

Clinical evaluation of a portable lactate meter in type I glycogen storage disease

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Summary: High lactate concentrations occur in type I glycogen storage disease (GSD) whenever glycogenolysis occurs. Not only does hyperlactataemia cause acute clinical deterioration, but chronic lactate elevations have also been associated with many of the long-term complications in GSD. A portable finger-stick blood lactate meter has recently been marketed as a training tool for high-performance athletes, but it has not been tested as a clinical diagnostic tool. This study was performed to assess the accuracy of the portable lactate meter in subjects with GSD I who are predisposed to high lactate concentrations. A total of 166 intravenous and 39 capillary samples from 13 subjects were tested concomitantly on three different lactate meters. The meter readings were compared with the lactate concentration determined by the laboratory gold-standard enzymatic colorimetric assay. Almost no inter-meter variability was found. The lactate meter values had outstanding correlation with the laboratory lactate determination, although the meters were found to run 0.5 mmol/L higher than the laboratory assay. The meter deviation was independent of lactate concentration. More variability was noted with finger-stick capillary lactate determinations, but monitoring of trends with capillary samples should prove valuable as a method for determining long-term control or acute deterioration. The portable lactate meter is a highly accurate tool for monitoring lactate concentrations, and should prove valuable for monitoring metabolic control in patients with GSD type I and other disorders associated with hyperlactataemia.

Type I glycogen storage disease (GSD I; McKusick 232200) is caused by a deficiency of hepatic glucose-6-phosphatase (EC 3.1.3.9), which is an integral part of both glycogenolysis and gluconeogenesis (Wolfsdorf and Weinstein 2003). Lack of this enzyme impairs normal glucose homeostasis, and fasting consequently results in severe hypoglycaemia. Not only is glycogenolysis ineffective in maintaining blood sugars, but glycogen degradation also results in hyperlactataemia, hyperlipidaemia, and hyperuricaemia. The provision of a constant supply of exogenous glucose minimizes hypoglycaemia, and usually results in amelioration of the biochemical abnormalities. This has allowed patients to survive into adulthood,

Table 1 Glucose-independent conditions associated with hyperlactataemia in GSD I

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- Illness
 - Stress
 - Puberty
 - Pregnancy
 - Surgery
 - Dietary intake of non-glucose carbohydrates (fructose, sucrose, galactose)
 - Medications (glucocorticoids, sympathomimetics)
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but long-term complications have become increasingly common (Weinstein and Wolfsdorf 2002a).

Type I GSD patients exhibit high lactate concentrations whenever glycogenolysis occurs (Fernandes et al 1984). Normally, glycogen degradation and hyperlactataemia occur during periods of fasting and hypoglycaemia. Hyperlactataemia, however, can also develop in the setting of normal blood sugars (Table 1) (Weinstein and Wolfsdorf 2002b). Elevated lactate can be associated acutely with vomiting, tachypnoea or systemic acidosis, and chronic lactate elevations have been associated with many of the long-term complications in GSD including hepatic adenomas, poor growth, nephropathy and anemia (Weinstein and Wolfsdorf 2002a).

Patients are easily able to routinely monitor their blood glucose concentrations using glucose meters, but lactate determinations are presently only performed in clinical laboratories, making frequent measurements away from a clinical setting impossible. Blood lactate concentrations fluctuate rapidly, and spot measurements do not accurately reflect overall control (Hagen et al 2000). Recently, a portable finger-stick blood lactate meter, the Lactate-Pro, has been marketed as a training tool for high-performance athletes. The meter employs a methodology similar to that of the finger-stick glucose meter, utilizing disposable test strips and an internal electrochemical (oxidation–reduction) reaction. Blood lactate concentrations are determined in 60 seconds. The Lactate-Pro test system has been given Waived Status by the US FDA. The manufacturer has statistical data that indicate a high correlation between lactate meter values and standard laboratory results (<http://www.fact-canada.com/LactatePro/lactate-pro-portable-analyzer.html>). However, the meter has not previously been tested as a clinical diagnostic tool and, in particular, it has not been used in a population that may be prone to very high lactate concentrations.

