Antisecretory vs. Antiproteasic Drugs in the Prevention of Post-ERCP Pancreatitis: The Evidence-Based Medicine Derived from a Meta-Analysis Study

Angelo Andriulli[1], Nazario Caruso[1], Michele Quitadamo[1], Rosario Forlano[1], Gioacchino Leandro[2], Fulvio Spirito[1], Giovanni De Maio[1]

[1]Division of Gastroenterology, Ospedale "Casa Sollievo della Sofferenza", IRCCS. San Giovanni Rotondo, Italy. [2]Division of Gastroenterology, Ospedale "C. De Bellis", IRCCS. Castellana Grotte, Italy

Summary

Uncertainties still exist about the clinical benefit of pharmacological prevention of post-ERCP pancreatitis by either antisecretory drugs such as somatostatin and its long-acting analogue octreotide, or protease inhibitors such as gabexate mesilate. Recent, large-scale prospective studies have reported a fourfold reduction in acute pancreatitis as compared to a placebo with the prophylactic administration of either gabexate mesilate or somatostatin, whereas octreotide was found to be ineffective. An initial meta-analysis of all available controlled trials on this topic has confirmed these findings. The indiscriminate use of these drugs in all patients is unlikely to be cost-effective, but the selective use of prophylaxis for high-risk patients might be advocated. Moreover, inasmuch as 85% of complications developed within 4 to 6 hours of completing the ERCP, it would be reasonable to infuse drugs only for this limited length of time.

A recent prospective trial, carried out on high-risk patients, has surprisingly documented a higher incidence, although a non-significant one, of pancreatitis in patients who received short-term prophylaxis with somatostatin or gabexate mesilate than those given a placebo: 11.5% and 8.1% vs. 6.5%, respectively. In order to explore this discrepancy, the original meta-analysis was updated by including data of this negative trial: heterogeneity among the trials was apparent. A careful scrutiny of the most recent studies has revealed differences in patient population, protocols of drug administration, technique and operator-related risk factors for complications among the trials, which could explain, by themselves, the contrasting results reported by the interventional studies.

In conclusion, current literature does not support the prophylactic use of either somatostatin or gabexate mesilate for the prevention of ERCP-related pancreatic damage, even in patients deemed to be at high risk for complications. At present, post-ERCP complications (and pancreatitis) can be prevented efficaciously by appropriate selection of patients, mastering of the technique and operator competence.

Introduction

Pancreatitis induced by ERCP or endoscopic sphincterotomy is a relatively frequent and, at times, medically serious event. Advances in our understanding of post-ERCP pancreatitis have recently occurred in several major areas: standardized outcome-based definitions are now available [1]; large-scale multicenter cohort studies, using multivariate analyses,

have allowed clearer identification of patient, technique, and operator-related risk factors for complications [2, 3, 4] and, finally, efficacy data on the pharmacological prevention of post-ERCP pancreatitis by administration of proactive drugs have recently been reported [5, 6]. The following review will focus on some uncertainties that still exist about the clinical benefit of pharmacological prevention of post-ERCP pancreatitis by antisecretory drugs such as somatostatin or its long-acting analogue octreotide, and protease inhibitors such as gabexate mesilate.

Review of Prophylactic Trials with Antisecretory or Antiproteasic Drugs

Gabexate mesilate has been used prophylactically in patients undergoing ERCP in Japan for several years with beneficial effects [7, 8]. In Europe, the first large-scale prospective study, published in 1996, reported impressive results: a fourfold reduction of acute pancreatitis as compared to the placebo groups (2% vs. 8%), and the occurrence of mild pancreatitis in all patients in the gabexate group vs. a necrotizing pancreatitis in about 25% of patients in the placebo group [5]. The drug was infused for 12 hours, a potential shortcoming of the study which has recently been overcome by the demonstration that a 6-hour infusion was as effective as a 12-hour infusion [9]. Further studies are needed to corroborate and extend these findings before this agent can be recommended on a widespread basis.

