Therapeutic Drug Monitoring Of Risperidone

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ABSTRACT
To develop a simple, reliable method for quantifying serum Risperidone concentrations and correlating them with clinical outcomes.61 Schizophrenic patients were included in the study of which 24 were females and 37 were males who were on Risperidone. Serum Risperidone concentrations were measured by using HPLC and a brief psychiatric rating scale was employed to assess the course of the illness. Statistical analysis was done using the Unpaired t-Test. The mean and standard deviation of a large sample comparison utilising an unpaired t-test were used to express the data.Out of 61 samples Serum Risperidoneconcentrations in 19 patients were found to be in therapeutic range, 38 patients were found to be in sub therapeutic range,4 are above therapeutic range.In order to optimize a patient's dosage and Clinical practice in psychiatric facilities must include monitoring of therapeutic drugsin order to establish a correlation between serum concentration using clinical assessment scales.
Keywords: Risperidone, High performance liquid Chromatography, Therapeutic range, Schizophrenia, Therapeutic drug monitoring.

INTRODUCTION:

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is a rationale tool for optimizing the drug therapy. The main reason to use therapeutic drug monitoring in psychopharmacology is to estimate and aid the interindividual pharmacokinetic variability of drug in patients.
Not all drugs require TDM to be performed, TDM in antipsychotics is particularly useful when switching a therapy from oral to depot or vice versa. It can avoid overdosing of antipsychotics which may lead to extrapyramidal side effects and thus improve the quality of life and safety[1].Therapeutic drug monitoring enables the individualization of the drug dosage by maintaining plasma or blood drug concentrations with in a targeted range called as the therapeutic range [2].Therapeutic range can be defined as the ranges of drug concentration in blood that would specify a lower limit below which a drug therapeutic response is unlikely to occur and an upper limit above which tolerability decreases [3].

Risperidone

Risperidone is an atypical antipsychotic agent used to treat schizophrenia belonging to class of benzoxazolederivatives.Risperidone has a combined D_2 and 5 HT_{2A} receptor antagonisms. It also has high affinity for 5 HT_{1A} and 5 HT_7 receptors. It lacks the extrapyramidal side effects at moderate therapeutic doses along with lack of antagonism for muscarinic receptors. It may have moderate weight gain and risk for dyslipidemia[4].

Risperidone is extensively metabolized in liver, primarily through hydroxylation to its active metabolite 9-hydroxy risperidone mediated through CYP2D6 isoenzyme. Renal clearance of Risperidone is about 12ml/min and this decrease with decreasing creatinine clearance. An average elimination half life of risperidone following oral administration is approximately 20 hours [5].

The primary goal of this study is to provide a simple, reliable method for measuring serum risperidone levels and establishing a clinical link with it using high-performance liquid chromatography (HPLC).

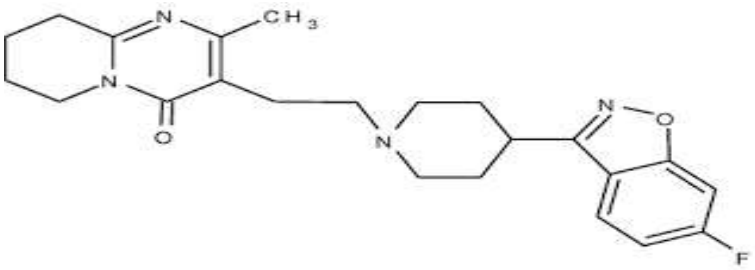

FIGURE 1 : Chemical structure of Risperidone

Experimental

Chemicals

We procured the drugRisperidone (internal standard [IS]) from a local manufacturer.HPLC-quality water from Fischer Scientific Corporation and acetonitrile, methanol, and potassium dihydrogen orthophosphate from Rankem Industries PVT Ltd.

Drug preparations

For the preparation of a Risperidone stock solution, mix 10 ml of ACN-water (1:1) and 10 mg of the medication. The concentration of working standard solutions was 10 µg/ml. Methanol was used to create the IS stock solutions. For up to seven daysStock and working solutions should be stored at 4°C for safety.To prepare the samples, blank serum was spiked with appropriate amounts of drug on the day of analysis.

Extraction procedure

10μl serum samples 50μl of internal standard was added and shaken. To this 100μl of methanol was added for protein precipitation and mixed and centrifuged at 10000rpm using ependorff centrifuge for 10 minutes. The obtained supernatant was collected and the HPLC column was filled with 15 millilitres of supernatant.

