Treatment of Opioid Dependence With Buprenorphine/Naloxone After Liver Transplantation: Report of Two Cases

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ABSTRACT

Opioid dependence is an increasing public health problem. One of the complications of intravenous opioid use is hepatitis C virus infection, which, in turn, is one of the most common indications for liver transplantations throughout the world. Therefore, the treatment of opioid dependence in a liver transplant recipient requires special attention in terms of graft function, drug interactions, and patient compliance. Buprenorphine is a semi-synthetic opioid-derived agent with analgesic effects. To prevent buprenorphine abuse, it is combined with the opioid antagonist naloxone. This buprenorphine/naloxone combination is the only drug approved for the treatment of opioid dependence in Turkey. Although the literature includes data about the safe usage of buprenorphine in liver transplantation in animals, there is no such evidence in either case reports or clinical trials for the same in humans. In this article, we present a report of our treatment of 2 opioid-dependent patients with buprenorphine/naloxone after liver transplantation due to hepatitis C virus–induced liver cirrhosis.

OPIOID dependence is a public health problem that has increasingly become more widespread in Turkey and all over the world [1,2]. With the increase in its prevalence, social, psychiatric, and medical problems associated with opioid use are also on the rise [2].

One of the most important medical problems associated with the intravenous use of opioids is hepatitis C virus (HCV) infection. Of individuals who use substances intravenously, 60%–90% become infected with HCV and it is now one of the principal reasons for liver transplantations in the United States and Europe [3].

The pharmacological agent used most commonly in the treatment of opioid dependence is methadone [4]. Methadone is a synthetic opioid agonist. There is data suggesting that the use of methadone is safe in the preoperative and postoperative period in patients undergoing liver transplantation [5–7]. However, methadone has still not been approved for use in Turkey.

Another agent used commonly in the treatment of opioid dependence is buprenorphine: a semi-synthetic opioid derivative exerting partial agonist effects on mu-opioid receptors and antagonistic effects on kappa-opioid receptors. As an effective analgesic, which is 25- to 40-fold more potent then morphine [8], it has been reported to be a useful agent in decreasing perioperative pain [9]. Buprenorphine is combined with the opioid antagonist naloxone to prevent misuse in opioid-dependent patients because, although naloxone has almost no effect when used sublingually, it exerts antagonistic effects if misused intravenously [1]. In Turkey, the combination of buprenorphine/naloxone was approved for the treatment of opioid dependence by the Ministry of Health in 2010. However, as far as we know, there are no reports in the literature suggesting that it can be used safely in patients undergoing liver transplantation. On the contrary, there are case reports stating that its use within therapeutic dose range can result in severe hepatotoxicity [3].

In this article, we describe our treatment of 2 opioid-dependent patients with buprenorphine/naloxone after liver transplantation due to HCV-induced cirrhosis.

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The informed consent of both patients has been obtained for this report.

CASE 1

A 56-year-old male patient living abroad was admitted to our outpatient unit in August 2014. He stated that his substance abuse had started with marijuana at the age of 15. In time, cocaine and heroin were added. In all, he has used heroin intravenously for the last 20 years (maximum dose 1 g/d). For the last 7 years, he has attended a methadone treatment program abroad (the methadone dose was initiated at 60 mg/d and was increased to 110 mg/d over time). While under methadone treatment, he continued to use heroine/cocaine once a week/month. HCV was first detected 20 years ago, with liver cirrhosis developing within the last 2 years. Upon the decision for liver transplantation, methadone use was gradually terminated and the patient was referred to a clinic in Turkey for the transplantation procedure. One month after the transplantation was carried out successfully from a live donor, discharge was planned. Meanwhile, he was referred to our unit due to his excessive demand for opioid analgesic (pethidine) reporting severe muscle pain, diarrhea, insomnia, and nervousness when pethidine was not administered. The patient was also diagnosed with diabetes mellitus and hypertension and in addition to immunosuppressive treatment he also used insulin, antihypertensive drugs, antivirals, antibiotics, and steroids. The immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil (MMF), and steroids. Steroid was withdrawn in 6 months. Tacrolimus dose was adjusted according to blood levels and MMF was given at 1000 mg/d.

In the ensuing psychiatric examination, opioid abstinence symptoms and severe craving for opioids were noted. He was diagnosed with Opioid Use Disorder according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5). At this stage, pethidine treatment was discontinued and buprenorphine/naloxone 2 mg/d was initiated with the dose increased incrementally over 3 days to 6 mg/d. He experienced no abstinence symptoms at this dose. Elevated liver enzymes due to the HCV recurrence at the onset of treatment decreased to normal ranges during follow-up and there were no problems with graft functions. The patient's difficulty in complying with drug treatment and diet also decreased with the buprenorphine/naloxone treatment. The patient has now been on buprenorphine/naloxone treatment for 1 and a half years and urinalysis yields negative results for illicit substance use. Liver function test results at the onset, 6th month, 12th month, and 18th month of buprenorphine/naloxone treatment are shown in Table 1.

CASE 2

A 44-year-old male patient living abroad was referred to our outpatient unit in August 2014. He had started to use heroine at the age of 20 and had begun intravenous use within approximately 1 year (maximum dose 3 g/d). HCV was detected in blood investigations carried out at the age of 23, and 1 year later he was diagnosed with HCV-associated cirrhosis. During periods when he discontinued heroin use, he joined a buprenorphine/naloxone treatment program and used buprenorphine/naloxone at the dose of 4 mg/d. With this treatment, his longest period of abstinence was 6 months. He underwent liver transplantation from a live donor at the end of July. With an overall improvement in his general condition, he was referred to our unit for evaluation of opioid dependence. He was on immunosuppressive, steroid, antiviral, and antibiotic treatment. The immunosuppressive regimen consisted of tacrolimus, MMF, and steroids. Steroid was withdrawn in 6 months. Tacrolimus dose was adjusted according to blood levels and MMF was given at 1000 mg/d.

