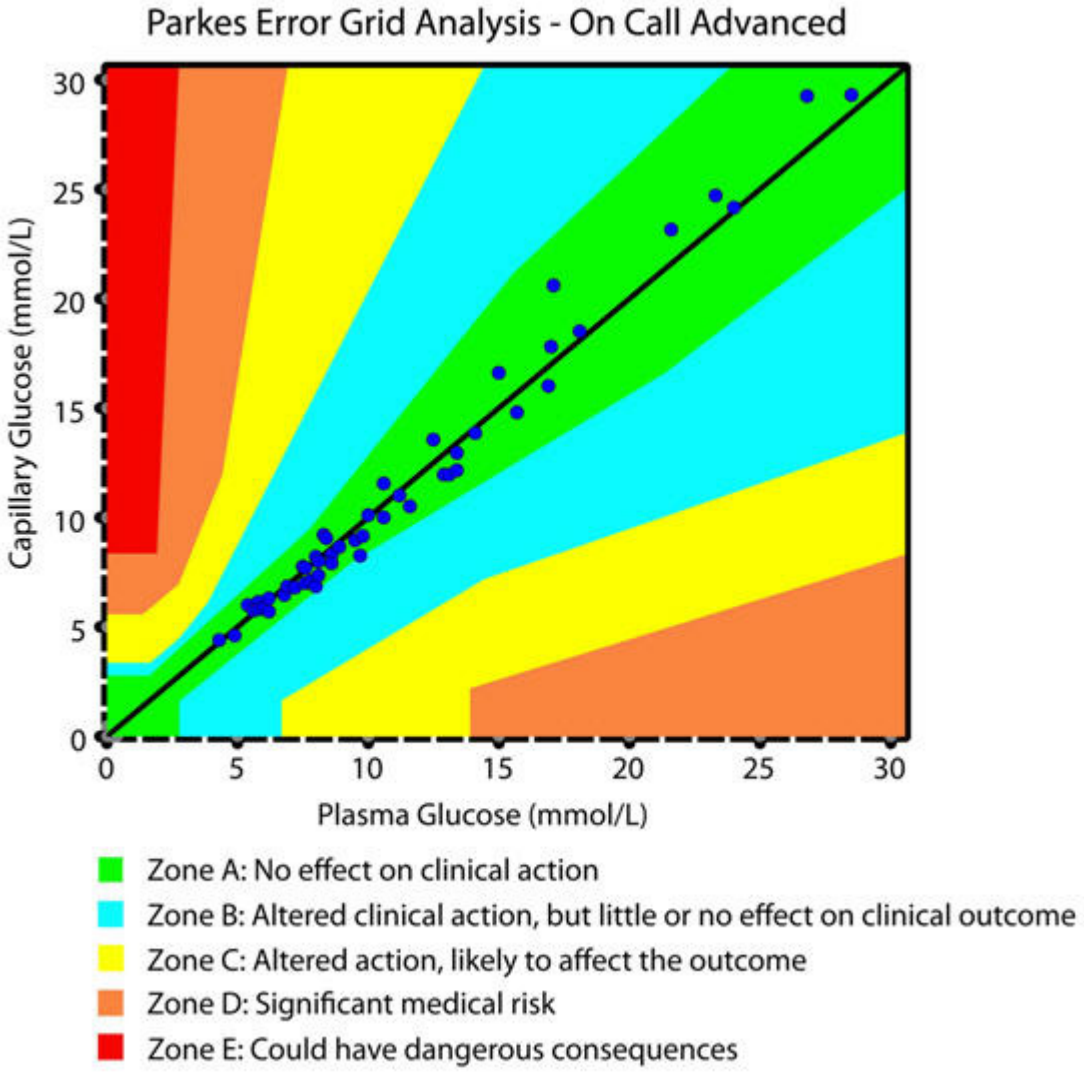
Figure 1b. Comparison of venous plasma with venous whole blood glucose (On Call Advanced)



Error grid analysis

Parkes error grid analysis is used to detect clinically significant errors in glucose measurement, when comparing capillary with laboratory plasma venous glucose results.[9] Using this visual method of analysis, method comparisons are intuitively easy to understand. The information in Figure 1a has been redrawn in Figure 2 as a Parkes error grid with a key showing how to interpret the zones contained within the grid. Error grid analysis of the different meters currently available in New Zealand is available on www.pharmac.govt.nz/usingmedicine and shows that all locally available meters perform to a satisfactory standard.

Figure 2. Comparison of simultaneously collected venous plasma with capillary glucose results



Clinical implications of limitations in meter accuracy and precision, in other settings

In other settings, for example in the ICU, factors related to patient pathology such as hypoxia, hypoperfusion and extremes of haematocrit may lead to additional sources of error.[5] Also, increased viscosity, which is common in severely dehydrated patients, may impair capillary strip filling and give an erroneous result with some older systems.[10] It is therefore of passing interest to note that one reason why very tight glycaemic control in some ICU settings may result in adverse clinical outcomes,[11] relates to the difficulty of safely achieving tight control with intravenous insulin, when insulin dose is determined using capillary meter glucose values.[12]

Another situation where meter inaccuracy and imprecision can amplify errors in glucose measurement is with CGM (continuous glucose monitoring) systems,[13] as the CGM biosensor requires ongoing calibration using finger stick readings from a conventional meter.

