Effect of the rectal administration of indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes

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RESUMEN

Introducción: hiperamilasemia y pancreatitis aguda representan las complicaciones más frecuentes a la colangiopancreatografía retrógrada endoscópica (CPRE), apareciendo en 1-30% de los casos.

Objetivo: determinar la incidencia de hiperamilasemia y pancreatitis aguda en el postprocedimiento, y evaluar la utilidad de indometacina rectal para la prevención de estos.

Material y métodos: estudio clínico controlado. En un período de 12 meses se incluyeron 150 pacientes. Estos fueron divididos en estudio (n = 75), a quienes se administró indometacina rectal 100 mg 2 horas previas al procedimiento, y control (n = 75) que recibió glicerina. Dos horas postprocedimiento se determinó el nivel de amilasa sérica y se clasificaron como: 0 = ≤ 150 UI/L, 1 = 151-599 UI/L, 2 ≥ 600 UI/L. Los episodios de pancreatitis clínica se cuantificaron y clasificaron de acuerdo a los criterios de Ranson.

Resultados: se dividió el estudio en grupo control (n = 75), a quienes se administró indometacina rectal 100 mg 2 horas previas al procedimiento, y control (n = 75), que recibió glicerina. Dos horas postprocedimiento se determinó el nivel de amilasa sérica y se clasificaron como: 0 = ≤ 150 UI/L, 1 = 151-599 UI/L, 2 ≥ 600 UI/L. Los episodios de pancreatitis clínica se cuantificaron y clasificaron de acuerdo a los criterios de Ranson.

Conclusions: indometacina rectal previo a CPRE disminuye el riesgo de hiperamilasemia y pancreatitis. La indometacina es accesible, de bajo costo con mínimos o nulos efectos secundarios.


ABSTRACT

Background: hyperamylasemia and acute pancreatitis represent the most frequent major complication after endoscopic retrograde cholangiopancreatography (ERCP), developing in 1-30% of cases.

Objective: to determine the incidence of hyperamylasemia and acute pancreatitis after ERCP, and to assess the utility of rectal indomethacin to prevent these events.

Material and methods: a randomized clinical trial. During a 12-month period 150 patients were included. They were divided up into a study group (n = 75), who received 100 mg of indomethacin rectally 2 hours prior to the procedure, and a control group (n = 75), which received rectal glycerin. Two hours after ERCP serum amylase levels were measured and classified as follows: 0 ≤ 150 IU/L, 1 = 151-599 IU/L, 2 ≥ 600 IU/L. Clinical pancreatitis episodes were quantified and classified according to Ranson’s criteria.

Results: Gender distribution: 100 women and 50 men. Mean age: 55.37 ± 18.0 for the study group, and 51.1 ± 17.0 for the control group. A diagnosis of benign pathology was present in 56 (74.7%) cases of the study group, and 59 (78.7%) control. Posterior to the procedure, 13 (17.3%) patients of the study group and 28 (37.3%) in the control group developed hyperamylasemia (p < 0.05). Se encontró una hiperamilasemia > 600 UI/L en 3 pacientes del grupo de estudio y 10 del control (p = 0.001). Se detectó pancreatitis leve en 5,3% de los pacientes del grupo de estudio y 16% del control (p < 0.05). No hubo mortalidad ni eventos adversos.

Conclusions: indomethacin before ERCP decreases the risk of hyperamylasemia and pancreatitis. Indomethacin is a feasible, low-cost drug with minimal or nil side effects.

Key words: Endoscopic retrograde cholangiopancreatography. Hyperamylasemia. Acute pancreatitis. Indomethacin.
INTRODUCTION

Hyperamylasemia and pancreatitis are events that frequently occur after endoscopic retrograde cholangiopancreatography (ERCP), and are seen in 1 to 30% of patients (1-5). The incidence of post-ERCP pancreatitis varies depending on the indications and the procedure conducted. Mortality rate ranges between 0.2 and 0.6% (6-8). Risk factors for post-ERCP pancreatitis include a history of pancreatitis (9), difficult pancreatic-duct cannulation (7), repeated injection of contrast in the pancreatic duct (9), pancreatic acinar opacification (10), sphincter of Oddi hypertension (SOH) (8,11), and precut sphincterotomy (3,8,9).

The pathogenesis of post-ERCP pancreatitis is unclear. It seems that the instrumentation and opacification of the pancreatic duct plays an important role in the inflammatory response (11). The initial intracellular events cause pancreatic acinar damage followed by a local inflammatory response that frees pro-inflammatory cytokines into the blood stream (12). The severity of the disorder is determined by the magnitude of the resulting systemic inflammatory response (13).

