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Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Background and Aims: Acute pancreatitis following endoscopic retrograde cholangiography presents a unique opportunity for prophylaxis and early modification of the disease process because the initial triggering event is temporally well defined and takes place in the hospital. We report a prospective, single-center, randomized, double-blind controlled trial to determine if rectal diclofenac reduces the incidence of pancreatitis following cholangiopancreatography.

Methods: Entry to the trial was restricted to patients who underwent endoscopic retrograde pancreatography. Immediately after endoscopy, patients were given a suppository containing either 100 mg diclofenac or placebo. Estimation of serum amylase level and clinical evaluation were performed in all patients.

Results: One hundred patients entered the trial, and 50 received rectal diclofenac. Fifteen patients developed pancreatitis (15%), of whom two received rectal diclofenac and 13 received placebo ($P < 0.01$).

Conclusions: This trial shows that rectal diclofenac given immediately after endoscopic retrograde cholangiopancreatography can reduce the incidence of acute pancreatitis.

Introduction

Pancreatitis is a complication that has plagued endoscopic retrograde cholangiopancreatography (ERCP) and occurs in 1–30% of cases.[1] Other ERCP-associated complications include bleeding, cholangitis and perforation. The estimation of post-ERCP pancreatitis incidence is inaccurate, as a mild type of the disease could be missed and 10% die before diagnosis.[2] An elevation in serum amylase concentration is common after ERCP, occurring in up to 75% of patients.[3] The incidence of post-ERCP complications varies according to the indications for the procedure and intervention performed.[4] Risk factors reported for ERCP-induced pancreatitis include prior post-ERCP pancreatits,[1] difficult cannulation,[1] repeated injection of pancreatic duct,[5] pancreatic acinar opacification,[1,6] sphincter of Oddi hypertension (SOH),[1,7] and needle-knife or precut endoscopic sphincterotomy.[4]

Although the pathogenesis of ERCP-induced pancreatitis is not clearly understood, it seams that the patient's inflammatory response to pancreatic duct imaging and/or instrumentation plays a critical role.[8] Initial intracellular events resulting in pancreatic acinar cell damage are followed by a local inflammatory response that in turn leads to the release of chemokines and proinflammatory cytokines into the general circulation.[9] The severity of the attack is determined by the magnitude of the resultant systemic inflammatory response.[10]

One hundred years ago, Chiari suggested that autodigestion by premature extraintestinal activation of the digestive enzyme precursors is responsible for the histopathological changes in acute pancreatitis.[11] Only recently has proof of intrapancreatic protease activation been found in both human[12] and experimental pancreatitis of different etiologies (subcellular kinetics of early trypsinogen activation in acute rodent pancreatitis).[13]

In the past, intracellular premature activation of trypsin protease leading to acinary cell necrosis was discussed as a causative agent of acute pancreatitis; however, this theory failed in the scope of coagulation necrosis of cells related much more to the organ's ischemic injury. Antitrypsin deficiency was mainly suspected as a cause of the chronic pancreatitis; however, a link to acute disease can be found in literature (Novis *et al.*),[14] but other studies have not proven any correlation between pancreatitis and antitrypsin deficiency. Prevention of intra-acinar trypsinogen activation to trypsin and the subsequent inflammatory cascade may be achieved mainly by using antiprotease agents after ERCP.

The results of several placebo-controlled trials using prophylactic agents such as glucagon,[15] calcitonin,[16,17] nifedipin,[18,19] octreotide[20] and corticosteroids[21] have been disappointing. Meta-analysis suggests that somatostatin, an antisecretory agent, and gabexate, a protease inhibitor, are effective in preventing post-ERCP pancreatits;[1] however, both agents must be given before ERCP and continued for a 12-h infusion afterward.[22] When

these drugs are given as a single dose, neither agent has been consistently effective.[23] Thus, to date, a single drug that is consistently effective in a single dose has not been found. Pretreatment with glyceryltrinitrate has been shown to reduce the incidence of post-ERCP pancreatitis, an effect that may, in part, be explained by relaxation of pancreatic sphincter hypertension. In 2001, Devière *et al*. reported a study showing that a single intravenous prophylactic dose of interleukin-10, a major anti-inflammatory cytokine, given 30 min before therapeutic ERCP at a dose of either 4 or 20 μg/kg can reduce the incidence of post ERCP pancreatitis.[24] Dumot *et al.*, however, failed to show any reduction in the incidence of pancreatitis following ERCP when interleukin-10 was given 15 min before the procedure at an intravenous dose of 8 μg/kg.[25]

