Acute hepatitis due to buprenorphine administration
Sophie Hervé, Ghassan Riachi, Catherine Noblet, Nathalie Guillement, Stephana Tanasescu, Odile Goria, Christian Thuille, Jean-Luc Tranvouez, Philippe Ducrotte and Eric Lerebours

Background Buprenorphine, a synthetic molecule derived from thebaine, has been commercialized in France since 1987 as a substitute treatment for pharmacodependence on opiates. Hepatotoxicity is poorly documented, since only few cases of hepatic injury have been reported.

Methods We report seven cases of acute cytolytic hepatitis due to buprenorphine. All patients were former drug addicts by the parenteral route and had been receiving withdrawal therapy with buprenorphine for an average of 91 days at a daily dosage ranging from 2 to 12 mg. Liver tests, complete viral screening and an abdominal computed tomography scan were performed in each patient.

Results Five out of seven subjects presented with acute icteric hepatitis without abdominal pain or fever. Average alanine aminotransferase levels were 39 times the normal rate. There was no sign of liver failure. All patients had anti-hepatitis C virus-positive serology and two had positive hepatitis C virus-RNA. Although no specific treatment was administered, buprenorphine doses were reduced whenever possible. Cytolysis and jaundice resolved rapidly in all cases, although treatment was continued at the same doses in four cases and the dosage was reduced by 50% in three other cases.

Conclusions Although buprenorphine hepatitis is uncommon and has spontaneously good evolution, we suggest better monitoring of hepatic profiles in patients whose mitochondrial function is already impaired by viral infections or other toxic factors. Eur J Gastroenterol Hepatol 16:1033–1037 © 2004 Lippincott Williams & Wilkins

Keywords: hepatotoxicity, drug addiction, buprenorphine, hepatitis C virus

Introduction Buprenorphine is a synthetic morphinan agonist-antagonist derived from thebaine, an opium alkaloid. It was discovered in the early 1970s and has been commercialized in France since 1987. Buprenorphine (Temgesic) was first prescribed for cancer and refractory pain in sublingual (0.2 mg) and injectable forms (0.3 mg). High dose sublingual buprenorphine (Subutex) has been administered in France since February 1997 as a substitute treatment for major opioid drug dependence. Daily doses are adapted to the degree of dependence and range from 0.8 to 16 mg/day taken once or twice a day. The slowly reversible link with mu-receptors in this drug explains the prolonged diminished need for narcotics in drug addicts [1].

Hepatotoxicity of this drug has been recently highlighted and isolated case reports mainly in relation to misuse of buprenorphine have been recently reported [2,3].

We report seven cases of acute hepatitis caused by buprenorphine administration for withdrawal from intravenous addiction to opiates at therapeutic doses.

Subjects and methods General practitioners and hepatologists of Upper Normandy participated in a care network allowing regular clinical and biological follow-up of subjects treated with buprenorphine to detect possible adverse effects, lack of observance or misuse. Each subject treated with buprenorphine was examined weekly by the same practitioner for treatment renewal. Buprenorphine was provided by the same chemist to avoid inappropriate drug use.

General practitioners from the network noted seven cases of acute hepatitis with buprenorphine. The seven patients (six men, one woman) were between 24 and 38 years old (median age, 30 years). All were former drug addicts by the parenteral route and had been receiving withdrawal therapy with buprenorphine at doses ranging from 2 to 12 mg/day for an average of 91 days (range, 30–135 days). Buprenorphine was...
administered by the sublingual route in six subjects and by intravenous injection in one. Once buprenorphine administration had begun, the seven patients stopped illegal drug use. Two of the subjects had been taking other prescribed drugs in addition to buprenorphine, one for 7 months and another for 24 months (Table 1).