Since the initial event is well identified, post-ERCP acute pancreatitis is a unique model for assessing the benefit of early immunomodulation (11-15).

The results from several controlled studies, where prophylactic agents such as glucagon (16), calcitonin (17), nifedipine (18), octreotide (19) and corticosteroids (20) have been used, have been little promising. Although initial studies failed to show a decrease in post-ERCP pancreatitis, recent trials have detected a beneficial preventive effect (21). It is thought that phospholipase A2 (FLA2) plays an important role in the initial inflammatory cascade that occurs in acute pancreatitis through the regulation of pro-inflammatory agents, including prostaglandins, leukotrienes, and platelet activating agents (22). The inhibition of FLA2 has been the aim of several therapeutic agents used to treat non-ERCP-dependent acute pancreatitis with promising results. It has been shown that nonsteroidal antiinflammatory agents (NSAIDs) are potent inhibitors of serum FLA2 in patients with acute pancreatitis (23), and have beneficial effects in other experimental models of murine pancreatitis (24).

The aim of this study was to determine the effect of rectal indomethacin on amylase levels and cases of post-ERCP pancreatitis.

MATERIAL AND METHODS

This was a controlled single-blind clinical trial carried out in patients who underwent ERCP within a 12-month period (June 2004 to May 2005) at the Endoscopy and Gastroenterology Departments of High Specialty Medical Unit, Specialties Hospital of IMSS Western National Medical Center, and Endoscopy Department at “Fray Antonio Alcalde” Civilian Hospital, University of Guadalajara. A total of 150 patients meeting the following criteria underwent ERCP out of a total population of 250 candidates:

—Patients over 18 years undergoing ERCP for suspected bile duct obstruction and accepting their enrollment in the study by signing an informed consent form.

—No patients with clinically evident acute pancreatitis or hyperamylasemia (≥ 150 IU/L) before the procedure, or having ingested NSAIDs a week earlier were enrolled in the study.

—Patients treated with anticoagulants or platelet anti-aggregants such as acetylsalicylic acid and plactixel, or with a prothrombin time with a difference of > 5 seconds versus the blind sample taken in a period no greater than 72 hours before the study.

—Patients allergic or hypersensitive to indomethacin or water-soluble contrast solutions, or those with active hemorrhage of peptic origin, or unable to lie on their backs for the endoscopic procedure.

We estimated that post-ERCP hyperamylasemia and/or acute pancreatitis episodes decreased by 15% with our intervention, for which we required 150 cases (25). Seventy-five patients were randomly assigned to the study group receiving 100 mg of indomethacin rectally two hours before the procedure, and 75 patients to the control group receiving 2 g of glycerin in suppositories.

Blood samples were drawn from all patients to determine serum amylase levels before the procedure and two hours later, and were classified usually as: grade 0: ≤ 150 IU/L, grade 1: 151-599 IU/L, and grade 2: > 600 IU/L.

All serum amylase values below 150 IU/L were regarded as normal. If amylase serum levels were > 150 and < 600 IU/L, and there was no evidence of acute pancreatitis (abdominal pain, nausea, vomiting), patients were discharged. If they were admitted, they were started on a liquid diet. If serum amylase was three times over the normal value and the patient had a sharp pain irradiating to his/her back, as well as nausea or vomiting, a diagnosis of post-ERCP acute pancreatitis was established in the absence of radiological evidence of pneumoperitoneum or emphysema in the retroperitoneal space. These cases were managed in the hospital with fasting, hydration with crystalloid solutions, and analgesics. Pancreatitis episodes were classified according to Ranson’s prognostic criteria (26).

Details concerning the endoscopic procedure, specifying difficulty for cannulation, number of pancreatic-duct injections, sphincterotomies, bile-duct characteristics, presence of cholelithiasis, and whether the procedure was diagnostic or therapeutic (endoprosthesis placement), were recorded. Previously the authors reported preliminary results from this protocol with 80% of cases evaluated, and published them in Revista de Gastroenterología de México late in 2006 (27).
Statistical analysis

Results are shown as average values, percentages, and means with standard deviations. Statistical inference was performed using the Chi square or Fisher’s exact test for qualitative variables, while Student’s T-test was used for quantitative variables. To explore the behavior of risk factors, relative risks and 95% confidence intervals were estimated. All p values lower than 0.05 were considered statistically significant. Finally, the reduction in absolute risk (RRA), the reduction in relative risk (RRR), and the number needed to treat (NNT) were analyzed in order to prevent an episode of pancreatitis.

