

Serial Blood and Urine Drug Concentration Measurement in a Patient With acute Intoxication By tramadol and Zolpidem Resulting in Qt Prolongation: Case Report

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Case report

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Abstract

Background: QT prolongation is a well-known complication when tramadol or zolpidem is ingested in large amounts acutely. However, the blood drug concentration resulting in QT prolongation or tachyarrhythmia when tramadol and zolpidem are ingested simultaneously in large amounts has not yet been reported. We report a case of acute intoxication by tramadol and zolpidem resulting in QT prolongation in a patient in whom serial blood and urine tramadol and zolpidem concentrations were determined.

Case presentation: A 38-year-old male patient presented to the emergency medical centre because of poisoning from 3 g of tramadol and 50 mg of zolpidem at 3 h before his emergency department (ED) visit. During supportive treatment, he developed QT prolongation without clinical manifestations. He was discharged five days after admission without any sequelae. We measured the blood and urine concentrations of tramadol and zolpidem at various time points, which revealed a blood tramadol concentration-dependent change in QTc intervals and increasing blood tramadol concentration at 8 h after the ED visit, with a sustained low zolpidem concentration. Tramadol and zolpidem are metabolized by the same enzyme, cytochrome P450 3A4. Therefore, competitive inhibition by a P450 3A4 isoenzyme may lead to increases in drug toxicity. The QT interval in patients acutely intoxicated by tramadol should be evaluated carefully, particularly when tramadol is co-ingested with other drugs.

Conclusions: Considering the half-life of tramadol or zolpidem and potential for continued absorption of drugs remaining in the gastrointestinal tract, it is necessary to observe patients via cardiac monitoring for more than 36 h after acute intoxication. The blood concentration of tramadol may increase and result in QT prolongation even after appropriate initial treatment.

Background

Tramadol and zolpidem are well-known analgesics and hypnotics widely used to treat pain or insomnia. Recently, cardiac safety concerns regarding administration of zolpidem have been raised by a case of long QT syndrome complicated by torsade de pointes tachyarrhythmia [1]. QT prolongation is a well-known complication that occurs when tramadol is ingested in large amounts acutely. The toxic and lethal blood concentrations of tramadol and zolpidem have been reported in post-mortem cases. However, the blood drug concentration resulting in QT prolongation or tachyarrhythmia when tramadol and zolpidem are ingested simultaneously in large amounts has not been reported. Herein, we report a case of acute intoxication from these drugs resulting in QT prolongation in a patient by evaluating serial blood and urine concentrations of the drugs.

Case Presentation

A 38-year-old male presented to the emergency department (ED) with a chief complaint of acute intoxication. He reported that he had ingested 60 tablets of Tridol® (tramadol hydrochloride 50 mg,

YUHAN, Seoul, South Korea) and 5 tablets of Zolpiram® (zolpidem tartrate 10 mg, Whan In Pharm, Seoul, South Korea) 4 h prior and had been treated for psychiatric disorders, including depression, anxiety, and insomnia, for many years. He had also been diagnosed with Wolff-Parkinson-White syndrome 6 years prior.

At the time of the visit, the patient scored 14 points (E3V5M6) on the Glasgow coma scale. His blood pressure was 152/105 mmHg, heart rate was 98 beats/min, breathing rate was 20 breaths/min, body temperature was 37.0 °C, and oxygen saturation was 95%. Neurological examination revealed no abnormal cranial reflex or brainstem signs. The results of an arterial blood test showed respiratory acidosis and hypoxemia (pH, 7.37; pCO₂ level, 52 mmHg; pO₂ level, 73 mmHg; HCO₃ level, 27.6 mmHg; O₂ saturation, 94%); the complete blood cell count test and electrolyte examinations (Na, K, Cl, Mg) showed normal values. He had been administered gastric irrigation and activated charcoal for poisoning treatment. A baseline electrocardiogram (ECG) on admission showed sinus tachycardia with 117 beats/min and a corrected QT (QTc) interval of 530 ms. The QRS interval was 98 ms, although a suspicious delta wave in the upstroke to QRS and PR interval of 130 ms were observed (Fig. 1). At 8 h after admission (12 h after exposure), an ECG showed a PR interval of 102 ms, QRS duration of 110 ms with a delta wave, and QTc of 543 ms, indicating Wolff-Parkinson-White syndrome with QT prolongation (Fig. 2). The QTc interval decreased to 524 ms, 485 ms at 24 h, 36 h after exposure respectively (Fig. 3,4).

