Flupirtine-induced Hepatic Failure Requiring Orthotopic Liver Transplant

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Abstract
We present the case of a 48-year-old otherwise healthy man who required an urgent liver transplant owing to acute liver failure after flupirtine treatment. After 3 months of daily flupirtine intake as treatment for pseudoradicular pain syndrome, he presented at our institution with signs of jaundice and hepatic encephalopathy. Laboratory results showed elevated liver transaminases, and the liver histopathology supported the assumed drug-induced liver injury. After listing him for an urgent liver transplant, he was given a liver graft from a 21-year-old man. Despite a rejection episode on day 11 after the surgery (which was successfully treated by steroid pulse therapy), the postoperative course was uneventful and the patient recovered completely. To the best of our knowledge, this is the first report of a liver transplant for acute liver failure after taking flupirtine.

Key words: Hepatotoxicity, Katadolon, Acute liver failure

Introduction
Flupirtine is a nonopioid analgesic that acts on the central nervous system and belongs to the pharmacologic group of selective neuronal potassium channel openers. It activates G-protein-coupled K⁺ channels, and leads to selective opening of voltage-independent K⁺ channels. The resulting outflow of K⁺ causes the resting membrane potential to stabilize, leading to reduced excitability of the nerve cell membrane. Flupirtine causes functional N-methyl-D-aspartate receptor antagonism by protecting against the inflow of Ca²⁺.¹ Thus, flupirtine is approved for treatment of acute and chronic pain such as increased muscle-tone of the postural and motor muscles, tension headaches, tumor pain, or pain after traumatic/orthopedic operations and injuries.² Varying degrees of additive hepatotoxic effects based on pre-existing liver damage have been reported. Therefore, flupirtine should not be prescribed in patients with pre-existing liver damage and/or alcohol abuse.³ To the best of our knowledge, this is the first report of flupirtine-induced hepatic failure in a patient without pre-existing liver damage or potential risk factors requiring an orthotopic liver transplant.

Case Report
We present the case of a 48-year-old otherwise healthy man who presented at an orthopedic institute with symptoms of pseudoradicular pain. Besides conservative, functional therapy, a single medication with flupirtine 400 mg at night as a continuous therapy was begun. After 3 months of daily flupirtine, the patient presented at our clinic with jaundice and hepatic encephalopathy (grade 2) according to West Haven criteria. There were no indices for a neurologic or cardiac cause of the symptoms. The laboratory results revealed elevated liver transaminases (aspartate aminotransferase, 34.82 µkat/L; alanine aminotransferase, 48.38 µkat/L; serum-bilirubin, 555.07 µmol/L; NH₃, 172 µmol/L;
prothrombin time, (52/sec); and international prothrombin time (52/sec) normalized ratio INR (22%). There were no known diseases or signs of substance abuse in the patient’s history. A computed tomography scan and abdominal ultrasound showed no diseased findings. The hepatitis serology and screening for autoimmune or infectious diseases were negative.

Within the next 24 hours, the patient became comatose and was intubated owing to aggravated encephalopathy; he came out of the coma on the third postoperative day. Possible causes for acute liver failure were excluded, and drug-induced liver failure was suspected. The flupirtine medication was stopped. This improved his liver test results in the laboratory (aspartate aminotransferase, 16.59 µkat/L; alanine aminotransferase, 33.62 µkat/L; serum-bilirubin, 596.79 µmol/L). The patient did not undergo hemofiltration or plasmapheresis, but adjunctive therapy with ornithine aspartate was begun. Within 3 days, the patient progressed to irreversible acute liver failure. Thus, with no contraindications, the patient was listed for an urgent liver transplant.

The patient underwent an uneventful orthotopic liver transplant and received a liver graft from a 21-year-old man. The preservation injury was severe, as indicated by postoperative values for aspartate aminotransferase, 21.69 µkat/L, and alanine aminotransferase, 12.69 µkat/L. Standard immunosuppressive therapy with tacrolimus and steroids was begun. Gross examination of the native liver explant showed acute, panlobular, confluent liver cell necrosis, with high-grade liver cell damage, surrounded by a lymphocytic tissue reaction (Figures 1 and 2). These findings were consistent with a toxic medical cause for his liver failure.

