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Case report

A possible interaction between linezolid and digoxin: A case report of therapeutic drug monitoring

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ABSTRACT

Drug-drug interactions lead to altered clinical effects, including adverse reactions. Therapeutic drug monitoring of digoxin is necessary due to its narrow therapeutic range. Linezolid can cause variable exposures in patients hospitalized in the intensive care unit owing to its possibility of drug-drug interactions. We present a patient with pneumonia and heart failure who experienced a possible drug interaction between linezolid and digoxin, resulting in high serum concentrations of both drugs. Also, the patient developed thrombocytopenia likely related to linezolid. The linezolid dose required to maintain sufficient levels had to reduce to 50% of the usual linezolid dose. A quarter dose of the standard digoxin dose was needed. Although the underlying mechanism of the drug interaction is unclear, we recommend conducting therapeutic drug monitoring when linezolid and digoxin are administered concurrently.

1. Introduction

Therapeutic drug monitoring (TDM) of digoxin is suggested because of its narrow therapeutic range. TDM is also recommended when new drugs are added that may potentially interact with digoxin, and when a patient has pathophysiological changes (e.g., deterioration in renal function, electrolyte disorders) that may increase the likelihood of digoxin toxicity. In general, patients with mild to moderate hepatic or renal impairment do not require a dosage adjustment of linezolid (Stalker and Jungbluth, 2003). Drug-drug interaction (DDI) may affect linezolid drug exposure leading to variable responses at the standard dose of linezolid. It is advisable to conduct TDM of linezolid when DDI is present (Pea et al., 2010; Töpper et al., 2016). We report a DDI case between linezolid and digoxin based on TDM. To the best of our knowledge, this case report is the first DDI between linezolid and digoxin.

2. Case

An 82-year-old man with severe pneumonia and congestive left heart failure was admitted to the respiratory intensive care unit. The body weight was 62 kg, height was 165 cm, and the body mass index (BMI) was 22.8 kg/m^2. On arrival, mental confusion, tachypnea, difficulty expectorating, widely distributed rales, and wheezes in both lungs were observed. On monitoring, his blood pressure was 138/80 mmHg, heart rate 120 beats per minute, respiratory rate 39 beats per minute, the temperature 39 °C, and peripheral oxygen saturation 70%. The patient had a normal renal function: glomerular filtration rate (GFR) (Levey et al., 2010; Wang et al., 2014) was 96.7 mL/min, and cystatin C was 1.1 mg/L. From day 1 to day 3, the patient received necessary life-support measures including respiratory support by tracheotomy and mechanical ventilation, bronchoscopic sputum aspiration, sedation and analgesia with midazolam and fentanyl, and maintenance of hemodynamic stability with norepinephrine.

Before this admission, the patient had been given empiric intravenous (IV) antimicrobial therapy with moxifloxacin (400 mg once daily) and cefoperazone/sulbactam (2 g/1g every 8 h) for 10 days. On hospital day 1, antibiotic treatment was changed to IV linezolid (600 mg every 12 h) and imipenem/cilastatin (500 mg/500 mg every 8 h) when the rapid sputum smear showed

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80% gram-positive cocci. Also, digoxin (0.25 mg once daily) taken orally was added for heart failure on day 1.

In our case, linezolid was measured by a validated high-performance liquid chromatography (HPLC) method with a Hypersil BDS C18 column (2.1 × 100 mm, 3.0 μm) and detection at 254 nm, using chloramphenicol as an internal standard. Digoxin was measured by an enzyme-linked immune-amplification with the Viva-E automatic biochemical analyzer. The methods were linear from 0.2 to 30.0 mg/L, 0.2 to 5.5 ng/mL, with a lower limit of quantification (LOQ) of 0.2 mg/L, 0.2 ng/mL in plasma for linezolid and digoxin, respectively.

