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Perspective

Ketamine: Therapeutic Monitoring Using UPLC-MS/MS

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INTRODUCTION

Serum ketamine and norketamine measurements have proved to be relevant and indicated in subjects receiving both oral and I.V. formulations. The method described by Armfield et al. utilises Ultra-High Performance Liquid Chromatography coupled to tandem Mass Spectrometry (UPLC-MS/MS) to resolve the complex nature of biological fluids such as serum or plasma. Biological fluids are naturally complex prior to acute and chronic pathological conditions where added xenobiotics and polypharmacy only complicates the sample further. Employment of good sample preparation and robust chromatography is the initial step in securing a UPLC-MS/MS method. Subsequent multiple reaction monitoring of mass transitions in optimized conditions provides the ideal detection method. Using this form of tandem mass spectrometry means method validation does not have a focus on base separation, but more the mass transitions. Multiple compounds can be measured in a single isocratic gradient. This is ideal in the clinical scenario such as therapeutic monitoring of multiple drugs or additional active metabolites. This is key to the success of the ketamine and norketamine measurements conducted at the Walton Centre NHS Foundation Trust.

DESCRIPTION

The method since introduction in May 2023 has proved robust. Inter-precision for ketamine=2.1% (mean=246.6 µg/L, n=20) and 4.4% (mean=1036.9 µg/L, n=25). Inter-precision for norketamine=2.5% (mean=249.3 µg/L, n=20) and 4.7% (mean=1144.7 µg/L, n=25). Retention time has remained stable at 1.24 mins for ketamine and 1.18 mins for norketamine since introduction to routine use, a small and acceptable change. Running accuracy assessments has proved difficult for this assay where no external quality assurance scheme exists. The neurosciences laboratories employ an internal quality assurance scheme in which blinded samples are cycled every quarter for accuracy assessments by the analyst. Any deviations are investigated, suffice for the assay's purpose.

Conflicting reports of peripheral ketamine concentrations have made it difficult to determine a therapeutic reference range to target for clinicians. 75 serum investigations have been conducted since May 2023. It is difficult to gauge true variability for ketamine in I.V. or oral formulations due to differing dosages tailored to a patient's clinical picture. A patient receiving I.V. route of administration normally has a titration of ketamine beginning at 75 µg/kg/hr to 900 µg/kg/hr throughout approximately 4 days. CV_i for patient sera measurements receiving 300 µg/kg/hr for ketamine=24.3% (range=197.3 µg/L) and for norketamine=45.6% (range=376.3µg/L). This data is not normalized for time into titration (4.15-50.15 hrs) (n=8). However, the difference in inter-variation between subject is also accounted for by pharmacodynamics and CYP3A4, CYP2B6 and CYP2C9 expression. Ketamine is heavily metabolized when administered orally, where post 50 mg dose at T=0.5 hrs, CV_i for norketamine is 30.5% (n=10) and all ketamine measurements <lower limit of quantitation. Again, a high variation is noticed even when controlled with dose and time. It has been clearly displayed in the literature that ketamine is extensively metabolised with pharmacological activity of some metabolites nominally norketamine. Succinctly, routine use of this assay has proven monitoring norketamine in oral dosed patients is principal.

CONCLUSION

The assay is supporting the pain relief patient pathway, offering more information rather than clinical observations alone. However, pharmacological work on this patient cohort is warranted. Free protein fractions of ketamine have been explored in which ketamine and norketamine affinity to protein is significantly different at 38.4% and 49.5% respectively (p=<0.001, n=18). Metabolism is evidently dependent on subject and could link to adverse reactions and drug efficacy. Tangible data measured by UPLC-MS/MS for ketamine, norketamine and other metabolites must be produced. The kinetic and dynamic profile of ketamine in this patient cohort should aid understanding of therapeutic monitoring and support patient experience. Chirality of ketamine is of chief interest. Ketamine exists as 2 optical enantiomers, S-ketamine (branded as Esketamine) and R-ketamine. The catalysis rate by P450 enzymes is stereoselective where S-ketamine is processed faster. Esketamine is often preferred by the clinician. The current

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method described does not account for chirality, measuring the racemate only. This is a rare case in which chiral separation may be used in the clinical setting. Clearly, laboratory method optimisation is paramount to the next phase of ketamine pharmacology monitoring.