This study was performed to assess the accuracy of the portable lactate meter in a clinical population predisposed to high lactate concentrations. The incorporation of a reliably accurate portable lactate meter into the treatment regimens of type Ia GSD patients would greatly improve the monitoring of control in this population, and would decrease the risk of lactate levels rising to the point of severe systemic acidosis during stress or illness.

METHODS

Subjects: All patients followed by the Glycogen Storage Disease Program of Children's Hospital Boston with proven type Ia glycogen storage disease (either documented low

glucose-6-phosphatase activity on liver biopsy or known mutation of the glucose-6-phosphatase gene) were eligible for participation. The subject population represents 13 consecutive admissions to the General Clinical Research Center, where patients were being admitted for evaluation of their metabolic control. These studies were approved by the Clinical Investigation Committee of Children's Hospital Boston, and informed consent (and assent from the child when under the age of 18 years) was obtained prior to enrolment in this study.

Research design and methods: Upon admission, a drawing intravenous line was placed, and heparinized saline (0.1 U/ml) was run at 10–20 ml/h. As part of routine clinical metabolic assessment, intravenous blood samples were drawn without a tourniquet for lactate determination every 1–3 h during a 24 h visit. At each time point at which a lactate concentration was determined as part of the clinical metabolic assessment, the lactate concentration was measured concurrently on three different lactate meters using 5 μ l of blood each. The meter readings were compared with the lactate concentration determined by the laboratory gold-standard enzymatic colorimetric assay (Cobas Integra; Roche Diagnostic Systems, Inc., Somerville, NJ, USA). At three time points, concurrent with laboratory draws, a capillary puncture was performed with a standard finger lancet, thus allowing comparison of the peripheral blood sample meter readings to the laboratory assay.

Statistical analysis: Data from intravenous and capillary samples were analysed separately. For intravenous blood data, the accuracy of the lactate meter readings was assessed by mixed-model linear regression of the meter values on the laboratory values, adjusted for differences among the three meters and for correlation within patient and sample. Capillary data were analysed similarly with the exception that, because all capillary samples were read on a single instrument, meter variability could not be included in the model. SAS software was used for all computations (SAS Institute, Cary, NC, USA).

RESULTS

The clinical characteristics of the subject population are summarized in Table 2. The subjects ranged in age from 1.4 to 33 years and their baseline control varied, allowing the spectrum of lactate values to be assessed using the new technology.

Each patient provided between 8 and 19 intravenous blood samples for analysis. In total, 166 samples and 498 readings were available for analysis, covering a range of lactate concentration between 0.49 and 10.54 mmol/L according to the laboratory assay. A total of 39 capillary blood results were available from 13 subjects, but five values were excluded from the analysis after it was learned that they were obtained from a heel-stick, which deviated from the protocol. The range of lactate concentrations compared with the capillary samples was between 0.57 and 8.19 mmol/L.

Regression analysis of the intravenous data is illustrated in Figure 1. The fitted line for meter readings plotted against the laboratory values lay significantly above the line of identity, indicating a positive bias in the meter readings of 0.57 ± 0.10 mmol/L (estimate \pm standard error). The slope of the fitted line did not differ significantly from unity (1.036, 95% confidence interval 0.986–1.086), indicating that the amount of bias in the meter readings was uniform across the measured range.

Table 2 Clinical characteristics of the study population

Subject	Age (years)	Gender	UCS ^a doses/day	UCS/day (g/kg)	Lactate range (mmol/L)	Mean lactate (mmol/L)
1	25	M	7	4.2	1.83–3.43	2.67
2	3	M	6	10.3	0.69–1.75	1.13
3	14	F	7	6.1	1.82–4.35	2.42
4	4	M	5	9.8	0.64–1.53	1.03
5	1.4	M	6	9.5	0.74–2.85	1.36
6	16	M	5	5.2	1.41–3.63	2.47
7	20	F	6	5.4	4.52–8.17	6.26
8	26	F	6	5.0	0.70–1.85	1.09
9	15	M	7	5.5	0.49–0.95	0.70
10	13	F	7	7.3	1.77–4.05	2.84
11	19	M	6	6.2	1.11–4.97	2.41
12	3	F	6	11.3	0.95–2.33	1.39
13	33	F	2	2.2	4.77–10.5	6.79
Average	14.8	7M/6F	5.8 ± 1.3	6.8 ± 2.7	0.49–10.5	2.50 ± 1.92

