Hypothesis: A worse clinical outcome might be expected in patients with acute pancreatitis (AP) who receive intravenous contrast medium for a nondynamic contrast-enhanced computed tomographic (CECT) study early during hospital admission.

Design: Cohort analytic study.

Setting: Tertiary care center.

Patients: Of 126 patients with mild AP, 52 patients underwent CECT to establish AP diagnosis (group 1), and the remaining 74 did not (group 2).

Main Outcome Measures: Survival and development of local or systemic complications during the hospital stay. Potential confounders were demographic, clinical, and biochemical data, as well as therapeutic measures. The Atlanta classification was used to define local and systemic complications.

Results: Mean age, etiology of AP, prognostic score on admission, and pharmacologic treatment were similar between groups. Local and systemic complications were more frequently observed in patients who underwent CECT (odds ratio, 11.4; 95% confidence interval, 2.0-64.8; \( P = .008 \)). Six patients, all in group 1, developed a pancreatic abscess (odds ratio, 20.8; \( P = .004 \)). In 5 of them, a second CECT showed more severe AP changes. The association between CECT and abscess development was more apparent in patients with a body mass index of 25 or more and/or nasogastric suction. Six patients in group 1 and 1 in group 2 had systemic complications (odds ratio, 9.5; \( P = .01 \)). There were no deaths.

Conclusions: The observed increased incidence of local and systemic complications in patients with mild AP who undergo CECT, particularly in those with a body mass index of 25 or more, suggests a potentially harmful effect of intravenous contrast medium. Until this issue is clarified, it seems reasonable to restrict the use of dynamic CECT to patients with severe AP, protracted clinical course, or suspected local septic complication.

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COMPUTED tomography (CT) is widely used in the clinical setting to confirm diagnosis and establish severity of acute pancreatitis (AP).\(^1\)\(^-\)\(^4\) It is now relatively easy to distinguish areas poorly perfused inside the pancreas using a high volume of iodinated contrast material.\(^5\) Much controversy has arisen since Foitzik et al\(^6\) showed that intravenous contrast medium (ICM) increases severity and mortality in an experimental model of AP in rats. Changes observed in these experimental models were attributed to pancreatic blood reduction induced by ICM.\(^7\)-\(^9\) If ICM reduces pancreatic blood flow in humans, as has been observed in animals, early contrast-enhanced CT (CECT) could worsen the course of AP. However, there are no controlled, prospective studies evaluating this issue. Some indirect evidence of the effect of ICM on the human pancreas is given by the retrospective analysis of McMenamin and Gates.\(^10\) They reported that the mean duration of clinical AP was significantly longer in patients who received ICM, although no major complications were observed in these patients.

In this study we evaluated the potentially harmful effect of ICM on the human pancreas by analyzing the clinical outcome of patients with AP who did and did not undergo CECT. We included only patients with mild AP in whom a low rate of local and systemic complications is expected.\(^11\) Thus, the possible deleterious effect of an external agent such as ICM could be fully evaluated.

RESULTS

On admission, no differences were found between groups 1 and 2 in terms of mean
PATIENTS AND METHODS

PATIENTS

All patients with mild AP admitted to the Instituto Nacional de la Nutrición Salvador Zubirán, Tláhuac, Mexico, between January 1, 1987, and December 31, 1996, were included in this analysis. The clinical diagnosis of AP was based on typical symptoms such as abdominal pain, nausea, and vomiting, with an elevation of serum amylase or lipase levels 5 times above normal. Severity of AP was assessed by means of an institutional prognostic score that has been previously validated and is widely used in Mexico (Table 1). The clinical usefulness of this score is equivalent to the Ranson’s criteria. Only patients with 0 or 1 alteration and without evidence of organic failure on admission were included. Hematocrit and serum urea nitrogen level were used to evaluate hemococoncentration.

Patients were classified in 2 groups. Group 1 included 52 patients who underwent CECT. In 31 of them, the scan was done on hospital admission while in the other patients the scan was performed between the second and the seventh hospital day. In all cases, CECT was performed to establish AP diagnosis. In group 2 were 74 patients who did not undergo CECT. Demographic variables, clinical and biochemical data, treatment, and outcome until discharge were evaluated in each case. The Atlanta classification system was used to define local and systemic complications. Sepsis was considered a systemic complication.

COMPUTED TOMOGRAPHY

Each patient received 1200 mL of water with 90 mL of iothalamate meglumide (Conray; Mallinckrodt Medical, St Louis, Mo) as oral contrast material. A rapid intravenous drip infusion of 300 mL of a solution containing iothalamate meglumide at 30% was started immediately before scanning. In no case was ICM injected as a bolus. The CT images were evaluated, according to the Balthazar classification, by a radiologist (P.B.-R.) blind to any clinical data.

