Serum Levels of Olanzapine in a Non-Fatal Overdose

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Abstract

Olanzapine is a widely used second generation antipsychotic drug. Case reports of intoxications have been published, but reports in the literature of non-fatal intoxications of olanzapine containing repeated measurements of serum levels are scarce. Therefore, this case of non-fatal olanzapine intoxication is presented, in which 19 blood samples were drawn during 2 weeks. The highest (initial) measured value was estimated at 800 µg/L. This patient ingested 550 mg of olanzapine resulting in clinical signs of intoxication, including seizures. Because the patient was found the day after the intoxication, the initial concentration had probably been higher. The pharmacokinetics of olanzapine has been described as linear and dose-proportional throughout the therapeutic dosing range. Large overdoses, however, have been described to show non-linear pharmacokinetics. In this study's series of serum concentrations, a two-phase elimination was seen, with an initial elimination half-life of about 24 h during the first 3 days, followed by a second phase with a half-life of about 2.5 days. The patient in this case recovered completely. Because the elimination time after intoxication can be considerably longer than expected, it is recommended that the patient's serum concentrations after intoxication be monitored.

Introduction

Olanzapine is an atypical antipsychotic with (in vitro) activity on dopamine D1, D2, D4, serotonin 5-HT2, histamine H1, alpha-adrenergic, and muscarinic receptors (1). Symptoms of olanzapine intoxication are somnolence, lethargy, coma, respiratory depression, hyperpyrexia, tachycardia, anticholinergic syndrome, confusion, agitation, delirium, miosis, dysarthria, convulsions/jerks/myoclonus, hypertension, orthostatic hypotension, and ECG changes (2-4). Doses ingested in fatal cases have been highly variable, and serum olanzapine levels between 237 and 5200 µg/L have been reported (3-7). The relationship between blood concentrations in clinical and post-mortem measurements is dependent on postmortem distribution (higher concentrations in heart blood than in femoral blood) as well as poor stability in postmortem blood (8). Non-fatal intoxications in children, 1-2.5 years of age, resulted in serum levels of 11-472 µg/L (3,9-11). In adolescents and adults, non-fatal toxic symptoms were seen at serum levels between 100 and 1500 µg/L (3,8,12-17). On the other hand, drug blood (serum and plasma) concentrations as high as 300 µg/L without adverse effects have been reported (4). Here, a case of non-fatal olanzapine (about 550 mg) overdose with symptoms of intoxication, in which levels of olanzapine were monitored for 14 days, is described.

Case History

A 36-year-old man with a diagnosis of paranoid schizophrenia was found in his home in a mentally confused state with signs of bowel and bladder incontinence indicating status post seizure. He had been vomiting and was pale and unsteady. It was estimated that the patient was found 24-36 h after the attempted self-poisoning with 55 10-mg olanzapine tablets. Because of a lack of compliance, he was not under regular treatment with olanzapine at the time of intoxication. Instead, his regular neuroleptic treatment consisted of injections of perphenazine decanoate (108 mg/mL, 2.5 mL every 2 weeks). On admission to the emergency unit at the hospital, the patient was conscious but agitated and showing psychotic symptoms. His heart rate was 78 beats/min, his blood pressure was 126/90 (mm Hg), and his body temperature was 36.9°C. Oxygen saturation at admission was 97%. No ECG abnormalities were detected. Liver affection was noted at the determination of laboratory enzyme levels. Aspartate aminotransferase (highest value, 2.43 µkat/L), alanine transaminase (highest value, 1.25 µkat/L), and lactate dehydrogenase (highest value, 13.6 µkat/L) were all elevated. The C Reactive Protein was also elevated to a highest level of 79 mg/L. Creatine kinase (CK) and creatinine kinase MB form (CKMB) were increased to 113 and 37 µkat/L, respectively, but troponine was not increased. A slight elevation of Leukocytes up to 10.4 x 10⁹/L was found. A CT scan of brain,
chest radiography, and abdominal ultra-sonography were normal. Initially, the patient was treated at the Department of Internal Medicine, but because of agitation and aggressive behavior, he was transferred to the Department of Psychiatry.

Methods

Serum concentrations of olanzapine were determined by a chromatographic method, which has been described in the literature (18). Briefly, 2 mL serum was mixed with 50 μL internal standard (IS), Lundbeck N-7084 (5-pyrrolidinylpropyliden)-10,11-dihydro-5-H-dibenzo (a,d) cycloheptene (Lundbeck A/S Copenhagen, Denmark), and 1 mL of 0.1M sodium acetate (pH 6.5). After mixing and centrifuging, the sample was applied to an Isolute HCX-cartridge for isolation of the analyte and IS. After washing and elution, the eluate was evaporated to dryness and the residue dissolved in 75 μL methanol. Three microliters were injected into the gas chromatograph for analysis.

