Case Report

Hepatitis after intravenous buprenorphine misuse in heroin addicts

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See Editorial, pages 334–336

Background: Sublingual buprenorphine is used as a substitution drug in heroin addicts. Although buprenorphine inhibits mitochondrial function at high concentrations in experimental animals, these effects should not occur after therapeutic sublingual doses, which give very low plasma concentrations.

Case reports: We report four cases of former heroin addicts infected with hepatitis C virus and placed on substitution therapy with buprenorphine. These patients exhibited a marked increase in serum alanine amino transferase (30-, 37-, 13- and 50-times the upper limit of normal, respectively) after injecting buprenorphine intravenously and three of them also became jaundiced. Interruption of buprenorphine injections was associated with prompt recovery, even though two of these patients continued buprenorphine by the sublingual route. A fifth patient carrying the hepatitis C and human immunodeficiency viruses, developed jaundice and asterixis with panlobular liver necrosis and microvesicular steatosis after using sublingual buprenorphine and small doses of paracetamol and aspirin.

Conclusions: Although buprenorphine hepatitis is most uncommon even after intravenous misuse, addicts placed on buprenorphine substitution should be repeatedly warned not to use it intravenously. Higher drug concentrations could trigger hepatitis in a few intravenous users, possibly those whose mitochondrial function is already impaired by viral infections and other factors.

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1. Introduction

Buprenorphine is a morphine/thebaine analogue with agonist/antagonist effects on morphine receptors [1]. This drug is used both as an antaligic agent in patients with chronic pain, and a substitution drug in heroin addicts [2]. The sublingual route is used to partly circumvent its low bioavailability due to extensive (90%) first pass metabolism during each pass through the liver [3,4].

Thanks to a milder initial effect and much longer duration of action than heroin, buprenorphine avoids the alternating periods of brief euphoria and severe withdrawal syndrome that characterize heroin addiction. Substituting sublingual buprenorphine for intravenous heroin has major advantages.

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observed in some heroin addicts during sublingual buprenorphine administration in clinical trials [7], and liver test abnormalities have also been reported in a non-addict patient given antalgic doses (0.8 mg daily) of buprenorphine for 3 months [8]. In this patient, liver tests promptly improved after buprenorphine withdrawal, but relapsed after a short rechallenge, with the liver biopsy then showing both steatosis and an inflammatory cell infiltrate without eosinophils [8].

In contrast, buprenorphine may be frankly toxic when used in large overdoses. Severe acute hepatitis and renal failure (without immune-mediated manifestations) has been reported 48 h after a massive oral overdose (112 mg of buprenorphine) in a patient who had been safely using 8 mg daily buprenorphine for the previous 22 months [9]. Another circumstance which might cause high systemic buprenorphine concentrations is intravenous use. Some heroin addicts misuse buprenorphine and inject it intravenously. Peak plasma buprenorphine concentrations are 80-times higher after an intravenous dose than after sublingual administration in rats [10].

We have observed four patients with severe hepatitis after intravenous misuse of buprenorphine. A fifth patient, who denied injecting buprenorphine intravenously, developed severe panlobular necrosis and microvesicular steatosis after using small doses of paracetamol and aspirin in addition to his sublingual buprenorphine treatment.

2. Case reports

2.1. Case 1

This 33-year-old man had a stable alcohol consumption of about 120 g daily and had been using heroin intravenously from 1993 to 1995. Since 1994 he had been treated with fluoxetine (40 mg daily), sulpiride (50 mg daily) and clonazepam (5 mg daily). An anti-HCV antibody was detected in December 1995.

Since the end of 1995, he had been taking sublingual buprenorphine (8 mg daily), but also occasionally injected it intravenously, sometimes twice a day. At the beginning of February 1996, he experienced asthenia and became jaundiced. On February 7, 1996, ALT was 1100 (N < 44), AST 770 (N < 44), alkaline phosphatase 235 (N < 30), and gammaplagutamyltransferase (GGT) at 334 (N < 50). The anti-HCV antibody was positive.

