Use of therapeutic drug monitoring of risperidone microspheres long-acting injection in hemodialysis: A case report

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Abstract

Limited evidence exists for the use of psychiatric medications in patients with end-stage renal disease on hemodialysis. Many psychotropic medications are not well-studied in this population, and optimal dosing of these medications is not well-established. Therapeutic drug monitoring is a useful tool in assessing the safety and efficacy of psychotropic medications; however, the use is unclear with long-acting injectable antipsychotics. We present a case of a 73-year-old male initiated on hemodialysis while on risperidone microspheres long-acting injection (RMLAI). Risperidone and 9-hydroxyrisperidone plasma concentrations obtained from this patient were relatively similar before and after initiation of hemodialysis, therefore it appears hemodialysis does not significantly influence clearance of RMLAI. Plasma concentrations in this patient were higher than those reported in the literature for equivalent doses, which may indicate accumulation of the medication secondary to renal impairment.

Keywords: risperidone, long-acting injection, hemodialysis, therapeutic drug monitoring, end stage renal disease, schizophrenia

Background

Treatment of psychiatric conditions in patients with chronic kidney disease is difficult because of limited research available using psychiatric medications in this population, including patients on hemodialysis. The American Psychiatric Association guidelines do not provide specific recommendations for the treatment of schizophrenia in patients with end-stage renal disease (ESRD) on hemodialysis.\textsuperscript{2} Risperidone is a second-generation antipsychotic available in oral and long-acting injection (LAI) formulations. Long-acting injection formulations include: a microsphere formulation administered intramuscularly every 2 weeks (risperidone microspheres long-acting injection [RMLAI]) and an extended-release formulation given subcutaneously every 4 weeks. The recommended starting dose of risperidone in patients with renal impairment (creatinine clearance <30 mL/min) is 0.5 mg oral twice daily, titrated to 2 mg daily. If 2 mg daily is well-tolerated, RMLAI 25 mg every 2 weeks is administered. Alternatively, 12.5 mg of RMLAI is considered, although efficacy of this dose is not well-established. No specific recommendations exist for patients on hemodialysis.\textsuperscript{2,3} The majority of active drug is not released until 3 weeks post injection, therefore oral overlap with risperidone is required during this time. The RMLAI reaches steady state after 4 injections (2 months).\textsuperscript{2,4} Risperidone undergoes extensive hepatic metabolism through CYP2D6 to the active metabolite, 9-hydroxyrisperidone, which has similar pharmacologic activity. The plasma protein binding of risperidone and 9-hydroxyrisperidone is 90% and 77%, respectively. Clinical effects result from the active moiety (risperidone + 9-
hydroxyrisperidone). Plasma concentrations of risperidone, 9-hydroxyrisperidone, and the active moiety follow linear kinetics. Risperidone and metabolites are predominately eliminated in the urine. Elimination half-life of RMLAI is 3 to 6 days. The clearance of oral risperidone and 9-hydroxyrisperidone are decreased by 60% in patients with moderate-severe renal disease. RMLAI was not studied in patients with renal impairment.2,3 Although it has a low molecular weight (410.49 Da), risperidone’s volume of distribution (1-2 L/kg), high protein binding, and insolubility in water make it unlikely to be removed by hemodialysis.5

Case Report

The patient is a 73-year-old male veteran with diagnoses of schizoaffective disorder and ESRD on hemodialysis. Past medical history includes chronic low back pain, hypothyroidism, mixed sleep apnea, iron deficiency anemia, hyperlipidemia, type 2 diabetes mellitus, hypertension, and vitamin D deficiency. Psychotropic medications at the time of this report include divalproex sodium extended-release tablet 1500 mg daily, benztropine 1 mg twice daily, and risperidone 2 mg daily. Five years prior to the initiation of hemodialysis, the patient was switched from oral risperidone tablets (6 mg daily) to RMLAI 25 mg every 2 weeks. The dose was increased 2 months later to 37.5 mg every 2 weeks. LAI formulation was chosen because of a history of medication nonadherence, which improved after LAI was initiated. At the time of RMLAI initiation, the patient had a diagnosis of chronic kidney disease, stage 3, with a serum creatinine of 2.0 mg/dL and creatinine clearance of 45 mL/min. No dose adjustments were made while his renal function further declined. Five years after RMLAI initiation with a serum creatinine of 10.1 mg/dL and creatinine clearance less than 10 mL/min, the patient began conventional hemodialysis with standard membrane, and RMLAI was continued at 37.5 mg every 2 weeks. The dose was decreased to 25 mg every 2 weeks 2 years following initiation of hemodialysis, because of suspected neuroleptic-induced tremor. The dose was further decreased 2 years later, to 12.5 mg every 2 weeks, because of somnolence and was subsequently discontinued 2 months later because of family preference in favor of oral risperidone 2 mg daily. Somnolence and tremor were reported to improve upon RMLAI discontinuation. Valproic acid levels were obtained periodically, none of which were supratherapeutic. Psychiatric symptoms remained relatively stable and well-controlled while on RMLAI and subsequently while on oral risperidone. The patient had no psychiatric hospitalizations after RMLAI initiation or after discontinuation.

