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Case Report

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정상 간기능을 가진 방광암환자에서 간효소 수치를 올리는 Tosufloxacin Tosylate: 증례보고

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Tosufloxacin Tosylate Increased the Liver Enzyme Levels in a Bladder Cancer Patient with Normal Liver Functions: a Case Report

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ABSTRACT

Summary: We report the first hepatic adverse effect of tosufloxacin tosylate in a muscle invasive bladder cancer patient with normal liver functions and with scheduling to undergo a surgical operation for a neobladder. Tosufloxacin tosylate 150 mg was administered to a 57-year-old man who maintained transurethral resection of bladder tumor (TUR-BT) postoperative multiple medications. His labs presented significant increases in alanine amino transferase (ALT) and aspartate amino transferase (AST) levels with 2-week compliance of 150 mg tablet three times a day. After discontinuing tosufloxacin tosylate, the levels slowly decreased and completely returned to normal ranges without any intervention in a few weeks. The Naranjo Causality Algorithm indicates a probable relationship between increased ALT and tosufloxacin. The patient was to have the second surgical operation as scheduled after getting normal range of ATL level. Therefore, tosufloxacin should be avoided in patients at risk for having liver dysfunctions or diseases if the patients have a schedule for any operation. **Background:** Tosufloxacin tosylate has been shown to have favorable benefits as an antibiotic. Tosufloxacin tosylate may be considered to have the adverse effects such as nauseas, vomiting, diarrhea, abdominal pain, stomatitis, tendonitis, tendon rupture, headache, dizziness, drowsiness, insomnia, weakness, agitation including hemolysis in the event of glucose-6-phosphate dehydrogenase deficiency as other fluoroquinolones. More severe adverse reactions of tosufloxacin tosylate over the above common adverse effects of fluoroquinolones were thrombocytopenia and nephritis. It also is not well known that tosufloxacin can cause hepatic problem. Here the study reports the first hepatic reaction from tosufloxacin and might arouse heath care providers' attention to appropriate drug choice for patients.

KEY WORDS: ALT, AST, tosufloxacin tosylate, liver function

The quinolones exert their antibacterial effects by rapidly inhibiting DNA syntheses through the cleavage of bacterial DNA in the DNA-enzyme complexes consisting of DNA gyrase and type IV topoisomerase. This event ultimately leads to rapid bacterial death.[1)]

The most commonly used quinolones in a clinical setting are

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fluoroquinolones with a fluorine atom attached to the central ring system, typically at the C-6 or C-7 position.

Fluoroquinolones are synthetic broad-spectrum antibiotics that play a critical role in the treatment of serious bacterial infections, especially hospital-acquired infections and others that may be resistant to older antibacterial classes. They are effective against both gram-positive and gram-negative bacteria by inhibiting DNA type IV topoisomerase and preventing DNA gyrase.[2)]

These are generally well tolerated due to contributing to mild to moderate adverse reactions.[3,4)] Their well-known adverse events include gastrointestinal problems, such as nausea, vomiting and diarrhea, as well as headache and insomnia.

Tosufloxacin is the third-generation quinolone with a bacterial activity specifically against streptococci; however, it has a dispute with its safety profile compared to other fluoroquinolones.[5,6)]

In this study, tosufloxacin gradually increased ALT and AST levels in a Korean male patient who had recently experienced TUR-BT for a bladder cancer without any detectable errors in laboratory tests.

CASE REPORT

A 57-year-old Korean male underwent cystoscopy TUR-BT under general anesthesia. His bladder was evaluated, and resection was performed with an electrocutting loop. He had no other comorbid diseases until the discovery of muscle invasive bladder malignancy.

He had smoked with 1 or 2 cigarettes a day for 20 years before 45 years old. He had also drunk 2 cups of coffee and 2 cans of beer a day before his tumor was found. He was 169 cm tall and weighed 70 kg. He was not allergic to any medications.

At the time of the hospital admission for TUR-BT, he did not have any problems of gastrointestinal, hepatic, renal, nervous, and endocrine systems as well as weight alteration. He also did not feel any fatigue. His mental status was alert, skin was warm, and respiratory efforts were normal. His vital signs included a blood pressure of 120/73 mmHg, pulse rate of 66 beats per minute, respiratory rate of 20 breaths per minute, body temperature 36.5°C and pulse oxygen saturation (SpO_2) of 97%. His laboratory data were Ca 8.5 mg/dL, inorganic Phos 3.3 mg/dL, fasting blood glucose 111 mg/dL, BUN 22 mg/dL, serum creatinine 1.08 mg/dL, uric acid 3.8 mg/dL, total cholesterol 154 mg/dL, total protein 6.4 g/dL, alkaline phosphate 43 IU/L, ALT 17 IU/L, AST 18 IU/L, Na 140 mmol/L, K 4.3 mmol/L, Cl 106 mmol/L and $PaCO_2$ 25 mmol/L.

