

Pharmacological Prevention of Post-ERCP Pancreatitis: Which Therapy is Best?

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Summary

The effectiveness of the pharmacological prevention of post-ERCP pancreatitis can be established only from large controlled randomized studies. Over the last decade, fifteen studies dealt with these characteristics and a cumulative series of about 3,000 non-selected patients were evaluated. Cumulating the data of the placebo groups, the median incidence of post-ERCP pancreatitis was 8.7% (mean 9.3%), the range varied from 1.6 to 17.7% likely due to case mix and/or different criteria defining acute pancreatitis. These variables, other than differences in the modalities of the administration of the drugs, could explain their contrasting effectiveness between the studies. Somatostatin and octreotide were the prophylactic drugs more frequently experimented (8 studies) followed by corticosteroids such as hydrocortisone, prednisone or methylprednisolone (four studies) and gabexate (three studies). While octreotide was confirmed to be ineffective, somatostatin and gabexate seem to be the best for the prevention of post-ERCP pancreatitis, but both can present some limits such as unreported sample size calculation in the statistical analysis for somatostatin studies and lack of widespread commercial availability for gabexate. Pharmacoeconomic studies are lacking in English language literature. On this point of view, it seems reasonable and preferable a selective as opposed to universal pharmacological prophylaxis but, actually, the experimented

pre-treatments in high-risk patients are ineffective.

The characteristics of the ideal pharmacological prevention of post-ERCP pancreatitis are fulfilled when it is effective, especially in those patients who potentially benefit the most from the treatment, but also when it is cost-effective. These characteristics include low cost, safety, a short infusion time and a shorter hospital stay than that of non-treatment. In fact, anything that decreases the risk of ERCP should be welcome, but everything must be placed in the cost equation [1].

The expected effectiveness of a drug is likely to be higher when it interferes with the etiopathogenetic mechanisms of post-ERCP pancreatitis.

Which drug is best?

- the one which inhibits proteolytic activity?
- the one which inhibits pancreatic exocrine secretion?
- the one which reduces ductal hypertension and/or inhibits the motility of the sphincter of Oddi?

Is it reasonable to pretreat only certain high-risk patients or all patients who will undergo ERCP?

Although many studies have been designed to answer these questions, the results have still not been able to clearly establish whether or not the prophylactic treatment of post-ERCP

pancreatitis is necessary, and to identify which drug is the best in preventing pancreatitis or which drugs are cost effective. In patients who did not receive any pharmacological agent, the ERCP drainage realized by sphincterotomy did not seem to constitute a protective maneuver in reducing the occurrence of post-procedural pancreatitis; on the contrary, it increased its frequency when compared with diagnostic ERCP [2].

Several drugs have been experimented in the prevention of post-ERCP pancreatitis but only few of them have been tested in controlled trials. In Table 1, the randomized controlled studies published in the last ten years are reported [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17].

The anti-secretory drugs, such as somatostatin and octreotide, are those which have been studied more frequently (8 of 15 reported studies) [4, 6, 9, 10, 13, 15, 16, 17] followed by corticosteroids, such as hydrocortisone, prednisone or methylprednisolone (4 studies) [6, 8, 11, 12] and anti-proteases, such as gabexate (3 studies) [3, 4, 14]. In single studies, the prevention of post-ERCP pancreatitis was evaluated using nifedipine [5], a calcium channel inhibitor which most likely relaxes the sphincter of Oddi [18], interleukin-10 [7], an anti-inflammatory cytokine that can limit the severity of experimental pancreatitis [19] or allopurinol [8], an inhibitor of oxygen-derived free radicals.

The low incidence of post-ERCP pancreatitis (less than 2%) in some non-treated and non-selected prospective large series [20, 21] would make a pharmacological prophylaxis costly and not even useful. A universal prophylaxis is likely to be ineffective when there is a low occurrence of the complication that we would like to reduce in the non-treated subset of patients.

Yet, an higher incidence of post-ERCP pancreatitis can be observed by cumulating the data of non-treated and non-selected patients (i.e. undetermined risk factors related to post-procedural pancreatitis) undergoing ERCP obtained both from recent large-scale

prospective series designed to establish the rate of post-ERCP complications (Table 2) [20, 21, 22, 23, 24, 25, 26] and controlled randomized studies designed to evaluate the efficacy of different prophylactic drugs (Table 1, 12 of 15 studies) [5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17]. In the former series the median incidence of pancreatitis referred to a population of about 12,000 patients was 5.4% (mean 4.7%; range 1.3-7.4%), in the latter series, it referred to the subset of the placebo group as part of about 3,000 randomized non-selected patients and was 8.7% (mean 9.3%; range 1.6-17.7%).

