CLOZAPINE TDM: A COMPARISON of LC/MS/MS, POINT of CARE and IMMUNOASSAY

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Introduction

Clozapine fulfils several criteria which make it a candidate for Therapeutic Monitoring (TDM) such as an identifiable reference range, unpredictable dose-concentration relationship between patients, many pharmacokinetic interactions with other drugs and a high probability of patient noncompliance. Therefore, TDM of clozapine assists with obtaining an optimal clinical response by minimizing drug-related CNS toxicity, assessing adherence thereby avoiding treatment failures. TDM has been reported in many clozapine studies and these have subsequently led to the development of practice guidelines and expert consensus recommendations[1,2]. Clozapine TDM is undertaken on venipuncture blood specimens that are sent to a specialist laboratory for drug determination. Transportation and analysis inevitably takes several days.

The present study has two aims:- 1) to validate the three title methods using a set of independently spiked clozapine samples and compare the performance between methods and; 2) to measure, plasma clozapine concentrations from venipuncture blood in patient samples by LC/MS/MS and compare the results with those determined using the MyCare Insite point of care device on capillary blood collected at the same time. In addition, to compare plasma concentration obtained by MyCare Psychiatry laboratory-based Immunoassay (IA) with the reference LC/MS/MS results.

Methods

The reference procedure involves extraction of small plasma samples using a 96 well AC extraction plate prior to injection into a LC/MS/MS[3]. The My Care Insite point of care device for determination of clozapine in capillary blood was calibrated and applied as described in ECNP poster P-878[4]. The liquid homogeneous Saladax Biomedical, Inc. (SBI) immunoassay for clozapine was performed at SBI using a Beckman Coulter AU480 analyser.

A set of 40 spiked plasma samples was prepared and blinded by Saladax. Initially this sample set was analysed by each of the headline methods. In addition 304 real patient samples were collected for method comparison during routine patient visits at two sites of the South London and Maudsley NHS Foundation Trust. Capillary whole blood samples were tested immediately by two operators each using two MyCare Insite analysers. An EDTA venous blood sample that was drawn at the same time and sent to the Viapath Toxicology laboratory through the routine system for analysis by LC/MS/MS. Residual plasma from the EDTA specimen was frozen at -20C and batch shipped to SBI for analysis using the MyCare Psychiatry Clozapine Test Kit immunoassay.

Results

Figure 1: Results of analysing the spiked sample set by the Viapath LC/MS/MS method which demonstrates excellent precision and accuracy.

Figure 1: Clozapine by Viapath LC/MS/MS vs. Clozapine Spike Concentration

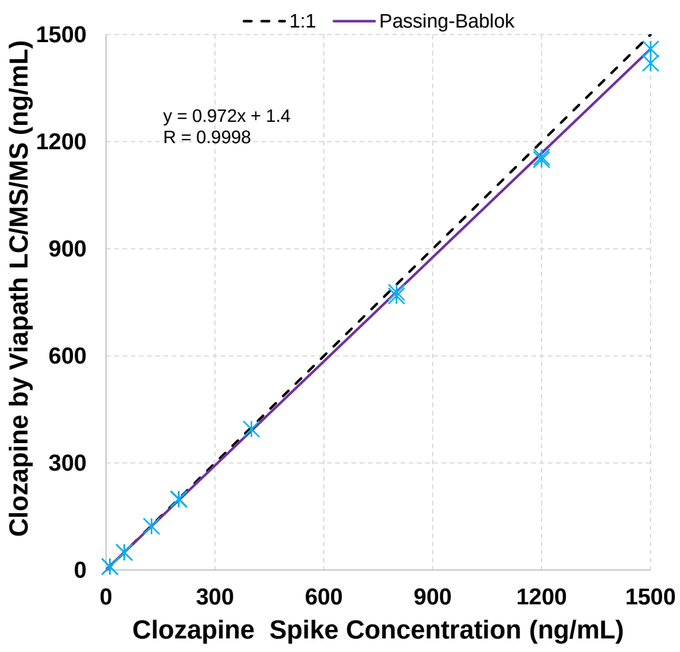


Figure 2: Comparison of analysis of the spiked sample set by SBI liquid immunoassay vs. Viapath LC/MS/MS, which demonstrates excellent comparability.