The patient was hospitalized in the intensive care unit for close cardiac monitoring. After informed consent was obtained, serial blood and urine samples were collected at 8- or 12-h intervals from the time of the ED visit and sent to the National Forensic Service of Korea for drug concentration analysis. Figure 5 shows the changes in the blood and urine concentrations of tramadol and zolpidem with the QTc interval change over time. Blood and urine concentrations of tramadol at the ED visit were 2.87 and 28.04 mg/L, respectively, and those of zolpidem were 0.02 mg/L and below the quantitative limit, respectively. Eight hours after the ED visit, the blood and urine concentrations of tramadol sharply increased to 4.03 and 96.86 mg/L, respectively. In contrast, the blood concentration of zolpidem decreased to 0.001 mg/L. The measured concentrations of tramadol peaked at 8 h after the ED visit and then began decreasing linearly over time. The change in the QTc interval was consistent with the change in the blood levels of tramadol. The patient was discharged without any complications after five days of hospitalization.

Discussion And Conclusions

This is the first report describing the determination of blood and urine concentrations of tramadol and zolpidem at regular time intervals in a patient. Tramadol, a synthetic opiate, is used in pain treatment. It is metabolized by the cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4, and its elimination half-life is known to be 9 h [2]. Several cases of tramadol poisoning have been reported, including lethal intoxications [3, 4], and the toxic concentration is known to be > 2 mg/L [5]. The blood drug concentration was reported to be 7.7 mg/L in one post-mortem case from acute tramadol poisoning death and 48.34 mg/L in other cases [6]. A previous study in 2016 reported prolonged QTc intervals in 18.4% of

1402 patients with tramadol poisoning [7]. In another study, Keller et al. reported that tramadol produced QTc prolongation that was well-correlated with plasma drug concentrations [8]. However, unlike the study by Keller et al., which was conducted while patients took prescriptions normally, this case involved a patient with acute overdose poisoning from an estimated total of 3 g of tramadol and 50 mg of zolpidem. In the present case, a serial blood tramadol concentration-dependent change in the QTc interval was observed, which is consistent with the findings of Keller et al. The patient's blood concentration and QTc interval simultaneously increased in the 8 h after the ED visit despite general treatment of the patient for acute poisoning. This suggests the potential for continued absorption of drug components remaining in the gastrointestinal tract, as the time to peak concentration is independent of the dose and depends only on the rates of absorption and elimination [9]. Zolpidem is also mainly metabolized by cytochrome P450 3A4 [10] and may have a synergistic effect in tramadol poisoning because it undergoes metabolism via the same pathway, and this interaction can enhance QT prolongation by decreasing drug clearance. However, in this case, zolpidem levels remained below the therapeutic concentration; thus, the effect of acute ingestion of zolpidem was minimal.

In conclusion, considering the half-life of tramadol or zolpidem and potential for continued absorption of drugs remaining in the gastrointestinal tract, it is necessary to observe patients via cardiac monitoring for more than 36 h in acute intoxication. The blood concentration of tramadol may increase and result in QT prolongation even after appropriate initial treatment, as observed in this case.

List Of Abbreviations

ED, emergency department; ECG, electrocardiogram; QTc, corrected QT

Declarations

Ethics approval and consent to participate

IRB No. CNUH 2020-06-073

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

WJ conceived the idea for the manuscript and supervised entire writing process. BL and JP helped to write the manuscript. SK, DK, DP, and HC analysed and interpreted data of the sampled blood and urine by liquid chromatography. CK and HJ treated patients in the intensive care unit under the supervision of YY, the ICU specialist. All authors read and approved the final manuscript