It has been shown that non-steroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of phospholipase A_2 (PLA_2) activity in the serum from patients with severe acute pancreatitis, with diclofenac second only in potency to indometacin.[26] NSAIDs have also been shown to have beneficial effects in experimental acute pancreatitis.[27] PLA_2 is proposed to play a key role in the initial inflammatory cascade of acute pancreatitis by regulating a number of proinflammatory mediators, including prostaglandins, leukotrienes, and platelet-activating factors.[28] Inhibition of PLA_2 has been the target of several agents used to treat non-ERCP-induced human acute pancreatitis with largely disappointing results. The role of these agents in the prevention of post-ERCP acute pancreatitis is more promising.[4] Murray *et al*., attempted to test the efficacy of a single dose of a drug to interrupt the inflammatory cascade leading to post-ERCP pancreatitis.[4] The result of their study has shown that rectal diclofenac given immediately after ERCP can reduce the incidence of acute pancreatitis.

We conducted a prospective, single-center, randomized, double-blind controlled trial to determine if a single diclofenac suppository given immediately after ERCP can reduce the incidence of post-ERCP pancreatitis.

Methods

Between November 2004 and January 2006, 180 patients fulfilled the inclusion criteria, among whom 100 patients were included in the final analysis. Patients were excluded if they had contraindications to diclofenac or had taken an NSAID during the preceding week. Entry to the study was restricted to patients advised to have endoscopic retrograde pancreatography ± cholangiography due to extrahepatic cholestasis and/or impaired liver function tests. These criteria were proposed to create a study group of patients with an increased risk of developing post-ERCP pancreatitis.

Patients were sedated with intra venous midazolam. In addition, intravenous hyoscine was given to control bowel motility. Xylocaine spray was used as a local anesthetic. Immediately on entering the recovery room, patients received a trial suppository containing either diclofenac (100 mg) or an inert placebo. The trial suppositories were prepared, sealed, and randomly numbered in batches of 20 in the pharmacy department. The content of each suppository remained unknown until the code was broken after 100 patients entered the study.

At the end of each procedure, the endoscopists recorded the ease or difficulty of cannulation, number of cannulations, number of pancreatic duct injections, presence, if any, of pancreatic acinar filling on radiography, and needle-knife sphincterotomy, if performed. None of the ERCP procedures lasted longer than 90 min. Pain was assessed shortly after the elimination of sedative drug effects, while its presence was the basis of post-ERCP pancreatitis diagnosis. Unfortunately, we did not apply pain intensity scoring. Implemented instruments were cannula sphingterotome, guidewire, and stone basket (Boston Scientific, Natick, MA, USA).

Patients were allowed water orally during the first 2 h after the procedure until determination of serum amylase level. If the serum amylase level was < 600 IU/L and there was no clinical evidence of acute pancreatitis, patients were allowed free oral fluids and diet, but if it was > 600 IU/L or if the patient exhibited epigastric pain with guarding, back pain, or nausea/vomiting, then the patient was fasted and intravenous crystalloid fluids with appropriate analgesia were prescribed. In addition to 2-h serum amylase, patient's blood tests were repeated at 4 and 8 hours after the procedure. Final blood analysis was ordered the next day, then a thorough physical examination was conducted, with special attention to clinical manifestations of acute pancreatitis. A diagnosis of acute pancreatitis was made based on a serum amylase level greater than fourfold the upper limit of normal for the reference laboratory (> 800 IU/L) in conjunction with epigastric pain, back pain, and epigastric rebound tenderness. Patients whose symptoms and signs did not settle within 48 h underwent contrast-enhanced computed tomography scanning. Fortunately, none of our patients were shown to have necrotizing pancreatitis. Surgery was not performed in any patient, while pancreatitis was conservatively managed in all subjects.