Figure 2: Clozapine by SBI Immunoassay (AU480) vs. Viapath LC/MS/MS

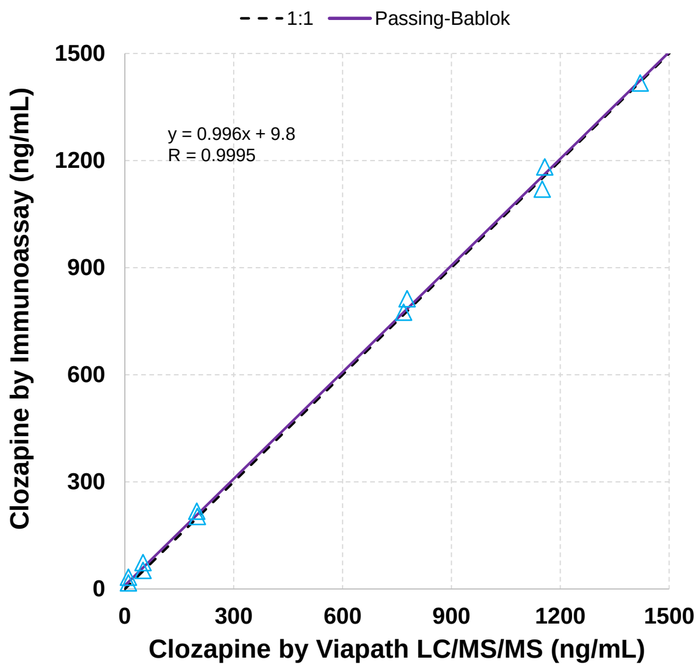


Figure 3: Comparative analysis of the spiked sample set by Viapath LC/MS/MS vs the MyCare Insite point of care device which indicates good comparability.

Figure 3: Clozapine by MyCare Insite POC vs. Viapath LC/MS/MS

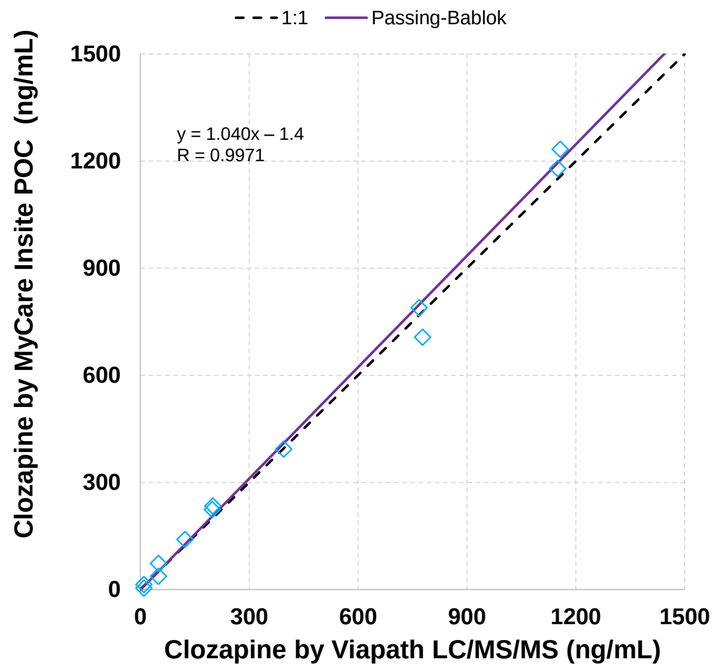


Figure 4: Comparison between LC/MS/MS vs MyCare Insite for 304 real patient samples. Five outliers were eliminated from the analysis as were four samples with results >1600ng/mL, the upper limit of linearity for MyCare Insite

