INVEGA® (paliperidone ER)
Use of INVEGA in Renal Dysfunction

SUMMARY

- INVEGA® dosing must be individualized according to the patient's renal function status.[1]
- **Mild Renal Impairment** (creatinine clearance (CrCl) ≥50 to <80 mL/min): For patients with mild renal impairment, the recommended initial dose of INVEGA is 3 mg once daily. The dose may then be increased to a maximum of 6 mg once daily based on clinical response and tolerability.[1]
- **Moderate to Severe Renal Impairment** (CrCl 10 to <50 mL/min): For patients with moderate to severe renal impairment, the recommended initial dose of INVEGA is 1.5 mg once daily, which may be increased to a maximum of 3 mg once daily after clinical reassessment.[1]
- **Creatinine Clearance <10 mL/min:** As INVEGA has not been studied in patients with CrCl<10 mL/min, use is not recommended in such patients.[1]
- **Dialysis:** Paliperidone is expected to be poorly dialyzable because of its large volume of distribution (extensive tissue binding).[2,3]
- Renal excretion is the primary route of elimination for paliperidone (around 80% of the administered dose), with 59% of the dose excreted unchanged in urine.[1]
- The disposition of a single dose INVEGA 3 mg tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl=50 to <80 mL/min), 64% in moderate (CrCl=30 to <50 mL/min), and 71% in severe (CrCl=10 to <30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8-fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥80 mL/min).[1]
- In a population pharmacokinetic (PK) model that examined many potential covariates, only altered renal function resulted in a sufficient change in the magnitude of exposure to paliperidone ER to necessitate a dose adjustment.[4]

BACKGROUND

There is no information regarding the effect of dialysis on paliperidone. The extent to which a drug is affected by dialysis is determined by several physiochemical drug characteristics. These drug characteristics include the molecular weight, protein binding, water solubility, and volume of distribution (Aronoff 1999).[5] It is also important to consider whether the drug has active metabolites that may or may not be removed by dialysis. Please see the table: Physiochemical Properties of Paliperidone that Influence Dialysis for a review of these properties.

Physiochemical Properties of Paliperidone that Influence Dialysis

Property	Value
Molecular Weight	426.49 daltons
Protein Binding	74%
Water Solubility	Practically Insoluble
Volume of Distribution	487 L
Metabolites	None of the metabolites have a relevant contribution to the pharmacologic activity of paliperidone

Winter et al (2004)[2] provide a formula to predict the dialyzability of a drug based on the apparent volume of distribution and plasma protein binding (volume of distribution/free fraction of the drug). For paliperidone this equation yields an unbound volume of distribution of 1,873 L or, 27 L/kg in a 70 kg individual. Since the unbound volume of distribution exceeds 3.5 L/kg, it is unlikely the drug will be dialyzable.

CLINICAL DATA

Railton et al (2005)[3] described the case of a 16-year-old female with worsening psychiatric symptoms and tics following a change in her hemodialysis program. The patient had a 10-year history of renal disease/failure. After years of peritoneal dialysis, she was switched to hemodialysis due to peritoneal sclerosis. Three years after initiating hemodialysis her treatment was changed to a nocturnal home procedure consisting of hemodialysis 10 hours per day, 6-7 days per week. Past medical history included stabilization of obsessive-compulsive disorder (OCD) and accompanying tics with risperidone 0.5 mg once daily at bedtime and fluoxetine 40 mg daily. Shortly after the change in dialysis treatments a worsening of tics and psychiatric symptoms occurred. Since psychiatric symptoms were controlled for more than one year prior to the start of nocturnal hemodialysis, risperidone and/or fluoxetine seemed to be the likely candidates responsible for control of CNS symptoms. Additional medications were ruled out as likely candidates (coumadin 1.5 mg daily, omeprazole 20 mg at bedtime, calcitriol 0.25 mg daily, replavite 1 tablet daily, clonidine 3 mg at bedtime, and clonazepam 0.5 mg twice daily as needed).