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Figures

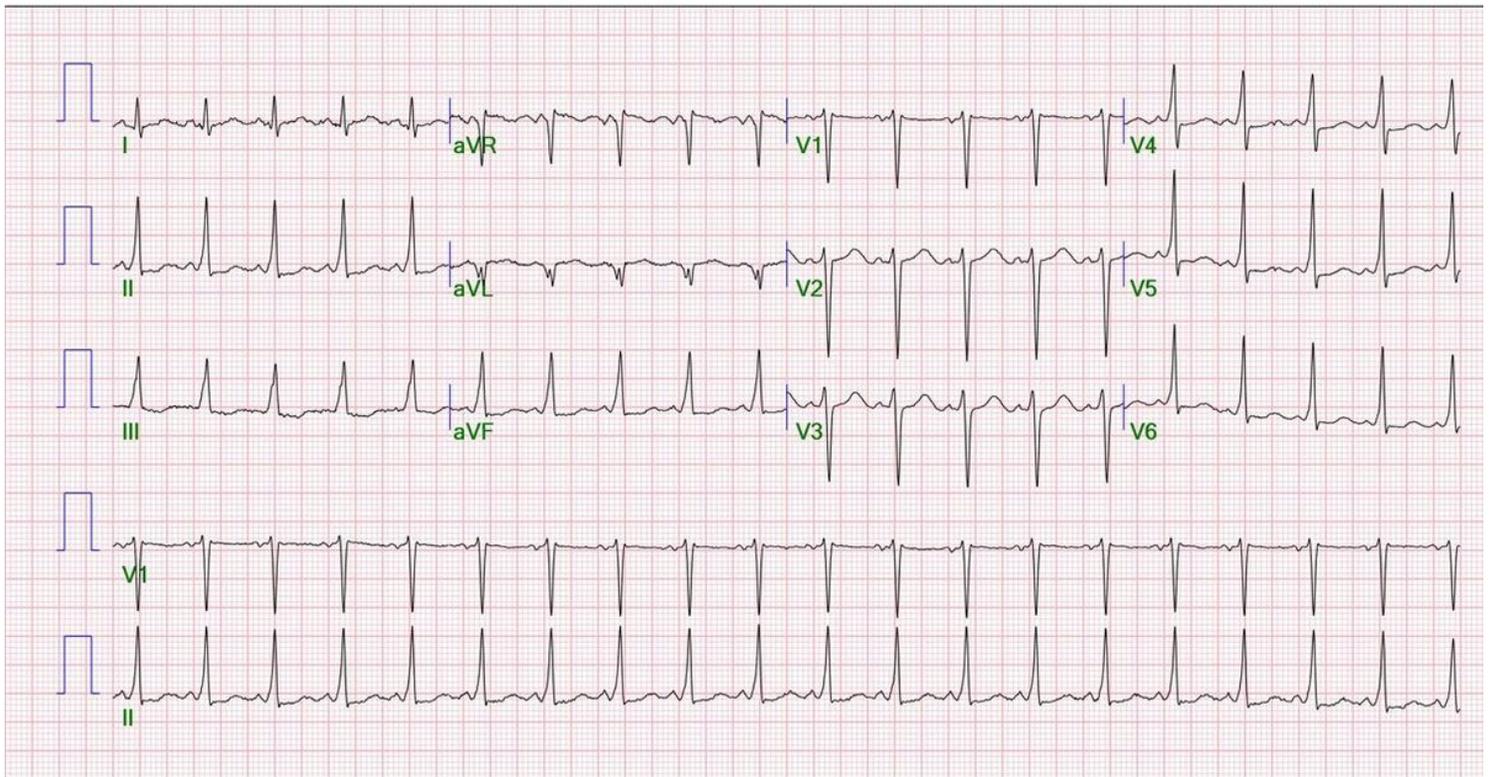


Figure 1

ECG at 4 hours after exposure, showing QTc prolongation of 530ms.

