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Comparison of plasma ammonia results from seven different automated platforms in use throughout Central Australia

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ABSTRACT

Introduction: The clinical catchment area for the Metabolic service at the Women's and Children's Hospital in Adelaide, South Australia, covers nearly 2.5 million km^2. Care of children with metabolic disorders in these remote areas is assisted from Adelaide, and at times, using plasma ammonia results from laboratories up to 3000 km away. There are seven different platforms measuring plasma ammonia within this vast clinical catchment area. Hence, a correlation study was conducted to examine the relationship between plasma ammonia results from the seven different platforms in use throughout central Australia.

Design & method: Multiple aliquots of plasma from remainder EDTA samples for haematological investigations were frozen. Samples were then dispatched on dry ice to the laboratories being correlated. At an agreed date and time correlation samples were thawed and plasma ammonia measured.

Results: Passing-Bablok regression analysis showed slopes ranging from 1.00 to 1.10 and y-intercepts ranging from −10 μmol/L to 1 μmol/L.

Conclusions: Despite the absence of a reference method or reference material and troublesome pre-analytical effects in ammonia measurement, plasma ammonia results from the different platforms in general compare well. The study also demonstrates that samples for ammonia measurement can be transported over great distances and still correlate well. Furthermore, a common reference interval for plasma ammonia may be a possibility.

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1. Introduction

Hyperammonaemia is a medical emergency, as elevated levels of free ammonia are neurotoxic, leading to cerebral oedema, coma and potentially death [1–5]. Hyperammonaemia is a significant complication of several metabolic disorders (not necessarily confined to children) including Urea Cycle Disorders, Organic Acidaemias, and Fatty Acid Oxidation defects [1–4]. Hyperammonaemia may be present in various acquired conditions for example, acute or chronic liver failure, Valproic acid treatment and L-Asparaginase therapy [1–5]. Investigation of ammonia levels is suggested in patients of any age with an unexplained change in consciousness, unusual or unexplained neurological illness, respiratory alkalosis, liver failure, or suspected intoxication [1–3]. The ability to rapidly measure plasma ammonia levels is important in the acute setting [1,2], as duration of hyperammonaemia and peak plasma ammonia concentration correlate with patient outcome [2].

The clinical catchment area for the Metabolic service of the Women's and Children's Hospital (WCH) in Adelaide covers an area of nearly 2.5 million km^2. In addition to South Australia (SA), this area includes the Northern Territory (NT), western New South Wales (NSW) and western Victoria.

Two public hospital laboratories measure plasma ammonia in the NT, the Royal Darwin Hospital (RDH) and the Alice Springs Hospital (ASH), 3000 km and 1530 km from Adelaide respectively. Furthermore, in western NSW, plasma ammonia is measured at the Broken Hill Hospital laboratory, 500 km from Adelaide. Care of patients with metabolic disorders in these distant areas is assisted by the Metabolic service from Adelaide, and if patients become acutely ill, they are retrieved to the WCH for management.

Within this large clinical catchment area, plasma ammonia is measured on seven different automated clinical chemistry platforms by thirteen different laboratories. The platforms used include Roche Diagnostic Cobas c501 and Modular P, Siemens Advia 2400 and Dimension, Beckman AU680 and AU640, and the Ortho Vitros 5,1 FS. Table 1 summarises the platforms used throughout Central Australia.

There are few recent studies comparing the relationship between plasma ammonia results from different platforms or different laboratories using the same platform [4–8]. We conducted a study using patient samples, to investigate the relationship between plasma ammonia results from the seven different platforms used within Central Australia.

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Table 1
Clinical chemistry platforms in use throughout Central Australia for the measurement of plasma ammonia.

Location	Platform	No. of labs.	Reagent	Method	Co-factor
Adel	Roche Cobas c501	1	Mnf	GLDH	NADPH
Adel	Roche Modular P	1	Mnf	GLDH	NADPH
Adel	Siemens Advia 2400	1	Mnf	GLDH	NADPH
Adel	Beckman AU680	1	TFI	GLDH	NADH
Adel + Reg	Beckman AU640	6	TFI	GLDH	NADH
Western NSW	Siemens dimension	1	Mnf	GLDH	NADPH
NT	Ortho Vitros 5,1FS	2	Mnf	Dry Slide	N/A

Adel - Adelaide Metropolitan.
Reg - Regional South Australia.
NSW - New South Wales.
NT- Northern Territory.
Mnf - Manufacture's reagent.
TFI - ThermoFisher Infinity reagent (Third party reagent).
GLDH - Glutamate dehydrogenase enzymatic method.
NAPDH - Nicotinamide adenine dinucleotide phosphate.
NADH - Nicotinamide adenine dinucleotide.
N/A - Not Applicable.

2. Materials and methods

Clinical samples of remainder blood collected into EDTA anticoagulant for haematological and transfusion investigations were used for the comparison study. EDTA anticoagulant was chosen, to reduce non-specific sample-buffer interactions, observed with lithium heparin samples in some methods [8,9]. Plasma ammonia concentrations increase when samples are stored as whole blood [10,11]. To obtain some correlation samples with a high plasma ammonia concentration, whole blood samples up to 72 h post-collection were selected. The EDTA samples were centrifuged at 1800*g* for 10 min at 14 °C. Plasma was then aliquoted into a number of daughter tubes and frozen at –80 °C.