Risperidone, 9-hydroxyrisperidone, and active moiety plasma concentrations were obtained prior to initiation of hemodialysis, after initiation of hemodialysis, and after a dose decrease (Table 1). Plasma concentrations were not obtained while the patient was on oral risperidone. Risperidone, 9-hydroxyrisperidone, and the active moiety plasma concentrations were obtained prior to initiation of hemodialysis, after initiation of hemodialysis, and after a dose decrease (Table 1). Plasma concentrations were not obtained while the patient was on oral risperidone. All concentrations obtained were peak concentrations at steady-state. RMLAI takes approximately 4 weeks to reach its peak, therefore peak concentrations were defined as 4 weeks after an injection. The reference serum concentrations of the active moiety provided by the processing laboratory (Quest Diagnostics, Secaucus, NJ) were based on oral risperidone dosing (Table 2). The laboratory did not specify if concentrations were based on peak or trough concentrations, defining them as mean steady-state. Per laboratory instructions, concentrations were to be drawn immediately prior to the next dose.

### Table 1: Risperidone peak plasma concentrations (ng/mL)

| Plasma Concentration Level | No. of Months Prior to Hemodialysis Initiation | No. of Months After Hemodialysis Initiation | RISP | OH-RISP | RISP + OH | RISP LAI Dose, mg (every 2 wk) |
|---------------------------|-----------------------------------------------|--------------------------------------------|------|---------|---------|---------------------------------|
| 1b                        | 2                                             | ...                                        | 18.9 | 51.1    | 70.0    | 37.5                            |
| 2b                        | 1                                             | ...                                        | 19.2 | 31.7    | 50.9    | 37.5                            |
| 3                         | ...                                           | 1                                          | 21.7 | 49.1    | 70.8    | 37.5                            |
| 4                         | ...                                           | 3                                          | 11.1 | 56.9    | 68.0    | 37.5                            |
| 5                         | ...                                           | 10                                         | 8.6  | 23.1    | 31.7    | 37.5                            |
| 6                         | ...                                           | 24                                         | 5.2  | 23.4    | 28.6    | 25                              |

LAI = long-acting injection; OH-RISP = 9-hydroxyrisperidone; RISP = risperidone; RISP+OH = active moiety.

*Reference plasma concentration for 25 mg is <22.9 ng/mL, 37.5 mg is 22.9-29.8 ng/mL.

*Plasma concentration prior to initiation of hemodialysis.

### Table 2: Active moiety reference ranges provided by laboratory

| Risperidone Oral Dose (mg) | Reference Serum Concentration (ng/mL) |
|---------------------------|--------------------------------------|
| 2                         | 14                                   |
| 6                         | 45                                   |
| 10                        | 73                                   |
| 16                        | 110                                  |

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indicating the concentration would likely be a peak as it would be 4 weeks after a dose.

Discussion

A literature search of PubMed was conducted on March 28, 2019, limited to the English language, using the keywords risperidone and hemodialysis. The search yielded 8 results, one of which was relevant to the use of RMLAI in hemodialysis. Xiong et al. published a case report of a patient with bipolar I disorder with psychotic features and ESRD initiated on RMLAI shortly after starting hemodialysis. The patient was stabilized on a regimen of RMLAI 25 mg every 2 weeks with no reported side effects. Risperidone plasma concentrations were not reported in this case.

Consensus guidelines for therapeutic drug monitoring recommend measuring plasma concentrations for neuropsychiatric drugs in patients with pharmacokinetically relevant comorbidities, such as renal or hepatic impairment. Plasma concentrations should be drawn immediately before the next injection for patients treated with depot formulations, although peak or trough is not specifically indicated. The therapeutic reference range provided in these guidelines for the active moiety of risperidone was 20 to 60 ng/mL with the comment that >40 ng/mL should only be targeted in cases of insufficient response to avoid neurological adverse reactions associated with higher concentrations. This proposed range is for oral risperidone and its application to patients on RMLAI is not established.

In a small (n = 13) pharmacokinetic trial of RMLAI in patients with schizophrenia, median peak plasma concentrations at steady state of risperidone, 9-hydroxyrisperidone, and the active moiety ranged from 4.7 to 15.4 ng/mL, 14.4 to 29.5 ng/mL, and 18.2 to 50.9 ng/mL, respectively. Higher doses correlated with higher plasma concentrations; the median steady state peak concentrations of the active moiety was 18.2 ng/mL in the 25 mg group, 33.6 ng/mL in the 50 mg group, and 50.9 ng/mL in the 75 mg group.