Chromatographic circumstances

To perform the chromatographic analysis, utilize a Shimadzu system with an50 µl permanent ring, a manual injector (Rheodyne 7725i), an LC 20AD (Kyoto, Japan) reciprocating pump, and an SPD 20 A UV-VIS sensor element with an uneven wavelength adjustment at 235 nm.The system is connected to a computer ,running LC Solution 1.25 software (Shimdazu).The chromatography was performed on a Varian Microsorb 100-5 C8 analytical column (250 mm × 4.5 mm).The mobile phase consists of potassium dihydrogen orthophosphate buffer and methyl alcohol in a 60:40 v/v ratio, with orthophosphoric acid used to adjust the pH to 3.0. A rate of 1.2 millilitres per minute is used for the degassed mobile phase.

MATERIAL AND METHODS

Study design

A nonrandomized, a Prospective Interventional studyexamination of TDM in individuals on risperidone and an assessment during a clinical meeting. KIEC (KMC Ethics

Committee) reviewed and approved the study design and the endorsement number was **KIEC/KMC/NCT/NIS//T28.**

Sample setting

The study's criteria were used to enrol patients. Patients with severe mental health issues and a diagnosis of schizophrenia who are between the ages of 18 and 60 are includedand responding to antipsychotic pharmacological therapy and, in particularto oral Risperidone.Other psychotic disorders, children, the elderly, and women who are pregnant or nursing are excluded. A sample of 61 patients37 men and 24 womenwere drawn from a Warangal tertiary care teaching hospital.

RESULTS AND DISCUSSION

Chromatogram

Olanzapine took 3.302 minutes and risperidone took 9.417 minutes to stabilise throughout the 12-minute test run. Figure 2a displays a chromatogram blank serum that has been tainted with risperidone and olanzapine at a known dosage.Figure 2b displays the patient's serum chromatogram treated with risperidone.