Comparison samples sent to the NT and western NSW were transported by express air freight and road transport. Adelaide metropolitan and regional SA laboratory correlation samples were transported by road freight. All comparison samples were transported with sufficient dry ice to ensure samples remained frozen for entire journey. Acknowledgment was sent to the coordinator, regarding the dry ice quantity remaining and specimen integrity, upon receipt at the destination laboratory. Samples were kept frozen at the destination laboratory at –20 °C or –70 °C if available.

Handling of ammonia samples prior to analysis was performed in a standardised manner. At an agreed date and time, all laboratories involved in the comparison thawed samples at room temperature. The moment samples were thawed they were centrifuged for 2 min at 1800*g* at 14 °C. Once spun, samples were loaded on board the analyser for stat plasma ammonia measurement. Due to sample volume limitations, the comparison was performed over four rounds, with up to seven laboratories correlated in one round.

Six platforms used an enzymatic method and one platform used a dry slide method for plasma ammonia measurement. The methodology for both the enzymatic and dry slide method is described by [6,7].

Manufacturer's reagent and calibrators were used on the following platforms: Roche Modular P and Cobas c501, Siemens Advia 2400 and Dimension, and the Ortho Vitros 5,1 FS. Two platforms, the Beckamn AU640 and Beckman AU680, used a third party Infinity ammonia liquid stable reagent and calibrators manufactured by ThermoFisher Scientific. Quality control performance for all laboratories on the day of correlations was within acceptable limits of performance.

The Roche Cobas c501 at the Adelaide WCH was used as the X-coordinate for statistical purposes of the correlation study. The rationale for this decision was there is no reference method or standard reference material available for ammonia measurement in human plasma. Furthermore, the WCH was the coordinating site for the comparison study and assistance from the Metabolic service is also conducted from this site. The range of ammonia results obtained from this platform was 25 to 339 μmol/L. For the Beckman AU640 platforms, one representative laboratory (Site B) was selected for the comparison amongst the different platforms. Statistical analysis was performed using Chemical Pathology-R (cp-R) v0.4 and R Project 3.2.2.

For method comparisons ethical approval is not required.

3. Results

Plasma ammonia results were returned for 830 of the 866 samples dispatched. A limited correlation study was done to confirm one site's previous results, hence results were not available for 36 samples. A further 22 results were removed from statistical analysis due to instrument flagging for haemolysed/icteric/lipaemic indices or technical difficulties during the analytical run. Some sites were correlated more than once due to updating of instrument parameter settings after the initial comparison. The highest plasma ammonia result achieved from the correlations was 353 μmol/L. No clinical samples were available for correlation at extreme ammonia concentrations greater than 1000 μmol/L. Ammonia results of this severity would result in an urgent retrieval to a hospital with a specialist metabolic service, regardless of assay correlation at this level.

Fig. 1 shows representative scatter and bias plots for each of the six platforms. Table 2 summarises the representative Passing-Bablok regression analysis and mean bias for the six platforms, using the Roche Cobas c501 at WCH as the X-coordinate. Table 3 displays the Passing-Bablok regression analysis and mean bias for the six laboratories using the Beckman AU640 platforms. Fig. 2 graphically displays the Passing-Bablok regression slopes and intercepts with 95% confidence intervals for the six platforms.

In general, the different platforms and laboratories all correlated well. The closest correlation was seen between the two Roche Diagnostics platforms, with a Passing-Bablok regression equation of Modular $P = 1.00 * c501 + 0$, and a mean difference (SD) of $-1(\pm 3)$ μmol/L., $R^2 = 0.99$.

The Siemens Advia 2400 platform Passing-Bablok regression equation was Advia $2400 = 1.03 * c501 + 5$, and a mean bias of $9(\pm 7)$ μmol/L. Similarly, the Dimension showed a regression equation of Dimension $= 1.08 * c501 + 0$, and a mean bias of $4(\pm 8)$ μmol/L, $R^2 = 0.98$.

The group representative for the Ortho Vitros 5,1 FS dry slide analysers in the NT demonstrated good correlation against the Roche Cobas c501. The regression analysis showed Vitros 5,1FS $= 1.03 * c501–10$, and mean bias of $-8(\pm 13)$ μmol/L, $R^2 = 0.97$.

The different laboratories using the Beckman AU640s and one site using the AU680 in general correlated well, with slopes for Passing-Bablok regression ranging from 1.07 to 1.14 and y-intercepts of −6 to 1 μmol/L. One notable exception was site D with a y-intercept of −15 μmol/L (95% CI = −20 to –12).

4. Discussion

In this study we investigated the relationship of plasma ammonia results from multiple platforms throughout Central Australia. Measurement of plasma ammonia and comparison of results from different platforms can be difficult due to pre-analytical effects, no reference method, or reference material for ammonia in human plasma. Our study shows that despite the absence of a reference method and material, plasma ammonia results generally correlate well between different platforms. Furthermore, samples for plasma ammonia measurement can be transported over great distances and still demonstrate good correlation.

The relationship observed between the two Roche Diagnostics instruments, the Modular P and the Cobas c501, was highly correlated. The only difference between the two methods is the reagent buffers, Triethanolamine in the Modular P reagent and *N*,*N*-bis(2-hydroxyethyl)-glycine (BICINE) in the Cobas c501 reagent. The

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