On day 4, blood samples through a separate venipuncture were taken to measure of linezolid and digoxin. Linezolid and digoxin serum concentrations are presented (Fig. 1). Linezolid belongs to the left y-axis, while digoxin corresponds to the left y-axis. Linezolid serum concentrations at 3 h were 28.8 mg/L, and 30 min before the next dose was 26.9 mg/L, respectively (trough reference range, 2.0 to 6.3, Wynalda et al., 2000). The digoxin trough concentration was 2.6 ng/mL (reference range, 0.5 to 0.9, Ziff and Kotecha, 2016). GFR was calculated to be 111.1 mL/min, and cystatin C was 1.7 mg/L. C-reactive protein (CRP) declined from 59.5 mg/L to 10.5 mg/L (normal range, < 10.0) and brain natriuretic protein (BNP) declined from 1710.0 pg/mL to 863.5 pg/mL (reference range, 0 to 450.0). Platelet count fell by over 30% from 241 × 10^9/L to 164 × 10^9/L (normal range, 100 to 300).

Linezolid-related hematological toxicity is associated with higher plasma concentrations. A level above 8.0 mg/L has been shown to inhibit the synthesis of platelet precursor cells by 50%. It is a significant predictor of thrombocytopenia during treatment (Adams et al., 2016; Boak et al., 2014). Therefore, linezolid dose was reduced 50% to 600 mg once daily, and digoxin dose was also reduced by 50% to 0.125 mg once daily. On day 6, imipenem/cilastatin was changed to cefoperazone/sulbactam (2.0/1.0 g every 12 h).

On day 8 (5 days after reducing the doses of linezolid and digoxin), linezolid concentrations were found to be 8.9 mg/L (3 h) and 5.9 mg/L (30 min) before the next dose. Platelet count continued to fall to below the normal range (66 × 10^9/L). Digoxin trough concentration was reported as 1.6 ng/mL, and the dose was reduced by 50% again to 0.125 mg every two days.

On day 16 (8 days after adjustment of digoxin dose), linezolid concentrations were 5.0 mg/L (3 h) and 3.6 mg/L (30 min) before the next dose. The platelet count rose to 110 × 10^9/L, and it was back to the normal range. In contrast, the digoxin trough concentration increased to 2.3 ng/mL, while BNP continued to decline to 277.5 pg/mL.

On day 18, repeat sputum and blood cultures were negative. Both linezolid and cefoperazone/sulbactam were discontinued on the assumption that the patient's pneumonia was cured. On day 24 (6 days after the discontinuation of linezolid), the platelet count was 212 × 10^9/L, and the digoxin trough concentration was 0.8 ng/mL.

The following day, his creatinines were 32 to 55 μmmol/L, and cystatin C values were 1.6 to 2.1 mg/L. However, the patient was unable to be discharged until day 40 due to respiratory failure related to his respiratory muscle weakness.

3. Discussion

This patient experienced high trough concentrations of both linezolid and digoxin during concurrent medication administration. The trough concentrations of both agents returned to therapeutic ranges upon subsequent dose reductions, and digoxin trough concentration further declined when linezolid was discontinued.

Digoxin is a typical substrate of P-glycoprotein (P-gp), and it may serve as a probe for P-gp. The use of P-gp inhibitors or inducers with P-gp substrates can lead to significant changes in substrate concentrations (Fenner et al., 2009). Studies point to the contribution of P-gp to enhanced digoxin elimination. Quinidine is a substrate and a potent inhibitor of P-gp. The inhibition of P-gp-mediated digoxin elimination plays a vital role in the increase of plasma digoxin concentration occurring with quinidine co-administration (Fromm et al., 1999). Rifampin reduced serum digoxin concentrations substantially after concomitant administration with digoxin, which occurred primarily due to an induced intestinal P-gp expression (Greiner et al., 1999).

Linezolid is not a substrate for the cytochrome P450 enzyme and has a low propensity to alter the pharmacokinetics of other drugs. However, linezolid has a potential for pharmacodynamic interactions through reversible inhibition of monoamine oxidase

