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REVIEW ARTICLE

Effectiveness of Gabexate Mesilate in Acute Pancreatitis

A Metaanalysis

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Since the effectiveness of gabexate mesilate in patients with acute pancreatitis is controversial, a metaanalysis of the published literature was conducted to address this problem. Five randomized trials were identified by our literature search. Three end points (mortality, complications, and complications requiring surgery) were evaluated. The results of our metaanalysis indicate that the treatment with gabexate mesilate does not affect mortality at 90 days ($P = 0.27$), but significantly reduces the incidence of complications requiring surgery (odds ratio = 0.61, 95% CI: 0.41–0.89; $P < 0.05$) and of complications in general (odds ratio = 0.69, 95% CI: 0.54–0.89; $P < 0.05$). Because the drug proves to be beneficial only to a low proportion of the treated patients, its clinical impact seems to be small. A pharmacoeconomic evaluation shows that its use in all patients with acute pancreatitis would imply a very high cost for preventing each complication. The administration of the drug to select patients who are at higher risk of complications could have a better cost–effectiveness ratio. However, specific studies on this point are still lacking.

KEY WORDS: gabexate mesilate; acute pancreatitis; metaanalysis; pharmacoeconomics.

A few clinical trials (1–5) have been conducted in patients with acute pancreatitis to assess the efficacy of gabexate mesilate (GM), a low-molecular-weight protease inhibitor. Some of these studies (2, 3) have shown that GM can improve morbidity, but other trials have failed to demonstrate any benefit (1, 4, 5). In this study, a metaanalysis was carried out to address this controversial issue.

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LITERATURE SEARCH

We searched the MEDLINE system on compact disk (Medline, Silver Platter Information, Norwood, Massachusetts; data from January 1990 to April 1994) using "gabexate mesilate" as the index term. This computer search was supplemented by consulting Current Contents (Current Contents on Diskette, Institute for Scientific Information, Philadelphia, Pennsylvania; diskettes from October 1991 to September 1994), the IOWA-IDIS compact-disk data base (Iowa Drug Information System, Iowa City, Iowa; data from January 1985 to September 1994), reviews, textbooks, and experts in this field. Additionally, we reviewed all the references listed in the trials we found.

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TABLE 1. CHARACTERISTICS OF FIVE STUDIES INCLUDED IN METAANALYSIS

Author	Patients (N)		Dose of GM (mg/kg/day)	Treatment duration (days)	Delay in GM treatment*			
					GM		Controls	
	GM	Controls			0–24 hr	24–72 hr	0–24 hr	24–72 hr
Buchler	115	108†	53	7	NR**	NR	NR	NR
Goebell	76	75†	12	7	NR	NR	NR	NR
Pederzoli	91	91‡	43§	7	35/65¶	30/65¶	29/51¶	22/51¶
Valderrama	51	49†	12	4–12	51/51	0/51	49/49	0/49
Yang	21	21	8.6	7–14	NR	NR	NR	NR

*Time elapsed between the diagnosis of acute pancreatitis and the beginning of treatment with GM.
†Placebo group.
‡Treated with aprotinin.
§Assuming body weight = 70 kg.
¶Data available only for a subgroup of 116 patients with necrotising acute pancreatitis.
**NR = not reported.

METAANALYSIS

All controlled clinical trials comparing the effectiveness of GM in comparison with a control group were eligible for our metaanalysis. Criteria for inclusion of the trials were the following:

1. The treatment with GM is started within 72 hr of the diagnosis of acute pancreatitis. The treatment duration is of at least four days.
2. Effectiveness of GM is evaluated in terms of lethality, incidence of complications, and incidence of pancreatitis-related operations.

Complications, as defined in the four full-length papers (1, 3–5), included shock, infectious complications (eg, sepsis, peritonitis, pancreatic abscess), bleeding, metabolic disorders, renal failure, and respiratory insufficiency. Since no specific definition of complications was given in Goebell's study (2), the number of patients with complications was estimated as the difference of the total number of patients minus the number of "totally normal" patients.

STATISTICAL TECHNIQUES

A conventional metaanalysis was performed using the Mantel-Haenszel method and the 95%-confidence-interval (95% CI) formulas of Breslow and Day (6). The study-specific 95% confidence intervals for the odds ratio were calculated by the method of Woolf (7). The pooled rates of incidence in the control group were computed directly from the crude data (ie, ratio of the sum of all numerators and the sum of all denominators). The pooled rates of incidence in the treatment group (with 95% CI) were estimated by the method of Laupacis et al (8). All mathematical calculations were performed using the META.EXE (Version 4.33) microcomputer program (9).

ASSESSMENT OF PUBLICATION BIAS

To keep the trial search and the metaanalysis data management in a context of independent institutions, no attempt was made to identify negative trials with the collaboration of pharmaceutical companies. The issue of publication bias (10) was addressed by the procedure of Rosenthal (11), which is based on the estimation of the minimum number, *m*, of negative (or null) studies required to lead a significant metaanalysis to nonsignificance. The value of *m* was calculated by the formula described by Klein et al (11).

