The underestimated role of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy

Anne DRUART-BLAZY, Alexandre PARIENTE, Philippe BERTHELEMY, Ramuntxo AROTÇARENA
Unité d'Hépato-gastroentérologie, Centre Hospitalier, Pau.

SUMMARY

Aims — Pain recurrence after cholecystectomy is often attributed to sphincter of Oddi dysfunction, whose diagnostic criteria and treatments remain uncertain. We performed a retrospective study to assess the possible precipitating role of opiate ingestion in this setting.

Methods — The retrospective study of the files of 147 consecutive patients investigated for post-cholecystectomy syndrome by endoscopic ultrasonography and/or endoscopic retrograde cholangiography yielded 37 cases of suspected biliary-type sphincter of Oddi dysfunction.

Results — Thirteen patients (30%) with suspected sphincter of Oddi dysfunction had taken opiate-containing drugs 1.5 minutes to two hours before the onset of pain (“Opiate group”). When compared with the 23 patients having not taken opiates (“Non-Opiate Group”), they were significantly younger (47 vs. 60 yrs), had a narrower common bile duct (5.0 vs. 7.7 mm), but had similar biochemical abnormalities and belonged to the same Milwaukee’s classes, mainly class II. None of the patients in the “Opiate group” were submitted to retrograde cholangiography or endoscopic sphincterotomy vs. 52% and 39%, respectively of the “Non-Opiate group”. After a mean follow-up of 3.5 years, there were three recurrences of biliary-type pain (1 choledochal stone, and 2 suspected sphincter of Oddi dysfunction) in the “Opiate group”, and 2 (1 choledochal stone, 1 after codeine intake) in the “Non-Opiate group”.

Conclusions — Opiate intake is a frequent cause of suspicion of sphincter of Oddi dysfunction after cholecystectomy, especially in young patients with a narrow common bile duct. A careful history taking is essential to avoid unnecessary and potentially harmful procedures.

RÉSUMÉ

Le rôle méconnu de la prise d’opiacés chez les malades suspects de dysfonction du sphincter d’Oddi

Anne DRUART-BLAZY, Alexandre PARIENTE, Philippe BERTHELEMY, Ramuntxo AROTÇARENA

Objectif — La récidive de douleurs biliaires après cholécystectomie est souvent attribuée à une dysfonction du sphincter d’Oddi dont les critères diagnostiques et le traitement restent discutés. Notre étude rétrospective avait pour but d’évaluer le rôle déclenchant de la prise d’opiacés dans ce contexte.

Méthodes — L’étude rétrospective des dossiers de 147 malades consécutivement explorés pour syndrome post-cholécystectomie par échoendoscopie et/ou cholangiographie rétrograde sélectionnait 37 cas de suspicion de dysfonction du sphincter d’Oddi.

Résultats — Treize malades suspects de dysfonction du sphincter d’Oddi avaient pris des médicaments opiacés 1.5 minutes à 2 heures (médiane 1 heure) avant le début de la douleur (Groupe O). Comparés avec les 29 malades n’ayant pas pris d’opiacés (groupe NO), les malades du groupe O étaient significativement plus jeunes (47 contre 61 ans), avaient une voie biliaire principale plus fine (5,0 contre 7,7 mm), mais avaient des anomalies biologiques similaires, et appartenaient aux mêmes classes de la classification de Milwaukee (principalement la classe II). Aucun n’avait eu de cholangiographie rétrograde ni de sphinctérotomie endoscopique (contre respectivement 48 % et 31 % des malades du groupe NO). Après un suivi moyen de 3,5 ans, il y eut 3 récidives de douleurs de type bilaire dans le groupe O (1 lithiase chéloïdienne, et 2 suspicions de dysfonction du sphincter d’Oddi) et 3 dans le groupe NO (1 lithiase chéloïdienne, 1 hypertrophie papillaire bénigne, et 1 après prise de codeine).

Conclusions — La prise d’opiacés est une cause fréquente de suspicion de dysfonction du sphincter d’Oddi, après cholécystectomie, particulièrement chez les malades jeunes ayant une voie biliaire principale fine. Un interrogatoire soigneux est essentiel pour éviter des explorations inutiles et potentiellement dangereuses.
opioid use, and found that it was a frequent occurrence. In this study, we report the characteristics of a consecutive series of patients with suspected SOD and opioid ingestion and compare them with patients with suspected SOD who did not take opioids.

**Methods**

**Study population**

The files of all cholecystectomized patients hospitalized in our unit for endoscopic biliopancreatic investigation (usually because of pain, abnormal liver biochemistry, and/or biliopancreatic echographic abnormalities) between January 1996 and June 2003 were retrieved. All the morphologic documents and reports were reviewed. The following characteristics were recorded: age, gender, the presence of biliary-type pain, the interval between cholecystectomy and symptoms, the eventual drug intake, the maximum value of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyltranspeptidase (GGT), total bilirubin, the maximum diameter of the common bile duct measured during endoscopic ultrasonography, the realization of endoscopic retrograde cholangiography (ERCP) and sphincterotomy, and the immediate outcome. The evolution after hospitalization was assessed by outpatient visits and telephone calls to the patients and their general practitioners.

