BJPsych | The British Journal of Psychiatry (2023)
223, 389–393. doi: 10.1192/bjp.2023.58

Paper

Point of care assay for blood aripiprazole concentrations: development, validation and utility

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Background

The antipsychotic aripiprazole is often used in the treatment of first-episode psychosis. Measuring aripiprazole blood levels provides an objective measure of treatment adherence, but this currently involves taking a venous blood sample and sending to a laboratory for analysis.

Aims

To detail the development, validation and utility of a new point of care (POC) test for finger-stick capillary blood concentrations of aripiprazole.

Method

Analytical performance (sensitivity, precision, recovery and linearity) of the assay were established using spiked whole blood and control samples of varying aripiprazole concentration. Assay validation was performed over a 14-month period starting in July 2021. Eligible patients were asked to provide a finger-stick capillary sample in addition to their usual venous blood sample. Capillary blood samples were tested by the MyCare™ Insite POC analyser, which provided measurement of aripiprazole concentration in 6 min, and the venous blood sample was tested by the standard laboratory method.

Results

A total of 101 patients agreed to measurements by the two methods. Venous blood aripiprazole concentrations as assessed by the laboratory method ranged from 17 to 909 ng/mL, and from 1 to 791 ng/mL using POC testing. The correlation coefficient between the two methods (*r*) was 0.96 and there was minimal bias (slope 0.91, intercept 4 ng/ml).

Conclusions

The MyCare Insite POC analyser is sufficiently accurate and reliable for clinical use. The availability of this technology will improve the assessment of adherence to aripiprazole and the optimising of aripiprazole dosing.

Keywords

Aripiprazole; schizophrenia; capillary blood sample; finger stick; point of care.

Aripiprazole is a widely used antipsychotic medication, and is often used in the treatment of first-episode psychosis[1] because it is less likely to be associated with long-term metabolic adverse effects such as weight gain.[2] Nevertheless, many people with psychosis are reluctant to take aripiprazole and non-adherence to antipsychotic treatment is common.[3] This reduces the effectiveness of treatment and is especially important in the management of first-episode psychosis, as non-adherence to treatment is the main factor associated with a subsequent relapse,[4] which has adverse effects on clinical, social, vocational and health economic outcomes.[5,6]

Medication adherence in people with psychosis is conventionally assessed by direct questioning. However, this approach does not usually provide an accurate measure and many patients report that they are taking medication when they are not.[7] Measuring the blood level of a medication provides an objective measure of adherence.[8] At present, this entails collection of a venous blood sample, which is then sent to a centralised laboratory for analysis, typically using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS).[9] The blood sample also has to be packaged and shipped, which adds to the logistical demands on the clinical team. Moreover, relatively few laboratories can perform the assay for aripiprazole. For example, in the UK there is only one laboratory with accreditation to support this analysis (Synnovis, at King's College Hospital, London). Once the sample reaches the laboratory, to optimise throughput, it may not be processed until there are other samples to run together in a batch, adding a further delay before receipt of the result. The delay between sampling and receiving the result can reduce the clinical value of the assessment, particularly in situations when decisions must be made quickly. A further consideration is that some patients with psychosis are reluctant to provide venous blood samples, as they dislike the procedure,[10] and clinical mental health teams may lack staff with the expertise to collect venous blood samples.

These logistical and acceptability issues could be overcome by using a point of care (POC) system to measure aripiprazole levels. Technologies are now available that provide precise and accurate measurements of drug concentrations using very small volumes of capillary blood. A capillary POC approach has recently been validated for use for clozapine.[11] This provides measurements of medication levels with similar accuracy to a conventional venous sample assay, and the sampling procedure is more acceptable to patients and staff than the traditional method.[12]

The aim of the present study was to validate a new POC test (POCT) for capillary blood concentrations of aripiprazole, using a nanoparticle turbidimetric immunoassay technology[13] developed by Saladax Biomedical.