Ethical considerations

The research protocol was reviewed and approved by the Research and Ethics Committees at the participating institutions. All patients signed informed consent forms prior to their taking part in the study. The study was supported with funds from both institutions.

RESULTS

The distribution by gender consisted of 50 men (33.3%) and 100 women (66.7%), for a 2:1 female:male ratio (p = 0.863). Gender distribution for the study group was 26 males and 49 females; in the control group there were 24 men and 51 women, with no significant differences (p = 0.86). Mean age for the study group was 55.37 ± 18.0 years, whereas for the control group it was 51.12 ± 17 (p = 0.985).

A benign diagnosis for both groups was reported in 115 (76.6%) patients, of which 56 were from the study group and 59 from the control group. Malignancy corresponded to 35 (23.3%) cases for both groups, 19 from the study group and the rest from the control group. Diagnoses reached are shown in table I.

Table II shows risk factors at the time of the endoscopic procedure. No statistically significant differences were found. Baseline amylase in the study group was 53.56 ± 22 IU/L, and it was 56.56 ± 22.8 IU/L in the control one (p = 0.38). Levels reached at 2 hours were 148.22 ± 190.6 IU/L in the study group, and 240.73 ± 256.2 IU/L in the control group (p = 0.013).

A total of 41 patients had hyperamylasemia (151-599 IU/L), 13 (17.3%) in the study group and 28 (37.3%) in the control group. Values higher than 600 IU/L were observed in 13 patients, with 3 corresponding to the study group (4%) and 10 (13.3%) to the control group (p = 0.04) (Fig. 1). Sixteen patients developed acute pancreatitis (10.7%), of which 4 correspond to the study group and 12 to the control group (p = 0.034). One female patient in the first group and two cases in the second group had amylase levels just below 600 IU/L at 2 hours. Twenty four hours after the procedure, the average serum amylase level was 1342.20 ± 345.3 IU/L. All cases were classified according to Ranson’s criteria at admission and at 48 hours as having mild pancreatitis, and were managed conservatively while evolving well. All patients were discharged within five days of treatment onset. No deaths were reported.

Table III shows the different risk factors analyzed and related to hyperamylasemia, finding statistical significance for preventing hyperamylasemia in the study group regardless of the nature of the biliary condition. In addi-
tion, there was a smaller number of cases of hyperamylasemia when sphincterotomy was performed in the study group (p = 0.03), when biopsies and brushings were done (p = 0.008), and during the cannulation of the pancreatic duct with marginal statistical significance (p = 0.06). No differences were found when a prosthesis was required (p = 1.0).

All patients developing clinically evident pancreatitis underwent sphincterotomy, cannulation or opacification of the pancreatic duct. Table IV shows the distribution of diagnoses and procedures conducted during ERCP.

We found an absolute risk reduction (ARR) equal to 10.7%, with a relative risk reduction (RRR) of 66%, and a number needed to treat (NNT) of 13 to avoid a clinically apparent episode of pancreatitis. No adverse events were recorded with the use of rectal indomethacin or glycerin suppositories.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Study group</th>
<th>Control group</th>
<th>*p value</th>
<th>RR</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign disease</td>
<td>14 (56)</td>
<td>29 (59)</td>
<td>0.01</td>
<td>0.56</td>
<td>0.35-0.90</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>2 (19)</td>
<td>9 (16)</td>
<td>0.01</td>
<td>0.26</td>
<td>0.07-0.92</td>
</tr>
<tr>
<td>Placement of prosthesis</td>
<td>1 (8)</td>
<td>2 (9)</td>
<td>1.0</td>
<td>0.67</td>
<td>0.12-3.35</td>
</tr>
<tr>
<td>Sphincterotomy</td>
<td>11 (39)</td>
<td>25 (49)</td>
<td>0.03</td>
<td>0.57</td>
<td>0.33-0.99</td>
</tr>
<tr>
<td>Cannulation and/or pancreatic duct opacification</td>
<td>2 (5)</td>
<td>6 (6)</td>
<td>0.060</td>
<td>0.25</td>
<td>0.08-0.83</td>
</tr>
<tr>
<td>Biopsy and brushing of bile duct</td>
<td>1 (15)</td>
<td>5 (8)</td>
<td>0.008</td>
<td>0.20</td>
<td>0.03-1.23</td>
</tr>
<tr>
<td>No endoscopic handling</td>
<td>1 (8)</td>
<td>0 (3)</td>
<td>1.00</td>
<td>1.43</td>
<td>0.95-2.14</td>
</tr>
</tbody>
</table>

*p value was obtained using Chi square and Fisher’s exact tests. Values between parentheses represent the total number of patients with the diagnosis or endoscopic handling. RR: relative risk; 95% IC: 95% confidence interval.