The true effectiveness of somatostatin in reducing post-ERCP pancreatitis remains to be clarified. Despite the fact that the topic has been the subject of investigation for a long time, the results still remain inconclusive, possibly due to the small number of patients included in most trials (beta error). In 1999, the largest trial concerning the efficacy of the prophylactic administration of somatostatin confirmed its positive effect: after a 12 hour infusion of the drug, a fourfold reduction of acute pancreatitis as compared to the placebo groups (2.8% vs. 9.9%) was observed [10].

A meta-analysis on the prophylactic use of antisecretory and antiproteasic drugs in patients undergoing ERCP [6] has reviewed 10 trials (8 randomized) of somatostatin, 8 trials (7 randomized) of octreotide, and 4 trials (1 randomized) of gabexate mesilate: both somatostatin (OR=0.38; 95% CI: 0.22–0.65) and gabexate mesilate (OR=0.27; 95% CI: 0.13–0.57) significantly reduced pancreatitis after ERCP while octreotide had no effect. Subsequently, the negative effect of octreotide has been confirmed in a large, randomized trial [11]. These data have supported the request for licensing the drugs for clinical use and establishment of guidelines for their appropriate use [12, 13, 14]. Anything that decreases the risk of ERCP pancreatitis should be welcomed, but everything must be subjected to the cost equation. Based on the meta-analysis, the number needed to be treated was 13 for somatostatin and 27 for gabexate [6]. These figures tell us that for every 100 patients undergoing ERCP under drug prophylaxis, the vast majority would receive the infusion needlessly. Therefore, the indiscriminate use of these drugs in all patients is not likely to be cost-effective [15]. A strong argument can be made for their use in high-risk groups, such as young patients and those with suspected sphincter of Oddi dysfunction, nondilated biliary ducts or a history of pancreatitis.

A further shortcoming of either the universal or the selective prophylaxis is the long-term infusion of the drugs as was the case in most studies. Indeed, the 12-hour infusional time requires an overnight hospitalization of patients, whereas, in recent years, outpatient ERCP has been gaining acceptance worldwide due to the observation of comparable complication rates in both in- and out-patient series [16, 17, 18]. A short-term infusion, if proved effective, would be cost efficient and be most warranted. As about 85% of complications developed within 4 to 6 hours of completing the ERCP [19, 20], it would be reasonable to infuse drugs only for this limited length of time. Reasoning along these lines, we designed a prospective trial on patients considered at high risk for post-

ERCP pancreatitis, and have used a 2.5-hour infusion of drugs, starting 30 minutes before the procedure [21]. Five hundred and seventy nine patients at high risk for post-ERCP pancreatitis were enrolled in the Italian multi-center trial and were randomly assigned to somatostatin, gabexate or a placebo. The unexpected results of the trial were that patients treated with somatostatin and gabexate had a higher incidence, although a non-significant one, of pancreatitis than those given a placebo: 11.5% and 8.1% vs. 6.5%, respectively. These negative data did not confirm the findings of the positive meta-analysis and gave statistically significant and opposite answers. As few will disagree with the use of large randomized, controlled trials

as the gold standard in the evaluation of the efficacy of therapeutic interventions, the value of antisecretory and antiproteasic drugs in the prophylaxis of post-ERCP pancreatitis remains a matter of debate.

Discrepancies between meta-analyses and large trials should be expected, given the variable characteristics and treatment response in different people, protocols, and populations. In order to explore the discrepancy, we have updated our previous meta-analysis [6] by including the data of this negative trial [21]. On visual inspection of the plots, there is considerable divergence between Andriulli's study and all previously published trials, with point estimates of the current study being on the opposite side of the

Table 1. Main characteristics of the 3 largest trials on the prophylaxis of post-ERCP pancreatitis by the administration of gabexate or somatostatin.