The processing laboratory provided reference concentrations based on oral risperidone doses that were extrapolated for RMLAI dosing. The RMLAI doses of 37.5 mg and 25 mg every 2 weeks are approximately equivalent to oral doses of 3 to 4 mg and less than 3 mg daily, respectively, based on equivalent doses suggested by a pharmacokinetic study. Expected plasma concentrations were calculated from reference levels provided using a trendline, assuming linear kinetics. It was estimated that RMLAI doses of 37.5 mg every 2 weeks and 25 mg every 2 weeks are equal to active moiety concentrations between 22.9 ng/mL and 29.8 ng/mL and less than 22.9 ng/mL, respectively.

Active moiety concentrations obtained in this patient were higher than expected, based on the laboratory reference concentrations and the plasma concentrations found in the small pharmacokinetic trial. Concentrations were relatively unchanged after initiation of hemodialysis. Higher plasma concentrations in this patient may indicate accumulation because of decreased renal clearance, as clearance of oral risperidone and 9-hydroxyrisperidone is decreased in patients with renal impairment. It should be considered that adverse effects the patient experienced (tremor, somnolence) may have been indicative of a supratherapeutic dose, although the highest plasma concentrations were prior to the onset of adverse effects. This may indicate that the adverse effects were not related to risperidone, or the plasma concentrations are not an accurate indicator of therapeutic effect. Supratherapeutic serum concentrations in the absence of significant adverse effects did not impact dosing decisions in this patient.

Based on risperidone therapeutic drug monitoring, it appears hemodialysis does not affect active moiety plasma concentrations. It is unclear why the fifth plasma concentration which was drawn approximately 20 months following initiation of dialysis was significantly lower than prior concentrations at a stable dose of RMLAI 37.5 mg every 2 weeks; the patient had no missed doses, and there was no noted change in renal function or other medical conditions at the time.

Conclusion

Evidence for use of psychotropic medications for the treatment of schizophrenia and schizoaffective disorder in patients with ESRD on hemodialysis is limited and guidelines provide no specific recommendations in this patient population. We present a case in which a patient with schizoaffective disorder and ESRD on hemodialysis was treated with RMLAI. Plasma concentrations were obtained in this patient for therapeutic drug monitoring. Based on the risperidone concentrations obtained in this patient, it is suggested that risperidone concentrations are unchanged by hemodialysis compared to a patient with severe chronic kidney disease not dependent on hemodialysis. Plasma concentrations were consistently higher than expected, likely because of accumulation related to decreased renal clearance. The use of therapeutic drug monitoring in this scenario is limited as reference ranges for RMLAI are not established; however, plasma concentrations were useful in ensuring risperidone clearance was
not substantially affected by initiation of hemodialysis in this patient maintained on a stable dose of RMLAI.

References

1. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(2 Suppl):1-56. PubMed PMID: 15000267.

2. Janssen Pharmaceuticals Inc. RISPERDAL CONSTA (risperidone) injection [Internet]. Bethesda (MD): National Library of Medicine (US); c2007 [updated 2018 Sep; cited 2019 Mar 28]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bb34ee82-d2c2-43b8-ba21-2825c0956691

3. Janssen Pharmaceuticals Inc. RISPERDAL (risperidone) tablet [Internet]. Bethesda (MD): National Library of Medicine (US); c2009 [updated 2018 Jul; cited 2019 Mar 28]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6afd70a6-fe7b-4096-8947-86c89c3b463f

4. Sheehan JJ, Reilly KR, Fu D-J, Alphs L. Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. Innov Clin Neurosci. 2012;9(7-8):17-23. PubMed PMID: 22984648.

5. Mirrakhimov AE, Barbaryan A, Gray A, Ayach T. The role of renal replacement therapy in the management of pharmacologic poisonings. Int J Nephrol. 2016;2016(3):1-12. DOI: 10.1155/2016/304729. PubMed PMID: 28042482; PubMed Central PMCID: PMC555094.

6. Xiong Y, Narang P, Lippman S. Injectable risperidone during hemodialysis. Prim Care Companion CNS Disord. 2018;20(2):17l02212. DOI: 10.4088/PCC.17l02212. PubMed PMID: 29701933.

7. Hiemke C, Bergemann N, Clement H, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. DOI: 10.1055/s-0043-116492. PubMed PMID: 28910830.

8. Gafvert O, Eriksson B, Persson P, Hellidin L, Björner A, Mannert E, et al. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. Int J Neuropsychopharmacol. 2005;8(1):27-36. DOI: 10.1017/S1461145704004924. PubMed PMID: 15710053.

9. Bai YM, Chen TT, Chen J-Y, Chang W-H, Wu B, Hung CH, et al. Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective, single-blind pharmacokinetic study. J Clin Psychiatry. 2007;68(8):1218-25. DOI: 10.4088/jcp.v68n0808. PubMed PMID: 17854246.

10. Janssen Pharmaceuticals Inc. INVEGA SUSTENNA (paliperidone palmitate) injection [Internet]. Bethesda (MD): National Library of Medicine (US); c2009 [updated 2018 Jul; cited 2019 Mar 28]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1af14e42-952d-424f-d856-5d5f8c38554