Original article

The value of serum procalcitonin in the early phase of post-ERCP pancreatitis

D. Kapetanos,[1] D. Christodoulou,[2] Ch. Fitili,[3] O. Christopoulou,[1] D. Sigounas,[2] E. Katodritou,[1] I. Avramidis,[1] E. Progia,[3] G. Kitis,[1] E. Tsianos[2]

SUMMARY

Objective: Procalcitonin is considered a possible predictive marker of severity in the early phase of acute pancreatitis. The variations of procalcitonin levels after ERCP and its contribution to the determination of the severity of post-ERCP pancreatitis were studied. Methods: Serum procalcitonin was measured with immunoluminometric assay (normal<0.5ng/ml) in 196 patients who underwent ERCP. Samples from all patients included in the study were collected 6 hours after ERCP. Samples from patients who experienced pancreatic type pain were also collected 24 hours after ERCP. Severity of pancreatitis was graded according to consensus criteria. Results: Ten patients developed pancreatitis, 3 severe, 1 moderate and 6 mild. Procalcitonin did not exceed 0.5ng/ml in any of them. Significant elevations of procalcitonin were observed when acute cholangitis was encountered. Conclusion: Procalcitonin was not useful in the prediction of the severity in the early phase of post-ERCP acute pancreatitis. The absence of organ failure and infective complications may have contributed to this result.

Key words: Procalcitonin; ERCP; Pancreatitis

INTRODUCTION

Pancreatitis is a disease with unpredictable course. Most of the cases have uneventful outcome after short-term hospitalization, but a small number experiences local and systematic complications, requiring intensive care and possibly surgery. Predictors of severity in the early phase of acute pancreatitis are needed, in order to decide about intensive care unit monitoring, early enteral feeding and antibiotic prophylaxis. Established predictors of severity are C-reactive protein (CRP), Ranson and APACHE II score after 24-48 hours. Research has been directed to the identification of inflammatory markers with predictive capacity of the severity of pancreatitis in the first 24 hours. IL-6, urine trypsinogen activation peptide (TAP), urine trypsinogen-2, serum amyloid AA (SAA) and serum PMN-elastase may contribute to the identification of severe cases. The role of other markers, such as procalcitonin, IL-8 or sTNFR (soluble TNFa receptor) is still controversial.[1-5]

Procalcitonin is a 116-amino acid propeptide of calcitonin with a molecular weight of 13kDa. It is an established marker of severe infection and inflammation.[6-12] The role of procalcitonin in the prediction of the severity of pancreatitis has been investigated with contradictory results.[13-23] An important limitation of those studies is that the time of onset of pancreatitis is not exactly known. Post-ERCP pancreatitis is a good model to examine the changes of the studied factors during time, because the patients are already hospitalized and the time of ERCP can be recorded.

In the present study, we explored the prognostic and diagnostic value of serum procalcitonin on post-ERCP pancreatitis as well as on the severity of the disease. Procalcitonin was also measured in patients without post-ERCP pancreatitis in order to serve as control group.

[1]George Papanikolaou Hospital, Gastroenterology Department, Thessaloniki, Greece, [2]1st Division of Internal Medicine, Gastroenterology Unit and Therapeutic Endoscopy Unit, Medical School, University of Ioannina, Greece, [3]Biochemical Laboratory, George Papanikolaou Hospital, Thessaloniki, Greece

Author for correspondence:

Dimitrios Kapetanos MD, PhD, George Papanikolaou Hospital, Gastroenterology Department, 57010 Thessaloniki, Greece, Tel: +30 2313307102, Fax: +30 2310 359217, e-mail: dkapetan@otenet.gr

Abbreviations:

CRP: C-reactive protein
SAA: Serum amyloid AA
sTNFR: soluble TNFa receptor
TAP: Trypsinogen activation peptide

METHODS

Patients who underwent ERCP for various indications were enrolled. ERCP was performed with a standard duodenoscope, by two experienced endoscopists. Midazolam, hyoscin-N-butyl bromide or meperidine, were used during the procedure. Iopamidol was used as contrast medium. Cannulation was performed with the guidewire method (i.e. the wire enters the duct before any injection). Hospital ethical committee approval was obtained and all patients signed an informed consent.