	Cavallini, 1996 [5]	**Poon, 1999 [10]**	**Andriulli, 2002 [21]**
Economic support	Industry	Investigators	Investigators
Participating centers	17	1	17
Total number of patients	418	220	579
Patient/center (mean)	24.6	-	34.0
Types of patients	All consecutive	All consecutive	Consecutive, high risk
Main indication for ERCP: biliary pain	53%	45%	81%
Exclusion criteria	Acute and chronic pancreatitis; cancer of pancreatic or papillary origin	Acute pancreatitis; previous sphincterotomy	Acute and chronic pancreatitis; cancer of pancreatic, papillary and biliary origin; previous sphincterotomy
Endoscopist's competence	Not assessed	Fully-trained	Each had performed more than 1,000 procedure; 9 high volume operators (250-400 procedures/year) and 8 low-volume operators (80-180 procedures/year)
Difficulty of ERCP	Not assessed	Easy vs. difficult: =<2 vs. 3 or more attempts	Schultz/Abbott scale
Definition of pancreatitis	Abdominal pain + raised amylase (x5 url)	Abdominal pain lasting for 24 hours + raised amylase (x3 url)	Abdominal pain lasting for 24 hours + raised amylase (x5 url at 4 hours post ERCP, x3 url at 24 hours post ERCP)
Pancreatitis score	US/CT data	Ranson score	US/CT data

url: upper reference limit

Table 2. Main characteristics of the 3 largest trials on the prophylaxis of post-ERCP pancreatitis by the administration of gabexate or somatostatin.

|	Cavallini, 1996 [5]		Poon, 1999 [10]		Andriulli, 2002 [21]		
Protocol	Placebo (mannitol, NaCl)	Gabexate	Placebo Saline	Somatostatin	Placebo Saline	Gabexate	Somatostatin
Infusion time (h)	12	12	12	12	2.5	2.5	2.5
Active drug:							
- Total dosage	-	1 gr	-	3 mg	-	0.5 g	0.75 mg
- Hourly dosage	-	83 mg	-	250 µg	-	200 mg	300 µg
- Dissolved in:	-	Saline or 5% glucose	-	Saline	-	Saline	Saline
Incidence of post-ERCP pancreatitis	8%	2%	10%	30%	6.5%	8.1%	11.5%
Severe type	31%	0%	0%	0%	0.5%	0.5%	0%

no-difference line. The statistical test for heterogeneity was not significant, but P values were near the level of significance for both somatostatin and gabexate (P=0.084 and P=0.062, respectively). Therefore, it might be misleading to compare the results of a single study with those of a meta-analysis without a careful examination of the studies that were included in order to evaluate the consistency of their results.

Heterogeneity Among the 3 Largest Trials of Prophylaxis of Post-ERCP Pancreatitis with Somatostatin or Gabexate Mesilate

Of the 1,745 patients included in the 19 studies on the prophylactic efficacy of gabexate mesilate or somatostatin and who were evaluated in the updated meta-analysis [21], 1,057 patients (60.6%) were enrolled in 3 studies only [5, 10, 21]. A fourth trial on gabexate mesilate has compared the effect of a short (6-hour) vs. a long (12-hour) infusion on 434 patients, but it cannot be included in the updated meta-analysis because a placebo group was lacking; moreover, at present, it is only available in abstract form [9]. We will attempt to highlight both similarities and differences in the design and findings of these 3 studies which have been summarized in Tables 1 and 2, in order to evaluate the consistency of their results.

