Effectiveness of Gabexate Mesilate in Acute Pancreatitis
A Metaanalysis

ANDREA MESSORI, PharmD, ROBERTA RAMPANZO, PharmD, GIOVANNA SCROCCARO, PharmD, ROSANNA OLIVATO, PharmD, CLAUDIO BASSI, MD, MASSIMO FALCONI, MD, PAOLO PEDERZOLI, MD, and NELLO MARTINI, PharmD

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.

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.
GABEXATE MESILATE: A METAANALYSIS

Table 1. Characteristics of Five Studies Included in Metaanalysis

<table>
<thead>
<tr>
<th>Author</th>
<th>GM (N)</th>
<th>Controls (N)</th>
<th>Dose of GM (mg/kg/day)</th>
<th>Treatment duration (days)</th>
<th>Delay in GM treatment*</th>
<th>Delay in Controls*</th>
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<tr>
<td></td>
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<td>24-72 hr</td>
<td>0-24 hr</td>
<td>24-72 hr</td>
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<tr>
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<td>108‡</td>
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<td>7</td>
<td>NR**</td>
<td>NR**</td>
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<td>75*</td>
<td>12</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
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<tr>
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<td>91*</td>
<td>43</td>
<td>7</td>
<td>35/65‡</td>
<td>30/65‡</td>
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<td></td>
<td></td>
<td></td>
<td>29/51‡</td>
<td>22/51‡</td>
</tr>
<tr>
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<td>12</td>
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<td>21</td>
<td>8.6</td>
<td>7-14</td>
<td>NR</td>
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</tr>
</tbody>
</table>

*Time elapsed between the diagnosis of acute pancreatitis and the beginning of treatment with GM.

‡Placebo group.

*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.