The study protocol was approved by the Ethics Committee of Shahid Beheshti Medical University. Adult patients without clinical or biochemical evidence of acute or severe chronic pancreatitis were requested to complete an informed consent form.

After 100 patients had entered the trial, the suppository content code was broken and the incidence of acute pancreatitis in the two study groups was compared. This initial data suggested a protective effect of diclofenac ($\chi^2 = 9.490$, d.f. = 1, $P < 0.01$), then for ethical reasons, we interrupted the trial.

Statistical analysis

The difference in the incidence of post-ERCP pancreatitis between the two study groups was subjected to statistical analysis using Fisher's exact test (two-tailed), with $P < 0.01$ indicating a significant difference. Serum amylase values were compared using an independent-samples *t*-test, and patient demographic and clinical factors were compared using Fisher's exact test or test, when appropriate. All statistical analyses were achieved using SPSS software (SPSS version 11.5, USA).

Results

A total of 100 patients entered the study; 50 received 100 mg diclofenac per rectum (diclofenac group), and 50 received an inert suppository (control group). Pancreatitis occurred in 15 patients (15%), of whom two belonged to the diclofenac group and 13 were controls (Table 1). Diclofenac has a protective effect in preventing post-ERCP pancreatitis. ($\chi^2 = 9.490$, d.f. = 1, $P < 0.01$)

Table 1 Occurrence of acute pancreatitis among patients receiving diclofenac (case group) and inert placebo suppository (control group)

	Drug group (no. patients)	Control group (no. patients)	Total (no. patients)
Post-ERCP pancreatitis			
Negative	48	37	85
Positive	2	13	15
Total	50	50	100

ERCP, endoscopic retrograde cholangiography.

Table 2 Risk factors for post-ERCP pancreatitis among diclofenac and control groups

Risk factors for post-ERCP pancreatitis	Diclofenac group ($n = 50$)	Control group ($n = 50$)
All patients	50	50
Age (years; mean ± SD)	57 ± 15	60 ± 17
Female	28	25
History of pancreatitis	0	2
Sphincterotomized patients	27	22
Difficult cannulation	32	34
Stent	3	2
Pancreatic acinary duct opacification	–	–
CBD stone	28	23

–, not seen; CBD, common bile duct; ERCP, endoscopic retrograde cholangiography.

There were 28 women in the diclofenac group and 25 women in the control group (NS). The mean ages (± SD) of patients in the diclofenac and control groups were 57 ± 15 and 60 ± 17 years, respectively (NS). Similarly, there were no statistically significant differences between the groups considering the procedures, and factors that might increase the risk of post-ERCP pancreatitis, including a previous history of acute pancreatitis, pancreatic acinar opacification and sphincterotomy (Table 2). The time between pancreatic duct imaging/instrumentation and suppository administration varied between subjects but did not exceed 60 min.

Two hours after the endoscopic procedure, the mean serum amylase level was 667 ± 146 (SEM) IU/L in the control group and 310 ± 45 IU/L in the diclofenac group; however, the day after, these values were 948 ± 179 lU/L and 324 ± 46 IU/L, respectively (Table 3). The difference in mean serum amylase value was statistically significant at 24 hours ($t_{55} = 3.366$; $P < 0.01$) (Table 4). Furthermore, there were significant differences in mean serum amylase values at 2, 4 and 8 hours following the procedure. Totally, 38 patients (38%) developed hyperamylasemia with a serum amylase level of >1000 IU/L during the first day following the ERCP.

Of the 49 patients who underwent endoscopic sphincterotomy, 14 (28.6%) developed hyperamylasemia, among whom only two cases belonged to the diclofenac group ($n = 27$).

Table 5 shows that the times of media injection were associated with serum amylase level.

All of our patients were discharged in good health and enjoyed a good quality of life thereafter. Meanwhile, a single NSAID dose (diclofenac) was not associated with severe side-effects.