STATISTICAL ANALYSIS

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated. Differences between groups 1 and 2 were assessed using nonparametric statistics, namely, χ², Fisher exact, and Wilcoxon rank sum tests. To adjust for confounding, stratified analysis was carried out by means of the Mantel-Haenszel χ² statistic.

Table 1. Institutional Prognostic Score

<table>
<thead>
<tr>
<th>Cardiovascular alteration</th>
<th>Hematologic alteration</th>
<th>Metabolic alteration</th>
<th>Renal alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia (&gt;100 beats/min) or hypotension (systolic blood pressure &lt;100 mm Hg)</td>
<td>Leukocytosis (16 × 10⁹/L [16 000 cells/mL]) or &gt;10% of bands</td>
<td>Hyperglycemia (&gt;11.1 mmol/L [&gt;200 mg/dL]) or hypocalcemia (2 mmol/L [&lt;8 mg/dL])</td>
<td>Serum urea nitrogen (&gt;2-fold above reference value)</td>
</tr>
</tbody>
</table>

*Acute pancreatitis is graded as mild when 0 to 2 alterations are present. This scoring system is equivalent to the criteria of Ranson. Patients are evaluated at hospital admission.

Table 2. Demographic and Clinical Characteristics of Patients With Acute Pancreatitis

<table>
<thead>
<tr>
<th>Group 1: CECT (n = 52)</th>
<th>Group 2: No CECT (n = 74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>28/24</td>
<td>.02</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>43.9</td>
<td>.8</td>
</tr>
<tr>
<td>BMI ≥25, No.</td>
<td>29</td>
<td>.05</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>13</td>
<td>.5</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Prognostic alteration, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32</td>
<td>.2</td>
</tr>
<tr>
<td>1†</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

*CECT indicates contrast-enhanced computed tomography; BMI, body mass index.
†Leukocytosis, hyperglycemia, or tachycardia. No patient had hypotension, renal failure, ascites, or a BMI >30.

Table 3. Medical Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group 1: CECT (n = 52)</th>
<th>Group 2: No CECT (n = 74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasogastric suction</td>
<td>20 (38)</td>
<td>16 (22)</td>
<td>.04</td>
</tr>
<tr>
<td>Analgesics</td>
<td>31 (60)</td>
<td>41 (55)</td>
<td>.6</td>
</tr>
<tr>
<td>Inhibitors of gastric acid secretion</td>
<td>38 (73)</td>
<td>55 (74)</td>
<td>.9</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>9 (17)</td>
<td>10 (14)</td>
<td>.6</td>
</tr>
</tbody>
</table>

Data are given as number (percentage). CECT indicates contrast-enhanced computed tomography.

Nitrogen level (5.7 mmol/L [15.9 mg/dL] in group 1 vs 5.0 mmol/L [13.9 mg/dL] in group 2; P = .1).

Pharmacologic treatment on admission was similar in both groups. More patients from group 1 received a nasogastric suction (P = .04, Table 3). Nine patients in group 1 and 10 in group 2 received antibiotics because of suspected biliary sepsis (8 and 9 cases, respectively) or urinary tract infection. In no case were antibiotics used as prophylaxis for AP.

age, etiology of AP, and prognostic criteria. A higher male-female ratio (P = .02) and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) (P = .05) were observed in group 1 patients (Table 2). Hematocrit on admission was similar in both groups (0.45 in group 1 vs 0.44 in group 2; P = .5). No significant difference was found in mean serum urea nitrogen level (5.7 mmol/L [15.9 mg/dL] in group 1 vs 5.0 mmol/L [13.9 mg/dL] in group 2; P = .1).

Pharmacologic treatment on admission was similar in both groups. More patients from group 1 received a nasogastric suction (P = .04, Table 3). Nine patients in group 1 and 10 in group 2 received antibiotics because of suspected biliary sepsis (8 and 9 cases, respectively) or urinary tract infection. In no case were antibiotics used as prophylaxis for AP.
In 19 cases the CECT scan was normal (grade A) or showed minimal inflammatory changes (grade B). More severe grades (C-E) were observed in 33 patients. Local severity of pancreatitis did not vary with the timing of CECT performance (Table 4).

Local or systemic complications developed in 7 patients in group 1 and 1 in group 2 (OR, 11.4; 95% CI, 2.0-64.8; \( P = .008 \)). In 6 patients, all in group 1, a pancreatic abscess was diagnosed between hospital days 7 and 13 (days 9 to 17 of the clinical course; OR, 11.4; \( P = .008 \)).

Of hospital stay in 2. Images were classified as grade C in 2 patients and as grade D in 4. Three patients received antibiotics before the scan. Diagnosis of pancreatic abscess was made 5 to 10 days after this first CECT. Due to clinical deterioration, and suspected pancreatic necrosis, a second CECT was performed 7 to 10 days after the first in 5 patients, showing more severe changes in all patients (Figure 1 and Figure 2). In 3 cases a guided percutaneous aspiration disclosed Gram-negative bacilli, leading to an open drainage. The other 3 patients underwent surgery because of clinically suspected pancreatic sepsis.