**Endoscopic procedure**

Endoscopic ultrasonography was done under general anesthesia, using an Olympus EUM 20 endoscope. Retrograde cholangiography and sphincterotomy were done during the same session, when judged necessary, by the same operator. In patients without clearly demonstrated stones, tumor or stenosis, the main indication for sphincterotomy was a suspicion of an organic disease at the papilla level, usually topped by a dilated common duct.

**Statistical analysis**

Results are expressed as median and/or mean ± SE. Group comparison were done using Chi-square test, exact probability test, t test after log transformation or Wilcoxon’s rank sum test when the distribution of values was not normal.

**Results**

During the study period, we investigated 151 patients previously cholecystectomized. We excluded four cases because of incomplete files. Final diagnoses are indicated in the figure 1. Forty-three patients had no detectable organic biliopancreatic disease; in six cases, there was no biliary-type pain, leaving 37 cases as putative SOD.

The patients with suspected SOD were mainly females (81%), with a mean age of 56 years (On average, fifteen years younger than patients with stones). The delay from cholecystectomy to symptoms ranged from 3 months to 32 years (median 10 years), and was slightly greater than in patients with stones.

Thirteen patients had taken opiates soon before the beginning of symptoms: analgesics containing codeine associated with paracetamol, in therapeutic doses (usually two tablets) in seven cases, and drugs for cough containing codeine or codethylin in 6 cases. One patient had taken syrup for cough containing codeine 24 hours before the occurrence of pain; because of this long latency period, we did not include this patient in the “opiate group”. In the other patients, the codeine intake had preceded the onset of pain by 15 min to 2 hours (median 1 hour). Codeine intake was only observed in 2 out of the 104 patients with no suspicion of SOD: the final diagnoses were intermittent small bowel obstruction in one, and liver dysfunction related to sepsis in the other. When compared with patients without opioid ingestion before the symptom-onset (tables I and II), the patients of the “opiate group” were significantly younger (47 vs. 60 years) and had a narrower common bile duct (5.0 mm vs. 7.7 mm), only one of them having a common bile duct of 7 mm or more, vs. 13/23 in the “non-opiate group”. None was submitted to ERCP or sphincterotomy (vs. 52% and 39% of the “non-opiate group”, with 1 case of mild post-procedure pancreatitis among 9 sphincterotomies). There was no significant difference concerning serum bilirubin, AST, ALT, PAL or GGT, although there was a tendency to higher aminotransferases and lower bilirubin and alkaline phosphatases in the “opiate group”. The patients belonged mainly to the class II of the Milwaukee’s classification (12/13 in the “opiate group” and 16/23 in the “non-opiate group”), without significant difference between the two groups (P = 0.25).

Six patients were lost to follow-up: one (8%) in the opiate group, and 4 (17%) in the non-opiate group. With a mean follow-up of 3.5 years there were 5 recurrences of biliary-type pain: 3 in the “opiate group” (in one case due to a choledochal stone 2.5 years after the initial episode, and 2 without detectable causes from 6 months to 7 years afterwards), and 2 in the “non-opiate” group (1 case of choledocholithiasis and one case after the intake of codeine, 4 and 2 years, respectively, after the initial episode).

<table>
<thead>
<tr>
<th>Presumptive SOD type</th>
<th>Definition: Biliary type pain plus…</th>
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<tbody>
<tr>
<td>Biliary type I</td>
<td>Classic: Abnormal HE + Dilated BD + delayed drainage</td>
</tr>
<tr>
<td>Biliary type II</td>
<td>Classic: Abnormal HE + Dilated BD</td>
</tr>
<tr>
<td>Biliary type III</td>
<td>Contemporary: Abnormal HE or Dilated BD or delayed drainage</td>
</tr>
</tbody>
</table>

SOD: sphincter of Oddi dysfunction; HE hepatic enzymes; Dilated BD: dilated bile duct (more than 12 mm); delayed drainage: delayed drainage of more than 45 min.
Table II. – Comparison of patients suspects of sphincter of Oddi dysfunction owing to opiate intake before the onset of symptoms.

Comparaison des patients suspects de dysfonction du sphincter d’Oddi en fonction de la prise d’opiacés avant le début des symptômes.