Such a difference in the occurrence of post-ERCP pancreatitis observed in these two kinds of studies could be due to their design, or case mix (technique and patient-related factors) and/or different criteria defining acute pancreatitis [27]. The expected frequency of the complication which one would like to reduce by pharmacological prophylaxis is an important variable in the calculation of the sample size, which often represents a crucial phase during statistical analysis in deciding whether or not a study on the prevention of post-ERCP pancreatitis can be carried out.

The inordinately high number of patients required in order to obtain an established difference in the rate of post-ERCP pancreatitis between the treated and the placebo group was the reason for terminating the study after an interim analysis in two [5, 6] of the 15 controlled reported studies.

A meta-analysis study [28] which referred to twenty-eight clinical trials showed that both prophylaxis with somatostatin and gabexate were effective in reducing the frequency of post-ERCP pancreatitis. In this study, from a pharmacoeconomic aspect, somatostatin was more effective than gabexate: 13 patients for somatostatin and 27 for gabexate needed to be treated to prevent a single case of post-ERCP pancreatitis. In any case, these results should emphasize the fact that universal prophylaxis is unlikely to be cost-effective. On the contrary, a prophylaxis only for patients considered at high-risk (selective prophylaxis) is the most warranted and theoretically gives the best advantages.

Table 1. Randomized controlled studies published in the last 10 years.

Study	Active treatment	No. of patients	Sample size calculation	Drug efficacy	% AP (Tx/PI)	% severe AP ^a (Tx/PI)	Notes
Masci 2003 [3]	Gabexate	430	Yes	---	1.8 ^{***} (1.4/2.3)	0.2 ^{b***} (0.4/0)	Equivalence's study
Andriulli 2002 [4]	Gabexate	579 [*]	Yes	No	8.6 (8.1/6.5)	0.3 ^b (0.17/0.17)	
Andriulli 2002 [4]	Somatostatin	579 [*]	Yes	No	8.6 (11.5/6.5)	0.3 ^b (0./0.17)	
Prat 2002 [5]	Nifedipine	155	Yes	No	15.5 (13.2/17.7)	0.6 ^b (0/0.6)	Interim analysis
Manolakopoulos 2002 [6]	Octreotide	354	Yes	No	10.0 (9.8/13)	0 ^c	Interim analysis
Manolakopoulos 2002 [6]	Hydrocortisone	354	Yes	No	10.0 (7.1/13)	0 ^c	
Deviere 2001 [7]	Interleukin-10	144	Yes ^{**}	Yes	13.2 (5.5/7.6)	1.4 ^c (0/1.4)	Pilot study
Budzynska 2001 [8]	Prednisone	300	Yes	No	10.7 (12/7.9)	1.3 ^c (3/0)	Interim analysis
Budzynska 2001 [8]	Allopurinol	300	Yes	No	10.7 (12.1/7.9)	1.3 ^c (1/0)	
Testoni 2001 [9]	Octreotide	114 [*]	Yes	No	13.1 (12/14.3)	0 ^c	
Poon 1999 [10]	Somatostatin	220	No	Yes	6.3 (3/10)	0 ^r	
De Palma 1999 [11]	Hydrocortisone	529	Yes	No	5.3 (5.7/4.9)	0.6 ^c (0.8/0.4)	
Dumot 1998 [12]	Methylprednisolone	255	Yes	No	10.5 (12.4/8.7)	Not specified	Interim analysis
Bordas 1998 [13]	Somatostatin	160	No	Yes	6.2 (2.5/10)	0 ^c	
Cavallini 1996 [14]	Gabexate	418	Yes	Yes	5.0 (2.4/7.6)	1.2 ^b (0/2.4)	
Arcidiacono 1994 [15]	Octreotide	151	No	No	6.6 (6.6/6.6)	1.3 (0/2.6) [?]	
Binmoeller 1992 [16]	Octreotide	245	Yes	No	2.0 (2.5/1.6)	0 ^c	
Sternlieb 1992 [17]	Octreotide	84	Yes	No	22.6 (35/11)	9.5 ^{npo}	Interim analysis

* High risk patients

** Only adequate to reduction of hydrolasemia as first primary end-point

*** Gabexate: 1 g in 13 hours vs. 0.5 g in 6.5 hours (no placebo)

AP: Acute pancreatitis

PI: Placebo group

Tx: Active treatment group

^a According to:

^b Balthazar [37]

^c Cotton [38]

^r Ranson [39]

^{npo} Number of days "nothing per os"

Table 2. Incidence of post-ERCP pancreatitis in prospective large series in non-selected and non-treated consecutive patients.