Among the 6 patients who developed pancreatic abscess, 5 had a BMI of 25 or more (OR, 6.5; \( P = .07 \)), and 4 received nasogastric suction (OR, 5.5; \( P = .06 \)). Stratification by these 2 confounders, taken separately and together, showed a persistently significant association between CECT performance and abscess development (OR, ≥9.2; \( P ≤ .01 \)).

Figure 2. A. Minimal peripancreatic inflammatory changes in a patient with biliary acute pancreatitis. Pancreas showed a heterogeneous density in the body. B. In a second contrast-enhanced computed tomography performed 8 days later, a lack of enhancement of the body and tail of the pancreas was observed. A guided percutaneous aspiration disclosed Gram-negative bacilli. An open drainage was performed.

Table 4. Contrast-Enhanced Computed Tomographic Findings

<table>
<thead>
<tr>
<th>Balthazar Classification</th>
<th>On Admission (( n = 31 ))</th>
<th>Hospital Days 2-7 (( n = 21 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>D</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Chapter: Impact of CECT on the Management of Biliary Acute Pancreatitis

**Figure 1.** A, Biliary acute pancreatitis with normal parenchyma enhancement. B, Second contrast-enhanced computed tomographic scan performed 7 days later, showing peripancreatic inflammatory changes with small foci of necrosis. An open drainage was performed because of clinically suspected sepsis. Escherichia coli was isolated from pancreatic debris.

**Table 5.** Hematocrit on Admission and Hospital Day 1

<table>
<thead>
<tr>
<th>Blood Parameter</th>
<th>On Admission (( n = 31 ))</th>
<th>Hospital Days 2-7 (( n = 21 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>35%</td>
<td>31%</td>
</tr>
<tr>
<td>Mean</td>
<td>37%</td>
<td>33%</td>
</tr>
</tbody>
</table>

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who developed abscess (Table 5). Sex was not associated with development of pancreatic abscess (P = .5).

Systemic complications developed in 6 patients in group 1 and in 1 in group 2 (OR, 9.5; P = .01). The 6 patients in group 1 were the same who developed pancreatic abscess. Three of them experienced systemic sepsis, 2 had multiple organ failure, and 1 had renal failure. The only patient in group 2 who developed a systemic complication had upper gastrointestinal tract bleeding.

Median hospital stay was 18.4 days in group 1 and 11.4 days in group 2 (P = .007). No fatal outcome was observed.

There is increasing evidence that impairment of the pancreatic microcirculation plays an important role in the transition of interstitial to necrotizing pancreatitis. Moreover, in experimental models the use of isovolemic hemodilution with dextran reduces acinar necrosis, improves survival, and counteracts the impairment of pancreatic microcirculation induced by ICM. Contrast-enhanced CT is the best method for defining local complications and for distinguishing pancreatic necrosis in patients with AP. The article by Foitzik et al, showing that ICM increases severity and mortality in experimental AP, raises some concern about the use of dynamic CECT in patients with AP. It is difficult, at least in the clinical setting, to prove that ICM produces in humans the same effects as described in animals. There are no controlled, randomized, prospective studies evaluating this issue. The only indirect evidence comes from a retrospective study showing that patients who received ICM took more time to recover from mild AP.

We evaluated the potentially deleterious effect of ICM on human pancreas by analyzing the clinical outcome of patients with AP who underwent nondynamic CECT shortly after hospital admission. We only included patients with clinically mild AP in whom a low rate of complications is expected to occur. We found that both local and systemic complications developed more frequently in CECT patients. It can be argued that these patients were sicker than those who did not undergo CECT, but prognostic score, hematocrit, and serum urea nitrogen values on admission were similar in both groups. Furthermore, after adjustment for other predictors of severe AP, the factor that was persistently associated with abscess development was nondynamic CECT performed to confirm the clinical diagnosis of AP.

Dynamic enhanced CT scan, using a large bolus of ICM, is the only nonsurgical method available for detecting pancreatic necrosis. A CT-guided fine-needle aspiration is used to detect bacterial infection early in the course of a necrotizing pancreatitis. No clinical data have shown that the ICM causes any adverse effect on the human pancreas. However, experimental studies have clearly shown that the nonionic contrast medium iopamidol reduces capillary flow in rats with severe AP. The high mortality observed by Foitzik et al has been attributed to both a direct toxic effect of ICM on the acinar cell and an indirect effect on the microcirculation. It is difficult to draw conclusions from these experimental studies. Important differences exist between an experimentally induced pancreatitis and a clinical AP. Foitzik et al administered ICM 7 hours after the induction of a severe AP in rats. In the clinical setting, a CT scan is rarely performed during the first 24 hours in patients with the clinical suspicion of pancreatitis. In many cases, patients are admitted several days after the clinical onset, and frequently they have already received medical treatment that can affect the clinical outcome. To avoid these sources of confusion, we exclusively analyzed patients with mild AP who had not received any medical treatment and in whom a nondynamic CECT was performed for diagnostic purposes shortly after hospital admission.

