Fulminant hepatic failure after intravenous injection of sublingual buprenorphine in a patient with hepatitis C

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Key Clinical Message
A 20-year-old indigenous Australian male was admitted to the intensive care unit with fulminant hepatic failure secondary to intravenous use of buprenorphine, which had been prescribed sublingually for opioid dependence. Intravenous buprenorphine-induced hepatitis is well recognized, however, life-threatening fulminant hepatic failure has not previously been reported.

Keywords
Buprenorphine, hepatitis C, liver failure, opioid dependence.

Introduction
A 20-year-old incarcerated indigenous Australian male, with a history of hepatitis C and intravenous drug abuse, was admitted to the intensive care unit with fulminant hepatic failure following a 5-day history of jaundice, nausea, and vomiting. The patient was opioid dependent but had been previously well with no relevant medical history. He had been prescribed sublingual buprenorphine in an effort to control his opioid dependence. He was not taking any other medications. He was noncirrhotic and treatment naïve for HCV. He was also HIV negative.

Investigations at the time of presentation revealed a severe acute hepatitis with marked synthetic dysfunction. The serum alanine aminotransferase (ALT) was 8768 U/L, bilirubin was 234 μmol/L, albumin was 31 g/L and the international normalized ratio (INR) was 9.0. His arterial lactate was 5.6 mmol/L, pH was 7.5 and serum ammonia was 132 μmol/L.

Viral serology revealed positive hepatitis C virus (HCV) antibodies and evidence of immunity to hepatitis B virus. HCV infection was confirmed with detectable HCV RNA. No other peripheral blood viral or autoimmune markers were found. Ultrasonography revealed patent hepatic vasculature without biliary abnormality.

History revealed recent intravenous use of prescribed sublingual buprenorphine. Corroborative history from prison medical staff revealed that the patient had thrice injected buprenorphine 1 day prior to the onset of his symptoms. He was known to share injecting paraphernalia with other inmates.

The patient developed life-threatening multiorgan failure as a consequence of the fulminant hepatic failure and met listing criteria for liver transplantation. The patient was managed as per the American Association for the Study of Liver Diseases acute liver failure guidelines [1]. He was commenced on broad-spectrum antibiotics, antifungal prophylaxis, an n-acetyl-cysteine infusion and continuous veno-venous hemofiltration. He required vasopressor support for the majority of his intensive care stay.

The patient survived with supportive intensive care management and was discharged from hospital after 42 days. Upon discharge, his liver function was improving with an ALT of 278 U/L, INR of 1.2, albumin of 24 g/L and serum bilirubin of 367 μmol/L, having peaked at 450 μmol/L.

Buprenorphine is a potent semisynthetic opioid derivative that is prescribed for the treatment of opioid dependence or for analgesic purposes. Buprenorphine acts as a
partial μ-opioid receptor agonist and a κ-opioid receptor antagonist. It undergoes extensive first pass hepatic metabolism utilizing the P450 (CYP 3A4) system [2]. Acute liver injury from the misuse of sublingual buprenorphine has been described in several case reports and case series. Almost all cases of significant hepatocellular injury have been associated with hepatitis C viremia [3–7]. It has been postulated that HCV induces mitochondrial toxicity, leading to more significant liver damage. Clearance of HCV has also been described following acute buprenorphine-induced hepatotoxicity [4].

The spectrum of hepatotoxicity following therapeutic administration, misuse or overdose of buprenorphine ranges from a mild-to-severe hepatitis. The majority of reported cases of intravenous buprenorphine-associated liver damage have been in the context of known or recently detected hepatitis C infection. Although intravenous buprenorphine-induced hepatitis is now well recognized, life-threatening fulminant hepatic failure due to this drug has not previously been reported.

Acute liver injury from intravenous buprenorphine use has been primarily attributed due to the high parenteral doses obtained from crushed sublingual tablets. The mechanism of toxicity is due to inhibition of mitochondrial respiration and fatty acid-b oxidation, leading to ATP depletion and hepatocyte necrosis, in rat models [2]. Most patients who have restarted conventional sublingual doses following an episode of toxicity have not had recurrent liver injury [3, 5].

The prevalence of hepatitis C virus (HCV) infections is high among opioid-dependent individuals. Hence drug interactions need to be undertaken when prescribing the newer classes of protease inhibitors; Simeprevir, Telaprevir, and Boceprevir that are metabolized via the P450 system.

In addition, the effect of alcohol on the liver contributes to the altered metabolism of buprenorphine via the CYP3A4 enzyme [8]. The additive CNS respiratory depressant effects of this combination have been fatal in overdose [9].

The possibility of intravenous misuse and drug interactions should not prevent clinicians from considering sublingual buprenorphine as a maintenance treatment for heroin addiction. However, caution should be applied in patients with chronic HCV infection and who are at risk of intravenous misuse.

Conflict of Interest
None declared.

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