Serum psychiatric drug concentrations were obtained. A trough fluoxetine level was within the therapeutic range (653 ng/mL; normal >500 ng/mL). Peak and trough risperidone levels were 11.8 nM and 5.5 nM, respectively, while 9-OH-risperidone (paliperidone) levels were 11 nM and 9.2 nM, respectively. Due to the subtherapeutic serum concentrations of risperidone and 9-OH-risperidone (combined therapeutic range=20-260 nM), the clinicians increased the risperidone dose to 0.75 mg at bedtime, 30 minutes prior to the start of dialysis. After 2 weeks of treatment risperidone drug concentrations were measured throughout a dialysis session. The results are presented in the Table: Risperidone/9-OH-risperidone Drug Concentrations at a Dose of 0.75 mg/day.

Risperidone/9-OH-risperidone Drug Concentrations at a Dose of 0.75 mg/day[3]

Time[a](hours following oral dose intake)	Risperidone (nmol/L)	9-OH-risperidone (paliperidone) (nmol/L)	Total Level(nmol/L)
1	42.5	22.1	64.6
3.83	40.0	21.7	61.7
5.83	46.9	26.1	73.0
7.83	32.9	20.8	53.7
9.83	32.8	20.7	53.5
11.83	33.5	23.7	57.2
24.75	10.5	17.0	27.5
[a]Hemodialysis administered between the 1-hour point and 11.83-hour point.			

Based upon the fluctuating concentration versus time curve, it is not clear if risperidone was poorly absorbed from the gut or subject to redistribution. The drug was likely not removed by dialysis, since levels of 9-OH-risperidone, a more water-soluble metabolite, were not markedly affected. Due to continued tics, the patient's risperidone dose was titrated upward, over 1 month, to a dose of 1.25 mg daily, administered 2 hours prior to dialysis. The patient and her family felt that the overall symptoms of her tic disorder improved. Again, risperidone drug concentrations were measured throughout a dialysis session. The

results are presented in the Table: Risperidone/9-OH-risperidone Drug Concentrations at a Dose of 1.25 mg/day.

Risperidone/9-OH-risperidone Drug Concentrations at a Dose of 1.25 mg/day[3]

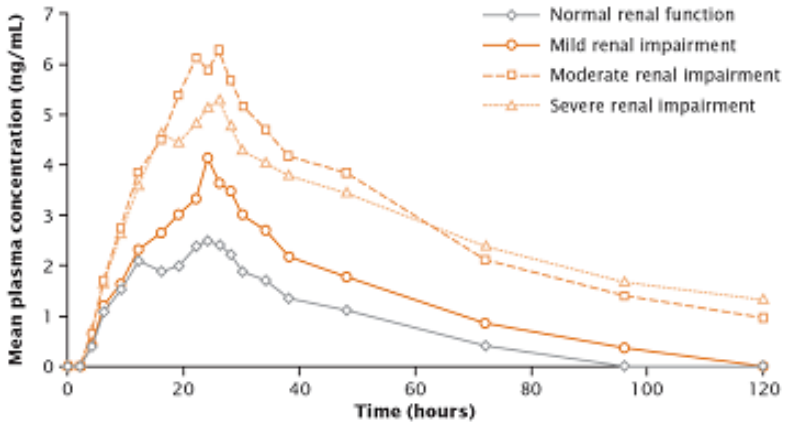
Time[a](hours following oral dose intake)	Risperidone (nmol/L)	9-OH-risperidone (paliperidone) (nmol/L)	Total Level (nmol/L)
2.21	43.5	52.7	96.2
4.21	34.5	40.8	75.3
6.21	39.0	56.2	95.2
8.21	30.0	53.0	84.0
10.21	26.6	45.0	71.6
12.21	28.0	50.8	78.8
26.13	8.6	49.4	58.0
[a]Hemodialysis administered between the 2-hour point and 12.12-hour point.			

