MIDAZOLAM ACTS SYNERGISTICALLY WITH FENTANYL FOR INDUCTION OF ANAESTHESIA

I. BEN-SHLOMO, H. ABD-EL-KHALIM, J. EZRY, S. ZOHAR AND M. TVERSKOY

SUMMARY

The induction dose–response of midazolam was compared with the dose–response of its combination with fentanyl and with that of fentanyl alone in three groups of 60 unpremedicated, ASA physical status I or II women undergoing minor gynaecological surgery. The end-point of induction of anaesthesia was inability to open eyes upon command. Dose–response curves were determined for each group with a probit procedure and compared with an isobolographic analysis. Midazolam was found to act in synergism with fentanyl for induction of anaesthesia. Twenty-five percent of the ED₅₀ of fentanyl was required in combination with 23% of the ED₅₀ for midazolam to achieve the ED₅₀ of the combination. This degree of synergism may explain mutual potentiation between opioids and benzodiazepines reported previously.

KEY WORDS

PATIENTS AND METHODS

Following informed consent, we studied 180 women (age 20–50 yr, ASA I or II) admitted for minor gynaecological procedures. The Institutional Review Board approved the study design.

Dose regimens used for the study are shown in Table I. Drugs were injected in a constant volume of 10 ml over 15–20 s. Two separate injections were administered at an interval of 1 min and the end-point of response to verbal command (open your eyes!) was evaluated 3 min after the first injection. In the combination group, midazolam was injected first, and in the other two groups saline was used as placebo. The drugs were labelled only as first and second, so that the administering physician was unaware of their nature. However, studies of the single-drug groups were concluded first, so that the doses for the combination could be planned.

Table I. Doses of midazolam, fentanyl, or a combination of the two, given to groups of 10 patients each in the study

<table>
<thead>
<tr>
<th>Combination</th>
<th>Midazolam (mg kg⁻¹)</th>
<th>Fentanyl (µg kg⁻¹)</th>
<th>Midazolam + Fentanyl (mg kg⁻¹) (µg kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.07</td>
<td>5.0</td>
<td>0.02 + 1.9</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>6.0</td>
<td>0.03 + 1.9</td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>7.0</td>
<td>0.04 + 1.9</td>
</tr>
<tr>
<td></td>
<td>0.19</td>
<td>7.5</td>
<td>0.06 + 1.9</td>
</tr>
<tr>
<td></td>
<td>0.26</td>
<td>8.0</td>
<td>0.08 + 1.9</td>
</tr>
<tr>
<td></td>
<td>0.37</td>
<td>8.5</td>
<td>0.10 + 1.9</td>
</tr>
</tbody>
</table>

Combinations of benzodiazepines and opioids are used for induction of anaesthesia and sedation. However, life threatening complications have been reported, indicating the importance of understanding the nature of their interaction. Although mutual potentiation of effects by specific drugs from these two groups was reported in several studies [1–6], none has attempted to define if this represents synergism or additivity.

The present study was designed to examine the specific interaction for induction of anaesthesia between midazolam and fentanyl.

IZHAR BEN-SHLOMO, M.D., SHIFRA ZOHAR, M.D. (Department of Obstetrics and Gynaecology); HALED ABD-EL-KHALIM, M.D., JOSEP EZRY, M.D., MARK TVERSKOY, M.D., PH.D. (Department of Anaesthesia); The 'Rebecca Sieff' Government Hospital, Safed, Israel 13100. Accepted for Publication: May 24, 1989.

Correspondence to I.B.S.
The percentage of patients in each dose group unable to open the eyes was converted into a probit value and plotted against a logarithmic value for the respective dose. Dose–response curves were determined with the use of probit analysis [7].

To define the type of interaction between midazolam and fentanyl, the three calculated ED\textsubscript{50} values were plotted as an isobologram [8]. Single-drug ED\textsubscript{50} points were placed on the dose coordinates, the combined ED\textsubscript{50} point in the dose field then representing the doses of each drug that were contained in the ED\textsubscript{60} of the combination.