^aUCS, uncooked cornstarch

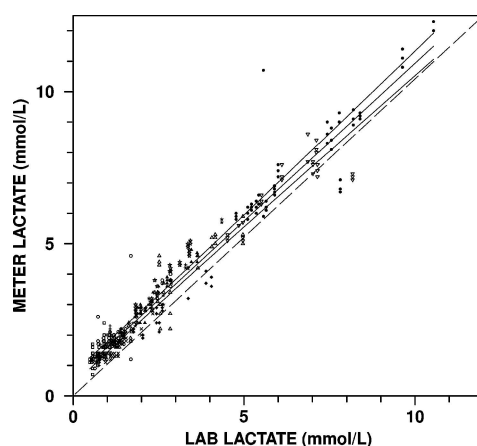


Figure 1 Regression analysis of lactate meter reading (vertical axis) vs laboratory gold-standard measurement (horizontal axis) in intravenous samples. Different plotting symbols represent 13 different patients providing 166 samples measured on three different instruments. Solid lines indicate the fitted linear relation with 95% confidence band, adjusted for correlation within patient and sample and for differences among instruments. The fitted line lies parallel to the line of identity (dashed) within statistical limits, but significantly above it, indicating upward bias in meter readings independent of lactate concentration

Almost no inter-meter variability was found. Modelled as a random effect, the maximum-likelihood estimate of meter–meter variance was zero; modelled as a fixed effect, the estimated difference among the three meters was negligible (3.25, 3.26 and 3.29 mmol/L at the mean laboratory value, 2.61 mmol/L; $p > 0.40$). Random variation in the readings

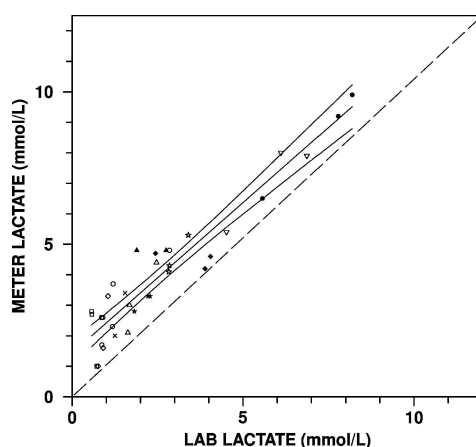


Figure 2 Regression analysis of lactate meter reading (vertical axis) vs laboratory gold-standard measurement (horizontal axis) in capillary samples. Different plotting symbols represent 12 different patients providing 34 samples measured on a single instrument. Solid lines indicate the fitted linear relation with 95% confidence band, adjusted for correlation within patient. The fitted line lies parallel to the line of identity (dashed) within statistical limits, but significantly above it, indicating upward bias in meter readings independent of lactate concentration

from intravenous samples at a given laboratory value was estimated at 0.26 mmol/L among GSD patients, 0.29 mmol/L among samples within a patient, and 0.31 mmol/L for residual measurement error.

Capillary data yielded similar results to those from the intravenous sampling (Figure 2). The upward bias of meter readings was more marked than for intravenous samples, amounting to 1.44 ± 0.20 mmol/L (estimate \pm standard error). The estimate of regression slope was less precise than that for the venous samples because of the smaller sample size and narrower range of laboratory values but was again indistinguishable from unity (0.986, 95% confidence interval 0.864–1.108), indicating that the amount of bias was not dependent on lactate level over this range. Random variation in the readings from capillary blood was considerably larger than that from intravenous samples. The standard deviation of the meter reading at a given laboratory value was estimated at 1.74 mmol/L among patients, 0.96 mmol/L among samples within a patient, and 1.08 mmol/L for residual measurement error.