The patient recovered completely. Preoperative dominating encephalopathy showed constant regression. An NH₃ level measured on the eighth postoperative day was normal (32 µmol/L). The patient was discharged 29 days after surgery. One year after the transplant, he presented with good liver graft function, and the results of his laboratory tests were within the normal ranges.

Discussion

Drug-induced liver damage is the second main cause of acute liver failure worldwide. In the United States and the United Kingdom, acetaminophen is the most-common cause of drug-induced liver failure, with increasing incidence. In other regions, antituberculous drugs or antibiotics are the leading causes for drug-induced liver injury. A search of a case safety report database (Vigibase) revealed 385 individual drugs associated with hepatotoxicity. A total of 83.1% of these listed drugs are associated with at least 1 report of acute liver failure.5

To the best of our knowledge, we report the first case of acute flupirtine-induced liver failure requiring orthotopic liver transplant. Besides the patient’s history (which revealed no signs of prior liver damage or predisposing diseases and risk factors for potential liver failure), the association of flupirtine intake as a cause of liver failure is underscored by the histopathologic findings and discrete improvement of the patient’s liver parameters after the medication was stopped. According to pharmacologic guidelines, an elevation of liver transaminases is listed as a rare adverse effect after flupirtine intake (1 out of 10 000 cases).2
In 2007, liver damage induced by flupirtine was reported by the Drug Commission of the German Medical Association. A 65-year-old woman had taken flupirtine 100 mg/day for 3 months owing to chronic pain. The alanine aminotransferase level was 7 times normal, the aspartate aminotransferase level was 5 times normal. Viral, autoimmune, metabolic and posthepatic pathologies were excluded. A histologic examination of a liver biopsy showed active chronic hepatitis in distinct fibrosis. Although the results of the woman’s liver values were normal 6 months earlier, it was assumed that the actual liver damage was attributed to an additive hepatotoxic effect of flupirtine and chronic liver damage. After the medication was discontinued, her liver values resumed normal levels. Re-exposure of the patient to flupirtine by self-medication led to immediate re-elevation of the liver values. The Drug Commission of the German Medical Association’s detection system showed 449 cases of unwanted adverse effects after flupirtine intake. Of these, 151 (33.6%) were associated with liver damage. Seventy cases of hepatitis are listed after flupirtine intake. Liver failure was reported in 7 cases. Four deaths due directly to flupirtine intake have been documented. Other adverse effects listed include nausea (72 cases) and dizziness (47 cases). Prescribing flupirtine to patients with a pre-existing liver disease or chronic alcohol abuse is contraindicated. In a study in which 20 patients with pre-existing liver damage were treated with 400 mg flupirtine daily, 6 patients developed signs of encephalopathy.

A potential hepatotoxic effect of flupirtine intake in patients with normal liver function might be underestimated. Another case of a 49-year-old man treated with diclofenac and flupirtine has been reported. Four months after starting treatment, he presented with jaundice and a progressive rise in his transaminase levels. Owing to his history as well as laboratory and histologic findings, diclofenac-induced hepatitis was assumed. Drug treatment was discontinued, and without any other treatment, all laboratory values returned to normal within 9 weeks.

A possible correlation of simultaneous use of flupirtine was not considered. This case suggests possibly more cases of acute liver failure from flupirtine. Nevertheless, the pathogenesis remains unclear. A genetic predisposition to drug-induced liver failure is discussed and might also play an important role in flupirtine-associated liver damage. An increased incidence of drug-induced liver failure has been seen with glutathione-S-transferase and manganese superoxide dismutase gene polymorphisms. In general, the outcome after acute drug-induced liver failure has been improved by using an emergency liver transplant (with a 1-year survival exceeding 80%).

Clinicians should be aware of potential hepatotoxicity with flupirtine treatment in adults with no underlying liver damage. Liver functions should be monitored carefully. If elevated serum liver enzymes are seen, flupirtine therapy should be discontinued immediately; otherwise, acute liver failure may result.

References

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