He stopped injecting buprenorphine on March 1, 1996, while continuing sublingual buprenorphine, other medications and his usual alcohol consumption. He felt better and jaundice disappeared within 1 week. On his first visit to the hospital, on March 7, 1996, no clinical abnormalities were found and liver tests had already markedly improved. Serum ALT was 180 (N < 40), AST 65 (N < 40), GGT 133 (N < 40), alkaline phosphatase 96 (N < 130) and total bilirubin 20 µmol/l. Serum prothrombin level was normal. Anti-HCV antibodies were present, but serum HCV RNA was negative by polymerase chain reaction (PCR). Antigen hepatitis B serum (HBS) and anti-HBc antibodies were absent, while anti-HBS antibodies were present. Anti-Hepatitis A virus (HAV) IgM antibodies and anti-HIV1/2 antibodies were absent. Anti-smooth muscle, anti-nuclear, anti-endoplasmic reticulum and antimitochoendrial antibodies were absent. Serum iron and ceruloplasmin were normal. The hemogram was normal. Abdominal ultrasonography was normal. Sulpiride was discontinued on March 8, 1996, while the other treatments were continued. On March 12, 1996, ALT was 64 (N < 44). On May 9, 1996 ALT was 25 (N < 44), AST 29 (N < 34), GGT 61 (N < 50).

The patient consulted again 1 year later, on March 6, 1997. He was still taking sublingual buprenorphine but no longer injected it. ALT was 157 (N < 40). HCV RNA (Amplicor Roche) was positive. A liver biopsy was performed on May 27, 1997 and showed chronic hepatitis of moderate activity with moderate portal and periportal fibrosis. In October 1997, buprenorphine was replaced by methadone. The patient was last seen on June 30, 1999. He was still taking methadone (10 mg daily). ALT was 66 (N < 40).

2.2. Case 2

This 27-year-old man was seen in our department for chronic hepatitis C, after a period of intravenous heroin use from 1987 to 1993. He was treated with interferon-α from September 1994 to March 1995, with a total dosage of 216 million units, but did not respond to treatment. On November 7, 1996, ALT was 69 (N < 30) and AST 49 (N < 27).

He did not consume alcohol, but had been taking bromazepam (12 mg daily) and loprazolam (1 mg daily) since 1992. From mid-November 1996 to December 10, 1996, the patient injected buprenorphine intravenously (8 mg each day), without consuming alcohol. On December 10, 1996, ALT was 1100 (N < 30), AST 620 (N < 27), GGT 257 (N < 40), alkaline phosphatase 235 (N < 130), and total bilirubin 13 µmol/l. Serum prothrombin was normal. The hemogram was normal. AgHBS and anti-HBc IgM were negative. Anti-HBS and anti-HCV antibodies were present. IgM anti-HAV antibodies and anti-HIV antibodies were absent. Antinuclear, anti-mitochondrial, anti-smooth muscle and anti-liver kidney microsomes type 1 (LKM1) antibodies were undetectable. Ceruloplasmin and serum iron were normal.

He stopped injecting buprenorphine and took it by the sublingual route, while continuing bromazepam and loprazolam at the same dosage. On February 1, 1997, ALT was 229 (N < 30) and AST 98 (N < 27). On November 5, 1997, ALT 97 (N < 30) and AST 46 (N < 30).
2.3. Case 3

