Dilated Bile Duct in Patients Receiving Narcotic Substitution

An Early Report

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Abstract

Narcotic substitution is now widely used. Morphine can induce a spasm of the sphincter of Oddi but dilation of bile duct has been reported only in an anecdotal case. In June 1995, we observed a first case of dilation of the common bile duct without organic obstacle in a hepatitis C virus (HCV)-infected patient who was under narcotic substitution, suggesting a causal relationship. We conducted a prospective study to evaluate the precise prevalence of bile duct abnormalities related to narcotic substitution in active intravenous drug or ex-intravenous drug users referred to our liver unit for histologic evaluation of HCV infection. We conducted a prospective study in a 30-month period of 334 HCV-infected patients, including 36 receiving narcotic substitution with methadone or buprenorphine. Biliary tract was analyzed by ultrasonography and by endoscopy ultrasound in cases of bile duct abnormalities. Of the 36 patients under narcotic substitution, 3 (8.3%) had asymptomatic dilated bile duct without organic obstacle—defined as a common bile duct ≥ 9 mm—compared to 1 of 298 (0.03%; p < 0.001) of those who did not receive substitution. Narcotic substitution may lead to bile duct dilation that does not require invasive diagnosis procedures.

Key Words: Hepatitis C virus—Narcotic substitution—Bile duct dilation.

Narcotic agonists are known to induce a spasm of the sphincter of Oddi and to increase the common bile duct pressure. They were used in isotope imagery to improve the visualization of the gallbladder and as diagnostic test for Oddi dysfunction. Dilated common bile duct related to morphine administration has not been reported except in one anecdotal case. Narcotic substitution by morphinomimetic drugs is now widely used in the treatment of intravenous drug users (IVDUs). After a first observation of nonobstructive dilated bile duct in a hepatitis C virus (HCV)-infected patient receiving narcotic substitution, we conducted a prospective study in HCV-infected IVDUs or ex-IVDUs to evaluate the precise prevalence of bile duct abnormalities related to morphine analogue substitutes.

METHODS

We prospectively analyzed bile duct abnormalities from July 1995 to December 1997 in the 334 IVDUs or ex-IVDUs who were referred to the liver unit for the histopathologic evaluation of HCV infection.

Laboratory Tests

Biological tests included serum aminotransferase, gamma-glutamyl-transferase, phosphatase alkaline activities, as well as bilirubin determination.

Morphologic Evaluation

Bile duct abnormalities were assessed by an ultrasonography that was performed by the same physician who was not aware of whether the patient was receiving narcotic substitution. When bile duct abnormalities were detected, endoscopic ultrasound was performed. Common bile duct dilation was defined by a diameter ≥ 9 mm in subjects younger than 60 years, without previous cholecystectomy. We did not perform manometry of Oddi sphincter, which may lead to severe side effects as acute pancreatitis, especially in patients with Oddi dysfunction.

Histologic Analysis

Because IVDU subjects were referred in our unit for liver evaluation, most of them underwent liver biopsy without complications, even in those with dilated bile duct. Histologic analysis was based on the hepatitis activity index according to Knodell et al., which permits semi-quantitative analysis of necrosis, inflammation, and fibrosis. All of the subjects in whom bile duct abnormalities were detected underwent liver biopsy. For these patients, precise analysis of lobular and interlobular bile duct were performed.

Patients

In June 1995, we observed a first case of a dilation of common bile duct in a 38-year-old HCV-infected patient. HCV...
infection was related to IVDU between 1993 and 1994, and he was given narcotic substitution with buprenorphine at 8 mg/24 hours since 8 months; he had no history of biliary disease. Ultrasonography performed before liver biopsy showed a common bile duct dilation of 10 mm without gallbladder abnormalities. Aminotransferases, alkaline phosphatase, and amylasemia activities were within 2-fold the normal values; bilirubin was normal. Endoscopic ultrasound ruled out obstructive biliary disease and the pancreas was normal. Liver biopsy showed chronic hepatitis with moderate activity without fibrosis; the lobular and interlobular bile ducts were normal. A link between narcotic substitution and common bile duct dilation was suspected.

Then, we performed a prospective study between July 1995 and December 1997 to evaluate the prevalence of bile duct abnormalities in the 334 consecutive anti-human immunodeficiency virus-negative HCV-infected IVDU or ex-IVDU subjects who were referred to our liver unit (Table 1). There were 216 men and 118 women with a mean age of 37 ± 9 years. For all of the subjects, biliary disease history (including gallstone gallbladder and history of hepatic colic), chronology of IVDU, and narcotic substitution intake was determined. None of patients under substitution had active use of morphine or codeine.

### RESULTS

Between July 1995 and December 1997, among the 334 IVDU or ex-IVDU subjects who were referred for HCV infection evaluation, 36 (10.8%) were given narcotic substitution with methadone (21 patients) or with high dosages of buprenorphine (15 patients). There were 27 men and 9 women with a mean age of 38 ± 7 years. Patients with (n = 36) or without (n = 298) narcotic substitution were comparable for age, sex, liver histology, and liver biologic tests. Of these 36, 3 (8.3%) had morphologic bile duct abnormalities with dilated common bile duct—defined by a common bile duct ≥9 mm—compared to 1 of the 298 (0.03%) without narcotic substitution (p < 0.001).