The seven patients were examined by a hepatologist and underwent a systematic evaluation including: (a) an abdominal scan; (b) biological tests – alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatases, gamma-glutamyl transpeptidase, total bilirubin; and (c) hepatitis B virus (HBV) and hepatitis C virus (HCV), serological markers [HBs antigen (HBsAg), anti-HBc antibody, anti-HBs antibody, anti-HCV antibody, HCV-RNA in reverse transcriptase-polymerase chain reaction, HBV-DNA in polymerase chain reaction], and HIV1, HIV2, cytomegalovirus and Epstein–Barr virus. In four patients, immunological tests were also performed (antinuclear antibody, liver–kidney microsomal antibody, smooth muscle antibody and anti-mitochondrial antibody). Histological liver examination was performed by a trained pathologist in two subjects due to positive HCV results, and histological lesions were classified according to the Knodell classification [4]. The pathologist was aware of the patient’s clinical record and medication.

Buprenorphine doses were reduced by 50% in patients whose degree of addiction made this possible (n = 3) and were maintained in the four other patients. The subjects were then examined every 7 or 10 days and ALT and AST tests were performed weekly until the liver test results were normal.

Causality assessment method
These seven cases were analysed according to the RUCAM/CIOMS scoring system now internationally recognized as the best method of causality assessment for drug hepatotoxicity [5,6]. This scoring system is based on chronological criteria, previous knowledge of drug’s toxicity, screening for non-drug-related causes, risk factors (age, alcohol consumption and pregnancy) and the use of concomitant drugs. Chronological criteria take into account the delay between initiation of therapy and the occurrence of hepatitis as well as its evolution after discontinuation or rechallenge. A high semiological score is only retained if exclusion of other possible causes of hepatic injury is possible.

Results
Clinical, biological and virological results for the seven patients are described in Tables 1 and 2. Five out of seven patients presented with acute icteric hepatitis without abdominal pain or fever. Alcohol consumption was assessed in all subjects and did not exceed 30 g alcohol/day. There was no acute intake of alcohol prior to the onset of jaundice.

The average ALT level was 39 times the normal rate (range, 9–68) and there were no signs of hepatic failure. Anti-HCV antibodies were positive in all patients and two patients had a positive HCV-RNA. Two patients were HBsAg carriers with no detectable viraemia for HBV. The remaining virological and immunological results were negative (Table 2).

The abdominal scan was normal in all subjects. The liver biopsy (subjects 4 and 6) was performed a certain amount of time after the acute episode in patients with chronic hepatitis C. The aim of the biopsy was to identify disease progression based on histological criteria. There were no signs of toxic hepatitis [7], and lesions showed persistent chronic hepatitis secondary to HCV infection, characterized by portal and peri-portal inflammation without fibrosis [4].

Evolution
Buprenorphine treatment differed in patients according to the degree of physical and psychological dependence on opiates. The treatment was continued at the same doses in four cases (subjects 1, 2, 3 and 7) and reduced by one-half in the three other cases (subjects 4, 5 and 6). Cytolysis and jaundice evolved favourably in all cases. For each subject, at least three hepatic biological check-ups were obtained during the follow-up. The maximum ALT ratio was observed as early as during

Table 1 Clinical and epidemiological characteristics of the subjects, route of administration of buprenorphine, and other drugs consumption

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration of drug abuse (years)</th>
<th>Buprenorphine (mg)</th>
<th>Time (days)</th>
<th>Route</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>27</td>
<td>5</td>
<td>8</td>
<td>30</td>
<td>Sublingual</td>
<td>Silymarine, hydroxyzine, zopiclone</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>32</td>
<td>10</td>
<td>6</td>
<td>135</td>
<td>Sublingual</td>
<td>Valproic acid, alprazolam, levomepromazine</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>31</td>
<td>8</td>
<td>8</td>
<td>153</td>
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<td>4</td>
<td>Male</td>
<td>29</td>
<td>10</td>
<td>3</td>
<td>135</td>
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<tr>
<td>5</td>
<td>Male</td>
<td>37</td>
<td>3</td>
<td>2</td>
<td>120</td>
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<tr>
<td>6</td>
<td>Male</td>
<td>24</td>
<td>3</td>
<td>4</td>
<td>100</td>
<td>Sublingual</td>
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<tr>
<td>7</td>
<td>Female</td>
<td>38</td>
<td>10</td>
<td>12</td>
<td>30</td>
<td>Intravenous</td>
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</table>
the second week of treatment. ALT returned to a normal level during the third week.