The *m* negative (or null) studies are hypothetical (simulated) trials in which the two treatments being compared have an identical effectiveness. A highly significant metaanalysis can be reversed to nonsignificance only by large values of *m* and *vice versa.*

RESULTS

Five trials were included in our metaanalysis (Table 1). Four of these compared GM with a placebo, while the fifth, conducted by Pederzoli et al (3), included a control group treated with aprotinin. The latter trial was not excluded from our metaanalysis because the presence of a possible effect of aprotinin [although unlikely in the light of the information presently available (12)] would have simply reduced the statistical significance of the metaanalysis without affecting substantially the interpretation of a statistically significant metaanalytical result. A trial conducted by Harada et al (13) did not meet the inclusion criteria

TABLE 2. END POINTS OF GM TREATMENT: RAW DATA EXTRACTED FROM 5 CLINICAL TRIALS AND OVERALL INCIDENCE RATES

	Mortality within 21 days		*Mortality within 90 days*		*Need for surgery*		*Complications*	
Author	*GM*	*Controls*	*GM*	*Controls*	*GM*	*Controls*	*GM*	*Controls*
Buchler	NR*	NR	18/115	16/108	23/115	23/108	56†/115	52†/108
Goebell	2/76	4/75	8/76	11/75	14/76	26/75	33/76	46/75
Pederzoli	3/91	4/91	9/91	12/91	7/91	13/91	14/91	24/91
Valderrama	0/51	2/49	0/51	2/49	1/51	1/49	14/51	15/49
Yang	3‡/21	4‡/21	3‡/21	4‡/21	0/21	2/21	3/21	5/21
Pooled % rates:	3.2	5.9	10.6	13.1	12.4	18.9	32.8	41.3
95% CI	1.4–7.4		7.1–15.4		8.8–17.2		27.6–38.4	

*NR = not reported.
†Excluding deaths.
‡No precise temporal details on mortality are given in this study.

because there was no patient group treated with placebo.

All studies employed a randomized design, with the exception of the trial by Yang et al (5). The randomization procedure was described in detail in the studies by Buchler et al (1) and by Valderrama et al (4), whereas no details on this point were given in the trials by Goebell (2) and by Pederzoli et al (3). In the study by Yang et al (5), the sequence of consecutive enrollments was the basis for the patients' assignment to the two groups (odd-number patients were assigned to treatment and even-number patients to controls). All studies adopted a double-blind design with the exception of the trial by Yang et al (5).

The criteria for diagnosing acute pancreatitis were rather uniform among the five trials. In the two studies by Pederzoli et al (3) and Yang et al (5), the diagnosis was mainly based on Ranson's criteria. Goebell (2) also enrolled exclusively patients in whom the diagnosis of moderate or severe acute pancreatitis was made on the basis of standard criteria. In the study of Buchler et al (1), the diagnosis of moderate or severe acute pancreatitis was documented by the presence of three obligatory criteria (namely, recent onset of symptoms, threefold enzyme elevations, upper abdominal pain) and of at least four of 10 additional facultative criteria. Valderrama et al (4) used the criteria of abdominal pain with hyperamylasemia (in the absence of other causes) and recent (<12 hr) onset of symptoms.

Table 2 shows the overall incidence rates (pooled metaanalytic rates) of mortality, complications requiring surgery, and total complications. For each of these three end points, Table 3 shows the study-specific values of odds ratio as well as the overall metaanalytical odds ratio. The statistical analysis shows that GM did not affect mortality at 90 days. In contrast, the treatment significantly reduced the incidence of total complications and of complications requiring surgery.

Although the limit of statistical significance was reached for two end points of our metaanalyses (total complications and need for surgery), the values of the pooled incidence rates indicate that the drug can be

TABLE 3. STUDY SPECIFIC VALUES OF ODDS RATIO AND RESULTS OF METAANALYSIS.*

	Odds ratio (95% CI)		
Author	*Mortality within 90 days*	*Need for surgery*	*Complications*
Buchler	1.07 (0.51–2.22)	0.92 (0.48–1.77)	1.02 (0.60–1.73)
Goebell	0.68 (0.26–1.81)	0.42 (0.20–0.90)	0.48 (0.25–0.93)
Pederzoli	0.72 (0.29–1.80)	0.50 (0.19–1.32)	0.51 (0.24–1.06)
Valderrama	† †	0.96 (0.06–15.8)	0.86 (0.36–2.04)
Yang	0.71 (0.14–3.64)	† †	0.53 (0.11–2.60)
Metaanalysis	0.78 (0.51–1.21)	0.61 (0.41–0.89)	0.69 (0.54–0.89)
Stat. signif.	$P = 0.27$	$P < 0.05$	$P < 0.05$

*All values are expressed as odds ratio of the GM group versus controls.
†Cannot be computed because of the presence of a zero frequency.

beneficial only to a low proportion of the treated patients (eg, the need for surgery is reduced from 18.9% to 12.4% with a difference of 6.5% only). Hence, the clinical impact of the use of GM seems to be rather small.

