INVEGA® (paliperidone ER)
INVEGA - Dosing - Plasma Concentrations

SUMMARY

- No therapeutic plasma concentration has been established for paliperidone (9-hydroxyrisperidone). Dosage adjustments, within the recommended range of 3 to 12 mg/day, should be based on the information provided in the INVEGA Prescribing Information and clinical assessment.
- A retrospective analysis was conducted examining the correlation between paliperidone serum concentrations (20-52 ng/mL) and improvement in clinical effects.[1]
- Dopamine D2 receptor occupancy of 70-80% may provide therapeutic efficacy with reduced dose-related extrapyramidal symptoms.[2] In two separate studies of dopamine D_2 receptor occupancy using mathematical models, plasma concentrations of 15.5-26.6 ng/mL[3] and 10-17 ng/mL[2] resulted in a D_2 receptor occupancy of 70-80% among patients receiving INVEGA.
- A study was conducted describing the methods for determining serum and urine concentrations of risperidone and 9-hydroxyrisperidone/paliperidone.[4]
- An additional study was conducted describing the use of the physiologically based absorption modeling approach to explore the absorption of paliperidone extended-release (ER) under fasting and fed conditions with a high-fat/high-calorie meal.[5]

PUBLISHED LITERATURE

Chung et al (2016)[6] conducted a study to predict treatment response as late as week 8 in first-episode psychosis patients in Korea, and included an analysis of the relationship between plasma concentrations for INVEGA at weeks 2 and 3 and the treatment responses at weeks 2, 3, and 8. First-episode patients included those with a DSM-4 diagnosis of first-episode schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder not otherwise specified. Their duration of illness was ≤5 years and there was no prior history of antipsychotics for ≥2 consecutive weeks or ≥6 weeks in total. Plasma samples were collected before drug administration on the mornings of days 14 and 21 and were analyzed using validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS).

Drug levels were measured in 30 patients at baseline and 29 at week 8. Average plasma concentrations were 17.08±9.30 ng/mL at week 2 and 21.51±14.82 ng/mL at week 3. There was a positive correlation between plasma concentrations and mean INVEGA doses (7.60 mg in week 2 and 8.38 mg in week 3). The plasma concentration at week 3 was a significant predictor of the treatment response at week 3 (treatment response based on ≥20% improvement in the Positive and Negative Syndrome scale (PANSS)-positive score and PANSS anxiety/depression score) and week 8 (treatment response based on ≥30% improvement in PANSS-positive score). No significant correlations were found between concentrations at week 2 and treatment responses at week 2 or 8.

Yeh et al (2015)[7] investigated, as a secondary endpoint, whether there was an association between plasma concentrations for paliperidone ER and clinical response at week 6 in Taiwanese adult patients meeting a DSM-4 diagnosis of schizophrenia or schizoaffective disorder. Responders were defined as those whose PANSS total scores were decreased by at least half after 6 weeks of treatment. Patients received a fixed dose of INVEGA 9 mg/day for the first 2 weeks and could be adjusted thereafter according to clinical judgment. Plasma concentrations were analyzed using high-performance liquid chromatography and ultraviolet detection. Comparable drug concentrations were found between responders (n=25; 41.6±34.1 ng/dl) and non-responders (n=5; 55.4±22.3 ng/dl) at week 6. No correlations

were observed between paliperidone concentrations and efficacy measures such as the PANSS, Clinical Global Impressions (CGI), and Personal and Social Performance scales.

Sheehan et al (2012)[8] conducted a study reviewing the peak-to-trough fluctuation of all long-acting injectable antipsychotics and their oral equivalents. The peak-to-trough fluctuations were determined by reviewing the literature and the US Prescribing Information for each product. The results illustrated that the steady-state peak-to-trough plasma-concentration ratios for oral antipsychotics varied between 1.47 (INVEGA) to 3.30 (active moiety risperidone) and for long-acting injectable antipsychotics varied between 1.56 (paliperidone palmitate) to approximately 4 (olanzapine pamoate). In addition, for antipsychotic formulations with similar dosing intervals, the antipsychotics with a longer time to maximum plasma concentration and terminal half-life contributed to a smaller peak-to-trough fluctuation.