Method

Assay development

Principle of the immunoassay

The immunoassay is a homogeneous, nanoparticle-based assay that capitalises on changes in the scattering of light that occur when the nanoparticles aggregate. It consists of two reagents: reagent 1 (R1), a buffer solution containing lysis reagents and a multivalent

https://doi.org/10.1192/bjp.2023.58 Published online by Cambridge University Press

aripiprazole conjugate, and reagent 2 (R2), a solution of nanoparticles that are coated with monoclonal antibodies selective for total aripiprazole (aripiprazole and its major active metabolite dehydroaripiprazole). Capillary whole blood from a finger-stick is directly added to the cuvette containing the R1, and the R2 reagent cap is snapped onto the cuvette. The prepared test cartridge is then placed in the MyCare™ Insite, a POC analyser that performs the sample measurement using the parameters from the test radio frequency identification (RFID) card. When the two reagents are mixed in the analyser, the antibodies bind to the multivalent aripiprazole conjugate and cause the nanoparticles to aggregate. This in turn causes the incident light to scatter. The change in absorption with time is measured by the Insite device. Competition for binding to the antibodies bound on the nanoparticle occurs between total aripiprazole in the sample and the aripiprazole conjugate. Aggregation of the nanoparticles is inhibited as total aripiprazole binds to the antibody and prevents binding to the aripiprazole conjugate, leading to less light scattering and a lower absorbance. Thus, the aggregation of the particles and absorbance are dependent on the concentration of total aripiprazole in the sample. The total aripiprazole concentration in the sample is then quantified using the pre-programmed calibration curve that is stored on the RFID card.

Assay method

Analytical performance testing of the precision, recovery, sensitivity, interferences and linearity of the total aripiprazole immunoassay was conducted at Saladax Biomedical, Inc. (Bethlehem, Pennsylvania, USA) on the MyCare Insite. Collection of patient samples for method comparison was performed at South London and Maudsley (SLAM) NHS Foundation Trust (London, UK) and Basurto University Hospital (Bilbao, Spain).

The MyCare Insite Total Aripiprazole Test reagents and controls as well as MyCare Insite analysers were provided by Saladax Biomedical, Inc. The reagent kits contained one RFID card containing test parameters, 16 R1 cuvettes and 16 R2 reagent caps, which is sufficient material to perform 16 measurements. The multianalyte MyCare Psychiatry Control Kit 2, which contains two sets of three control levels (low, medium and high) were supplied in dropper vials; medium (192 ng/mL) and high (818 ng/mL) controls have concentrations within the measuring range of the aripiprazole POCT.

Sample preparation

Total aripiprazole-spiked dipotassium ethylenediaminetetraacetic acid (K3-EDTA) whole blood samples were prepared from stock solutions of aripiprazole and dehydroaripiprazole in dimethyl sulfoxide (DMSO) (compounds obtained from MilliporeSigma, St Louis, Missouri, USA). Samples were spiked such that the ratio of dehydroaripiprazole to total drug was 0.45, the ratio observed in patients at steady state.[14] Additionally, the amount of DMSO in each sample was <0.01% w/w. The samples were prepared in bulk, aliquoted into 0.25 mL volumes and stored frozen at −80°C. On each testing day, aliquots were thawed at 2–8°C for at least 1 h before use. Aliquots were not refrozen and were discarded after 12 h at 2–8°C.

Testing procedures

Repeatability and within-laboratory precision of the assay were validated using the two assay controls and four total aripiprazole-spiked whole blood pools at concentrations of 150, 500, 750 and 1000 ng/mL. Sample concentrations were chosen to include the medical decision points at the proposed therapeutic target range, a supratherapeutic level and the alert level.[14] Each sample was measured in duplicate twice a day for 20 days, for a total of 80 replicates per sample, in accordance with the Clinical and Laboratory Standards Institute (CLSI) guideline EP05-A3.[15] Results were evaluated using the Complex Precision module in EP Evaluator, Version 12 for Windows (build 12.1.0.18, Data Innovations). Recovery of the precision samples was calculated with respect to the spike concentration.

