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Dear Dr Lucire,

Thank you for requesting information on Zyprexa® (olanzapine) and:-

1. therapeutic window
2. blood levels and how are they measured
3. why are some people slow metabolisers
4. what cytochromes of ugts are involved in poor metabolisers

We appreciate the opportunity to be of assistance.

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The underlying pharmacodynamic mechanisms for therapeutic windows are unknown [16].

As stated by Perry [17], a reasonable therapeutic window for olanzapine would be 9.3 to 20.6ng/ml. However, additional research is needed to conclusively establish a therapeutic range for olanzapine in schizophrenia.

Detailed below is information on measuring the plasma levels of olanzapine. Eli Lilly cannot recommend specific diagnostic centres for testing of olanzapine plasma concentrations. However we are aware these are usually measured by a routine high performance liquid chromatography (HPLC) method.

SUMMARY

Information on oral olanzapine and plasma concentration monitoring is briefly summarized below. Information excluded may pertain to trial methods and limitations,

patient population, non-endpoint results, and statistical information. Please refer to the sections that follow for further details.

- Plasma concentrations of oral olanzapine were linear and dose proportional in trials studying doses from 1 to 20 mg. However, there is considerable intersubject variability in olanzapine pharmacokinetics. In addition, plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, age, and concomitant medications.
- An analysis of pooled data from premarketing approval studies in patients with schizophrenia did not demonstrate a clear relationship between measures of efficacy and olanzapine plasma concentrations.
- Several published studies have also examined the potential relationship between olanzapine plasma concentrations and clinical response.

INTRODUCTION

Plasma concentration monitoring may be useful in optimizing response to several antipsychotic medications. Benefits of therapeutic plasma level monitoring include optimizing dosing regimens, minimizing potential adverse events, guarding against toxicity, and assessing adherence[1].

Plasma concentrations of olanzapine were linear and dose proportional in trials studying doses from 1 to 20 mg[2]. During one pharmacokinetic study, doses of olanzapine 10 mg daily achieved an average steady-state concentration of approximately 14 to 15 ng/mL (C_{min} 10 ng/mL; C_{max} 19 ng/mL)[2]. However, there is considerable intersubject variability in olanzapine pharmacokinetics[2]. In addition, plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, age, and concomitant medications[2-7].

Premarketing approval studies comparing olanzapine plasma concentration to measures of efficacy did not demonstrate a clear relationship between response and plasma concentration[2]. Presented below is a summary of studies examining the potential relationship between oral olanzapine plasma concentrations and clinical response.

OLANZAPINE PLASMA CONCENTRATION AND CLINICAL RESPONSE

Pooled data from three premarketing approval studies[8-10] that had either fixed-dose treatment groups or fixed dosage ranges were analyzed[2]. Plasma samples from 592 patients who had been receiving olanzapine (dose range 1 to 17.5 mg/day) for at least 3 weeks were included in the analysis. There was extensive variability in endpoint olanzapine concentrations (mean 15.07 ng/mL, range 0.04 to 108.11 ng/mL). Olanzapine plasma concentrations plotted against percent change in Brief Psychiatric Rating Scale (BPRS) total score did not show a clear relationship between response and plasma concentration.

Olesen and colleagues[7] evaluated olanzapine serum concentrations in 56 psychiatric patients (33 male, 23 female) treated with olanzapine therapy (median 15 mg/day, range 5 to 30 mg/day). Patients were treated with a constant dose of olanzapine for at least 1 week and plasma levels were drawn 12 hours postdose. Eighty percent of all patients (n=56) had olanzapine serum concentrations between 6.9 and 45.6 ng/mL. In the group receiving olanzapine monotherapy (n=22), 80% of patients had a serum concentration between 8.7 and 47.2 ng/mL. Based on these observations, the authors suggested a therapeutic range for olanzapine of 7.8 to 46.9 ng/mL. The authors found only a weak

correlation between daily dose and serum concentration due to a large interindividual variability.

Perry et al.[11] analyzed data from 79 patients with schizophrenia (61 male, 18 female) who participated in a clinical trial comparing olanzapine (1 and 10 mg/day) to placebo[2]. Response was defined as a ≥20% reduction in BPRS or Positive and Negative Symptom Scale (PANSS) scores. The analysis included patients who had completed 1 to 3 weeks of therapy and had olanzapine plasma samples obtained 24 hours after the last dose. The results of this analysis suggested a minimum threshold for optimal response to be 9.3 ng/mL. Olanzapine plasma concentrations ≥9.3 ng/mL resulted in a response rate of 45% compared to a response rate of only 13% when olanzapine plasma concentrations were <9.3 ng/mL[7].