Table 3 Serum amylase level following the ERCP procedure in diclofenac and control groups

Drug, placebo	Amylase 2 h	Amylase 4 h	Amylase 8 h	Amylase 24 h
Diclofenac group				
Mean (IU/L)	310.28	337.48	425.70	324.22
SEM	45.342	55.711	115.855	46.903
% of total sum	31.7%	23.1%	24.0%	25.5%
Sum	15 514	16 874	21 285	16 211
Control group				
Mean (IU/L)	667.80	1122.74	1347.88	948.86
SEM	146.252	237.202	254.857	179.563
% of total sum	68.3%	76.9%	76.0%	74.5%
Sum	33 390	56 137	67 394	47 443
Total				
Mean (IU/L)	489.04	730.11	886.79	636.54
SEM	78.262	127.473	146.776	97.514
% of total sum	100.0%	100.0%	100.0%	100.0%
Sum	48 904	73 011	88 679	63 654

SEM, standard error of mean.

Discussion

We have shown that a single dose of diclofenac suppository (100 mg) given immediately after ERCP can reduce the incidence of post-ERCP pancreatitis. The incidence of acute pancreatitis after ERCP varies according to the indications for the procedure, patient characteristics, and type of intervention performed. It is perhaps optimistically reported as 1–2% for diagnostic ERCP, 1–4% for endoscopic sphincterotomy, 4–8% for pancreatic sphincterotomy and 8–11% for sphincterotomy in patients with SOH.[29–31] The 10-year audit of the principal investigator of this report (B.M.) shows an all-corners post-ERCP pancreatitis rate of 3.8% (76 of 2004).

The overall incidence of post-ERCP pancreatitis in the present study was 15%, with a control group incidence of 26% and a drug group incidence of 4%. These figures are high when compared with all-comers data but reflect the study design, which intentionally created a study population with a high incidence of post-ERCP pancreatitis by restricting study entry to patients who had ERCP and pancreatic duct instrumentation. Indeed, a remarkable proportion of the subjects in our study turned out to have bile duct stones. This can present a rather selected group of patients to create a study group of patients with an increased risk of developing post-ERCP pancreatitis. However, this approach may decrease comparability with other studies, but our results could be compared with studies surveying similar patient groups. This trend can be seen in several recent studies of post-ERCP pancreatitis with reported incidences of pancreatitis in the control groups of 11.3%,[32] 15%,[33] 18%[24] and 24%.[25]

Accepted risk factors for ERCP-induced acute pancreatitis were prospectively audited in this study, and no significant difference was found between the diclofenac and control groups. It is a fact that post-manipulation sphincter spasm or post-sphincterotomy edema resulting in an increased pressure in the pancreatic duct outlasts the protective effects of diclofenac in patients with SOH; however, some other studies have shown that prophylaxis with

Table 4 Differences in mean serum amylase value between the two groups at 2,4,8, and 24 hours after ERCP

Independent samples test	Levene's test for equality of variances		*t*-test for equality of means						
			t	d.f.	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
	F	Sig.						Lower	Upper
Amylase 2 h									
Equal variances assumed	5.272	0.024	2.335	98	0.022	357.520	153.119	53.661	661.379
Equal variances not assumed			2.335	58.333	0.023	357.520	153.119	51.056	663.984
Amylase 4 h									
Equal variances assumed	12.801	0.001	3.223	98	0.002	785.260	243.657	301.731	1268.789
Equal variances not assumed			3.223	54.390	0.002	785.260	243.657	296.838	1273.682
Amylase 8 h									
Equal variances assumed	12.798	0.001	3.294	98	0.001	922.180	279.955	366.619	1477.741
Equal variances not assumed			3.294	68.422	0.002	922.180	279.955	363.602	1480.758
Amylase 24 h									
Equal variances assumed	18.401	0.000	3.366	98	0.001	624.640	185.588	256.348	992.932
Equal variances not assumed			3.366	55.655	0.001	624.640	185.588	252.813	996.467

Sig, significance.

Table 5 Association between the time of media injection and mean serum amylase level

Times of media injection	No. patients	Mean serum amylase value at 24 h after ERCP (IU/L)
None	27	257
Once	9	265
Twice	20	374
Three times	13	713
>Three times	31	835

ERCP, endoscopic retrograde cholangiography.

diclofenac is not effective in patients with SOH.[34] Thus, we did not detect SOH manometrically in our study patients.