<table>
<thead>
<tr>
<th></th>
<th>Opiate group</th>
<th>Non-Opiate Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 13*</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>47 ± 14 (49)</td>
<td>60 ± 19 (61)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female gender</td>
<td>13 (100 %)</td>
<td>16 (69 %)</td>
<td>0.03</td>
</tr>
<tr>
<td>Delay from cholecystectomy (months)</td>
<td>86 ± 88 (63)</td>
<td>125 ± 128 (78)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bilirubin (μmol/L)</td>
<td>17.6 ± 11.2 (16.0)</td>
<td>28.5 ± 27.9 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline phosphatase (x ULN)</td>
<td>1.1 ± 0.2 (1.0)</td>
<td>1.4 ± 0.6 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Gamma-GT (x ULN)</td>
<td>4.7 ± 7.5 (2.0)</td>
<td>5.2 ± 5.0 (2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspartate aminotransferase (x ULN)</td>
<td>6.3 ± 7.6 (4.0)</td>
<td>3.9 ± 3.3 (2.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Alanine aminotransferase (x ULN)</td>
<td>7.1 ± 8.4 (3.0)</td>
<td>4.0 ± 3.4 (2.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Main bile duct diameter (mm)</td>
<td>5.0 ± 2.3 (5.0)</td>
<td>7.7 ± 3.5 (7.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Retrograde cholangiography</td>
<td>0 (0 %)</td>
<td>12 (52 %)</td>
<td>0.002</td>
</tr>
<tr>
<td>Endoscopic sphincterotomy</td>
<td>0 (0 %)</td>
<td>9 (39 %)</td>
<td>0.01</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>46 ± 28 (46)</td>
<td>34 ± 23 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrence</td>
<td>3/12 (17 %)</td>
<td>2/21 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Milwaukee type (I/II/III)</td>
<td>0/12/1</td>
<td>3/16/4</td>
<td>NS</td>
</tr>
</tbody>
</table>

* One patient, who had taken codeine 24 hr before the onset of pain, was excluded from the analysis. Values are given as mean ± SD or exact values. Median or percentages are between brackets. ULN: upper limit of normal values.
NS: not significant

Discussion

The role of opiates (mainly morphine and codeine) in the triggering of biliary pain in cholecystectomized patients is established for a long time [6-8], and attributed to the association of spasm of the sphincter of Oddi induced by the drug and the loss of the reservoir-damper role played by the gallbladder. After subcutaneous injection of morphine, the biliary pressure increases from the first 5 minutes, is maximal after approximately 15 minutes and persists at least 2 hours [10]. After intramuscular injection of morphine, the lag-time is 30 minutes, and the effect can be antagonized by coerulein [8]. However, the muscular injection of morphine, the lag-time is 30 minutes, and the effect can be antagonized by coerulein [8].

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In our experience, a third of cholecystectomized patients with suspected biliary-type SOD were found to have taken codeine in therapeutic doses 15 minutes to 2 hours before the onset of pain. This high prevalence, not previously reported in the literature, could appear surprising, but is related, in our opinion, to two factors: a general increase in the consumption of codeine-containing analgesics during the last decade on the one hand, and careful history taking on the other. In our patients, the codeine intake was sometimes forgotten or neglected: one patient had to be questioned on three separate occasions to remember having chewed two tablets containing codeine for a vague sorethroat; for another patient, who stated having taken paracetamol alone for a headache, careful interrogation revealed combined codeine-paracetamol ingestion given to her by her migraine-suffering daughter. In our unit, comprising 3 senior gastroenterologists, we have been sensitised by our previous experience since 1994 [9] to be extremely rigorous with respect to drug ingestion in such patients.

Therefore, we believe that the collection of these data was as appropriate as in a prospective study, at least concerning patients with an unidentified cause for post-cholecystectomy syndrome. The comparison between our patients suspected of SOD having or not taken opiates before pain seems therefore to be accurate.

Although patients having taken opiates were younger and had a narrower common bile duct than patients having not taking opiates before pain, the presentation of patients in the opiate group was similar. Most belonged to the Milwaukee’s class II classification, and this compared to the majority of patients [4, 5] in the two controlled studies having established the efficacy of endoscopic sphincterotomy in biliary-type SOD in the subclass of patients with sphincter of Oddi’ hypertony. In these two studies, a morphine-prostigmine test was performed. In the study by Geenen et al. [4], the test was positive in only 7/35 patients tested (however apart from pain, a 5-time increase in the basal value of serum enzymes was also required for the test to be considered positive). In the study by Touli et al. [5], the test was positive in 48 of 81 patients, however a positive result required only a supranormal value of serum enzymes. The positivity of the test was correlated neither with the basal sphincter pressure nor with the symptomatic efficacy of sphincterotomy in these two studies. The correlation between a positive morphine-neostigmin test and the common bile duct diameter was not indicated, and yet, according to the presumed pathophysiology [8], a positive test had to be more frequent when, as in our patients, the bile ducts are thin. The onset of pain after the spontaneous ingestion of opiates was not indicated in these two studies as an exclusion criterion. We agree with the general opinion that, because of poor specificity and sensitivity, the morphine-prostigmine test has to be discarded [1].
In conclusion, the ingestion of opiates is, in our experience, a frequent cause of presumptive biliary-type SOD in cholecystectomized patients. These patients are younger, and have a narrower common bile duct diameter than patients with presumptive SOD having not taken opiates before the onset of pain. They need to be identified by a careful questioning, to avoid unnecessary and potentially harmful investigations or therapy. Cholecystectomized patients should be instructed not to take opiate-containing drugs, and this precaution should be written on these drug boxes.

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REFERENCES