Linearity of the assay was evaluated using 14 total aripiprazole-spiked whole blood pools prepared at assay values throughout the measuring range using admixes of a high- and low-spiked sample. Each sample was measured 7 times in accordance with CLSI guideline EP06.[16] All testing occurred on one day. Results were analysed as directed in the CLSI guideline.

The limit of blank (LOB), limit of detection (LOD) and limit of quantification (LOQ) of the assay were determined using total aripiprazole-spiked samples in whole blood from five (LOB, LOD) or four (LOQ) individual donors. Testing was performed according to the minimum design requirements of CLSI guideline EP17-A2.[17] For LOB and LOD, each sample was measured 4 times on two lots of reagents for 3 days, for a total of 60 replicates per sample per reagent lot. For LOQ, each sample was measured 3 times on two lots of reagents for 3 days, for a total of 36 replicates per sample per reagent lot. The LOB was defined as the 95th percentile value of the 60 replicate data-set of the 0 ng/mL total aripiprazole sample. The LOD was defined as the median value observed at the lowest spiking concentration for which the 60 replicate data-set had ≤5% of results below the LOB. The LOQ was defined as the mean value observed at the lowest spiking level for which the 36 replicate data-set had a total error ≤35% by the Westgard model, as described in CLSI Guideline EP17-A2. The LOB, LOD and LOQ calculations were performed separately for each reagent lot, and the determined value for each was the higher of the two reagent lots.

Endogenous substances rheumatoid factor (Rf), human serum albumin (HSA), human immunoglobulin G (hIgG), bilirubin (BIL), triglycerides (TRI), hemolysate and haematocrit were tested for interference in the immunoassay according to CLSI guideline EP07.[18] Interference from these endogenous substances was measured in whole blood spiked with total aripiprazole at low and high concentrations of 150 and 1000 ng/mL. Samples spiked with total aripiprazole without additional interferences added were used as controls. All samples were measured 6 times. Interference in the assay was measured by calculating the assay bias of the sample containing interferent with respect to the control sample without interferent.

Calibration and standardisation

Aripiprazole is known to partition in whole blood,[19,20] so whole blood and plasma concentrations are not the same. Since clinicians are familiar with aripiprazole results in plasma, the calibrator values were value assigned to provide whole blood results equivalent to the concentration in serum or plasma. Forty-six paired patient samples were measured: capillary finger-stick whole blood was measured by the immunoassay POCT and the corresponding venous plasma was measured by the HPLC-MS/MS reference laboratory. These data were then split into two groups based on their HPLC-MS/MS plasma value and fit separately to linear regression equations (Supplementary Fig. 1, available at https://doi.org/10.1192/bjp.2023.58). The total aripiprazole concentrations used in the calibration curve programmed on the RFID card were then adjusted such that the capillary whole blood values measured using the immunoassay were statistically equivalent to the obtained venous plasma

https://doi.org/10.1192/bjp.2023.58 Published online by Cambridge University Press

values. Standardisation of the assay was validated in the method comparison study.

Assay validation

Patient sample for method comparison

We recruited patients who were already being treated with aripiprazole as part of their routine clinical care from the South London and Maudsley NHS Foundation Trust (SLAM) and Basurto University Hospital, Bilbao. Samples were collected over 14 months, starting from July 2021. All patients had a diagnosis of schizophrenia. When patients were providing a venous blood sample (3 ml K3-EDTA) for monitoring aripiprazole concentration as part of their clinical care they were asked if they would be willing to also provide a finger-stick capillary sample for testing. In those who agreed, capillary whole blood and venous blood were taken at the same visit.