The peak concentration of diclofenac given by suppository occurs between 30 and 90 min after insertion, and bioavailability is complete. The elimination half-life of plasma is 2 h; however, 90% of the drug clearance occurs 3–4 h after administration.[35] In our study, all patients received medical care in hospital for at least 1 day following their ERCP procedure. In contrast, acute pancreatitis was even diagnosed or reconfirmed by clinical examination and measurement of serum amylase level the day following the ERCP procedure (15–22 h after the procedure); hence, it was well beyond any possible analgesic-masking effect from the 100-mg diclofenac suppository given to one-half of the study patients.

The mechanisms of ERCP-induced pancreatic injury are not clearly understood, and a number of hypotheses exist. Trauma or thermal injury to the papilla can cause edema or spasm of the sphincter of Oddi and lead to temporary obstruction of the pancreatic duct. Contamination of the pancreatic duct by bacterial proteases during cannulation may activate pancreatic proenzymes intraductally.[18] Hydrostatic pressure from overfilling of the pancreatic duct may cause acinar damage and initiate pancreatitis. Whatever the mechanism of injury, the host inflammatory response to endoscopic instrumentation seems to play an important role in the pathophysiology of acute pancreatitis.[8] A time delay of several hours (median of 4.5 h) exists between pancreatic injury during ERCP and the onset of symptoms.[8] This 'therapeutic window' invites the use of anti-inflammatory strategies to modulate the premature intracellular activation of proteolytic enzymes and acinar cell damage followed by a local inflammatory response that, in turn, leads to the release of chemokines and proinflammatory cytokines into the general circulation.[9]

It has been widely accepted that the mechanism of action of NSAIDs is the inhibition of prostaglandin synthesis. However, the exact role of prostaglandins in acute pancreatitis is unclear and studies of NSAID administration in animal models of acute pancreatitis have shown conflicting results. NSAIDs have anti-inflammatory mechanisms of action other than inhibition of prostaglandin synthesis.[36] NSAIDs have been shown to be potent inhibitors of PLA activity in the serum of patients with acute pancreatitis when tested *in vitro*. Mäkelä *et al*. showed that diclofenac was second only to indomethacin in its PLA inhibitory activity.[26] PLA catalyzes the hydrolysis of cell membrane phospholipids, leading to the production of numerous inflammatory mediators, and is believed to play a critical role in the initial inflammatory cascade in acute pancreatitis by generating prostaglandins, leukotrienes, kinins and platelet-activating factor, which, in turn, lead to tissue damage and autodigestion of the pancreas.[37]

Because inhibition of PLA results in suppression of several important classes of proinflammatory lipids (prostaglandins, leukotrienes, platelet-activating factor, and lysophospholipids), the use of PLA inhibitors has been considered an attractive therapeutic strategy in the treatment of inflammation-related diseases and tissue injury. However, most studies concerning PLA inhibitors in the prevention of tissue injury in experimental models of severe acute pancreatitis have been disappointing. This may be because the stimulus used to induce acute pancreatitis in these animal models is too potent for a prophylactic or treatment benefit to be seen.[18]

However, the proteolytic enzyme inhibitor, gabexate mesilate, has been shown to have a beneficial role in the prevention of

post-ERCP acute pancreatitis.[38,39] It has been reported that several NSAIDs, including diclofenac, strongly inhibit neutrophil/endothelial cell attachment, thus preventing accumulation of neutrophils at the site of tissue damage, a key event in the inflammatory response.[35] NSAIDs have been shown *in vitro* to inhibit certain phenomena associated with neutrophil activation, such as synthesis of adenosine 3′, 5′-cyclic monophosphate, generation of superoxide anions, and the release of lysosomal enzymes.[40] Furthermore, NSAIDs can inhibit the expression of inducible nitric oxide synthase *in vitro*, an enzyme clearly associated with inflammation and cell damage.[41]

A weakness of our study was that we did not record duration of pain and did not use a standard pain scaling/characterization method. We simply considered whether epigastric pain was present or absent after ERCP. This can decrease comparability with other studies. In addition, our criteria to diagnose pancreatitis may seem simplistic because we only considered hyperamylasemia and pain as criteria to diagnose pancreatitis. These all might, to some extent, obscure the exact proportions of pancreatitis among diclofenac-treated and placebo groups. However, several prior studies applied the same criteria to diagnose post-ERCP pancreatitis.[42–44]