Differences in Schedules of Administered Drugs

The hourly dosage, which has been adopted in the negative trial on gabexate [21], was almost three times higher than the one given in the positive study [5], whereas for somatostatin the same hourly dosage was used. Perhaps more important was the infusional time: a short time of infusion (2.5 hours) employed by Andriulli *et al*. [21] was considerably different from the 12-hour infusion in the two positive studies [5, 10]. Could such a difference explain the different rates of post-ERCP pancreatitis among these trials? We do not think so for several reasons. The first one refers to the time in which complications and, more specifically, pancreatitis develop after the endoscopic procedure: it is widely assumed that by 6 hours after ERCP, more than 80% of patients have symptoms [19], and those with ongoing pancreatitis can be picked up by measuring serum amylase levels at 4 hours after the procedure [20]. Unfortunately, the time at which pancreatitis was first recognized was not reported in the 3 trials. Furthermore, Mariani *et al*. have recently reported a beneficial effect on post-ERCP pancreatitis with a relatively short (6 hours) infusion of gabexate [9]. Finally, we have re-analyzed the data on the prophylactic benefit of
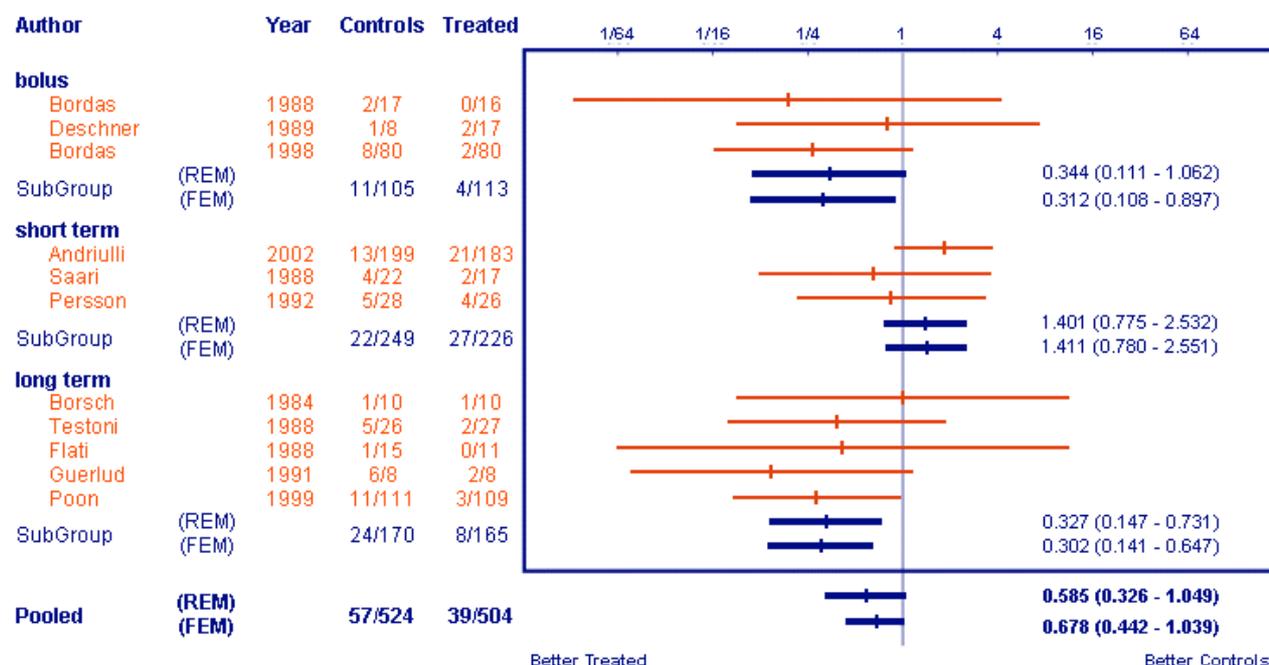
Figure 1. Prophylactic administration of somatostatin for post-ERCP pancreatitis. Three different meta-analyses were carried out by sorting out all available controlled trials according to the infusional time: bolus injection, short-term, and long-term infusion. The data have been evaluated either by a random effect model (REM) or a fixed effect model (FEM).

somatostatin administration by sorting out all the studies according to the length of infusional time; the results are shown in Figure 1. In 3 studies [22, 23, 24] which used a single bolus injection of the drug, a pooled, significant benefit was found: OR=0.312 (95% CI: 0.108–0.897). In 3 other trials [6, 25, 26] that used a short term infusion (2.5 hours), a pooled, non-significant effect was found. A long term infusion of somatostatin was employed in 5 clinical trials [10, 27, 28, 29, 30] and a significant benefit was shown: OR=0.302 (95% CI: 0.141–0.647). These results are not consistent with each other and are difficult to explain.