Drug concentration of blood, urine and QT interval over time

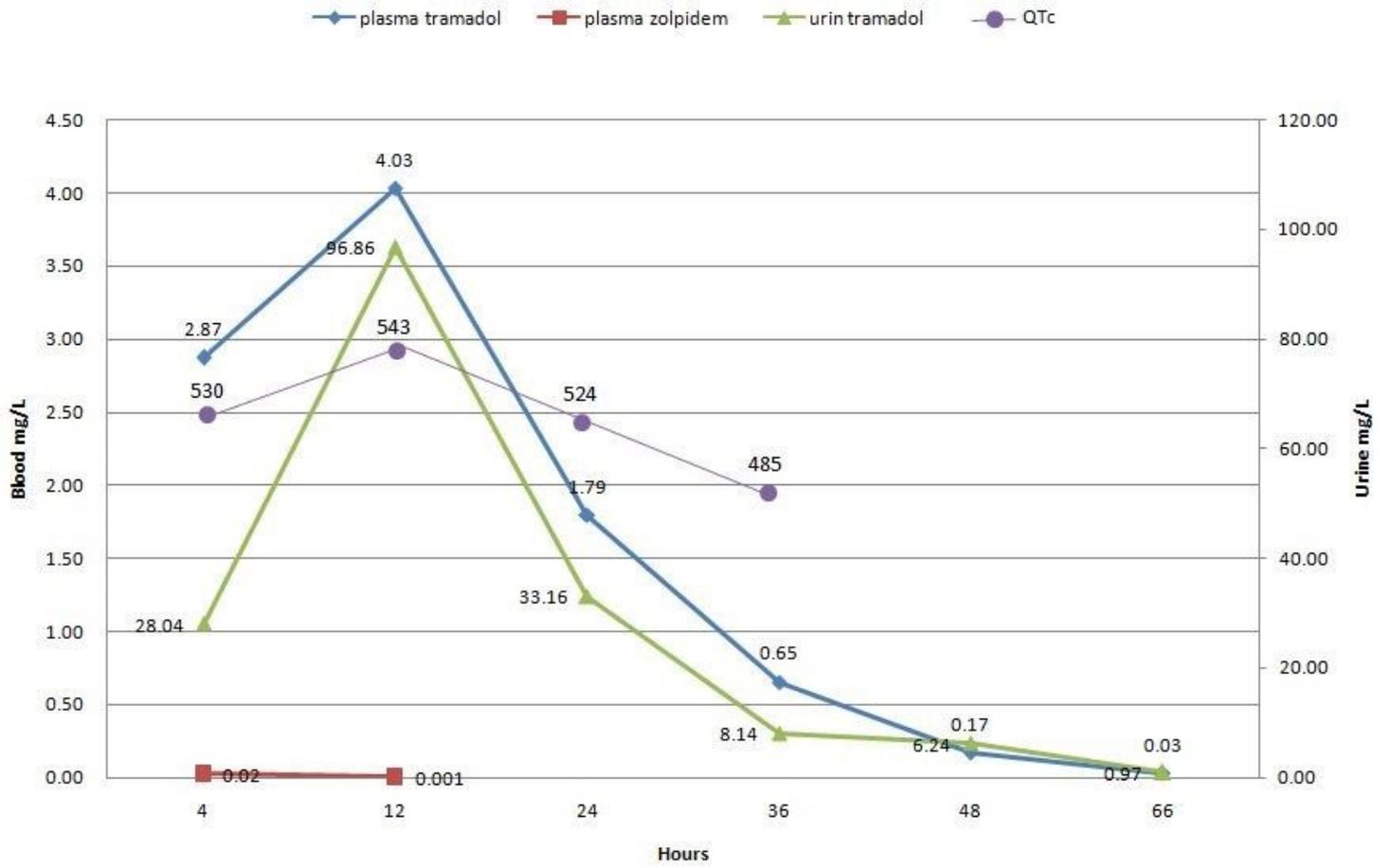


Figure 2

ECG at 12 hafter exposure, showing QTc prolongation of 543ms.