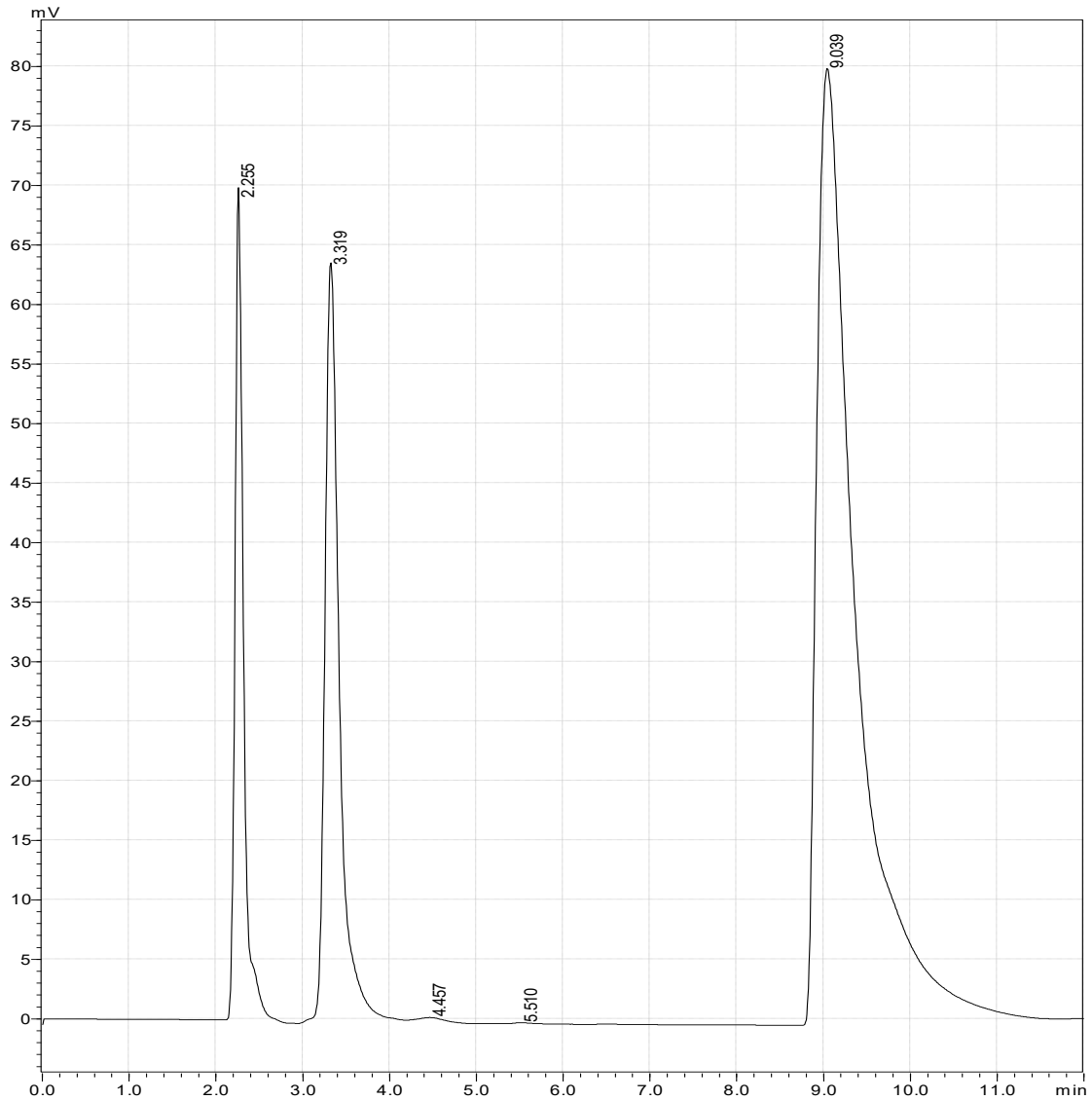

Figure 2a: Chromatograph of drug with blank serum

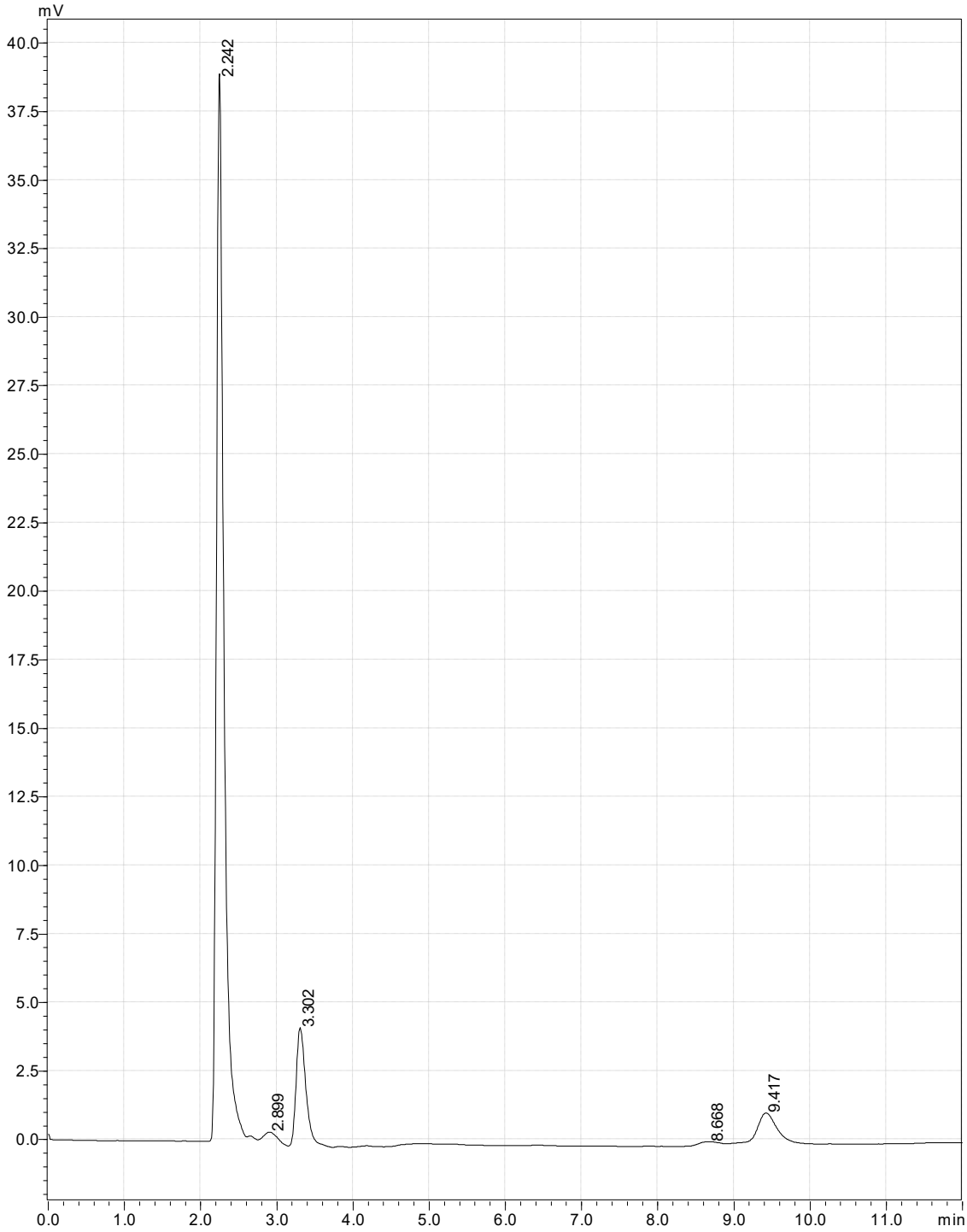

Figure 2b: Chromatograph of patient sample

Serum concentrations and assessment of brief psychiatry rating scale in patients

The Therapeutic Drug Concentrations of Risperidone were found to be 20-60ng/ml.In this study, 38 patients had sub-therapeutic drug concentrations, likely due to poor adherence or ultra-rapid metabolism, and showed poor symptom control with higher rates of psychotic, depressive, and cognitive symptoms, including relapse. Adverse effects correlated with drug levels; concentrations >40 ng/mL should be targeted only when response is inadequate, with dose titration and close follow-up.4 patients had concentrations above the therapeutic alert range, possibly due to poor metabolism or CYP2D6 inhibitor interactions (e.g., fluoxetine), and experienced extrapyramidal symptoms, cardiovascular risk, hyperprolactinemia, and amenorrhea. Regular drug monitoring and dose adjustment are recommended, BPRS scores showed greater symptom

severity in patients with sub-therapeutic levels. 19 patients were within the therapeutic range, had good adherence, and responded well to treatment.Brief Psychiatry Rating Scale was done in all the patients under study. Most of them found to present with somatic concern, anxious behaviour, hallucinations, suspiciousness and guilt feeling. Especially it is more predominant in patients with sub therapeutic concentrations. At sample removal, patients were evaluated using a brief psychiatric assessment scale. As indicated in Table 2, each of the parameter's mean and standard deviation were determined.

Linearity, precision, and accuracy

Risperidone was added to blank serum to produce a difference of 100–800 ng/ml, which was then interpreted using the method outlined. Olanzapine typically has a linear curve with a 0.997 coefficient of correlation. The degradation stripe formula is y = 89.254x + 329.38. According to Table 1, accuracy varied from 97.5% to 101.9%.

Limit of quantification and limit of detection

The limit of quantification (LOQ) was 150.33 ng/ml, whereas the limit of detection (LOD) was 40.6 (µg/ml).

The current study has an equal LOD to Basavaiah et al.'s reverse phase HPLC-UV technique [6].

The brief psychiatric rating scale's mean and standard deviation

Variables	**Mean**	**SD**
Somatic concern	2.42	1.49
Anxiety	2.12	1.28
Depression	2.19	1.33
Suicidality	1.74	1.14
Guilt	1.79	1.04
