COMPARISON OF FLUMAZENIL WITH AMINOPHYLLINE TO ANTAGONIZE MIDAZOLAM IN ELDERLY PATIENTS

A. N. SIBAI, A. M. SIBAI AND A. BARAKA

SUMMARY

We have compared, in a double-blind study, the efficacy of flumazenil with that of aminophylline in antagonizing the effects of midazolam in 60 patients (ASA I-II, mean age 66 yr) undergoing transurethral resection of prostate under spinal anaesthesia. All patients received midazolam 0.075 mg kg\(^{-1}\) i.v. and the test drugs were given 5 min after its administration. Patients were allocated randomly to receive i.v. flumazenil 0.01 mg kg\(^{-1}\), aminophylline 2 mg kg\(^{-1}\) or placebo saline 0.1 ml kg\(^{-1}\). One minute after administration, aminophylline caused 42\% reversal of sedation, 66\% of disorientation and 73\% of lack of co-operation in comparison with placebo, although there was marked individual variation. Flumazenil caused complete and rapid antagonism of sedation, disorientation and lack of co-operation.

KEY WORDS


Flumazenil (Anexate) has been introduced recently into clinical practice as a specific benzodiazepine receptor antagonist. Aminophylline, a non-specific central nervous system (CNS) stimulant drug, has been shown to antagonize the sedation induced by benzodiazepine derivatives such as flurazepam [1], lorazepam [2] and diazepam [3, 4]. Stirt [3] has suggested that aminophylline may also be useful in antagonizing midazolam sedation, but this was not confirmed by Sleigh [5] and Mathews and colleagues [6]. The purpose of our study was to compare the effects of flumazenil with those of aminophylline in antagonizing the actions of midazolam.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed consent was obtained from all patients, who comprised admissions for transurethral resection of prostate (TURP). The following patients were excluded: ASA III and above; insulin-dependent diabetics; patients receiving benzodiazepine derivatives, aminophylline, sedative or stimulant CNS drugs; those suffering from impaired memory, hearing or consciousness; and patients with renal or hepatic insufficiency, cardiac problems or chronic obstructive pulmonary disease.

Sixty male patients, ASA I and II, were allocated randomly to three groups (n = 20) to receive flumazenil, aminophylline or placebo. All patients were premedicated with glycopyrrolate 0.3 mg i.m., 1 h before operation. In the anaesthetic room, a cannula was inserted into a peripheral vein and Hartmann's solution infused i.v. All patients received a spinal block via the L2-3 or L3-4 lumbar interspace with amethocaine 4–5 ml. In the operating room, patients were placed in the lithotomy position for TURP. Arterial pressure, heart rate and ECG were monitored.

Patients received an i.v. bolus of midazolam 0.075 mg kg\(^{-1}\). Five minutes later, flumazenil 0.01 mg kg\(^{-1}\), aminophylline 2 mg kg\(^{-1}\) or saline 0.1 ml kg\(^{-1}\) was given randomly as an i.v. bolus in a double-blind manner. The volume and the colour of the three solutions were comparable. During operation, any hypotension was treated with...
TABLE I. Evaluation of the codes used to score the central nervous system variables: sedation, disorientation and lack of co-operation. A greater score indicates improved antagonism for the three outcome variables.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Asleep and not responding to painful stimuli (pinching)</td>
</tr>
<tr>
<td>1</td>
<td>Asleep and responding to painful stimuli</td>
</tr>
<tr>
<td>2</td>
<td>Asleep and responding to verbal order</td>
</tr>
<tr>
<td>3</td>
<td>Awake and drowsy</td>
</tr>
<tr>
<td>4</td>
<td>Fully awake</td>
</tr>
<tr>
<td>Disorientation to space and time (Where are you? What day is it today?)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Fully disoriented</td>
</tr>
<tr>
<td>1</td>
<td>Partially oriented</td>
</tr>
<tr>
<td>2</td>
<td>Fully oriented</td>
</tr>
<tr>
<td>Lack of co-operation and collaboration (Lift your hand, with or without imitation)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Fully unco-operative (order not executed)</td>
</tr>
<tr>
<td>1</td>
<td>Partially co-operative (order executed by imitation)</td>
</tr>
<tr>
<td>2</td>
<td>Fully co-operative (order executed by verbal command)</td>
</tr>
</tbody>
</table>

Increments of i.v. phenylephrine hydrochloride 100 µg. Blood loss was replaced adequately.

Measured variables

CNS variables were measured according to Nisbet and Norris [7] and Ricou and colleagues [8], with modifications as presented in Table I. Baseline data recorded before and after spinal block included the level of wakefulness, orientation and co-operation. Scores for sedation, disorientation and lack of co-operation were noted at 1, 3 and 5 min after administration of midazolam, and at 1, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90 and 120 min after the administration of the test drug or placebo.