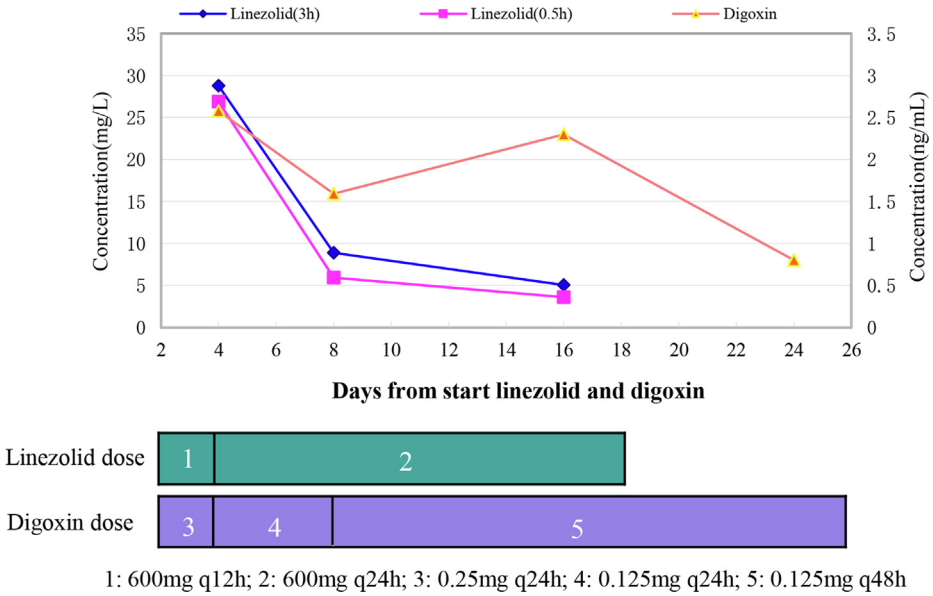

Fig. 1. Serum concentrations of linezolid and digoxin (1: 600 mg every 12 h; 2: 600 mg every one day; 3: 0.25 mg every one day; 4: 0.125 mg every one day; 5: 0.125 mg every two days).

A and B. Linezolid is not devoid of pharmacokinetic interactions, and it is susceptible to interact with other drugs via the P-gp efflux pump. Several studies have reported that rifampin, a proven P-gp inducer, reduced the serum concentration of linezolid (Egle et al., 2005; Gebhart et al., 2007). Whereas clarithromycin and amiodarone, classical P-gp inhibitors, increased linezolid concentrations (Gebhart et al., 2007; Bolhuis et al., 2010). These studies demonstrate that there may be potential drug-drug interactions between linezolid and the substrates of P-gp inhibitors or inducers.

The patient did not have any symptoms of digoxin toxicity. Although the patient had normal BMI, liver, and kidney function, pathological and physiological needed to consider the influence of pharmacokinetics. The elderly (median age of 79 [70–92] yeas, MDRD equation 62.8 [47.2–86.8] mL/min) may require linezolid dose adjustment due to high plasma concentrations (Tinelli et al., 2017), the patient's first drug level of 26.9 mg/L was twice the median drug level of 13.0 mg/L. Therefore the main reason for our patient's high trough concentration was not due to age or renal function.

On day 6 from imipenem/cilastatin to cefoperazone/sulbactam, with the consistent end of cefoperazone and linezolid use on day 18, cefoperazone/sulbactam was suspected and evaluated. Some data reported cefoperazone's ability to modulate MDR1 through competitive inhibition of the pump (Gosland et al., 1989; Petrini et al., 1993). The literature above only mentioned that the cefoperazone was a P-gp substrate *in vitro*, and we did not retrieve information on clinical effects in the drug interaction database. Although cefoperazone could not be completely ruled out, the available evidence was minimal. So was imipramine/cilastatin.

However, we observed an elevated digoxin concentration of 2.3 ng/mL on combination therapy with reduced daily doses of both agents (linezolid 600 mg and digoxin 0.125 mg once daily). The digoxin concentration was back to the normal range at 0.8 ng/mL after the discontinuation of linezolid for 6 days. This case was assessed as a probable interaction using the Drug Interaction Probability Scale (Horn et al., 2007). Although there is little information about the DDI between linezolid and digoxin in clinical practice, Medscape's drug interaction database indicates that linezolid increases the level or effect of digoxin by altering the intestinal flora.

The combined administration of linezolid and digoxin, leading to high serum concentrations of both agents, has not been reported previously. In our patient, thrombocytopenia developed after high linezolid serum concentrations were measured, and improved gradually after halving the dose. The Naranjo Adverse Drug Reaction Probability Scale was used to assess the causality between the platelet effect and linezolid. A score of 9 was obtained, indicating that a definite adverse drug reaction has occurred.

In conclusion, although the underlying mechanism of DDI is unclear, a possible interaction is observed between linezolid and digoxin requiring therapeutic drug monitoring. This report underscores the importance of TDM in managing this drug-drug interaction for a patient on concomitant digoxin and linezolid therapy.

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