Figure 4: Patient Clozapine by MyCare Insite POC vs. Viapath LC/MS/MS

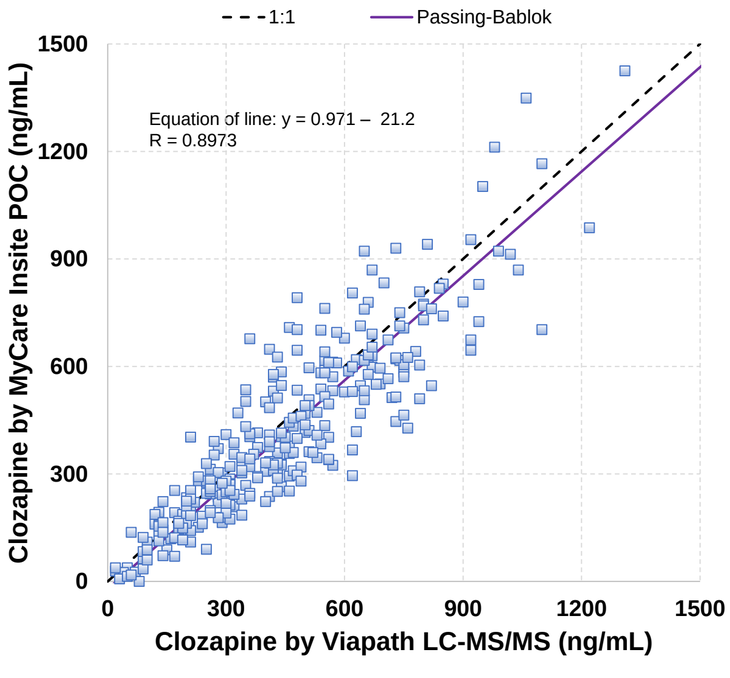
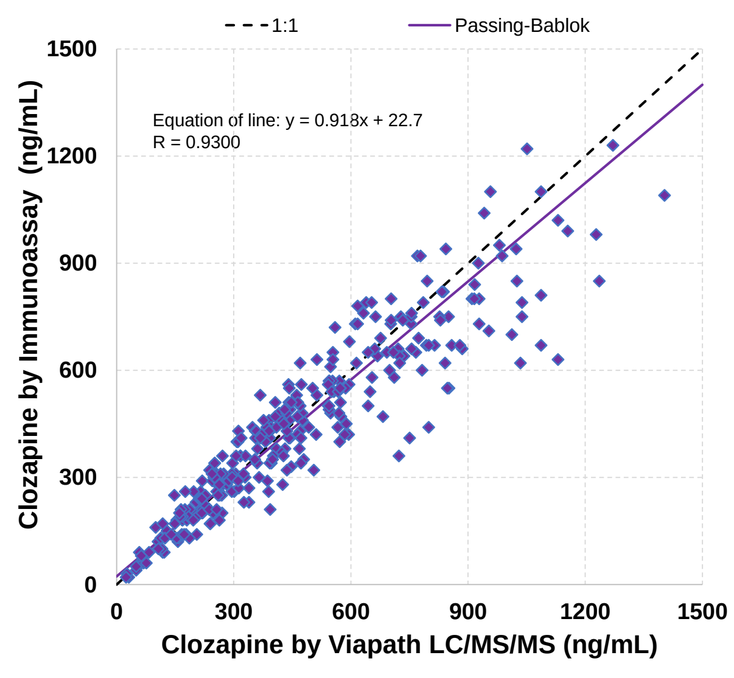


Figure 5: Comparison between LC/MS/MS results vs SBI liquid immunoassay for 303 real patient samples. Three were excluded, two because they exceeded the SBI calibration range and one high flier.

Figure 5: Patient Clozapine by SBI Immunoassay (AU480) vs. Viapath LC/MS/MS



Conclusions

- The Viapath LC/MS/MS clozapine method is accurate, unbiased and suitable for providing a routine laboratory-based service, particularly if norclozapine measurement is required
- The SBI Immunoassay is accurate, unbiased and suitable for providing a clozapine TDM service based in a routine clinical laboratory
- MyCare Insite produced satisfactory results for the spiked trial set of plasma
- Capillary blood samples from 304 patient tested by MyCare Insite produced a good comparison with the results derived by LC/MS/MS on matching venipuncture plasma drawn at the same time
- 303 patient plasma samples tested by SBI IA produced a satisfactory comparison with the results derived by LC/MS/MS
- MyCare Insite is a small, portable device for near patient testing which can measure clozapine levels in finger prick blood within 7 minutes
- LC/MS/MS remains the gold standard, particularly if norclozapine concentrations are required

1. Hiemke C et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropharmacology. Pharmacopsychiatry 2018; 51:9-62.
2. Taylor D et al. The Maudsley Prescribing Guidelines in Psychiatry. 13th Ed. Hoboken, NJ: Wiley; 2018.8.
3. Couchman L et al. Ultra-fast LC-MS/MS in therapeutic drug monitoring: Quantification of clozapine and norclozapine in human plasma. Ther Drug Monit. 2016;38(1):42-9.
4. Taylor D et al. ECNP poster P-878

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