DISCUSSION

Indomethacin was introduced in 1963 for the treatment of rheumatoid arthritis and related disorders. It has antiinflammatory, analgesic, and antipyretic properties, similar to salicylates. Therapeutic effects are a consequence of their property for inhibiting the synthesis of prostaglandins.

The first enzyme participating in the synthesis of prostaglandins is synthetase-end peroxide or fatty-acid cyclo-oxygenase. This enzyme transforms arachidonic acid into unstable intermediary products. Two forms of cyclo-oxygenase exist –cyclo-oxygenase-1 (COX-1), and cyclo-oxygenase-2 (COX-2). The former is the constitutive isoenzyme found in the blood stream, stomach, and kidneys, whereas the latter is often seen in inflammatory situations induced by cytokines and inflammatory mediators. The biotransformation of cyclo-oxgenase products PGH2/PGF2 differs from one tissue to the next one, and depends on the metabolizing enzymatic activities of that particular PGH2/PGF2. Arachidonic acid can also be transformed into diverse leukotrienes via 5-lipoxygenase. Indomethacin and the rest of NSAIDs inhibit cyclo-oxgenase and prostaglandin production, but does not suppress lipoxygenase or leukotriene formation. It also inhibits death in polymorphonuclear leukocytes. In contrast to other NSAIDs, it uncouples oxidative phosphorylation to supratherapeutic concentrations and depresses the biosynthesis of mucopolysaccharides (28).

Indomethacin and the greater part of NSAIDs are organic acids. While different from acetylsalicylic acid, they constitute competitive reversible inhibitors of cyclo-oxygenase activity. As organic acids, these compounds are almost always absorbed after ingested, avidly bind plasma proteins, and are excreted by glomerular filtration or tubular secretion. For this reason, indomethacin, aspirin, and other NSAIDs accumulate in inflammatory sites, which constitute an attractive pharmacokinetic property for products intended to be used as antiinflammatory agents. After the administration of single oral doses of 25 or 50 mg, indomethacin is easily absorbed and reaches peak serum concentrations of 1 and 2 μg/ml, respectively, at approximately two hours after administration. Bioavailability is practically 100%, and after four hours 90% of the dose is absorbed. Elimination is via the kidneys, with metabolic transformation, biliary excretion, and considerable enterohepatic circulation. Its half-life has been estimated around 4.5 hours. Absorption via the kidneys is slightly higher (80-90%) (28).

Within the limits of variation of therapeutic plasma concentrations, approximately 99% of indomethacin binds to plasma proteins. It also passes the blood-brain and placental barriers (29). Regarding the mechanisms related to pancreatic damage, phospholipase A2 (PLA2) plays an important role in the initial inflammatory cascade through the regulation of proinflammatory mediators, including prostaglandins, leukotrienes, and...
platelet-activating factors (22). FLA inhibition has been the objective of several therapeutic agents used to treat acute pancreatitis—not induced by ERCP— with acceptable results. In previous studies, only gabexate mesylate proved to prevent ERCP-related pancreatic damage and decrease its incidence (30).

Ebbehoj et al. (31) have reported the results of a controlled clinical trial in patients with acute pancreatitis where 50 mg of indomethacin were administered rectally twice a day, decreasing pain and the need for opiate analgesics in the treated group. These promising results supported our research idea for the development of this project. Previously, Murray et al. (32), in a randomized clinical trial, demonstrated that the rectal application of diclofenac, 100 mg two hours after an ERCP, reduces the incidence of pancreatitis episodes—such events developed in 6.4% of patients in the study group, and in 15.5% of patients in the control group (p ≤ 0.05). In our study the incidence in the first group was 5.3%, and 16% in the control group (p ≤ 0.05). Fortunately, all acute pancreatitis episodes in our study were catalogued as mild, contrary to Murray's study, where two patients (8.3%) developed severe necrotic acute pancreatitis from a total of 24 cases.