The time of ERCP, cholangiography, pancreatography, number of pancreatic duct entrances, sphincterotomy, precut sphincterotomy, presence of diverticulum, stone extraction and bile duct stent placement, were recorded. The patients remained fasted for 24 hours after the procedure and were discharged the next day if there were no complications.

Serum procalcitonin was measured with immunoluminometric assay in a Liaison analyzer (Dia Sorin) (normal <0.5ng/ml) 6 hours after ERCP and 24 hours later, if the patient complained of pancreatic type pain. Samples for serum amylase measurement were collected before, 6 and 24 hours after ERCP. Amylase was measured with enzymatic colourimetric test (normal value<90 IU/L).

Pancreatitis was diagnosed and graded according to previously published consensus criteria.[24] Mild pancreatitis was defined as clinical pancreatitis and serum amylase at least 3 times higher than normal at more than 24h after the procedure, requiring admission or prolongation of planned admission for 2-3 days. Pancreatitis was graded moderate if it required hospitalization for 4-10 days and severe if it required hospitalization for more than 10 days or an intervention (percutaneous drainage or surgery) or if a pseudocyst was diagnosed.

Statistical analysis for categorical data was performed with the Pearson chi-square test with Yates correction and Fisher exact test when appropriate, while numerical data were analyzed with the Mann Whitney U test, with 5% significance level. SPSS, (version 12 for Windows; SPSS Inc. Chicago, Ill) was used as software.

RESULTS

Two hundred and twenty two patients were enrolled. Twenty-six were excluded because procalcitonin was not measured due to inability to collect blood samples. None of the excluded patients developed pancreatitis. One hundred ninety six patients, 101 male and 95 female, with mean age 65(SD:14.6) years (range 17-89) were finally included. Pancreatitis developed in 10 patients (5.1%), 2 male and 8 female with mean age 58(SD:14.1) years. Mild pancreatitis was diagnosed in 6 patients, moderate in 1 and severe in 3. Eight patients had pancreatic type pain with less than 24-hour duration. Patients' characteristics, with and without pancreatitis are shown in Table 1. Procedures' characteristics are shown in Table 2. More pancreatographies and more pancreatic entrances were performed in patients with pancreatitis.

Table 3 shows serum procalcitonin and amylase values in patients with and without pancreatitis. In patients with pancreatitis serum procalcitonin did not exceed normal limits at any time, even in the severe cases. In patients without pancreatitis procalcitonin was significantly increased when ERCP was performed during the acute phase of cholangitis (3 patients), as expected. When patients with acute cholangitis were excluded there was no difference in procalcitonin levels of the group with pancreatitis compared to that without pancreatitis.

DISCUSSION

Pancreatitis may result in infective complications that should be recognized as soon as possible, in order to promptly administer the appropriate treatment. C-reactive protein (CRP), Ranson and APACHE score are used to assess the severity of pancreatitis, but 24-48 hours are required with those particular indicators for a reliable prediction. Research has focused on the identification of novel markers such as procalcitonin, for earlier assessment of the severity of pancreatitis.

Procalcitonin is a factor indicating bacterial infection, endotoxinaemia and multiple organ failure. It does not significantly increase in viral infections and in non-infectious

Table 1. Patients' characteristics and indications for ERCP

	Pancreatitis (n=10)	**No pancreatitis (n=186)**
Mean age(SD)	58(14.1)	65(14.6)
Sex (M/F)	2/8	99/87
Choledocholithiasis	5	93
Jaundice	1	25
Cholangitis	0	22
Biliary colic (possible choledocholithiasis)	3	31
Bile duct dilation	0	10
Bile duct stenosis	0	3
Postcholecystectomy bile leak	0	2
Possible PSC	1	2
Recurrent pancreatitis	0	1

Table 2. Procedure characteristics

	Pancreatitis (n=10)	No pancreatitis (n=186)	p
Cholangiography	10	168	0.6
Pancreatography	9	89	0.018
Biliary sphincterotomy	8	175	0.135
Mean(SD) no. of pancreatic duct cannulations	4.8(4.8)	2.4(3.9)	0.01
Stone extraction	2	75	0.321
Precut sphincterotomy	1	33	1
Biliary stent placement	0	22	0.6
Periampullary diverticulum	1	33	1

inflammatory conditions. Endotoxin is a potent stimulator of the production and release of procalcitonin and its components. The site of procalcitonin production is not known but it has been demonstrated that procalcitonin can be found in peripheral blood mononuclear cells.[10] Ammori et al have also shown that plasma concentrations of calcitonin precursors correlate with serum endotoxin and reflect the derangement in gut barrier function.[25]