Epidemiologic, clinical, and histologic characteristics of subjects under narcotic substitution did not differ, whether they had or not bile duct abnormalities. There was no differences between the 3 patients with and the 33 without bile duct abnormalities in age (38 ± 10 vs. 39 ± 7), gender ratio (men:women; 2:1 vs. 25:8), duration of substitution (15 ± 8 vs. 21 ± 35 months), or doses of buprenorphine (6.0 ± 2.8 vs. 5.0 ± 3.4 mg). Biologic liver tests were similar for aspartate transaminase (47 ± 27 vs. 60 ± 70 UI/L), alanine transaminase (71 ± 38 vs. 79 ± 83 UI/L), gamma-glutamyl-transferase (57 ± 38 vs. 124 ± 196 UI/L), alkaline phosphatase (63 ± 17 vs. 74 ± 40 UI/L), bilirubin (12 ± 8 vs. 9 ± 5 μmol/L), and cirrhosis (1/4 vs. 3/36). The doses of methadone were paradoxically higher in patients without bile duct abnormalities (61 ± 37 vs. 25 ± 21 mg; p < 0.05). In association with the common bile duct dilation, dilation of the cystic, Wirsung, and intrahepatic bile ducts was observed in two, one, and two patients, respectively. Subjects with bile duct abnormalities had no biliary symptoms, including colic hepatic, fever, or jaundice. None had hyperbilirubinemia or phosphatase alkaline activity >2-fold the normal values. Endoscopy ultrasound performed in three patients with bile duct dilation excluded biliary obstruction, tumor, papillary stenosis, gallbladder, or pancreatic abnormality. None had intra- or interlobular bile duct abnormalities or histopathologic signs of cholangitis at liver biopsy. Among the 298 IVDUs without narcotic substitution, only 1 (0.03%) had bile duct abnormalities with a 13-mm common bile duct dilation that did not require diagnostic procedure because it was assumed to be due to previous cholecystectomy.

### DISCUSSION

Our study showed an unreported cause of common bile duct dilation linked to narcotic substitution. Of HCV-infected patients receiving narcotic substitution, 8% have a common bile duct dilation—defined by a diameter ≥9 mm—compared to none of those without narcotic substitution and previous cholecystectomy. Other morphologic abnormalities of the biliary and pancreatic ducts, including cystic and Wirsung canal dilation, may be associated with common bile duct dilation.

Increases in the pressure of sphincter of Oddi and bile duct have been reported with narcotic analogues, mainly with morphine; and, they were used in isotope imagery to improve the visualization of the gallbladder and as diagnosis test for Oddi dysfunction in subjects with biliary pain after cholecystectomy. Dilated common bile duct related to morphine administration has been reported in only one anecdotal case. To the contrary, a double-blind placebo-controlled ultrasonographic study of 12 patients undergoing cholecystectomy showed a constriction of the common bile duct after a single intravenous dose of 0.2 mg/kg of morphine.

It is noteworthy that common bile duct enlargement is not related to age (all of subjects were aged <50 years) or to previous cholecystectomy, because no patients underwent cholecystectomy. Endoscopic ultrasound analysis ruled out obstruction of the biliary tract. Thus, we assume that morphologic bile duct abnormalities are related to narcotic substitution, probably by a modification of the biliary pressure, mainly at the Oddi sphincter level. We did not analyzed this hypothesis by manomet-

### TABLE 1. General characteristics of IVDU or ex IVDU with or without substitution

<table>
<thead>
<tr>
<th></th>
<th>Under substitution†</th>
<th>Without substitution‡</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (y)*</td>
<td>38 ± 7</td>
<td>37 ± 8.5</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>27/9</td>
<td>216/118</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatitis activity index*</td>
<td>7.0 ± 5.0</td>
<td>6.0 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>% Cirrhosis</td>
<td>10</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>% Bile duct abnormalities</td>
<td>10.8 ± 0.03</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>AST (UI/L)</td>
<td>58 ± 66</td>
<td>58 ± 73</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (UI/L)</td>
<td>79 ± 79</td>
<td>90 ± 103</td>
<td>NS</td>
</tr>
<tr>
<td>GGT (UI/L)</td>
<td>117 ± 155</td>
<td>82 ± 147</td>
<td>NS</td>
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<tr>
<td>Ph Alc (UI/L)</td>
<td>73 ± 38</td>
<td>125 ± 53</td>
<td>NS</td>
</tr>
<tr>
<td>Bilirubinemia (μmol/L)</td>
<td>10 ± 5</td>
<td>12 ± 10</td>
<td>NS</td>
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*Mean ± SD. †n = 36. ‡n = 298.
ric study of Oddi sphincter because such an exploration could be deleterious.6

The reasons why orally narcotic substitution (methadone and buprenorphine), contrary to intravenous heroin, can lead to bile duct enlargement is unknown. Route of administration (oral vs. intravenous), timing of administration (regular vs. irregular), or intrinsic properties of methadone and buprenorphine cannot be ruled out; but, we recently observed a new case of dilation under sulfate of morphine substitution.

Physicians should be aware of this substitution-related bile duct dilation. Such a dilation in subjects under narcotic substitution, in whom biologic hepatic abnormalities are frequent due to chronic alcohol intake or chronic viral hepatitis, does not require invasive and potentially deleterious procedures. However, we underline the need of an absence of clinical or biologic evolution in favor of biliary obstruction to not perform invasive procedures. Whether such bile duct abnormalities can be found in patients without liver disease remains to be determined.

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REFERENCES