All cases were reported to our regional pharmacovigilance centre.

Causality assessment results
Chronologically, the time to onset is ‘suggestive’ of causality in subjects 1 and 7 and ‘compatible’ in the others (subjects 2, 3, 4, 5 and 6). The evolution is ‘inconclusive’ in all the patients since the treatment was continued in all.

Considering the screening for other causes of hepatitis, even if alcohol could be considered as a positive risk factor for drug toxicity in all the patients an alcoholic hepatitis could be excluded based upon the following observations: (a) the daily alcohol intake in each of the patients was less than the dose considered to be toxic (50 g/day) [8], (b) there was no acute alcoholization preceding the onset of jaundice or cytolysis, and (c) the profile of the cytolysis (ALT/AST ratio > 1) did not suggest an alcoholic origin. A hepato-biliary scan excluded the presence of hepatic, biliary or pancreatic disease. None of the patients had an acute recent hypotension history. Results of viral screening showed only two patients out of seven (subjects 2 and 4) to be carriers of HBsAg, and negative HBV-DNA excluded cytolysis in connection with HBV re-activation. The roles of the cytomegalovirus, and Epstein–Barr virus were excluded either by negative serologies or by a lack of clinical or epidemiological evidence of recent infection. Finally, all patients were negative for HIV1 and HIV2 serology.

All patients were carriers of HCV. HCV infection is very common in intravenous drug users with a prevalence of approximately 70% [9]. In patients 3, 5 and 7 acute hepatitis C was suggested since the pre-buprenorphine liver tests were normal. This hypothesis was ruled out in subjects 3 and 7 since only patient 5 was viraemic. In this patient, the last potentially infectious intravenous injection had occurred more than 3 months before. This excludes acute hepatitis since the usual term for seroconversion is 8 weeks [10]. Chronic hepatitis C was also a possibility in patient 5. The ALT levels were 50 times above normal, whereas during the chronic viral replication ALT levels are most of the time lower than 10 times above normal, and usually range from 1.5 to five times the normal level. These data strongly suggest that HCV was not the aetiological agent responsible for acute cytolysis despite the lack of hepatic histology [6].

Only two patients (subjects 1 and 2) were taking drugs other than buprenorphine. In the first patient, associated drugs were silymarine (420 mg/day), hydroxyzine (150 mg/day) and zopiclone (1.5 mg/day). None of those molecules is known to be hepatotoxic. In the second patient, the associated drugs were valproic acid (1500 mg/day), alprazolam (1.5 mg/day) and levomepromazine (25 mg/day). This treatment had been taken for several years without any recent change in dosage. Levomepromazine and alprazolam have been shown to result in acute hepatitis during phase III clinical studies in, respectively, 2.7% and 0.4% of patients. The maximum delay before the occurrence of hepatitis was 3 weeks–21 months after the onset of the treatment. Finally, valproic acid has also been shown to cause acute hepatitis with a maximum frequency of 0.02% and a delay ranging from 3 days to 17 weeks, suggesting that acute toxicity from this substance was improbable [11].

According to these data the global RUCAM/CIOMS score in our patients was 6 (patients 2–6) or was 7 (patients 1 and 7). The diagnosis of buprenorphine-induced hepatitis could be considered ‘probable’.

Discussion
We noted seven cases of acute hepatitis in subjects undergoing withdrawal therapy and treated with buprenorphine at doses ranging from 2 to 12 mg/day.