The value of procalcitonin as an early prognostic indicator of the severity of pancreatitis is controversial. Differences in assay techniques, time of blood sampling and variation of the percentage of patients with severe pancreatitis and organ failure included in several studies, may contribute to the conflicting results. Kylanpaa-Back et al found that measurement of procalcitonin with a semiquantitative strip test is more effective than CRP after 12 hours of admission and CRP, APACHE and Ranson score 24 hours after admission.[17,18] Procalcitonin was also a better index than CRP in the studies of Pindac et al (12 hours after admission),[15] Rau et al (2 days after admission)[21] and Riche et al (3 days after admission),[16] while Ammori et al showed that calcitonin precursors on the day of admission are more accurate predictors than APACHE score.[13]

At variance, Modrau et al[19] and Pezzili et al[14] found that CRP was better than procalcitonin 48 hours and 5 days after admission respectively, while Muller et al found CRP and procalcitonin of similar value 1 week after admission.[20] In addition, Melzi et al concluded that CRP was a better predictor of the severity of pancreatitis than procalcitonin during a 6-day follow up.[23] In the study of Frasquet et al procalcitonin had poor sensitivity, positive predictive value and negative predictive value.[22]

In a recent meta-analysis, Purkayastha et al demonstrated that procalcitonin displays moderate sensitivity but high specificity and accuracy.[26] On the contrary, Shafiq et al found in a meta-analytic approach that procalcitonin is not a good marker for assessing the severity of acute pancreatitis.[27] All of the previously mentioned studies bear limitations, mostly because the exact time of onset of pancreatitis was unknown and all measurements started after admission to the hospital.

The study of the consecutive changes of inflammatory markers in post-ERCP pancreatitis could ameliorate this limitation, because the time of ERCP and initiation of symptoms can be exactly determined. The single published study that evaluated procalcitonin as a marker of severity of post-ERCP pancreatitis, failed to show that procalcitonin increased beyond the normal limits (0.5ng/ml) at any time. Blood samples were collected before, 40 min, 2, 6, 24, 48 and 72 hours after ERCP.[28] All twelve patients studied had mild pancreatitis, which may explain the low procalcitonin levels observed.

We also studied serum procalcitonin variations in patients who underwent ERCP, 6 hours after the procedure and 24 hours later, if they had pain of pancreatic type. Ten patients developed pancreatitis, 3 of them severe. Procalcitonin did not exceed normal limits, even in the severe cases. Normal values were also measured in patients with pancreatic type pain with less than 24 hours duration. Significant elevations of procalcitonin were observed in patients with acute cholangitis, who had obvious infectious inflammatory reaction. Pancreatic manipulation in patients without pancreatitis was not associated with increased pro-

Table 3. Serum procalcitonin and amylase values

	Pancreatitis	No pancreatitis (without cholangitis)	p
Mean(SD) Procalcitonin (ng/ml)			
Sixth hour	0.18(0.1)	0.38(0.7)	>0.5
24th hour	0.26(0.14)	0.27(0.23)	>0.5
Mean(SD) Amylase (IU/L)			
Baseline	46(14)	64(60)	0.47
Sixth hour	1755(1068)	260(411)	<0.001
24th hour	1625(720)	218(361)	<0.001

calcitonin levels. We should address that, none of our patients with severe pancreatitis developed organ failure or infective necrosis, which may explain the negative results. It may be argued that infection or organ failure is required for procalcitonin elevation. Classification of patients in the severe pancreatitis group may include those with pseudocyst formation or multiple Ranson and APACHE criteria but without infective or systematic complications. Procalcitonin may not be increased in those patients; therefore the diagnostic accuracy of the test is reduced.

The study was not designed to compare the standard criteria of severity (CRP, Ranson, APACHE) with procalcitonin, because the expected incidence of severe pancreatitis in the studied population (post-ERCP patients) is generally low, and therefore, the results could hardly reach statistical significance.

In conclusion, procalcitonin was not elevated in our patients with pancreatitis, even in the severe cases. The absence of organ failure and infective complications may have contributed to this result. Procalcitonin was not elevated after ERCP, in patients without pancreatitis, except for those with cholangitis.

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