Analytical process for method comparison

Venous blood samples (3 ml K3-EDTA) were transported from the clinical teams to a central laboratory at King's College Hospital where HPLC-MS/MS[21] was performed. This was used as the reference standard method. Samples collected in London were transported to the laboratory, where they were processed into plasma and tested within 72 h from the time of collection. Samples collected in Bilbao were processed into plasma onsite by centrifugation at ≥10 000 rpm for 10 min, then aliquoted into a 2 mL cryovial with 1.5 mL of sample in each. The plasma aliquots were then deidentified, stored frozen and later shipped frozen to the laboratory at King's College London for HPLC-MS/MS analysis.

Capillary whole blood (20 µL) was collected into a neutral Sarstedt Minivette® POCT capillary. The blood sample was then pipetted into the test cuvette containing the R1, the R2 reagent cap was snapped onto the test cuvette, and inserted into a MyCare Insite POC analyser in the clinic room or ward by a trained operator. The Insite provided a quantitative measurement of the aripiprazole concentration in 6 min. The Insite POC analyser is a fully portable and compact device that has IT integration functionality using both LAN port and WIFI technologies.

Statistical analysis

A Deming regression analysis[22] and Bland–Altman analysis[23] were conducted for the results of the method comparison. Deming regression analysis is a statistical analysis method that differs from a simple linear regression in that it accounts for imprecision in both measurement procedures that are being compared. EP Evaluator, Version 12 (build 12.1.0.18, Data Innovations) was used to generate both the regression and Bland–Altman plots.

Ethics statement

This investigation was defined as a service development by SLAM's local Drug and Therapeutics Committee. Our trust policies dictate that medicines-related audits and service developments are considered by the Drug and Therapeutics Committee and approved or modified by that committee. Ethical committee approval is sought only when the Drug and Therapeutics Committee considers is appropriate. In the case of this investigation, the Committee approved it as a service development not requiring ethical committee approval or formal written consent from potential participants (SLAMDTC2020/3). All patients had the simple finger-stick procedure explained to them and were asked if they were willing to provide two samples. The reason for taking two samples (the testing of a new device) was also explained to them.

Table 1 Characteristics of the patient sample

Characteristic	Result
Total evaluable patients, *n*	101
Gender, *n*	
Male	75
Female	26
Age, years: median (range)	32 (19–66)
Time on aripiprazole, weeks: mean (range)	34 (1–208)
Aripiprazole oral dose, mg/day: mode (range)	20 (5–35)
Aripiprazole LAI dose, mg/4 weeks: mode (range)	400 (150–400)
Aripiprazole oral dose, mg/day: range, *n*	
5–10	26
15–25	46
30–35	6
Aripiprazole LAI dose, mg/4 weeks: range, *n*	
150	3
300	9
400	11

LAI, long-acting injection.

Results

Assay development

Precision and recovery

The repeatability and within-laboratory precision coefficients of variation (CV) of the two assay controls (192, 818 ng/mL) and four spiked total aripiprazole whole blood samples (150, 500, 750 and 1000 ng/mL) were calculated and are shown for each sample in Supplementary Fig. 2. The CVs were ≤4.5% for all samples, except the lowest spiked sample at 150 ng/mL, where the CVs were 6.0 and 10.9% for repeatability and within-laboratory precision respectively. Mean deviation from spike concentration was ±12% for all samples.

Linearity

Linearity was considered acceptable if non-linearity was ≤15%. The assay was found to be linear over an assay range of 41 to 1081 ng/mL