The sublingual administration of buprenorphine prevents its degradation in the intestine, and the important effect of the first hepatic pass. Thus, the absolute biodisponibility of buprenorphine ranges from 35% to

<table>
<thead>
<tr>
<th>Patient</th>
<th>HCV</th>
<th>HCV-RNA</th>
<th>HBsAg</th>
<th>HBV-DNA</th>
<th>HIV</th>
<th>EBV</th>
<th>CMV</th>
<th>Anti-nuclear antibody</th>
<th>Mitochondrial antibody</th>
<th>Smooth muscle antibody</th>
<th>Liver–kidney microsomal antibody</th>
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</tbody>
</table>

HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; EBV, Epstein–Barr virus; CMV, cytomegalovirus.
55%, and the plasmatic peaks are obtained 90 min after administration [12]. Absorption is followed by a phase of rapid distribution with a plasmatic half-life of 2–5 h. Buprenorphine spreads very rapidly in the tissue, especially the liver. This strong tissue fixation is responsible for its long-lasting action despite the plasmatic half-life with brief elimination [13]. The metabolism of this molecule is mainly hepatic through dealkylation and glucuroconjugation, and elimination of 80% mainly occurs through biliary excretion of the glucuroconjugated metabolites, with the rest eliminated through urine [12].

Recently, Berson et al. investigated the mitochondrial effects and metabolic activation of buprenorphine in isolated rat liver mitochondria and microsomes and its toxicity in isolated rat hepatocytes [14]. They demonstrated that buprenorphine concentrates within mitochondria, where it uncouples and inhibits mitochondrial toxicity in isolated rat hepatocytes [14]. They demonstrated that buprenorphine concentrates within mitochondria, where it uncouples and inhibits mitochondrial respiration and also inhibits fatty acid β-oxidation. In isolated rat hepatocytes it causes adenosine triphosphate depletion, liver cell necrosis, and steatosis. In animal models hepatotoxic effects of buprenorphine are mainly due to its mitochondrial effects, but these effects require higher buprenorphine concentrations than those obtained in humans. Berson et al. also reported five cases of former heroin addicts infected with HCV placed on substitution therapy with buprenorphine who exhibited a marked increase in the serum ALT [3]. Four patients injected buprenorphine intravenously, and the other used sublingual buprenorphine and small doses of paracetamol and aspirin. The authors hypothesized that, in humans, intravenous buprenorphine could trigger decompensation in a few patients whose mitochondrial function is already compromised by other factors. Only one of our patients injected buprenorphine intravenously. However, even in the other patients, who used sublingual buprenorphine, mitochondrial toxicity remained the more documented hypothesis. In our patients either viral infection known to affect directly mitochondrial function, daily alcohol intake, drugs such as valproic acid or the combination of all these factors may have promoted the mitochondrial toxicity of buprenorphine [15–20].

The association between buprenorphine-induced hepatitis and HCV infection had been noted by Berson et al. but the five patients were vireamic [3]. The increased risk of hepatotoxicity in HCV carriers has already been suggested in patients with the presence of serum HCV-RNA and chronic hepatitis on liver biopsies [21]. However, there is no clear evidence that beyond viral disappearance this risk remained increased. Most patients that use buprenorphine as a substitute treatment have the epidemiological profile for the exposure to HCV. The association between buprenorphine hepatotoxicity and HCV infection could also have been fortuitous. However, in patients with positive HCV-RNA a mitochondrial dysfunction induced by the virus remains a strong hypothesis. In our study all the patients were anti-HCV-positive but only two of them were RNA-positive. It is important to take into account that the sensitivity of the RNA assay employed at this time was lower than those used nowadays and that some patients could have been considered as non-viraemic falsely.

In conclusion, buprenorphine-induced hepatitis remains uncommon but can appear even if patients do not misuse the drug. In all cases the evolution is favourable independent of treatment. We suggest better hepatic biological monitoring in patients presenting many possible sources of hepatic function impairment in whom mitochondrial function is already impaired by viral infections or other factors.

Conflict of interest
None declared.

Authors’ contributions
The digestive tract research group analysed and described all the cases, and reviewed and discussed similar cases already published. The Regional Pharmacovigilance Group helped to assess the causality of the drug and to discuss the mechanism involved in buprenorphine.

References