DISCUSSION

Hyperlactataemia in GSD I is associated with both acute deterioration and many of the long-term complications (Daublin et al 2002; Weinstein and Wolfsdorf 2002a), yet measurement of this critical marker of control has been problematic. Rapid elevations of lactate concentration with use of a tourniquet often makes measurement with phlebotomy inaccurate, and in-patient admissions have been required if lactates are used to titrate treatment regimens in GSD I. The data in this study indicate that the portable lactate meter is a reliable tool for measuring blood lactate concentration almost instantaneously in GSD I.

While the intra-meter consistency was outstanding, the lactate meters were found to consistently run 0.5 mmol/L higher than the laboratory values when intravenously drawn samples were compared with the traditional laboratory lactate determination. Slightly more variability was found with finger-stick lactate measurements, but capillary samples run on the portable lactate meters had an excellent correlation with the intravenous sample values. The meter deviation from the laboratory lactate values was independent of lactate concentration. Of note, however, occasional significant elevations in lactate measurements occurred with finger-stick determinations when a good sample was not obtained and significant squeezing of the digit was required.

Although capillary sample readings were less precise than those of intravenous samples, monitoring of the trends should be very valuable as a method for determining long-term control or acute deterioration. The level of precision for the portable lactate meter is similar to that of devices currently used to monitor blood sugars (e.g., the Cygnus Glucowatch Biographer or the Medisense Continuous Glucose Monitoring System), where measurement of low blood sugars is problematic (Koschinsky et al 2003). Trends for glucose fluctuations rather than precise concentrations are often used in these devices, and similar trends can be followed with the lactate meter. The lack of strict precision compared to the laboratory and the possibility of false positives limit the use of the meters for interpreting individual lactate determinations. Individual values should not be used in isolation for clinical decision-making, but tracking of the trends can be useful. Using the trends, the small difference between the laboratory values and the meter readings would not result in inappropriate clinical response.

Monitoring of blood lactate concentrations with the portable lactate meter will supplement currently available methods for assessing control in GSD I. Measurement of urinary lactate concentrations has been used as a noninvasive way of monitoring control in patients with GSD I (Hagen et al 2000). Urinary lactate concentrations correlate well with blood lactate concentrations in individuals, but urinary lactate excretion differs significantly among individuals owing to variations in lactate reabsorption and renal tubular dysfunction (Hagen et al 2000; Lee et al 1996). As a result, it is difficult to extrapolate blood lactate concentrations from urinary lactate values. Urinary lactate measurements are also not routinely available in many places, and often results are not available for several days. Thus, while urinary lactate concentrations are simple and a noninvasive method for assessing chronic control in patients with GSD I, they cannot be used to determine the acute metabolic status of a patient. In contrast, the lactate meter provides almost instantaneous results, and it can be used to more precisely assess the timing of suboptimal control. Most importantly, in situations where lactic acidosis may occur in the setting of normoglycaemia, determination of blood lactate concentrations in real time should allow interventions prior to development of systemic acidosis and vomiting.

We envision the Lactate-Pro lactate meter being used to supplement traditional glucose monitoring. Glucose monitoring will remain the standard for titration of treatment regimens, but lactate monitoring should help to improve control in populations prone to hyperlactataemia in the setting of normoglycaemia, such as in patients with partial enzyme activity or the conditions outlined in Table 1. The main use of lactate monitoring will be during illness, when the stress response can result in rapid development of lactic acidosis. In these situations, specific values are not as important as whether lactate concentrations

are decreasing or increasing rapidly. When higher lactate concentrations are documented, interventions aimed at slowing counterregulation can occur, including administration of glucose and cornstarch. Lowering of lactate concentrations during illness should prevent the acute deterioration associated with acidosis often seen in patients with GSD I, and fewer hospitalizations are predicted. Of note, use of the lactate meter is likely to be specifically limited to patients with type Ia GSD. Patients with type Ib GSD often have normal or even low lactate concentrations when well treated, even during puberty, and lactate elevations only occur during severe stress or illness (Rake et al 2002). Consequently, monitoring of lactate concentrations in patients with type Ib is likely to be of limited value.

In summary, the Lactate-Pro portable lactate meter is a highly accurate tool for monitoring of lactate concentrations. This should improve monitoring in GSD Ia patients, and would probably be of use in other disorders associated with hyperlactataemia, including disorders of gluconeogenesis and mitochondrial disorders.

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