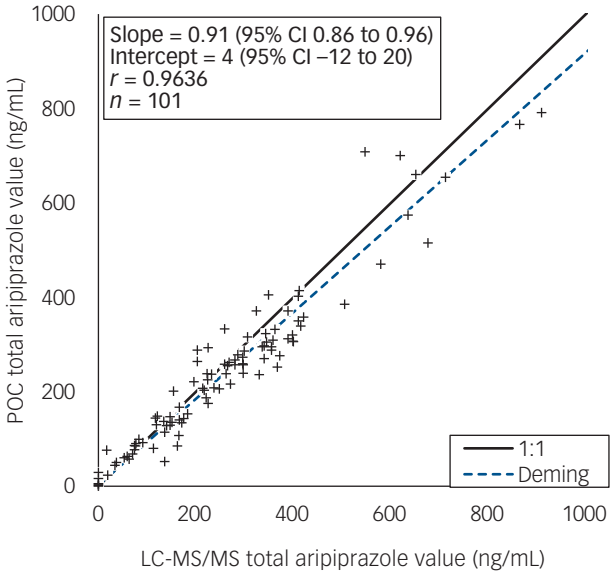

Fig. 1 Method comparison: point of care versus high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) (*n* = 101).

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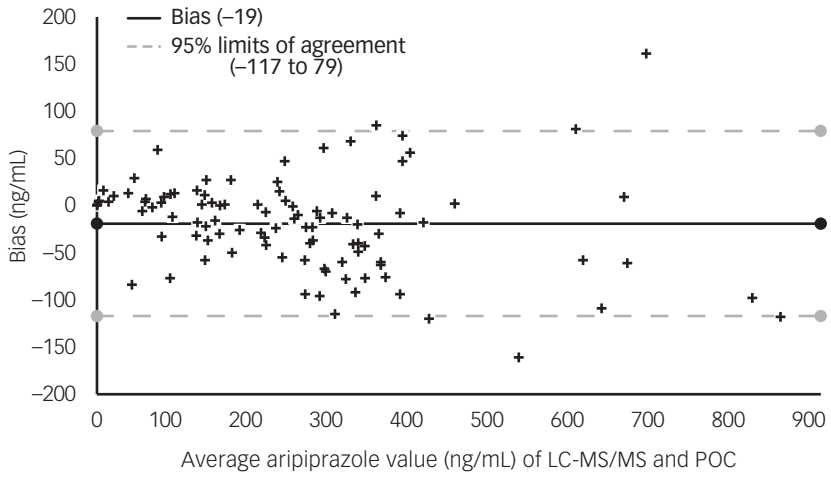

Fig. 2 Bland-Altman plot for the difference between POC and high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) against the mean of both methods ($n = 101$).

(Supplementary Fig. 3), with deviations from linearity ranging from −8 to 12% (Supplementary Fig. 4). The results yielded a slope of 0.9992, an intercept of 4 and a correlation coefficient (r) of 0.9990.

Sensitivity

The assay LOB was determined to be 0 ng/mL from the measurement of five individual donors' whole blood negative for total aripiprazole. The LOD was determined as 24 ng/mL and the LOQ was determined as 51 ng/mL.

Interferences

Assay bias caused by endogenous substances Rf, HSA, hIgG, TRI, BIL, hemolysate and haematocrit ranged from −12 to 3% (Supplementary Table 1) and was not clinically significant.

Assay validation

Method comparison

In total, 101 patients agreed to having a finger-stick capillary sample taken along with a venous blood sample. Characteristics of the patient sample can be seen in Table 1.

Plasma aripiprazole concentrations as assessed by HPLC-MS/MS ranged from 17 to 909 ng/mL, and from 1 to 791 ng/mL using POC testing. The correlation (r) between the plasma aripiprazole levels measured by HPLC-MS/MS and those measured by the Insite POC device from capillary whole blood was 0.96, with a slope of 0.91 (95% CI 0.86 to 0.96) and an intercept of 4 (95% CI −12 to 20) (Fig. 1). Mean biases as determined by Bland-Altman plot analysis for plasma aripiprazole measurements by HPLC-MS/MS and capillary whole blood aripiprazole measurements by the Insite POC device was −19 ng/mL (−7.6%) (95% CI −118 to 79) (Fig. 2). Biases at intervals across the range of results were determined and are as follows: for 0–150 ng/mL, mean bias was 3 ng/mL (3%) (95% CI −43 to 48) where $n = 31$; for 151–500 ng/mL, mean bias was −27 ng/mL (−8%) (95% CI −117 to 63) where $n = 61$; and for 501–950 ng/mL, mean bias was −39 ng/mL (−5%) (95% CI −153 to 74) where $n = 9$. Across the patient sample, we found no notable differences in accuracy by gender or age.