Minimising sources of error in the real world setting

The above discussion on meter performance is based predominantly on tests undertaken under controlled conditions by trained technicians. In the real world setting,[14] end-user (patient or health practitioner) error, including problems with interpretation of glucose results, may have negative clinical consequences. In theory, errors can be minimised by reviewing patients' meter technique on a regular basis,[1] and also by undertaking quality control checks using commercial control solutions supplied by meter manufacturers for use with their specific meter. In practice, a combination of cost of these control solutions and their short shelf life after opening, limits their use to selected service providers such as hospital based point of care co-ordinators.

End-user error is minimised by the multiple safety features embedded into currently available meter systems but many potential sources of error remain. The clinical cases below describe extreme examples of real world problems that can occur with current meter systems. We hope that these illustrations will help improve clinicians' awareness of potential problems, as well as help them with troubleshooting. Although major errors in glucose measurement are rare, minor errors are not uncommon. Further descriptions of common potential sources of error are given in Table 2.

Case studies

Case 1—Meter not coded for current batch of test strips

A patient was diagnosed with Type 1 diabetes 2 years previously and undertook frequent glucose testing. He had a year-long discrepancy between his home glucose results, which were consistently <10mmol/L and his laboratory glucose results which were >10mmol/L. During the same year his HbA1c increased from 8.5% to 11%. Thus there was a discrepancy between his finger stick and laboratory values. On reviewing meter technique, he was found not to have recoded (recalibrated) his meter since the time of diagnosis. The combination of an old strip batch code and currently available test strips produced meter glucose results that were much lower than their real value, leading to significant under-dosing of insulin. The patient was given structured meter education at the time of diagnosis but does not recall receiving instructions about calibration and did not recall any update on meter use at any subsequent appointment.

Comment: This problem is common.[15,16] Another common problem is inadvertent use of time expired strips,[2] which is less likely to occur in systems that use a strip calibration code which also signals that the strip batch is past its expiry date . Regular review of meter technique is recommended, but it may be difficult to achieve in our resource constrained environment.

Table 2. Commoner potential sources of error in glucose meter measurement in the ambulatory setting

Description of source of error	Comment
Simultaneously collected capillary and venous plasma samples show slightly discrepant results	Capillary meter results should read within ± 20% of a laboratory plasma venous sample, 95% of the time. A higher discrepancy than this may point to an additional source of error (see below)
Meter not calibrated (using the calibration chip) to read the current batch of test strips	A common potential source of error – up to 25% of patients may be using an incorrectly calibrated meter/strip system
Contamination of test finger surface	Glucose rich foodstuffs on fingers may elevate the measured glucose value. Inadequate hand drying after washing may produce a dilutional error
Time expired and/or 'spoiled' strips	Strip performance is likely to be suboptimal, once past the strip expiry date. Performance may also be affected by prolonged exposure to adverse environmental conditions e.g. heat, humidity. Some (but not all) strip/meter systems will signal an error in these situations
Pathophysiological factors present in the patient, which may affect glucose meter / strip accuracy	More common in the inpatient (e.g. ICU) rather than ambulatory setting, but occasional ambulatory patients may experience extremes of haematocrit (e.g. anaemia) hypoxia (including acrocyanosis) and hyperviscosity syndromes, sufficient to affect the accuracy of glucose readings
Interfering substances present in the patient's blood	Icodextrin (found in dialysis fluid) can produce marked pseudohyperglycaemia. Many other compounds may produce interference, including aspirin, high dose vitamin C and paracetamol. These substances have a much smaller effect on glucose values compared to icodextrin. Interference is not always predictable and is in part dependent on the interaction between the interfering substance and the specific meter and strip system used for testing
Use of meter/strip systems in extreme environmental conditions	Meters and strips tend to perform suboptimally under 'extreme' conditions. This includes the high atmospheric pressure used in hyperbaric chambers

Case 2—Dilutional error

An adolescent on insulin had a history of recurrent diabetic ketoacidosis. She had a 'contract' with her parents to show them her latest glucose value recorded on her meter. Her parents reported observing satisfactory glucose results. Computer download of her meter's memory demonstrated clusters of tests undertaken over several minutes. A typical series of glucose results was: 21mmol/L at initial testing followed by 18, 10 and 6mmol/L over the next 5 minutes.

Comment: It is physiologically impossible to drop glucose levels by this magnitude over 5 minutes. It was assumed she was manipulating results by undertaking self-

dilution of samples, so that the glucose on the meter display read 6mmol/L, rather than 21mmol/L. Downloading glucose results from memory meters and comparing this with self recorded glucose results often highlights discrepancies in self reported results.[17] The concentration of salivary glucose is much lower than that of blood,[18] thus 'licking fingers clean' prior to testing may also cause a dilutional error, as can hand washing followed by incomplete hand drying. These errors are usually unintentional, but can on occasions be intentional.