This 28-year-old male heroin addict was hospitalized for jaundice on January 26, 1998. Thyroidectomy had been performed for Basedow disease in 1996 and he had been taking levothyroxine (175 \( \mu g \) daily) ever since. He had intermittent periods of alcohol abuse and also took several benzodiazepines (lorazepam, clorazepate, and bromazepam). He was known to carry the HBS antigen and to have chronic viral hepatitis C. Since July 1997, he had been taking sublingual buprenorphine (16 mg daily). From November 1997 to January 25, 1998, he injected buprenorphine intravenously, 8 mg in the morning and 8 mg in the evening. He was increasingly asthenic and became jaundiced on January 20, 1997. On January 26, ALT was 520 \( (N < 40) \), AST 440 \( (N < 40) \), GGT 169 \( (N < 40) \), conjugated bilirubin, 176 \( \mu mol/l \). HBS antigen was positive but anti-Hbe antibodies were absent and serum HBV DNA was negative by PCR. Antigen delta and anti-delta antibodies were negative. Anti-HCV antibodies were positive. There was no anti-HIV or anti-cytomegalovirus (CMV) antibodies and no Epstein–Barr virus (EBV) IgM antibodies. Ceruloplasmin and serum copper were normal. Ultrasonography showed slight hepatosplenomegaly.

Buprenorphine was discontinued and there was clinical and biological improvement. On February 7, 1998 ALT was 375 \( (N < 40) \), AST 360 \( (N < 40) \), GGT 189 \( (N < 40) \), and bilirubin 46 \( \mu mol/l \). A liver biopsy on February 13, 1998 showed normal liver architecture without fibrosis. Foci of necrosis were observed in the whole hepatic lobule with an inflammatory cell infiltrate. Limiting plates showed piecemeal necrosis and there was a slight inflammatory infiltrate in the portal space.

2.4. Case 4

This 31-year-old male patient was admitted on April 16, 1998 for acute hepatitis. He was a former heroin addict, consumed alcohol occasionally, and had been taking valproamide (300 mg daily) and meprobamate (800 mg daily) for the last 3 years. During the first 2 weeks of April, 1998, he had injected buprenorphine intravenously (8 mg each day). He became jaundiced, and asthenic, with no other clinical abnormalities. On April 14, 1998, ALT was 1980 \( (N < 40) \) and AST 665 \( (N < 40) \). On April 16, 1998, ALT was 1960 \( (N < 40) \), AST 724 \( (N < 40) \), GGT 521 \( (N < 40) \), alkaline phosphatase 200 \( (N < 130) \), total bilirubin 55 \( \mu mol/l \), prothrombin level 89% of normal. Anti-HCV antibodies and HCV RNA were positive. HBS antigen was absent, with positive anti-HBS and anti-HBc antibodies. Anti-HAV IgM antibodies were negative. Anti-HIV and anti-HTLV antibodies were negative. The hemogram was normal. Ultrasonography was normal.

Liver tests quickly improved after buprenorphine discontinuation, while valpromide and meprobamate were continued. On April 24, 1998, ALT was 352 \( (N < 40) \), AST 74 \( (N < 40) \), GGT 255 \( (N < 40) \), alkaline phosphatase 106 \( (N < 130) \), total bilirubin 29 \( \mu mol/l \). On May 13, ALT was 66 \( (N < 40) \), AST 29 \( (N < 40) \), GGT 89 \( (N < 40) \), alkaline phosphatase 168 \( (N < 130) \), total bilirubin 15 \( \mu mol/l \). A liver biopsy performed at this late stage showed chronic hepatitis of moderate activity. A recent acute hepatitis episode was suspected from the presence of microgranulomatous inflammatory foci surrounding necrotic hepatocytes in the liver lobule and the polymorphic portal cell infiltrate with mononuclear cells, macrophages and polymorphonuclear cells, with rare eosinophils. Liver tests were normal on July 28, 1998 and February 2, 1999.