His medications for hospitalization were normal saline, N-l-alanyl-L-glutamine 20000 mg/100mL, zinc sulfate, pancreatin enteric coated (EC) microtablet 457.7 mg capsule, aceclofenac

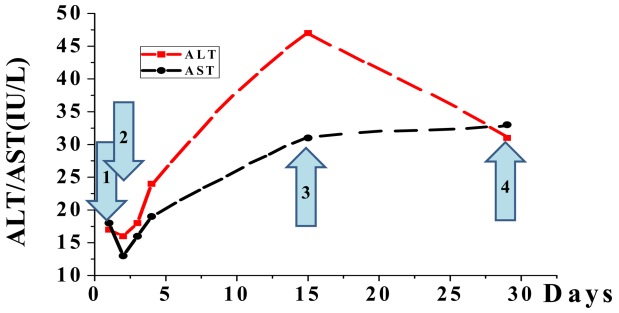

Fig. 1. The change of ALT/AST on administration of tosufloxacin. 1: The first operation date for TURBT, 2: The starting date of tosufloxacin, 3: The stopping date of tosufloxacin, 4: The second operation date for a neobladder.
ALT (alanine aminotransferase); AST (aspartate aminotransferase).

100 mg/tablet, lactitol powder 20000 mg/pack, ultracet (acetaminophen 650 mg/tramadol hydrochloride 75 mg) extended release (ER) tablet, rebamipide 100 mg/tablet. He received pancreatin EC microtablet 457.7 mg capsule three times per day (TID) after meals (PC), rebamipide 100 mg tablet, lactitol 1000 mg power TID PC, aceclofenac 100 mg tablet TID PC as need (PRN), tosufloxacin tosylate 150 mg tablet TID PC and ultracet ER tablet TID PC PRN on the discharge day after TUR-BT.

When he revisited the hospital after 2 weeks, his ALT level was increased by 47 IU/L, three folds from baseline (Fig. 1) and AST level was slightly increased. He had completed pancreatin EC, rebamipide and tosufloxacin doses at that time. He had also taken ultracet ER during the first two days after hospital discharge. He did not complain of any signs or symptoms except for fatigue and loss of appetite. He discontinued all medications on the day of the revisit because he rescheduled to take the second operation for a neobladder.

His ALT levels were found to have decreased after stopping tosufloxacin, 30 days post-operatively (Fig. 1). Then, he was going to have a surgical operation for neobladder as scheduled after ALT levels decreased to the normal range (0~40 IU/L).

DISCUSSION

This is the first case showing the buildup of ALT and AST upon completion of 14-day-course of tosufloxacin tosylate in a Korean male. This case suggests that the adverse effect of tosufloxacin may be caused by some predisposing factors such as the concomitant use of ultracet ER®. The patient had been administered with tosufloxacin for 14 days and ultracet ER® for the first five days.

Ultracet ER® consists of acetaminophen 650 mg and tramadol 75 mg. Although acetaminophen frequently causes hepatotoxicity, total daily dose (1950 mg) of acetaminophen for five days

may rarely have a negative effect on the liver in patients with normal hepatic functions because its half-life is only 1-4 hours after oral administration[7)]

Tramadol, a centrally acting opioid analgesic, is a serotonin releaser, norepinephrine reuptake inhibitor, and weak μ-opioid receptor agonist.[8,9)] It undergoes hepatic metabolism via the cytochrome P450 isozymes such as CYP2B6, CYP2D6, and CYP3A4. It induces hepatic problems in only very rare cases with accountability. Therefore, neither acetaminophen nor tramadol is likely to be responsible for the increased levels of ALT and AST. In addition, any studies have not been reported that the concomitant use of ultracet ER® and tosufloxacin negatively affect levels of ALT and AST.

Tosufloxacin belongs to the class of quinolones that have a safety profile and tolerability similar to those of other antimicrobial classes.[3,4)] Although adverse events of quinolones are uncommon, some reactions, such as tendinitis and CNS-related side effects, are more common than those of other antimicrobial classes.[2)] Adverse drug reactions such as torsades de pointes, glycemias and hepatotoxicity are rarely described for some of the floroquinolones.[3)] However, hepatotoxicity was reported for trovafloxacin, one of the floroquinolones.[6)]

Tosufloxacin caused severe thrombocytopenia, nephritis and eosinophilic pneumonitis.[3,6)] A total adverse drug reaction (ADR) rate of 3.6% was found for tosufloxacin, compared to total ADR rates of 1.3% for levofloxacin and 4.5% for gatifloxacin according to a five-year-post marketing surveillance study in Japan.[6)] However, tosufloxacin associated hepatotoxicity was not reported yet.

The patient had been administered with tosufloxacin alone for nine days after its concomitant use with ultracet ER®. Thus, tosufloxacin is likely to have exerted a strong influence on the increased ALT and AST in the patient.

In this patient, the hepatoxicity of tosufloxacin was presented through an increased level of ALT. The Naranjo scale indicates that a probable relationship exists between the increased ALT and tosufloxacin. Because the concept that tosufloxacin might cause ALT/AST elevations is not well known, it is weighty to be alert of medication choice. Careful monitoring of the liver also is needed for patients taking tosufloxacin, regardless of their hepatic conditions if particularly they make a reservation for any surgery. Further studies are necessary to identify the adverse drug reactions of tosufloxacin in the liver.

IRB: The study was approved by the Institutional Review Board (IRB) at Gyeongsang National University (GIRB-A14-Y-0033) and it was processed with the written informed consent by the patient.

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