Case 3—Change of meter from one calibrated to whole blood glucose, to a system calibrated to plasma glucose

A patient with Type 1 diabetes had tight glucose control (HbA1c 6.4%), frequent minor hypoglycaemia and hypoglycaemic unawareness. He updated his meter system but was unaware that his old meter was calibrated to read as whole blood yet his new meter read as venous plasma equivalent. Glucose values from the new meter therefore 'read higher' than those from the old meter. The patient concluded that glycaemic control had deteriorated and increased his insulin. He then had a hypoglycaemic fall and sustained a fracture.

Comment: All subsidised meters in New Zealand read glucose as plasma and this calibration related scenario is therefore now uncommon. However there are some countries that still use meters calibrated to whole blood,[2] thus patients with diabetes who move to New Zealand may need additional education when changing meters. This case also highlights the fact that patients become familiar over time with how their own meter functions and reads and they incorporate meter performance characteristics into their everyday self care.

Case 4—Interfering substances

A 53-year-old with insulin treated diabetes was commenced on peritoneal dialysis. He experienced unexplained severe hypoglycaemic symptoms despite apparently normal or elevated glucose readings using the Accuchek Perfoma meter. His high mean glucose value from the Performa meter contrasted with his normal HbA1c value of 5.4%. Paired glucose meter tests were then done using both the Performa meter (strips use a glucose dehydrogenase system) and Glucocard meter (strips use a glucose oxidase system).

A Performa glucose reading of around 8.0mmol/L corresponded to 2.0mmol/L using the Glucocard. The attending clinical team was advised by the local laboratory that systemic absorption of 7.5% icodextrin from the peritoneal dialysis fluid was a source of interference for the glucose dehydrogenase based strip systems using pyrroloquinoline quinone as a cofactor (which include Performa, Freestyle Lite, On Call Advanced, but not the Xceed or CareSens systems). Thus interference from icodextrin resulted in artefactually high glucose levels.[5,13] This was rectified by changing the patient to a glucose oxidase based meter/strip system.

Comment: Many other substances, including high dose ascorbic acid and aspirin,[5,13] may also interfere with glucose measurement (see Table 2) but, in contrast to icodextrin, they usually produce only a small change in measured glucose value.

Case 5—Meter reading glucose values as mg/dL

A teenager with Type 1 diabetes switched meters and inadvertently set his new meter to the mg/dL setting (i.e. to the glucose units used in the USA and several other countries) rather than to mmol/L. The conversion factor between the two units is 18:1. The patient was unclear how to interpret results, but worked on the assumption that 100mg/L equated to 10mmol/L.

He therefore titrated his insulin dose to achieve results between 40mg/L and 100mg/L (i.e. 2.2 to 5.6mmol/L), assuming erroneously that this was equivalent to 4 to 10mmol/L. Over the next four months, the patient's HbA1c dropped from 8.7% to 5.9%. He experienced frequent hypoglycaemia and excessive weight gain and developed hypoglycaemic unawareness. Fortunately all these negative clinical developments reversed when the error was identified and corrected.

Comment: Whilst this patient's persistent misinterpretation of results was unusual, we have witnessed patients making similar errors for short periods of time. The Care Sens meters are able to be set to read glucose units as either mg/dL or mmol/L. This may be advantageous for occasional patients who move between countries and health systems that utilise different units.

Conclusions

Meter analytical performance and ease of use has improved markedly over recent years. Safety features in the meter and strip systems may result in potentially erroneous values being 'disallowed', for example by giving an error message. Also, there are now far fewer potential sources of errors in measurement, but errors in measurement and in interpretation of results can nevertheless occur. An understanding of glucose physiology and meter performance should help minimise meter related errors and help with trouble shooting.

Most published data about meter performance is based on assessments undertaken in controlled environments. The error contribution made by end users (i.e. patients and health care practitioners), in real world settings is acknowledged to be large. There are however few systematic studies of the reasons for and magnitude of this source of error. Patients and their health practitioners therefore need to remain vigilant about the possibility of meter error. Undertaking occasional comparisons between simultaneous laboratory and finger prick samples measured on the patient's own meter system and undertaking regular reviews of meter technique remain important tools for minimising errors.

Clinicians want their meter derived glucose results to show close agreement with a plasma laboratory value. There are however challenges in achieving this, which relate in part to intrinsic physiological differences between these two specimens. Although current meter systems are accurate, they lack precision and only 95% of results might fall within 20% of the reference plasma laboratory value. Clinicians need to be aware of this fact, especially in situations such as diabetes in pregnancy and insulin pump therapy, where the patients and their health care team are aiming for tight glucose control. In practice, patients who use the same, familiar meter system over a prolonged period seem to be the least troubled by issues related to meter accuracy and imprecision. This may in part be because regular use of the same meter system yields

consistent readings in similar situations. From the health practitioner's perspective, an understanding of the differences between currently available funded meter systems should enable practitioners to select meters that best fulfil their patients' and their practice's needs. Encouraging staff and patients within your practice to become very familiar with one or two meter systems allows for an in depth understanding of the behaviour of that particular meter system and its related software for downloading of meter results, in the real world setting.

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