Discussion

The data indicate that the sensitivity, precision, recovery and linearity of the total aripiprazole capillary POC immunoassay are satisfactory for clinical use in the management of patients being treated with aripiprazole. The proposed therapeutic range is 150–500 ng/mL, with an alert limit of 1000 ng/mL,[14] a linear measuring range from 51 to 1200 ng/mL, within-laboratory precision CV ≤10.9% and recovery of ±12%. Additionally, the results demonstrate that the immunoassay provides reproducible results that are not affected by endogenous substances such as proteins (HSA, hIgG), rheumatoid factor, bilirubin, triglycerides, hemolysate and haematocrit.

Our findings indicate that the MyCare Insite device provides clinically acceptable measures of aripiprazole concentrations compared with the gold standard HPLC-MS/MS, as demonstrated by the close correlation between the respective measurements ($r = 0.96$). The MyCare Insite device uses very small volumes (20 uL) of capillary finger-stick blood, which makes this method of testing more acceptable to both patient and clinician.[12] Moreover, because the results are available in just 6 min, they can be shared with the patient at the time of testing.

The overall analytical measuring bias, and biases at defined intervals, were minimal and clinically acceptable. Based on a 12 h trough, using a response therapeutic threshold for total aripiprazole of 150 ng/ml and a maximal target level of 500 ng/mL[14] (at which concentration striatal D_2 receptor occupancy is approximately 100%[24]), the mean biases around these target levels were just 8 and 9% respectively. The speed with which results can be obtained by this method permits immediate decision-making in relation to the management of treatment adherence and the assessment of the therapeutic response and tolerability. Immediate access to antipsychotic blood levels can reduce the time required to titrate the dose to a therapeutic level and to identify adherence or pharmacokinetic issues that may result in subtherapeutic blood levels. This could facilitate identification of when treatment has reached 'a point of futility',[24] when further increases in blood levels are unlikely to lead to a therapeutic response. Confirmation that the absence of a response to treatment is not attributable to subtherapeutic aripiprazole levels can also support the diagnosis of treatment resistance.[25]

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https://doi.org/10.1192/bjp.2023.58 Published online by Cambridge University Press

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First received 4 Jan 2023, final revision 6 Apr 2023, accepted 18 Apr 2023

Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2023.58.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Author contributions

Study conceptualisation: M.A., P.M., M.R.H., I.B., D.T., S.J.S. Methodology and supervision: M.A., M.R.H., I.B., A.C., P.M., R.H., D.T. Testing and data collation: M.R.H., A.C., N.D., E.C., T.R., L.D., M.A. Data analysis: M.A., M.R.H. Manuscript writing: M.A., M.R.H., P.M., D.T. Manuscript review: M.A., D.T., A.C., N.D., E.C., T.R., I.B., M.R.H., L.D., R.H., S.J.S., P.M.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

D.T. has received personal fees from H Lundbeck and Janssen unrelated to this manuscript and has received consultancy payments from Mylan, a manufacturer of clozapine, again unrelated to this manuscript. P.M. reports consultancy fees from Takeda, Janssen, GW Pharmaceuticals, Roche and Sunovion outside the submitted work. P.M. is a member of the *BJPsych* editorial board and did not take part in the review or decision-making process of this paper. M.R.H., I.B. and S.J.S. work for the manufacturer of the device, Saladax Biomedical, Inc. T.J.R. is supported by an MRC Clinical Research Training Fellowship, MR/W015943/1.

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