Patient Selection

Criteria for excluding and including patients in the 3 trials have also varied. Patients with acute pancreatitis, pancreatic cancer and cancer of the papilla of Vater were excluded from all studies, whereas those with chronic pancreatitis were excluded from two studies [5, 21], and those with a previous sphincterotomy were not included in two studies [10, 21]. Patients with biliary cancer

were excluded from only one of the 3 trials [21]. Consequently, the population of patients included appears to differ from one study to the other. For instance, 81% of patients included in Andriulli's study were complaining of biliary pain [21], whereas the value dropped to 53% and 45%, respectively, in Cavallini's study [5] and in Poon's study [10].

Differences in the Definition of Acute Pancreatitis

In an exhaustive review of prospective studies, Gottlieb and Sherman tallied a cumulative rate of pancreatitis of 5.2% for diagnostic ERCP and 4.1% for therapeutic biliary ERCP [31] in patients undergoing the procedure without drug prophylaxis. The incidence of pancreatitis in control patients included into the 3 trials under evaluation are noticeably higher than these rates, by approximately a factor of 2. Whereas the prospective American studies of complications refer to patients at generic risk, the higher rate of pancreatitis found in the trial on high-risk patients had to be expected

[21]. It is more difficult to find an explanation for the higher than expected rates of post-ERCP pancreatitis reported in the other two studies [5, 10]. One possibility lies in the subtle differences in defining pancreatitis. The consensus criteria for diagnosing acute pancreatitis after the endoscopic procedure require the occurrence of persistent abdominal pain with an amylase level at least three times above normal at more than 24 hours after the procedure [1]. The duration of pain is crucial for defining post-procedure pancreatitis. However, in one study, the time after the endoscopic procedure at which pain and serum amylase had to be found elevated in order to diagnose acute pancreatitis was not mentioned [5]. As the distinction between clinical mild pancreatitis and hyperamylasemia with transient abdominal discomfort is somehow arbitrary, it seems likely that an overdiagnosis of pancreatitis might have occurred. As a matter of fact, an independent data monitoring committee which had to validate the data from the multicenter trials was set up and operated in only one study [21].

Endoscopist's Experience and Competence

Seventeen different centers with an unknown number of participating operators were involved in 2 studies [5, 21], whereas in the single institution study carried out in Hong Kong, five different operators were involved. It may be likely that all these operators had a different degree of competence; no statement about this point was given in one study [5], and only a generic definition in another trial [10]; only the third study specifies that all operators had personally performed at least 1,000 ERCPs and had been in practice for 5 to 12 years [21].

Univariate vs. Multivariate Analysis of Data

The problem of preventing post-ERCP pancreatitis is a complex one, as several factors, namely patient features, technical difficulties and operator competence all interact with each other and all of these with drug prophylaxis in determining or preventing pancreatitis after ERCP. All these details were not evaluated in Cavallini's study [5]. Difficult common bile duct cannulation and repeated pancreatic duct injections were significantly associated with post-ERCP pancreatitis in the Hong Kong study [10], but, unfortunately, no multivariate analysis of data were reported so that one might wonder whether the observed difference between treated and control patients reflects the efficacy of the therapeutic intervention or the different endoscopic procedures. Several endoscopic details were also associated with pancreatitis in Andriulli's study and were evaluated, in conjunction with the drugs administered, by multivariate analysis; only the difficulty of obtaining biliary access and a long sphincterotomy, but not drug prophylaxis, were independent predictors of post-ERCP pancreatitis.