A straight line joining the single-drug ED\textsubscript{50} points is termed the “additivity line” and deviation of the ED\textsubscript{50} of a combination to its left indicates synergism. This deviation is measured perpendicular to the additivity line. The standard error of this distance was computed by the method of propagation of error [9]. Error estimates from the combined ED\textsubscript{50} point, in addition to single-drug ED\textsubscript{50} points, were used. An approximate \( t \) test used to test the assumption of additivity was obtained as the ratio of measured distance to its standard error [10].

**RESULTS**

The groups were comparable with respect to age and weight. The ED\textsubscript{50} calculated from the fentanyl dose–response curve (fig. 1) was 7.7 \( \mu \)g kg\textsuperscript{-1} (95% confidence limits 7.5–8.0 \( \mu \)g kg\textsuperscript{-1}). The dose–response curve of midazolam was displaced to the left by combination of midazolam with fentanyl 1.9 \( \mu \)g kg\textsuperscript{-1} (25% of the calculated ED\textsubscript{50})

![Fig. 1. Fentanyl quantal dose–response curve for induction of anaesthesia. Each point represents a subgroup of 10 patients at the indicated dosage.](https://academic.oup.com/bja/article-abstract/64/1/45/355628)

![Fig. 2. Midazolam quantal dose–response curves for induction of anaesthesia with the addition of fentanyl 0.019 mg kg\textsuperscript{-1} (M + F) or saline (M + S). Each point represents a subgroup of 10 patients at the indicated dosage.](https://academic.oup.com/bja/article-abstract/64/1/45/355628)

![Fig. 3. ED\textsubscript{50} isobologram for the anaesthetic interaction of midazolam and fentanyl. The dashed line connects the ED\textsubscript{50} values of each drug. See text for details.](https://academic.oup.com/bja/article-abstract/64/1/45/355628)

ED\textsubscript{60} values were 0.19 mg kg\textsuperscript{-1} (0.17–0.22) and 0.044 mg kg\textsuperscript{-1} (0.037–0.051) for midazolam alone and in combination, respectively.

The difference between the slopes was not significant by this method of analysis. However, the midazolam–fentanyl isobologram for ED\textsubscript{50} doses (fig. 3) reveals that the combined ED\textsubscript{50} point deviates to the left of the additivity line, indicating synergism \( (P < 0.001) \). Comparing the sum of fractional doses given of each drug alone with that given in the combination further demonstrates this synergism. Twenty-three percent of midazolam ED\textsubscript{50} combined with 25% of fentanyl ED\textsubscript{50} (48% of ED\textsubscript{50}) were included in the ED\textsubscript{50} of the combination (calculated degree of synergism = 2.1).
DISCUSSION

Fentanyl is used in anaesthesia mainly for its pronounced analgesic effect. Stanley and Webster [11] used fentanyl alone to achieve anaesthesia in all patients (the end-point was inability to open the eyes) and found that the average dose required was $11 \pm 3 \mu g \ kg^{-1}$. Although derived by a different methodology, our dose–response curve agrees with this value. ED$_{50}$ value for midazolam calculated in this study ($0.19 \ mg \ kg^{-1}$) is within the range of values described for this drug for the same end point [12, 13].

In a previous study we found that midazolam and morphine acted additively for sedation [14]. However, several studies report potentiation between opioids and benzodiazepines [15–17], leading in some cases to life-threatening complications such as respiratory and cardiac arrest [18]. The current study supports these qualitative reports and provides an estimation of the degree of synergism. We have no explanation for the different nature of the interactions between midazolam–morphine and midazolam–fentanyl. The difference between the two opioids may be attributable either to the differing end-points (anaesthesia vs sedation), or to their different structures, as differences in the degree of synergism between midazolam and agents from other groups are known to exist, for example with barbiturates [19, 20].

REFERENCES