With this patient, there was a history of opioid abstinence symptoms, opioid tolerance, and continuing opioid use, despite his awareness of having a continuing problem. In his psychiatric evaluation, a craving for opioids was detected and he was diagnosed with Opioid Use Disorder according to DSM-5. Buprenorphine/naloxone 2 mg/d was initiated and the dose was increased incrementally to 6 mg over 3 days, at which dose the patient reported experiencing no more craving. Elevated liver enzymes due to the HCV recurrence at the onset of treatment decreased at follow-up. No problems were experienced in graft functions or in compliance to drug treatment and diet. The patient has been on buprenorphine/naloxone treatment for 1 and a half years now and urinalysis yields negative results for illicit substance use. Liver function test results at the onset, 6th month, 12th month, and 18 month of treatment are shown in Table 1.

DISCUSSION

In this article we presented 2 opioid-dependent patients who underwent liver transplantation due to HCV-induced cirrhosis. After transplantation, buprenorphine/naloxone treatment, which is the only treatment option in Turkey for opioid dependence, was commenced. Opioid abstinence

Table 1. Liver Function Test Results of the Patients

	Treatment Onset	6th Mo	12th Mo	18th Mo	Reference Ranges
Case 1					
ALT (IU/L)	130.8	37	61	57	0.00–41.00
AST (IU/L)	44.9	34	63	61	10.00–40.00
Total bilirubin (mg/dL)	1.49	1.5	1.7	0.89	0.01–1.20
Prothrombin time (sec)	14	13	11	12	11.00–15.50
INR	1.09	1.05	0.9	1.09	0.80–1.20
Case 2					
ALT (IU/L)	987	25	45	32	0.00–41.00
AST (IU/L)	252	30	40	24	10.00–40.00
Total bilirubin (mg/dL)	1.84	0.9	0.8	1.1	0.01–1.20
Prothrombin time (sec)	12.4	14	12	11	11.00–15.50
INR	0.97	1.2	1	1	0.80–1.20

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio.

symptoms (in Case 1) and opioid craving (in Cases 1 and 2) were brought under control at the dose of 6 mg/d. During the follow-up period, no problems were observed in graft functions and, in Case 1, incompliance with drug treatment and diet improved after buprenorphine/naloxone treatment. During the bi-monthly follow-up of both patients carried out at our outpatient clinic for the last 1 and a half years, no recourse to substance use including opioids has been seen. In both cases, this is their longest recorded period of abstinence.

Buprenorphine is a drug metabolized in the liver [8]. Because 90% of the drug undergoes first-pass metabolism in the liver, a sublingual form has been developed to increase its bioavailability [10]. It is a lipophilic drug concentrated in the liver. In animal studies, buprenorphine has been demonstrated to impair mitochondrial functions when in high concentrations [11]. However, with the doses used in opioid dependence (8–16 mg/d), peak plasma concentrations are very low, so it is expected that mitochondrial effects should not occur or should be minimal [12]. In support of this, some case reports state that buprenorphine may be used safely in cases with acute HCV infection. Buprenorphine/naloxone treatment was started in 4 cases of opioid dependence, in the presence of acute HCV infection, and while alanine transaminase (ALT) and aspartate transaminase (AST) levels were high. In the follow-up period, ALT and AST levels were found to have decreased without any complications [13].

However, other case reports describe the development of hepatotoxicity as a result of buprenorphine use. In these cases, ALT levels increased considerably as a consequence of the use of buprenorphine at therapeutic doses both sublingually [14] and intravenously [14,15], with the development of jaundice in some cases. In the report by Herve et al [14], it was stated that the buprenorphine dosage was halved in 3 cases and maintained at the same dose in 4 patients and that cytolysis and jaundice were reversed in a short period, despite no treatment being administered. In the report by Berson et al [15], the drug use was discontinued in 2 of the 4 cases and in the remaining 2, the use of sublingual form was maintained with a reversal of clinical and laboratory findings in all cases. In both of these reports, HCV infection was present in almost all cases as well as an additional drug (such as paracetamol and valproic acid) and alcohol use in some. Therefore, it is thought that viral infections, which were already present in the cases, and toxic effects such as the use of additional drugs and alcohol may have led to mitochondrial damage, which in turn may have facilitated the development of buprenorphine-associated hepatotoxicity [14–16].

It has been suggested that buprenorphine may exert a negative effect on graft functions [17]. Nevertheless, in rats undergoing liver transplantation, it has been demonstrated that the use of buprenorphine as analgesic in the postoperative period does not lead to a significant increase in ALT, AST, and bilirubin levels or to any adverse effects on the recipient and liver graft [17]. As far as we know, there is no study in humans with liver transplantation reporting the use of buprenorphine for the treatment of opioid dependence or as an analgesic. However, in our cases buprenorphine/naloxone treatment, initiated for the treatment of opioid dependence following liver transplantation, did not lead to any increase in ALT, AST, or bilirubin levels; in follow-up, laboratory test results were similar to those of normal patients undergoing liver transplantation; there were no postoperative complications or any adverse events associated with buprenorphine/naloxone use.

In conclusion, opioid dependence, which is increasing in Turkey, as in the rest of the world, is a significant condition owing to its associated complications. Herein, 2 cases with opioid dependence that underwent liver transplantation due to HCV cirrhosis are presented. The significance of this report is its indication that buprenorphine/naloxone treatment can be safely administered after liver transplantation. However, the evidence of this case report should be supported by other case reports and clinical studies.

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