Without any doubt, a wide variety of risk factors have been identified for the development of post-ERCP pancreatitis. In a recent study, Loperfido et al. (33) identified three risk factors related to post-ERCP pancreatitis: non-dilated bile duct, pancreatic duct opacification, and age younger than 70 years. A second multicenter study from Italy (34) demonstrated three statistically significant risk factors: inability to eliminate bile-duct stones, precut sphincterotomy, and age younger than 60 years. An American multicenter study (7) revealed several other risk factors such as: a history of post-ERCP pancreatitis, biliary balloon sphincter dilation, difficult cannulation, pancreatic sphincterotomy, more than one pancreatic contrast injection, dysfunction of the sphincter of Oddi, female gender, normal serum bilirubin, and absence of chronic pancreatitis. Finally, a French study (8) supported precut sphincterotomy and the presence of sphincter of Oddi dysfunction as independent variables that increased the risk of pancreatitis. In our cases, we found a clear protective effect of indomethacin regardless of disease nature and endoscopic procedure, with the exception of stent application.

With the identification of several patient-related risk factors (i.e., young age, female gender, history of post-ERCP pancreatitis, etc.), endoscopists can now use this information in a risk-benefit analysis when deciding whether to perform an ERCP.

A majority of cases of post-ERCP pancreatitis are mild and uncomplicated; however, severe cases of pancreatitis occur in up to 20% of cases, with development of necrosis, pseudocysts, abscesses, or multiple organ system failure. While most (22/24; 92%) patients developing post-ERCP pancreatitis in the study by Murray had only mild pancreatitis, 8% (2/24) of them progressed to severe pancreatitis (32). In our trial all cases had a mild form, without clinical evidence of pancreatic or peripancreatic necrosis.

The prevention of this complication is of utmost importance. A great variety of pharmacological drugs to avoid post-ERCP pancreatitis have provided only marginal benefits. The most promising agents are somatostatin and gabexate, with significant benefits according to Andruilli et al. (21). Nonetheless, neither agent is available in the United States, and both need to be administered intravenously (33). Andruilli compared each to placebo and found no protective effect by either. Octreotide, an analogue of long-acting somatostatin, has proven effective in the prevention of post-ERCP pancreatitis.

Other agents such as IL-10 (34,35) and glyceryl trinitrate (nitroglycerin) (36,37) have shown promising results. However, data on IL-10 are inconsistent, and the hypotension induced by nitroglycerin limits its use. In another study, heparin proved preventive in an effective manner (38). Further controlled trials are required to confirm such results.

In addition to pharmacotherapy, mechanical methods have been used to prevent pancreatitis, including the placement of a stent in the pancreatic duct of high-risk patients. Evidence currently available shows an important protective effect that, although encouraging, requires confirmation through controlled studies (9,39).

Recently, Menis (40) and Mahjoub (41) reported two cases of pancreatitis probably induced by indomethacin. Both were male patients older than 50 years, and both were suffering from rheumatoid arthritis under treatment with oral indomethacin for at least three weeks. In the first cases gallbladder lithiasis was identified; in the second, pancreatic-duct dilation; however, both authors considered that the only etiologic factor was the ingestion of this drug. They did not establish any etiologic mechanism, but supposed that pancreatitis had developed as a response to a decrease in glutathione levels, as well as a decrease in superoxide activity, and an increase in oxidative stress. In the most recent version of the catalog of drug-induced pancreatitis, published by Trivedi and Pitchumonj (42) the authors included NSAIDs as class-III drugs (among them they emphasized diclofenac and other NSAIDs, but indomethacin was not included) or drugs probably related to drug-induced pancreatitis with less than 10 reported cases in the literature. To consider a drug definitively associated to pancreatitis—a class-I drug— at least 20 cases must be found in the literature with pancreatitis resolution upon discontinuing the drug and at least 1 case with positive rechallenge. When this protocol was designed, we established among inclusion criteria that patients must not have hyperamylasemia or...
any previous ingestion of NSAIDs for a week before ERCP. The authors consider that even in patients with pancreatitis in the study group, episodes were related to the endoscopic maneuver rather than the rectal application of a single indomethacin dose.

In conclusion, when conducting this procedure, 13 patients (17.3%) from the study group and 28 (37.3%) from the control group had hyperamylasemia. Levels over 600 IU/L were reported in 3 (4%) cases of the study group and 10 (13.3%) of the control group. Clinically apparent post-ERCP pancreatitis was found in 4 patients in the study group (5.3%) and 12 (16%) patients in the control group (p = 0.034, RR = 0.33). Our results indicate that the use of rectal indomethacin prior to ERCP decreases the incidence of hyperamylasemia and clinical pancreatitis. We suggest the use of rectal indomethacin especially in those patients with risk factors for the development of pancreatitis.

REFERENCES