2.5. Case 5

This 34-year-old male patient had stopped taking heroin in 1997. Seropositivity for HIV was detected in 1991 and for HCV in 1995. On March 5, 1998, he was apyretic, but asthenic and jaundiced. He exhibited asterixis and was hospitalized. For several months, he had been using flunitrazepam (4 mg daily) and sublingual buprenorphine (16 mg daily). He denied having used buprenorphine intravenously. He had also taken small doses of paracetamol and asparin over the three preceding days (a total of 5 and 2 g, respectively over this whole period). ALT was 6595 \( (N < 40) \), AST 2831 \( (N < 40) \), GGT 168 \( (N < 40) \), alkaline phosphatase 306 \( (N < 130) \), total serum bilirubin, 192 \( \mu mol/l \). Plasma prothrombin factor V levels were 22 and 34% of normal, respectively. Blood urea was 32.1 mmol/l and plasma creatinine 699 \( \mu mol/l \). The hemogram was normal. Ultrasonography was normal. HBS antigen and Anti-HBc IgM were absent, while anti-HBS antibodies were present. Anti-HCV antibodies and HCV RNA (Amplicor, Roche) were positive. HIV RNA was present at 440 copies/ml (Monitor, Roche). CD4 counts were 280/mm\(^3\), with a CD4/CD8 ratio of 0.4. Anti-CMV IgM, anti-EBV IgM, anti-Herpes IgG, anti-human herpes virus 6 (HHV6) IgG, anti-human T-cell leukemia virus (HTLV), anti-delta, anti-parvovirus B19 IgM, anti-‐Hantaan virus IgG were negative. Hemocultures and serodiagnostic tests for leptospirosis were negative. CMV viremia was absent. Anti-nuclear, anti-mitochondrial, anti-smooth muscle, and LKM1 autoantibodies were absent. Serum copper and ceruloplasmin were normal. An electroencephalogram, on March 6, 1998 suggested incipient hepatic encephalopathy. A transjugular liver biopsy was also performed on March 6, 1998 and showed panlobular necrosis, microvesicular steatosis and a mononuclear cell inflammatory infiltrate (Fig. 1). The microvesicular steatosis was confirmed by an Oil Red O stain.

All medications were interrupted and the patient quickly improved. On March 23, 1998, ALT was 97 \( (N < 40) \), AST 37 \( (N < 40) \), conjugated bilirubin 24 \( \mu mol/l \) and creatinine 94 \( \mu mol/l \). ALT and GGT were normal on March 2000.
Fig. 1. Liver lesions in patient 5. This high magnification photograph of an H/E stain shows microvesicular steatosis in hepatocytes, an acidophlic body (large arrow) and some infiltrating mononuclear cells (small arrows).

3. Discussion

Recognizing a drug-induced etiology is difficult in heroin addicts who usually have several other potential causes of liver disease. The five patients reported above were infected with HCV and one also had HIV. Although they no longer used illicit drugs, all were taking diverse psychoactive medications (fluoxetine, diverse benzodiazepines, valproamide and meprobamate), and three of them also consumed alcohol.

Nevertheless, we believe that hepatitis was triggered by buprenorphine injections in the four patients with acknowledged intravenous misuse (cases 1–4). These four patients exhibited a marked increase in ALT activity (i.e., 30-, 37-, 13- and 50-times the upper limit of normal, respectively) after injecting buprenorphine, and three of them also became jaundiced (cases 1, 3 and 4). All four patients promptly improved when buprenorphine injections were stopped, even though other drugs and ethanol intake were continued. The lack of fever, rash or blood eosinophilia in these patients and their recovery despite continued sublingual administration in two of them, may suggest concentration-related direct toxicity rather than an immunooallergic phenomenon.

In addition to these four patients, we also observed a fifth patient with possible buprenorphine-associated hepatitis (case 5). This patient developed severe hepatitis with asthenia, jaundice, ALT 165-times the upper limit of normal, and decreased plasma prothrombin levels after using both sublingual buprenorphine (without acknowledged intravenous use) and small doses of paracetamol and aspirin. An early transjugular liver biopsy showed both severe panlobular necrosis and microvesicular steatosis. The patient quickly improved and serum ALT activity was only twice normal three weeks after buprenorphine withdrawal.