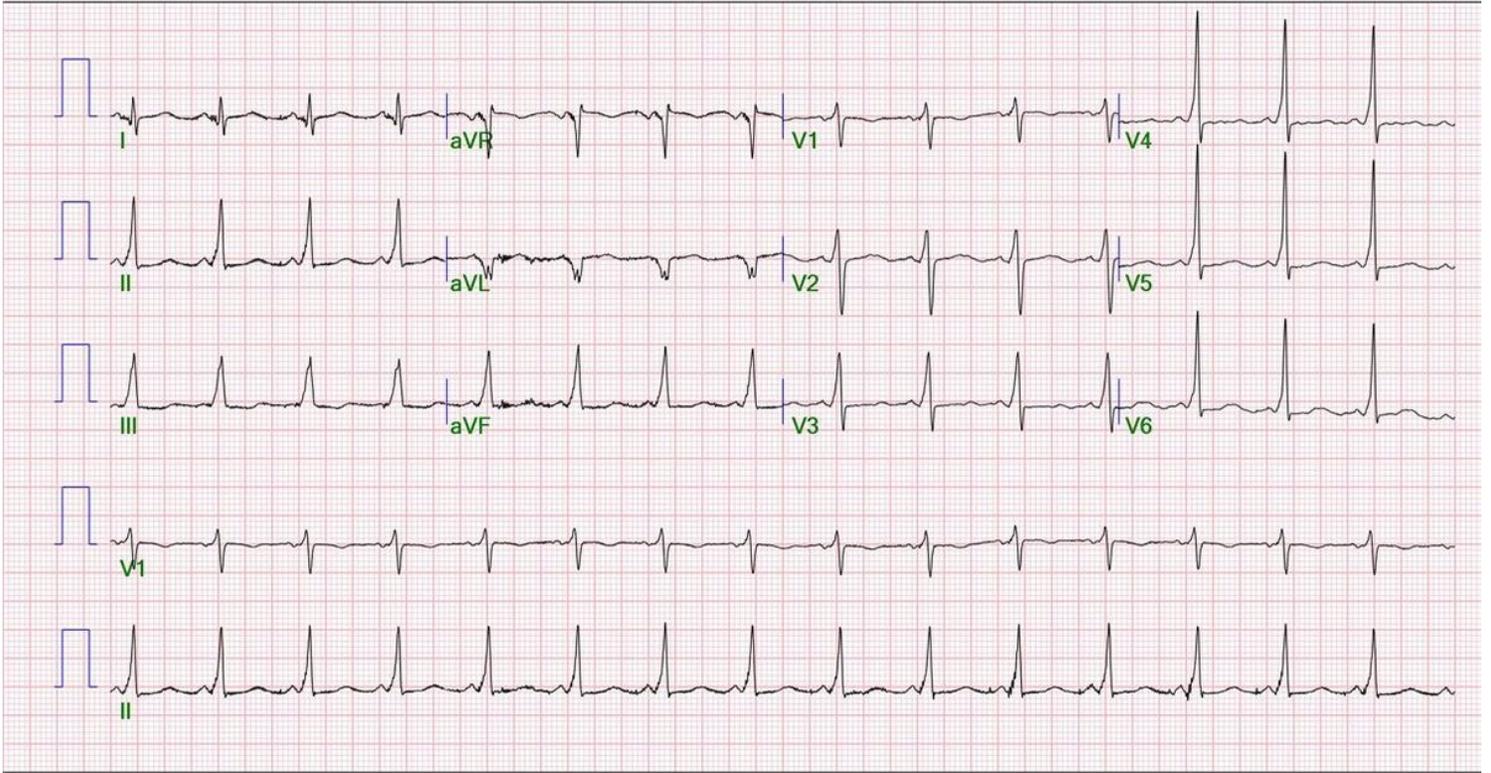


Figure 3

ECG at 24 hafter exposure, showing QTc prolongation of 524ms.