Hostility	2.01	1.13
Elevated mood	1.29	0.81
Grandiosity	1.15	0.71
Suspiciousness	2.05	1.30
Hallucinations	1.87	1.25
Unusual thought content	1.21	0.74
Bizarre behavior	1.01	0.45
Self-neglect	1.15	0.77
Disorientation	0.97	0.31
Conceptual disorganization	0.92	0.19
Blunted affect	1.17	0.71
Emotional withdrawal	1.13	0.72
Motor retardation	1.13	0.67
Tension	1.69	1.05
Uncooperativeness	0.97	0.39
Excitement	0.97	0.41
Distractibility	0.91	0.16
Motor hyperactivity	0.90	0.11
Mannerisms & posturing	0.88	0.00

SD=Standard deviation

Table 1: Accuracy of spiked serum in Risperidone

Concentration (ng/ml)	Accuracy (%)
50	97.5
250	101.9
550	94.5

Table 2: Precision of spiked serum in Risperidone

Concentration(µg/ml)	Standard deviation
150	350.6
250	1098.1
450	2012.2

CONCLUSION

The developed method is sensitive, straightforward, and precise. It is fully validated, demonstrating excellentlinearity, LOD, LOQ, accuracy, and precision.This approach supports routine monitoring of serum olanzapine levels and enables clinicians to link concentrations using clinical rating systems for tracking disease progressionusing BPRS in this analysis. Such correlations aid in identifying severe side effects.

Motor effects were seen in those whose serum levels were higher than 60 ng/mL.Increasing weighta frequent adverse effect of olanzapine, occurred in those with concentrations between 20 and 60 ng/mL. Individuals with levels below 20 ng/mL primarily showed positive symptoms. Smokers displayed notably lower serum concentrations.The method also facilitates regular risperidone serum monitoring. Overall, this work connects TDM outcomes to clinical scales, equipping clinicians with insights into patient status for optimized therapy.

In conclusion, substantial inter-individual variability in serum risperidone levels requires individualized dose adjustments via TDM. Elevated concentrations correlated with clinical response and adverse reactions; subtherapeutic levels necessitate caretaker monitoring of adherence. Drug interactions identified demand caution with combinations. Routine TDM is feasible, aiding dose optimization, compliance checks, ADR management, and treatment adjustments. Regular antipsychotic TDM is recommended to monitor concentrations, dose-related ADRs, subtherapeutic doses, and interacting drugs impairing effectiveness.

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Nil

Conflicts of interest
There are no conflicts of interest.

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