While all our patients had clinically mild AP, only in 19 cases did the initial scan show minimal inflammatory changes or a normal pancreas. Grade C, D, or E pancreatitis was observed in the remaining 33 patients. These findings are similar to those reported by Balthazar et al, who described grade C to E pancreatitis in 57% of their patients with 2 or less Ranson’s prognostic signs. Seven (12.5%) of these 56 patients developed a pancreatic abscess. In our study, 6 patients (11.5%), all in group 1, developed an abscess. We cannot exclude that in these cases the unexpectedly worse course was actually due to the natural history of AP and to the fact that more patients in this group received nasogastric suction and had a BMI of 25 or more. Nasogastric suction and a BMI of 25 or more were significantly associated with abscess development but this association did not neutralize the one due to CECT. This means that abscess development in CECT patients is more likely to occur in obese patients and/or in those who require nasogastric suction. Our patients were not randomly allocated to CECT, and, therefore, we are not able to assure comparability of our study groups. Besides BMI and nasogastric suction, we could neither identify nor suspect other potential sources of selection bias that might have determined the systematic performance of CECT on patients who developed complications afterward. If this is true, clinical misclassification of severity on admission would be expected to occur with similar frequency in both of our study groups and irrespective of the decision to perform a diagnostic CECT.

The incidence of pancreatic abscess in our study is different from earlier series when CECT was not routinely used. In 1977, Ranson and Spencer reported pancreatic abscess in 2.7% from patients with 2 or fewer
Ranson’s prognostic signs. Later, in 1985, Ranson and Balthazar found an abscess in 12.5% of patients with mild clinical AP who underwent CECT. None of our patients in group 2 developed an abscess. Thus, pancreatic abscesses seem to be more frequently observed in patients with mild AP when CECT had been previously performed: 12.5% vs 2.7% in both Ranson’s series and 11.5% vs 0% in groups 1 and 2 of our study, respectively.

Human pancreatic toxicity induced by ICM has not been demonstrated. The contrast medium circulates rapidly through the pancreas and is not retained within the gland. In fact, a rapid scan speed and a large bolus of ICM is needed to obtain a dynamic CECT. In the experimental model used by Foitzik et al., ICM increased acinar cell necrosis and the level of trypsinogen activation peptides. These changes suggest a toxic effect on the acinar cell. However, the severity of an AP seems to be mediated more by activated polymorphonuclear leukocytes and their products than by activated pancreatic enzymes. Besides, patients are usually hospitalized when AP is well established, several hours and even days after the clinical onset. Therefore, a toxic effect of the ICM on the acinar cell seems unlikely. On the other hand, the high susceptibility of the pancreas to ischemic necrosis has been clearly demonstrated in clinical studies. The transition of pancreatic edema into pancreatic necrosis was showed experimentally by Popper et al. in dogs. They were able to produce pancreatic necrosis by occluding the main pancreatic artery for 15 minutes after inducing pancreatic edema through ligation of the pancreatic duct and intravenous administration of large doses of secretin. Recently, Schmidt et al. showed a significant reduction of total capillary flow (especially in low-flow capillaries) in rats with severe AP who received ICM. There is no clinical evidence that ICM could turn an interstitial pancreatitis to a necrotizing one. Some of our findings suggest an association: more severe grades of AP were observed in a second scan performed on 5 of our 6 patients who developed a pancreatic abscess. These changes were seen between days 7 and 10 following performance of the first scan. In 4 of these patients the initial CECT was done on admission. Although the timing of ICM application could play a role in the progression from mild to severe AP, we did not find any difference to support this association. It is possible to speculate that in some cases ICM decreases blood flow in poorly perfused areas, leading to necrosis and eventually infection.

In conclusion, results of our study show an increased incidence of local and/or systemic complications in patients with mild AP, particularly those with a BMI of 25 or more, who underwent CECT shortly after hospital admission. Although other factors cannot be excluded, such as severity not adequately identified, this association suggests a potentially harmful effect of ICM. Further studies, ideally prospective and controlled, are required to clarify this important issue. At this point, and given that CT scan findings early in the course of an AP have little practical implications, it seems reasonable to restrict the use of a dynamic CECT to patients with severe AP, a protracted clinical course, or suspected local septic complication.

This work was presented as a poster at the Digestive Disease Week, Washington, DC, May 11 to 14, 1997.

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REFERENCES