Study	No. of patients	Pancreatitis
Sherman 1994 [22]	690	7.4%
Freeman 1996 [23]	2,347	5.4%
Loperfido 1998 [21]	2,769	1.3%
Masci 2001 [20]	2,462	1.8%
Freeman 2001 [24]	1,963	6.7%
Christoforidis 2002 [25]	556	3.3%
Vandervoort 2002 [26]	1,223	7.2%
Total	12,010	

Yet, in the two large controlled studies [4, 9] in which pharmacological prevention was administered to high-risk patients, gabexate, somatostatin and octreotide were found to be ineffective in reducing the incidence of pancreatitis. In one of these studies, the strategy of the Authors [4] was to assess if a short term infusion of gabexate (30 minutes before ERCP and two hours afterward) could result the most warranted effective and cost-effective prophylaxis, but this gabexate regimen was ineffective.

In high-risk patients, while further use of octreotide does not seem to be indicated due to its inefficacy also in non-selected risk patients [6, 15, 16, 17], the use of somatostatin and gabexate need to be further evaluated in larger series of patients and with appropriate dosing regimens [29].

While pharmacological prophylaxis failed to be effective in high-risk patients, in non-selected series, it significantly reduced the incidence of post-ERCP pancreatitis in four controlled studies: somatostatin in two [10, 13], gabexate [14] and interleukin-10 [7] each in one. Which universal prophylaxis for post-ERCP pancreatitis using these drugs is the best? Interleukin-10 prophylaxis was effective but a pilot study in which the sample size was calculated vs. an expected reduction rate only referred to hydrolasemia; for this reason, further and larger case studies using interleukin-10 prophylaxis are necessary, as in the case of somatostatin. In fact, the two somatostatin studies [10, 13] which differ from each other in dosage and modality of the

administration of the drugs, gave positive data but the sample size was not reported. The gabexate study [14] was effective in reducing post-ERCP pancreatitis in non-selected patients when the prophylaxis was administered from 30-90 minutes to twelve hours after the procedure. A recent equivalence study [3] showed that gabexate prophylaxis could be administered in outpatients: 0.5 g infused for 6.5 hours was as effective as 1 g for 13 hours. Compared with the latter, the shorter gabexate prophylaxis can potentially be both more economical and cost-effective. It has to be noted that, nowadays, gabexate prophylaxis is only commercially available in some countries and the reported published ERCP data only refer to the Italian series.

Regarding the theoretical or speculative economic considerations just now postulated, there are no published prospective pharmacoeconomic studies specifically designed to verify if the different agents tested in the prevention of post-ERCP pancreatitis are really cost-effective.

The only English language study was published in abstract form [30]. It analyzed whether or not gabexate versus no prophylaxis was cost-effective according to a theoretical economic analysis when administered to patients at undefined risk for post-ERCP pancreatitis. The following three variables were considered: a) a 50% reduction in the incidence of post-ERCP pancreatitis with 13-hour infusion of gabexate [14]; b) dollar 280 as a direct cost for gabexate administration per patient; c) dollar 2,927 as an average cost of mild pancreatitis. A positive economic impact for universal gabexate prophylaxis was obtained only when the estimated incidence of pancreatitis in the untreated patients was higher than 5%. In Italy, gabexate prophylaxis could gain further economic advantages if it is considered that euro 87 is the actual costs for the administration of a 13-hour infusion of 1 g gabexate and euro 43.5 for the shorter and equivalent effective dosing regimen (6.5-hour infusion of 0.5 g) [3]. A further cost decrease

could be expected if one of these two dosing regimens of gabexate were to be confirmed to be effective in the subset of high-risk patients. Two Italian language studies have made some pharmacoeconomic evaluations about gabexate and somatostatin prophylaxis [31, 32]. The first study showed that Cavallini data [14] are cost-effective in Italy with a cost saving of euro 67.6 per gabexate-treated patient. In the second study [32], the results of six controlled studies, three experimenting with somatostatin [33, 34, 35] and three with octreotide [16, 17, 36] were analyzed taking into account the cost of drugs, nursing, endoscopic devices and hospitalization (in Italy). The analysis of the differential costs between the prophylaxis with these two agents and that of non-treatment resulted cost-effective only for somatostatin (euro 38 saving per patient).

Conclusions

Nowadays, which pharmacological agent is the best is not well established; encouraging data are obtained by gabexate and somatostatin infusion. A selective as opposed to universal pharmacological prophylaxis seems reasonable and preferable, but actually the experimental pretreatments in high-risk patients are ineffective. Conclusive evidence on the effectiveness of the pharmacological prevention of post-ERCP pancreatitis will only come from further large prospective controlled studies and the results would be better if they were accompanied by appropriated pharmacoeconomic analyses.

Keywords Acute Disease; Adrenal Cortex Hormones; Allopurinol; Chemicals and Drugs Category; Cytokines; Gabexate; Hormones; Hormones, Hormone Substitutes, and Hormone Antagonists; Hormones, Synthetic; Nifedipine; Octreotide; Primary Prevention; Pancreatitis; Protease Inhibitors; Serine Proteinase Inhibitors; Somatostatin

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