The data analysis for this paper was generated using SAS/STAT software, Version 9 of the SAS System for Windows (SAS Institute Inc., Cary, NC).

Results

In this case the diagnosis of olanzapine intoxication was confirmed by the analysis of multiple serum specimens of olanzapine, and the clearance of the drug was observed by analysis of a series of serum concentrations in all consisting of 19 measurements during a period of 14 days. The samples were drawn once or twice a day at 8:00 a.m. and/or 8:00 p.m.

The first serum concentration was drawn at the time of hospital admission, approximately 24–36 h (24 h being used as the starting point in Figure 1 and Table I) after the olanzapine intake, and showed to be the highest level during this series of measurements (815 μg/L) (Table I). The following measurements showed a rapidly declining pattern, which would imply that the maximal serum level of olanzapine probably had passed its top level and was considerably higher during the first 24–36 h after the intoxication event (Figure 1).

The regression for this trend was best in accordance with a two-phase elimination model. This elimination model consisted of an initial phase during the first 3 days after hospitalization (which would be 4–4.5 days after the intoxication event), with a faster elimination and a calculated half-life of 22 h for olanzapine ($R^2$ 0.9865, $P < .0001$). The second phase was showed to have a much slower rate of elimination with a calculated half-life of 2.3 days ($R^2$ 0.9734, $P < .0001$).

Discussion

One previously published case describing a series of serum concentration determinations related to intoxication with olanzapine was found (14). In that case report, a series of five serum concentration determinations during the first 100 h (4 days) after intoxication with 800 mg of olanzapine was presented. Even though the number of determinations of olanzapine in serum was lower than in this case, the authors’ interpretation of their material was that the data indicated a first period of faster decline during the first 24 h after intoxication, which was a result of drug distribution to the tissues as well as metabolism to inactive metabolites. The results in our case seem to confirm this interpretation. Thus, a similar graphic pattern was found, although the faster decline during the first phase of elimination in our material seems to be considerably longer, at 3–3.5 days. The two-phase model is possibly explained mainly by redistribution from plasma to tissue during the first fast phase, and mainly by elimination of the drug during the second slow, phase. Olanzapine has been described to be metabolized via the Cytocrome P 450 liver enzymes, mainly by CYP1A2 and CYP2D6 (1,2,4,19,20). The range of elimination half-life times have been estimated at 27 to 38.6 h in young, healthy volunteers. Smoking and male gender has been related to higher CYP1A2 activity. In this case, our patient should have had a faster rate of elimination because he was both male and a...
smoker, in contrast to the patient in the other case mentioned, who was a non-smoking woman. Our patient was under long-term treatment with perfenazine, administered as decanoate by injection. Perfenazine is metabolized via CYP2D6. Theoretically, if both drugs are metabolized via this enzyme, the elimination of perfenazine might influence and prolong the elimination of olanzapine (21). However, there have been somewhat diverging results concerning the metabolism of olanzapine because in another study, the authors concluded that neither CYPIA2 nor CYP2D6 seemed to have a dominant role in the metabolism of olanzapine after intake of a single-dose (18). No therapeutic serum concentration window has been defined for olanzapine. However, toxicity has been described at serum concentrations above 100 µg/L (8). This study suggests serum concentrations greater than approximately 100 µg/L as potentially toxic when making clinical decisions concerning the caretaking of intoxicated patients. Thus, in our patient the serum concentration was at a potentially toxic level for about 4–5 days, using this suggested definition.

Conclusions

The patient in this case report was found 24–36 h after intoxication with 550 mg of olanzapine. He was found with signs of status post seizures, liver affection, slight leukocytosis, and elevated CK and CKMB. The serum concentration determinations showed a rather slow elimination of olanzapine and the elimination appears to be best described by a two-phase elimination model. Because of the risk of a decreased elimination rate, it is recommended that, if possible, serum concentrations after olanzapine intoxications are followed until non-toxic levels are detected as an aid for clinical caretaking decisions. This study suggests serum concentrations above 100 µg/L as potentially toxic. Calculated from the elimination half-life described for therapeutic doses of olanzapine, symptoms of intoxication and elevated serum concentrations may be found during a period of time that is longer than expected.

References


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