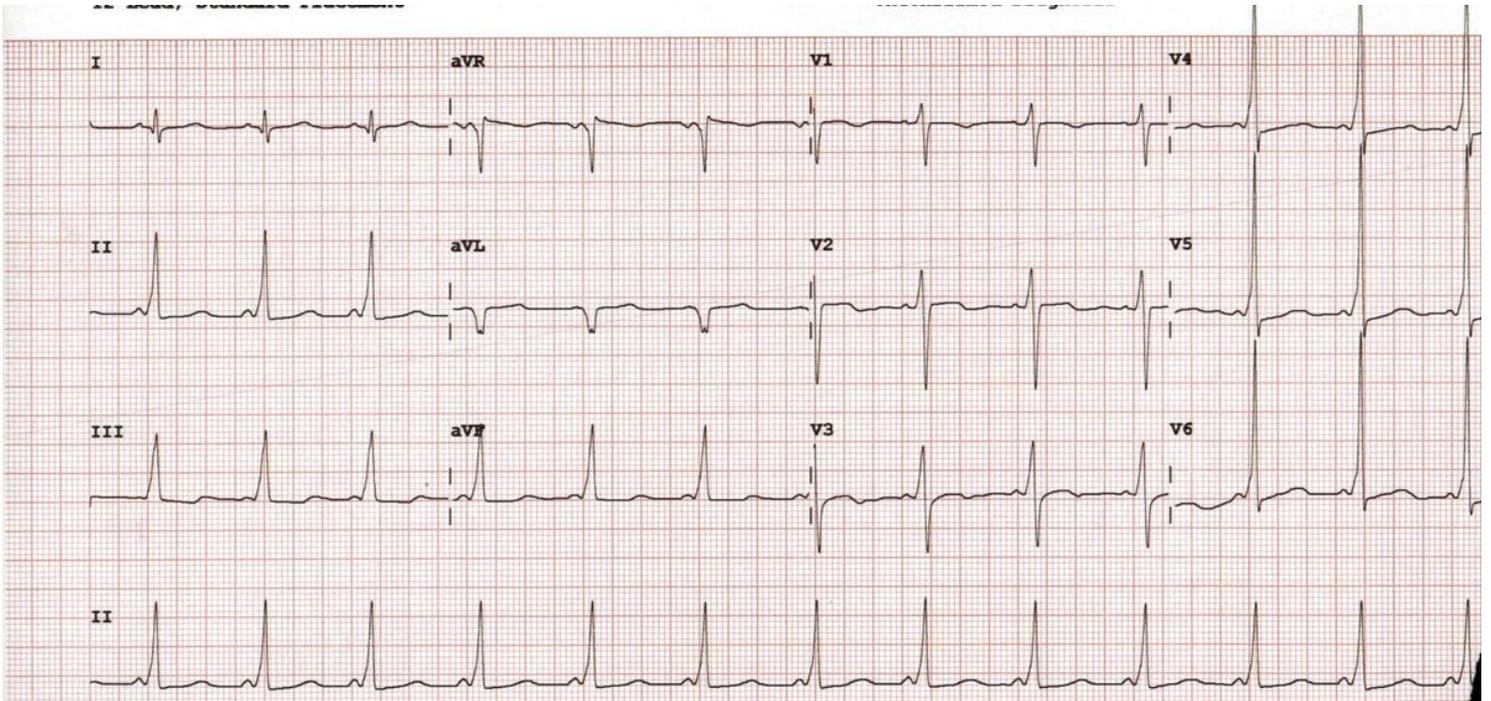


Figure 4

ECG at 36 hafter exposure, showing QTc of 485ms.

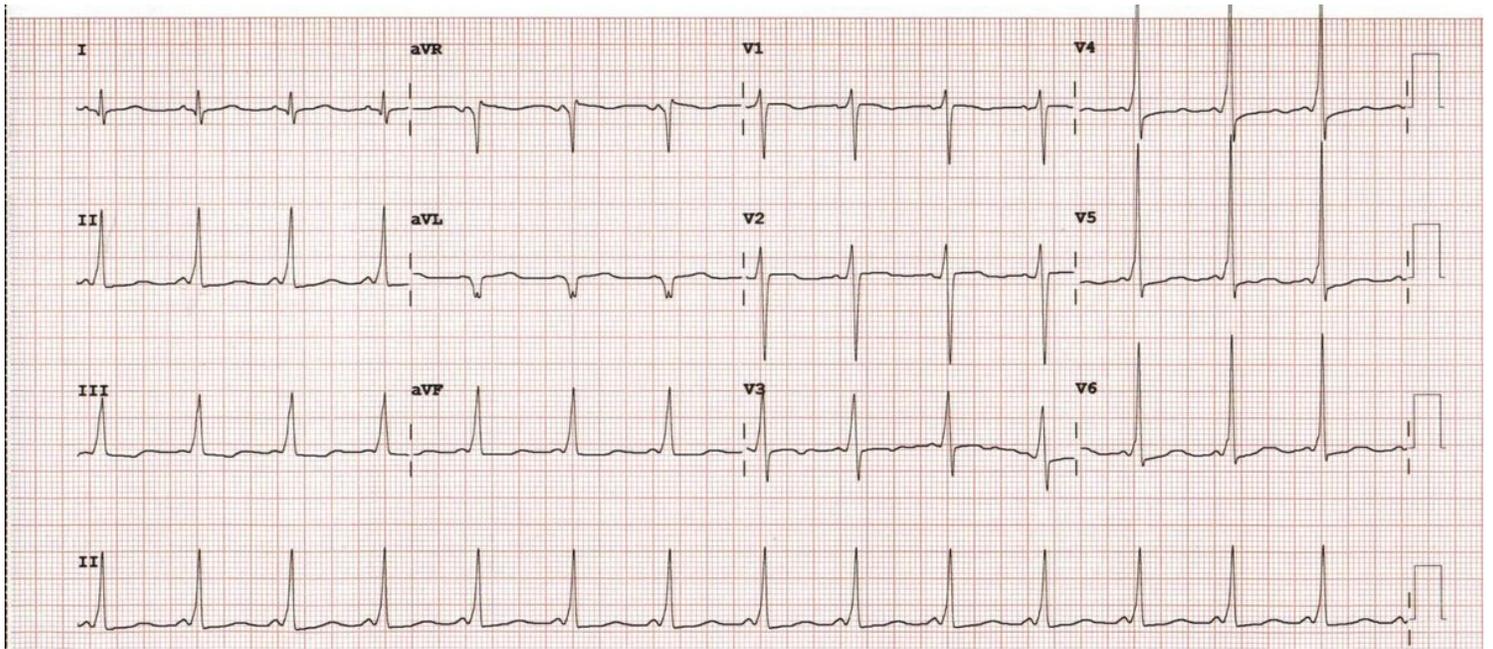


Figure 5

QT intervals and drug concentrations in blood and urine over time

Supplementary Files

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