Nazirizadeh et al (2010)[1] conducted a retrospective analysis examining the correlation between paliperidone serum concentrations and clinical effects in 217 patients (mean age: 38.1 years). Patients were diagnosed with schizophrenia spectrum psychoses (67.4%), schizoaffective disorder (16.4%), bipolar affective disorder (5.2%), depression (6.1%), and other psychiatric disorders (3.8%). Patients were markedly ill with a mean CGI-Severity of 5.9 with variable responses to INVEGA treatment (CGI-Improvement 2.6). The mean daily dose of INVEGA was 7.8 mg/day (range 3-18 mg/day) yielding a mean paliperidone steady-state serum trough concentration of 35.7 ng/mL (25th-75th percentiles 19.5-46.0 ng/mL). The mean dose-corrected paliperidone concentration (concentration/dose) was 4.7 ng/mL/mg. In 106 patients receiving INVEGA as antipsychotic monotherapy, improvement CGI scores were available for 63 patients of which 32 were very much or much improved. Mean serum concentrations in these patients were 43 ng/mL (25th-75th percentiles 20-52 ng/mL) similar to the recommended range of 20-60 ng/mL for risperidone plus 9-hydroxy-risperidone (paliperidone). In patients who demonstrated minimal or no improvement the mean paliperidone serum concentration was 33 ng/mL. Adverse events included somnolence (18.9%), extrapyramidal disorder (16.8%), and agitation (3.2%).

The authors commented that the power of the data was not sufficient to evaluate a therapeutic range, however the range of serum levels were found to be similar to the range reported for the sum of concentrations of risperidone plus 9-hydoxyrisperidone (20-60 ng/mL).

Arakawa et al (2007)[3] measured dopamine D_2 receptor occupancy in adult male patients (mean age 29.4 years) with schizophrenia during an open-label Phase II trial in Japan. Inclusion criteria included a PANSS score <120, and good symptom control with one oral antipsychotic during the 4 weeks prior to the study. Patients received 3 (n=6), 9 (n=4), or 15 (n=3) mg/day of INVEGA for 6 weeks. After 2 to 6 weeks, patients received a positron emission tomography scan with [^{11}C] raclopride and [^{11}C] FLB 457 to measure striatal and extrastriatal dopamine D_2 receptor occupancy, respectively.

A plasma concentration of 6.65 and 7.73 ng/mL resulted in 50% dopamine D_2 receptor occupancy (ED_{50}) in the striatum and temporal cortex, respectively. Based on this ED_{50}, a plasma concentration of 15.5-26.6 ng/mL may provide therapeutic efficacy (>70% D_2 receptor occupancy) with a reduced trend in dose-related extrapyramidal symptoms (<80% D_2 receptor occupancy).

DeMeulder et al (2008)[4] described two validated LC-MS/MS methods for the quantitative analysis of risperidone and the enantiomers of 9-hydroxyrisperidone (paliperidone) in plasma (down to 0.2 ng/mL) and for the quantitative analysis of the enantiomers of 9-hydroxyrisperidone in human urine (down to 1 ng/mL).

UNPUBLISHED LITERATURE

Karlsson et al (2005)[2] conducted an open-label, single-dose study in four healthy Caucasian subjects (median age 24 years) to evaluate the pharmacokinetics and dopamine D_2 receptor occupancy of INVEGA 6 mg. Administration of a single dose of INVEGA resulted in a peak plasma concentration of 11.7 ng/mL at 25.1 hours. The investigators estimated the plasma concentration at which 50% of the target receptor is occupied (K_D^{app}) as 4.4 ng/mL. Based on the K_D^{app} values, a plasma concentration of 10-17 ng/mL may result in a suitable 70-80% D_2 receptor occupancy.

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 19 August 2024.

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