Conclusion

This prospective, single-center, randomized, double-blind clinical study has revealed that the incidence of post-ERCP acute pancreatitis can be reduced by giving an inexpensive 100-mg diclofenac suppository immediately following the endoscopic procedure. It is theoretically possible that the observed benefit of rectal diclofenac is due to its ability to inhibit PLA activity and hence downregulate the inflammatory cascade that would otherwise lead to acute pancreatitis. This observation requires validation, more detailed biochemical investigation, and pharmacological manipulation related to the choice of drug, route of delivery, and timing of administration.

References

1 Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest. Endosc.* 2004; **59**: 845–64.
2 Baker S. Diagnosis and management of acute pancreatitis. *Crit. Care Resusc.* 2004; **6**: 17–27.
3 Pieper-Bigelow C, Strocchi A, Levitt MD. Where does serum amylase come from and where does it go? *Gastroenterol. Clin. North Am.* 1990; **19**: 793–810.
4 Murray B, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2003; **124**: 1786–91.
5 Podolsky I, Haber GB, Kortan P, Gray R. Risk factors for pancreatitis following ERCP: a prospective study (Abstract). *Am. J Gastro Enterol.* 1987; **82**: 972A.
6 Bilbao MK, Dotter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography (ERCP). A study of 10 000 cases. *Gastroenterology* 1976; **70**: 314–20.
7 Barthet M, Lesavre N, Desjeux A *et al.* Complications of endoscopic sphincterotomy: results from a tertiary referral center. *Endoscopy* 2002; **34**: 991–7.
8 Messman H, Vogt W, Hoistege A *et al.* Post-ERCP pancreatitis as a model for cytokine induced acute phase response in acute pancreatitis. *Gut* 1997; **40**: 80–5.
9 Karne S, Gorelick ES. Etiopathogenesis of acute pancreatitis. *Surg. Clin. North Am.* 1999; **79**: 699–710.
10 Bhatia M, Brady M, Shokuhi S, Christmas S, Neoptolemos JP, Slavin J. Inflammatory mediators in acute pancreatitis. *J. Pathol.* 2000; **190**: 117–25.
11 Braxel C, Versieck J, Lemey G, Vanballenberghe L, Barbier F. Alpha 1- antitrypsin in pancreatitis. *Digestion* 1982; **23**: 93–6.
12 Grandaliano G, Monno R, Ranieri E *et al.* Regenerative and proinflammatory effects of thrombin on human proximal tubular cells. *J. Am. Soc. Nephrol.* 2000; **11**: 1016–25.
13 Beynon RJ, Kay J. Letter: enteropancreatic circulation of digestive enzyme. *Nature* 1976; **260**: 78–90.
14 Novis BH, Young GO, Bank S, Marks IN. Chronic pancreatitis and alpha-1- antitrypsin. *Lancet* 1975; **2**: 748–9.
15 Silvis SE, Vennes JA. The role of glucagon in ERCP. *Gastrointest. Endosc.* 1975; **21**: 162–3.
16 Ohnhaus EE, Witzel L, Halter F, Stauffacher W. [The effect of salmon calcitonin on pancreatic enzymes and hormones before and after retrograde cholangiopancreatography]. *Schweiz. Med. Wochenschr*. 1981; **111**: 750–4. (In German.)
17 Odes HS, Bovis BN, Bank S. Effect of calcitonin on serum amylase levels after ERCP. *Digestion* 1977; **16**: 180–4.
18 Sand J, Nordback I. Prospective randomized trial of the effect of nifedipine on pancreatic irritation after endoscopic retrograde cholangiopancreatography. *Digestion* 1993; **54**: 105–11.
19 Prat F, Amaris J, Ducot B *et al.* Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. *Gastrointest. Endosc.* 2002; **56**: 202–8.
20 Manolakopoulos S, Avgerinos A, Vlachogiannakos J *et al.* Octreotide versus hydrocortisone versus placebo in the prevention of post-ERCP pancreatitis: a multicenter randomized controlled trial. *Gastrointest. Endosc.* 2002; **55**: 470–5.
21 Sherman S, Blaut U, Watkins JL *et al.* Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. *Gastrointest. Endosc.* 2003; **58**: 23–9.
22 Andriulli A, Clemente R, Solmi L *et al.* Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial. *Gastrointest. Endosc.* 2002; **56**: 488–95.
23 Andriulli A, Caruso N, Quitadamo M *et al.* Antisecretory vs. antiproteasic drugs in the prevention of post-ERCP pancreatitis: the evidence-based medicine derived from a meta-analysis study. *JOP* 2003; **4**: 41–8.
24 Devière J, Le Moine O, Van Laethem J-L *et al.* Interleukin-10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology.* 2001; **120**: 498–505.
25 Dumot JA, Darwin CL, Zuccaro G *et al.* A randomized, double blind study of interleukin 10 for the prevention of ERCP-induced pancreatitis. *Am. J. Gastroenterol.* 2001; **96**: 2098–102.
26 Mäkelä A, Kuusi T, Schrdder T. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. *Scand. J. Clin. Lab. Invest.* 1997; **57**: 401–8.
27 Wildenhain PM, Melhem MF, Birsic WI, Sell HW, Rao KN. Acute hemorrhagic pancreatitis in mice: improved survival after indomethacin administration. *Digestion* 1989; **44**: 41–51.
28 Gross V, Leser HG, Heinisch A, Scholmerich J. Inflammatory mediators and cytokines: new aspects of the pathophysiology and assessment of severity of acute pancreatitis? *Hepatogastroenterology* 1993; **40**: 522–30.