Based upon the measured drug concentrations during hemodialysis and the volume of distribution of risperidone, the authors felt that dialysis did not enhance the elimination of risperidone or 9-hydroxyrisperidone. The authors concluded the patient's long history of peritoneal dialysis and peritoneal fibrosis may have affected intestinal physiology, thereby decreasing the extent of risperidone absorption.

Thyssen et al (2007)[6] conducted a single-dose, parallel-group study (n=48; age 18-75 years) to evaluate the impact of renal impairment on plasma and urine PK of orally administered INVEGA 3 mg in subjects with varying degrees of impairment compared to healthy subjects with normal renal function. The subjects (mean age 57.3 years) were divided into a normal renal function group (CrCl ≥80 mL/min), mild renal impairment group (CrCl 50-≤80 mL/min), moderate renal impairment group (CrCl 30-<50 mL/min), and severe renal impairment group (CrCl <30 mL/min), and all groups were balanced with regard to age, weight, body mass index, sex and ethnicity.

The plasma protein binding did not significantly differ among the four groups (mean: 26.8-30.1%). Please see figure 1: *Mean Paliperidone Plasma Concentration-time Plot* for a graphical comparison of the drug disposition.

Mean Paliperidone Plasma Concentration-time Plot[6]



Please refer to the table: Paliperidone Pharmacokinetic Parameters (mean) for a comparison of the PK among the four groups of subjects. The volume of distribution decreased 25-30% in renally impaired subjects compared to healthy subjects.

Paliperidone Pharmacokinetic Parameters (mean)[6]

	Healthy Subjects (n=12)	Mild Renal Impairment (n=11)	Moderate Renal Impairment (n=12)	Severe Renal Impairment (n=10)
C_{max}, ng/mL	**2.63**	**4.29**	**6.65**	**5.55**
AUC_{∞}, ng.h/mL	114	169	416	429
t_{max}[a], h	20.5	24.0	24.0	24.0
$t_{1/2}$, h	23.2	23.6	40.2	51.0
CL/F, mL/min	561	433	271	217
CL_R, mL/min	70.5	49.2	21.9	12.9
Ae, % dose	13.2	15.2	9.80[b]	7.47

Abbreviations: C_{max}: peak plasma concentration; AUC_{∞}: area under the plasma-concentration-time curve from time zero to infinity; t_{max}: time to reach peak plasma concentration; $t_{1/2}$: elimination half-life; CL/F: apparent total plasma clearance; CL_R: renal clearance; CL_{NR}: non-renal clearance; Ae: amount renally excreted; [a]median (range); [b] n=11

Ninety-one percent, 83%, 100%, and 100% of subjects in the normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment groups, respectively, reported adverse events. No patients reported severe or serious adverse events, and no subjects discontinued treatment because of an adverse event.

Cirincione et al (2007)[4] constructed a PK model using data from nine Phase 1 studies and four Phase 3 studies. The doses and formulations of paliperidone ranged from 3-15 mg extended-release oral tablets to 1 mg immediate-release intravenous infusion. The study included 21,183 paliperidone plasma concentrations from 1,368 subjects (65% male, mean age 40 years). Potential covariates included subject demographics, laboratory parameters, and other variables.

After refinement, the plasma concentration of paliperidone ER was described by a linear, 2-compartment model with consecutive zero- and first-order absorption and first-order elimination from the central compartment. In a population with normal renal function (CrCl 114.4 mL/min) receiving 6 mg of INVEGA at steady-state, the $AUC_{SS(0-\tau)}$ decreased from 484 to 410 ng•hr/mL as lean body mass increased from 42.8 to 67.5 kg. Furthermore, for any

given lean body mass, as renal impairment changed from normal (CrCl 114.4 mL/min) to mild impairment (CrCl 72.7 mL/min), mean exposure was predicted to increase by about 20%. However, based on these results only the magnitude of change in exposure caused by altered renal function necessitates a dose adjustment. None of the other covariates analyzed, including CYP2D6 phenotype, significantly contributed to the interindividual variability in any of the PK parameters.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 02 January 2024.

REFERENCES

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