Conclusion

The issue as to whether it is possible to prevent pancreatic damage by administering drugs prophylactically is still open to discussion. Available studies do not support the use of either somatostatin or gabexate mesilate for this purpose, even in patients deemed to be at risk for complications. The observation that whenever it develops after ERCP, pancreatitis is usually mild and spontaneously disappears within the following few days without medical intervention is a further theoretic argument against the need for pharmaceutical prophylaxis. Efforts should be devoted to delineate factors which are associated with the development of severe pancreatitis after the endoscopic procedure, but unfortunately studies on this medically-relevant topic are lacking. Post-procedure pancreatitis should be regarded as an unavoidable event when biliary cannulation is difficult; its occurrence has to be expected even in the hands of an expert endoscopist. At present post-ERCP pancreatitis (and other complications) can be

prevented efficaciously by appropriate selection of patients, mastering of the technique and operator competence.

Key words Cholangiopancreatography, Endoscopic Retrograde; Gabexate; Pancreatitis; Somatostatin

Abbreviations CI: confidence interval; OR: odds ratio

Correspondence
Angelo Andriulli
Division of Gastroenterology
Ospedale "Casa Sollievo della Sofferenza", IRCCS
71013 San Giovanni Rotondo (FG)
Italy
Phone: +39-0882-410.263
Fax +39-0882-411.879
E-mail address: angelo.andriulli@tin.it

References

1. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991; 37:383-93. [AN 91301427]

2. Fleischer DE. Better definition of endoscopic complications and other negative outcomes. Gastrointest Endosc 1994; 40:511-4. [AN 95011353]

3. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc 1998; 48:1-10. [AN 98347799]

4. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol 2001; 96:417-23. [AN 21122345]

5. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariani A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. Gabexate in digestive endoscopy--Italian Group. N Engl J Med 1996; 335:919-23. [AN 96365276]

6. Andriulli A, Leandro G, Niro G, Mangia A, Festa V, Gambassi G, et al. Pharmacologic treatment can prevent pancreatic injury after ERCP: a meta-analysis. Gastrointest Endosc 2000; 51:1-7. [AN 20092786]

7. Hajiro K, Tsujimura D, Inoue R, Yamamoto H, Yamamoto T. Effect of FOY on hyperamylasemia after endoscopic retrograde cholangiopancreatography. Gendai Iryo 1978; 10:1375-9.

8. Shimizu Y, Takahashi H, Deura M. Prophylactic effects of preoperative administration of gabexate mesilate (FOY) on post-ERCP pancreatitis. Gendai Iryo 1979; 11:540-4.

9. Mariani A, Frullloni L, Masci E, Curioni S, Tittobello A, Cavallini G, and the "Gruppo Gabesato Endoscopia Digestiva". Comparison of two-dosing regimens of gabexate mesilate in the prevention of post-ERCP pancreatitis: results of a multicentre controlled trial. Dig Liv Dis 2001; 33(Suppl 1):A36.

10. Poon RT, Yeung C, Lo CM, Yuen WK, Lin CL, Fan ST. Prophylactic effect of somatostatin on post-ERCP pancreatitis: a randomized controlled trial. Gastrointest Endosc 1999; 49:593-8. [AN 99246296]

11. Testoni PA, Bagnolo F, Andriulli A, Bernasconi G, Crotta S, Lella F, et al. Octreotide 24-h prophylaxis in patients at high risk for post-ERCP pancreatitis: results of a multicenter, randomized, controlled trial. Aliment Pharmacol Ther 2001; 15:965-72. [AN 21314850]

12. Pasricha P. Prevention of ERCP-induced pancreatitis: success at last. Gastroenterology 1997; 112:1415-7. [AN 97252463]

13. Kozarek RA. ERCP economics. Gastrointest Endosc 1999; 49:660-2. [AN 99246313]

14. Haber GB. Prevention of post-ERCP pancreatitis. Gastrointest Endosc 2000; 51:100-3. [AN 20092814]

15. Pasha TM, Therneau T, Petersen BT. Economic analysis of gabexate mesilate in post-ERCP pancreatitis. Gastroenterology 1997; 112:471A.