A second report by Perry et al.[12] analyzed data from 84 patients with schizophrenia (71 male, 13 female) who participated in a clinical trial comparing olanzapine with haloperidol and placebo. Patients received daily dosages of olanzapine ranging from 2.5 to 17.5 mg/day for up to 6 weeks. The analysis included patients who had received a fixed dose of olanzapine for at least 2 weeks and had the plasma sample obtained between 10 and 16 hours (mean 11.7 hours) postdose. Response was defined as ≥20% decrease in total BPRS (scale of 1 to 7) and either an endpoint Clinical Global Impression (CGI) severity score of ≤3 or an endpoint BPRS score of ≤35. The results of the plasma concentration analysis suggested a minimum olanzapine plasma concentration of 23.2 ng/mL for optimal response. Olanzapine plasma concentrations ≥23.2 ng/mL resulted in a response rate of 52% compared to a response rate of 25% when olanzapine plasma concentrations were <23.2 ng/mL. Additionally, an olanzapine concentration of ≥23.2 ng/mL was also found to be a predictor of negative symptom response in the Scale for the Assessment of Negative Symptoms (SANS). The authors did find a relationship between olanzapine plasma concentration and dose, as well as plasma concentration and gender, with males requiring a higher olanzapine dose to reach the minimum threshold concentration compared to females. This observation is consistent with prior findings that olanzapine clearance is approximately 30% lower in females than males[5].

Kinon et al.[13] assessed the pharmacokinetic characteristics of oral olanzapine doses (10, 20, or 40 mg/day) in acutely ill, non-treatment-resistant patients with schizophrenia or schizoaffective disorder enrolled in a randomized, double-blind, 8-week study. Olanzapine is indicated for the treatment of schizophrenia with a dosing range of 5 to 20 mg/day in adult patients. Steady-state olanzapine plasma concentrations were determined for a subset of patients (10 mg/day, n=133; 20 mg/day, n=125; 40 mg/day, n=122) from blood samples collected after daily administration of fixed doses for 2 and 6 weeks. Steady-state olanzapine plasma concentrations did not differ at 2 and 6 weeks and were pooled for analysis. Median steady-state olanzapine plasma concentrations of 17, 34, and 69 ng/mL were proportional to doses of 10, 20, and 40 mg/day, respectively. There was a lack of correlation between olanzapine plasma concentration and change from baseline in PANSS total score at 8 weeks (r=-.09, p=.123). Steady-state plasma olanzapine concentrations were proportional to doses up to 40 mg/day and typical covariate effects (smoking, gender) were observed. There was a significant difference between the 10 and 40 mg/day dose groups (p=.002) for mean change in weight (1.9 kg [10 mg/day], 2.3 kg [20 mg/day], 3.0 kg [40 mg/day]; p=.002). However, there was a lack of correlation between olanzapine plasma concentration and weight change from baseline (8 weeks: r=-.03, p=.614). There was also a significant difference between the 10- and 40-mg/day (p<.001), 20- and 40-mg/day (p=.004), and 10- and 20-mg/day (p=.018) dose groups for mean change in prolactin levels and a significant correlation between olanzapine plasma concentrations and absolute prolactin levels at 8 weeks (r=.46, p<.001).

The pharmacokinetics of oral olanzapine are similar between adolescent and adult patients[2]. In clinical studies, the average steady state olanzapine concentrations were approximately 27% higher in adolescents than in adults. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors likely contribute to the higher average exposure observed in adolescents. Similar to adult populations, a clear relationship between efficacy and plasma olanzapine concentrations has not been established for the treatment of schizophrenia or bipolar I disorder[2]. Please note that olanzapine therapy is currently not approved for use in adolescent patients.

Fellows et al.[14] evaluated the potential use of olanzapine plasma concentration monitoring as an indicator of clinical response in 53 patients with schizophrenia (mean age 32 years; 40 male, 13 female) in an open-label study. Response was defined as a $\geq$20% reduction in PANSS scores. After 6 weeks of therapy, patients were receiving olanzapine doses ranging from 5 to 30 mg/day (median dose 15 mg/day). The mean plasma olanzapine concentration was 32 microgram/L at a median of 13.5 hours following the dose. Although plasma concentrations in responders and nonresponders were similar, the authors stated that monitoring for olanzapine concentrations $\geq$23 to 25 microgram/L may be useful as an adjunct to clinical evaluation of response.

In a 2-week, open-label study, Mauri et al.[15] examined olanzapine use (dose range 5 to 20 mg/day, mean dose 15.27 $\pm$ 5.53 mg/day) in 54 patients with schizophrenia (age range 18 to 75 years; 38 male, 16 female). Olanzapine plasma levels were determined 12 hours following the last dose and ranged from 5 to 120 ng/mL (mean 33.15 $\pm$ 28.28 ng/mL), exhibiting high interindividual variability. A statistically significant positive correlation between olanzapine plasma concentration and dose was observed ($r=0.42$, $p<.01$). In addition, the data showed a statistically significant curvilinear relationship between olanzapine plasma levels and percent improvement in BPRS, PANSS, and Hamilton Rating Scale for Depression.

In addition, we have enclosed some clinical papers relating to slow metabolisers and ugts in relation to poor metabolisers which may be of interest.

The details of your query have been recorded on our database for any follow up by you or by Lilly if required. Please do not hesitate to contact us if you have any further questions or comments.

Yours sincerely,
ELI LILLY AUSTRALIA PTY. LIMITED

Vicky J Foster B. Nursing
MEDICAL INFORMATION CONSULTANT

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