Oral Presentation - 19

Determination of Tramadol and Its Major Metabolites (M1, M2 and M5) Concentration in Plasma of Human Poisoning By HPLC and Its Relation with Clinical Symptoms

Mahnaz Ahmadimanesh[1], Shahin Shadnia[2], Mohammad-Reza Rouini[3], Sara Ahsaninasab[1], Mahmoud Ghazi-khansari[4]

[1]Pharmacology Department, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[2]Toxicological Research Center, Clinical Toxicology Department, Loghman Hakim Hospital Poison Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]Biopharmaceutics and Pharmacokinetics Division, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[4]Department of Biostatistics and Epidemilogy, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Objectives: Tramadol hydrochloride is a novel synthetic opioid with a centrally acting analgesic effect. Tramadol produces analgesia by binding weakly to the μ-opioid receptor and inhibits re-uptake of monoaminergic hormones (norepinephrine and serotonin). It is rapidly metabolized in the liver into O-desmethyl-tramadol (M1), N-desmethyl-tramadol (M2) and N, O-didesmethyl-tramadol (M5). CYP2D6 primarily is involved in M1 formation, CYP2B6 and 3A4 are involved in M2 formation and CYP 2D6, CYP 2B6 and 3A4 are involved in M5 formation. The CYP2D6 has high genetic polymorphism affecting the CYP enzymes in human and any co-ingested drug with potential effect on CYP2D6 such as tricyclic antidepressants, phenothiazines, and selective serotonin reuptake inhibitors may affect blood levels of M1. The pharmacological activity of M1 is most important. The main and common side effects of tramadol include nausea, vomiting, vertigo, drowsiness, fatigue, sweating, dry mouth, and in overdose tachycardia, CNS depression, respiratory depression, seizure and coma. The serious side effect of tramadol may be depended to genetics, renal failure and metabolism. Although tramadol-related seizure may happen with overdose, several reports showed that it could occur even at therapeutic doses. The exact cause and mechanism of induction of seizure in some users of tramadol remains unclear.

Method: In this study, blood samples were collected from 120 patients admitted to the Emergency Department of the Logman Hakim Hospital with a history of tramadol intoxication. A high performance liquid chromatography (HPLC) with fluorescence detection was used to measure tramadol and its major metabolites (M1, M2, and M5) concentrations. Additionally, tramadol and its major metabolites (M1, M2, and M5) concentrations were correlated with the main symptoms.

Results: Of all the investigated symptoms, only seizure had significant correlation with respect to sex and increased concentration. Male patients had seizure more significantly greater than females ($p < 0.001$). It also showed that the average concentration of M2 in male is significantly greater than female ($p=0.003$). Our results also indicated that there is a significant correlation between increased tramadol ($p=0.006$) and its metabolites (M1; $p=0.017$, M2; $p=0.023$, M5; $p=0.011$) concentrations in plasma with respect to seizure symptom. Also with increasing ratio of M1/M2, decrease in the risk of seizure (0.26-fold, $p=0.02$) was found.

Conclusions: It is suggested that there might be a relationship between tramadol and its metabolites plasma concentrations with regard to sex and seizure. Also, the risk of seizure increases with higher concentration of the drug.