16. Elfant AB, Bourke MJ, Alhalel R, Kortan P, Haber GB. A prospective study of the safety of endoscopic therapy for choledocholithiasis in an outpatient population. Am J Gastroenterol 1996; 91:499-502. [AN 96322159]

17. Ho KY, Montes H, Sossenheimer MJ, Tham TC, Ruymann F, Van Dam J, Carr-Locke DL. Features that may predict hospital admission following outpatient therapeutic ERCP. Gastrointest Endosc 1999; 49:587-92. [AN 99246295]

18. Freeman ML, Nelson DB, Sherman S, Haber GB, Fennerty MB, DiSario JA, et al. Same-day discharge after endoscopic biliary sphincterotomy: observations from a prospective multicentre complication study. Gastrointest Endosc 1999; 49:589-6. [AN 99246294]

19. Gottlieb K, Sherman S, Pezzi J, Esber E, Lehman GA. Early recognition of post-ERCP pancreatitis by clinical assessment and serum pancreatic enzymes. Am J Gastroenterol 1996; 91:1553-7. [AN 96322170]

20. Testoni PA, Bagnolo F, Caporuscio S, Lella F. Serum amylase measured four hours after endoscopic sphincterotomy is a reliable predictor of postprocedure pancreatitis. Am J Gastroenterol 1999; 94:1235-41. [AN 99249279]

21. Andriulli A, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, 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. [AN 22233811]

22. Bordas JM, Toledo V, Mondelo F, Rodes J. Prevention of pancreatic reactions by bolus somatostatin administration in patients undergoing endoscopic retrograde cholangio-pancreatography and endoscopic sphincterotomy. Horm Res 1988; 29:106-8. [AN 88297533]

23. Deschner K, Kalloo A, Collen M, Cattau EL, Maher KA, Fleischer DE, Benjamin SB. Somatostatin: an evaluation of its utility as adjunctive medication for ERCP. Gastrointest Endosc 1989; 35:A149.

24. Bordas JM, Toledo-Pimentel V, Llach J, Elena M, Mondelo F, Gines A, et al. Effects of bolus somatostatin in preventing pancreatitis after endoscopic pancreatography: results of a randomized study. Gastrointest Endosc 1998; 47:230-4. [AN 98199942]

25. Saari A, Kivilaakso E, Schroder T. The influence of somatostatin on pancreatic irritation after pancreatography. An experimental and clinical study. Surg Res Comm 1988; 2:271-8.

26. Persson B, Slezak P, Efendic S, Haggmark A. Can somatostatin prevent injection pancreatitis after ERCP? Hepatogastroenterology 1992; 39:259-61. [AN 92371924]

27. Borsch G, Bergbauer M, Nebel W, Sabin G. Der einfluss von somatostatin auf die amylasespiegel und pankreatistrate nach ERCP. Med Welt 1984; 35:109-12. [AN 84141123]

28. Testoni PA, Masci E, Bagnolo F, Tittobello A. Endoscopic papillo-sphincterotomy: prevention of pancreatic reaction by somatostatin. Ital J Gastroenterol 1988; 20:70-3.

29. Flati G, Porowska B, Negro P, Flati D, Chiarinelli MG, Carboni M. Efecto de la somatostatina sobre las secuelas de la colangiopancreatografia retrograda endoscopica. Rev Esp Enf Ap Digest 1988, 74:17-9. [AN 89018422]

30. Guelrud M, Mendoza S, Viera L, Gelrud D. Somatostatin prevents acute pancreatitis after pancreatic duct sphincter hydrostatic balloon dilation in patients with idiopathic recurrent pancreatitis. Gastrointest Endosc 1991; 37:44-7. [AN 91169195]

31. Gottlieb K, Sherman S. ERCP and endoscopic biliary spincterotomy-induced pancreatitis. Gastrointest Endosc Clin N Am 1998; 8:87-114. [AN 98070870]