29 De Palma GD, Catanzano C. Use of corticosteroids in the prevention of post-ERCP pancreatitis: results of a controlled prospective study. *Am. J. Gastroenterol.* 1999; **94**: 982–5.
30 Rabenstein T, Hahn EG. Post-ERCP pancreatitis: new momentum. *Endoscopy* 2002; **34**: 325–9.
31 Freeman ML, Disario JA, Nelson DB *et al.* Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest. Endosc.* 2001; **34**: 991–7.
32 Laferla G, Gordon S, Archibald M, Murray WR. Hyperamylasaemia and acute pancreatitis following retrograde cholangiography. *Pancreas* 1985; **1**: 160–3.
33 Moretó M, Zaballa M, Casado I *et al.* Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: a randomized double-blind trial. *Gastrointest. Endosc.* 2003; **57**: 1–7.
34 Tarnasky PR, Palsech YY, Cunningham IT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998; **11**: 1518–24.
35 Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. *Clin. Pharmacokinet.* 1997; **33**: 184–213.
36 Diaz-Gonzalez F, Sanchez-Madrid F. Inhibition of leukocyte adhesion: an alternative mechanism of action for the anti-inflammatory drugs. *Immunol. Today* 1998; **19**: 169–72.
37 Niederau C, Schulz HU. Current conservative treatment of acute pancreatitis: evidence of animal and human studies. *Hepatogastroenterology* 1993; **40**: 538–49.
38 Italian Digestive Endoscopy Group: Cavallini G, Tittobeilo A, Frulloni L, Masci E, Mariani A, Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. *N. Engl. J. Med.* 1996; **335**: 919–23.
39 Matsunga E, Sato J, Nakashima H, Deguchi T, Kojima H, Sagara K. Effect of Foy prevention of the occurrence of pancreatitis after ERCP. *Gendai lryo.* 1979; **11**: 1213.
40 Simon LS. Actions and toxicity of nonsteroidal anti-inflammatory drugs. *Curr. Opin. Rheumatol.* 1996; **8**: 169–75.
41 Zurier RB, Quagliata F. Effect of prostaglandin El on adjuvant arthritis. *Nature* 1971; **234**: 304–5.
42 Loperfido S, Angelini G, Benedetti G *et al.* Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest. Endosc.* 1998; **48**: 1–10.
43 Cheon YK, Cho KB, Watkins JL *et al.* Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacification. *Gastrointest. Endosc.* 2006; **63**: 385–93.
44 Thomopoulos KC, Pagoni NA, Vagenas KA *et al.* Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. *Gastrointest. Endosc.* 2006; **64**: 726–31.