Our publication bias calculations showed that two (hypothetical) null studies were sufficient to reverse the results of the metaanalysis on total complications to statistical nonsignificance and, similarly, two null studies were sufficient also for the metaanalysis on the need for surgery. Overall, these findings suggest that the statistically significant results obtained from the two metaanalyses on complications have a low level of statistical robustness because both analyses can be reversed to nonsignificance by a very small number of hypothetical null trials.

The trial by Yang et al (5) differed from the other four because it was not based on a double-blind design, and so the end points were presumably determined less objectively. To assess the statistical contribution of this trial, our three metaanalyses were rerun excluding the study by Yang et al (5) and thereby using the data of four trials only. However, the results remained virtually unchanged (data not shown).

DISCUSSION

Our metaanalyses show that GM has a significant effectiveness in reducing the risk of pancreatitis-related complications requiring surgical treatment; the incidence of total complications also is significantly reduced. However, our metaanalyses confirm also the indication emerging from most clinical trials that mortality (at three months) is not affected by the treatment with GM.

Some explanations can be proposed to interpret the apparently different effect of GM on mortality and on complications. It should be stressed that no metaanalysis could be done in our study to assess the effect of GM on early mortality because the study by Buchler et al (1) provided no mortality data at 21 days. In patients with acute pancreatitis, late mortality is known to be affected by a variety of factors, which are mainly related to the occurrence of septic complications (14) (on which protease inhibitors like GM can obviously have no effect). Thus, the results of our metaanalysis preclude a conclusive assessment about a possible effect of GM on short-term mortality, but nonetheless demonstrate that a "hard" end point, such as mortality at 90 days, is not influenced by the treatment with GM.

A simpler interpretation of our results concerning complications is that GM produces a small although statistically significant effect. The clinical relevance of this effect remains uncertain because the robustness of its statistical significance is low (as shown by our publication bias analysis) and also because the cost–effectiveness ratio does not seem to be particularly favorable. This latter conclusion is supported by the following simplified pharmacoeconomic analysis.

The treatment of a patient with GM at a dose of 3 g/day for a week costs 9,366,000 Italian lire, which correspond to $6130 (US$ 1 = 1528 Italian lire, as of October 29, 1994). As a result, the cost for treating 100 patients is about US$613,000. Our metaanalysis shows that the treatment of 100 patients can avoid, on average, 6.5 complications requiring surgery (95% CI: 1.7–10.1) and a total of 8.5 complications of any kind (95% CI: 2.9–13.7). This means that the cost for avoiding each complication requiring surgery is around US$94,300 (= US$613,000/6.5) with 95% CI of US$61,000–361,000, while the cost for avoiding a complication is approximately US$72,000 (= US$613,000/8.5) with 95% CI of US$45,000–211,000.

The first of these two cost–effectiveness estimates is more interesting because the definition of a complication requiring surgery was relatively homogeneous across the trials. In contrast, the definition of a complication of any type was less objective and presumably had a much higher degree of heterogeneity. To extend this cost–effectiveness analysis to a cost–benefit evaluation, it would be useful to draw an estimate of the cost for treating a complication of acute pancreatitis. Unfortunately no specific cost estimates are reported in the literature and, additionally, no reliable data are available from the retrospective cases observed at our institution.

The results of our metaanalysis must be viewed with caution because of the well-known limitations of all metaanalytic studies (10, 15). It should be stressed, in particular, that our pooling process has involved a series of trials having a certain degree of heterogeneity in terms of diagnostic criteria and definition of pancreatitis-related complications. Regardless of these differences, however, the trend observed in all five trials was relatively homogeneous in that the treatment arm generally tended to fare slightly better in terms of incidence of complications, whereas mortality was little affected.

Even though no cost–benefit analysis has been made in this study, our pharmacoeconomic evaluation suggests that the cost–effectiveness ratio of a universal treatment with GM of all patients with acute pancreatitis is probably poor because the costs

for preventing each complication seem to be very high. This finding raises the need to identify a selected subgroup of patients with acute pancreatitis at higher risk for complications and who could maximally benefit from the treatment with GM.

In conclusion, in the light of the results of our metaanalysis, the question of the effectiveness of GM remains open. Further trials in select patients are therefore needed to better define the role of this controversial drug.

After the submission of our paper, an article published by S.G. Thompson has emphasized the need to quantify the inter-trial heterogeneity in the event rates for each end-point evaluated in a meta-analysis study (BMJ 1994;309:1351–5). The three meta-analyses reported herein, which considered the end-points of mortality within 90 days, need for surgery, and incidence of complications, had a low level of inter-trial heterogeneity (chi-square values of 2.4, 3.8, and 4.2 for these three end-points, respectively, which correspond to p-values of 0.66, 0.43, and 0.38, respectively, with 4 degrees of freedom). These calculations are based on the method of Collins et al. (BMJ 1985;290:17–25).

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