Buprenorphine is a lipophilic, protanable amine which concentrates within mitochondria where it uncouples and inhibits mitochondrial respiration and also inhibits fatty acid β-oxidation [5]. Buprenorphine causes ATP depletion and liver cell necrosis, together with some steatosis, in isolated rat hepatocytes [5]. These mitochondrial effects, however, require higher buprenorphine concentrations (25 μM or more) than those occurring in humans [5]. After an 8 mg sublingual dose, the peak plasma concentration of buprenorphine is only 0.02 μM, due to slow absorption and extensive metabolism during each pass through the liver [6]. This important safety margin may explain the good tolerance of buprenorphine after sublingual use. After intravenous injection, however, rapid dilution of the drug in the plasma volume may result in a much higher initial concentration (3 μM). Although this concentration is still less than the concentrations causing marked mitochondrial dysfunction in rat mitochondria or necrotic cell death in rat hepatocytes [5], a minor effect of intravenous buprenorphine could trigger decompensation in a few patients whose mitochondrial function is already compromised by other factors.

This basal mitochondrial impairment could have several different causes. First, intravenous buprenorphine may depress ventilation and cause anoxia [11]. Second, heroin addicts frequently abuse alcohol, which oxidatively cuts mitochondrial DNA and causes mitochondrial DNA deletions [12–14]. Patient 5 also ingested small doses of paracetamol and aspirin, which inhibit mitochondrial respiration [15] and β-oxidation [16], respectively. These two drugs may have added their mitochondrial effects to those of sublingual buprenorphine in this patient. Finally, our five patients with buprenorphine-associated hepatitis had mild chronic hepatitis C and one also had asymptomatic HIV infection (patient 5). HCV, HIV and also HBV may directly affect mitochondrial function [17–20] and these viral infections also cause inflammatory cells to overexpress nitric oxide, interferon-α, tumor necrosis factor-α and Fas ligand, which all impair mitochondrial function [21]. With this probable combination of added factors, it may be purely academic to try to distinguish between the potentiation of buprenorphine-induced toxicity by viral infections, cytokines, alcohol and, sometimes, other drugs (as in patient 5), the potentiation of the mitochondrial toxicity of these other drugs (paracetamol and aspirin) by buprenorphine in this patient, and/or the potentiation of viral- and-immune-induced cytotoxicity by buprenorphine.

The concept that viral infections and drugs can have added cytopathic effects has several precedents. Aspirin releases salicylic acid which inhibits β-oxidation [16]. Although lethal overdoses of aspirin cause microvesicular steatosis, therapeutic doses do not, unless aspirin is given during viral infections in children [16]. Isoniazid metabolites impair mitochondrial function and cause ATP depletion [22]. In patients receiving antituberculous polytherapy including isoniazid, the risk of developing drug-associated hepatic cytolysis is increased 5-fold in HCV-positive patients, 4-fold in HIV positive patients, and 14-fold in...
both HCV and HIV carriers [23]. This risk is also increased 3-fold in HBSAg carriers [24]. Chronic viral hepatitis also increases the risk of severe hepatotoxicity during antiretroviral therapy in HIV patients [25].

Although we have observed several cases of buprenorphine-induced hepatitis, this is probably a most uncommon complication even after intravenous misuse, considering the large number of patients (about 65 000) placed on buprenorphine substitution, and the likelihood that a certain number may (admittedly or not) misuse it and inject it intravenously.

The possibility of intravenous misuse should not prevent physicians from prescribing sublingual buprenorphine to help heroin addicts stop using illicit drugs. As mentioned in the introduction, this substitution has major advantages, and sublingual buprenorphine is probably very safe. However, these patients should be repeatedly warned not to inject buprenorphine intravenously. Severe hepatitis can occur in a few intravenous users, possibly those whose mitochondrial function is already impaired by viral infections and other factors.

References