Statistics

Data were analysed statistically using the Mann-Whitney U test. Cochran's method of analysis of comparison of slopes was used to compare the course of action of aminophylline with that of midazolam following their threshold effects. All data are presented as mean (SD). P < 0.05 was considered significant.

RESULTS

The ages of the patients included in this study were 50–86 yr (mean 66 yr). Patients had a mean ASA score of 1.6 (0.5). There was no significant difference in age, weight, height or ASA score between the three groups (table II).

Figure 1 compares the actions of flumazenil, aminophylline and placebo on sedation, which was maximal (grand mean (SD) (n = 60) 1.1 (0.52)) 5 min after administration of midazolam. One minute after flumazenil, patients in this group (n = 20) were fully awake, with no incidence of anxiety (mean score 4 (0)). This was maintained with minimal non-significant variations thereafter. At 1 min, the mean sedation score of patients in the aminophylline group was 2.35 (1)—an increase of 42% antagonism of sedation in comparison with placebo (saline). At 35 min, there was no significant difference in the sedation score between flumazenil and aminophylline (P = 0.146), and at 45 min there was no significant difference in the score between placebo and either flumazenil (P = 0.378) or aminophylline (P = 0.176).

TABLE II. Characteristics of patients in the three groups (mean (range or SD)). No significant differences between groups (Mann-Whitney U test).

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I Flumazenil (n = 20)</th>
<th>Group II Aminophylline (n = 20)</th>
<th>Group III Placebo (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67 (57–86)</td>
<td>66 (50–78)</td>
<td>66 (51–83)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 (9)</td>
<td>73 (1)</td>
<td>69 (11)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 (8)</td>
<td>167 (5)</td>
<td>166 (7)</td>
</tr>
<tr>
<td>ASA (I–II)</td>
<td>1.5 (0.5)</td>
<td>1.4 (0.5)</td>
<td>1.6 (0.4)</td>
</tr>
</tbody>
</table>

Fig. 1. Mean sedation score in the flumazenil (□), aminophylline (+) and placebo (△) groups. Shaded boxes indicate timings at which comparisons between each pair of the groups were not significant (P > 0.05, Mann-Whitney): at 35 min for comparison between flumazenil and aminophylline groups, and at 45 min for comparison between the placebo and either flumazenil or aminophylline groups.
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Fig. 2. Regression analysis of mean sedation score for aminophylline (+) and placebo (△) against time. No significant difference between regression slopes (P > 0.05).

Figure 2 represents the regression lines obtained when mean sedation scores for aminophylline and placebo were plotted against time. The data presented were restricted to those obtained 1–30 min after administration of antagonist. Using Cochran's method of analysis, there was no significant difference in the slopes of both regression lines (P > 0.05).

Figures 3 and 4 present the actions of flumazenil, aminophylline and placebo on disorientation and lack of co-operation, respectively. Maximum disorientation and lack of co-operation (grand mean (sd) (n = 60): 0.23 (0.48) and 0.22 (0.51)) occurred 5 min after administration of midazolam. One minute after flumazenil, there was full orientation and co-operation of all patients in this group (n = 20) (mean score of 2 (0)) and this was maintained thereafter. At 1 min, the disorientation and unco-operation scores of aminophylline were 1.45 (0.89) and 1.55 (0.83), respectively—an increase of 66% antagonism of disorientation and an increase of 73% antagonism of lack of co-operation in comparison with those in the placebo group. At 20 min, there was no significant difference between aminophylline and placebo in both disorientation and lack of co-operation scores (P = 0.249 and P = 0.12, respectively). At 15 and 25 min, there was no significant difference in the lack of co-operation and disorientation scores between the flumazenil and aminophylline groups (P = 0.154 and P = 0.324, respectively). At 30 and 35 min, there was no significant difference in the lack of co-operation and disorientation scores between the flumazenil and placebo groups (P = 0.13 and P = 0.154, respectively).

Fig. 3. Mean disorientation score in the flumazenil (□), aminophylline (+) and placebo (△) groups. Shaded boxes indicate timings at which comparisons between each pair of the groups were not significant (P > 0.05, Mann–Whitney): at 20 min for comparison between aminophylline and placebo groups, at 25 min for comparison between aminophylline and flumazenil groups, and at 35 min for comparison between flumazenil and placebo groups.

Fig. 4. Mean lack of co-operation score in the flumazenil (□), aminophylline (+) and placebo (△) groups. Shaded boxes indicate timings at which comparisons between each pair of the groups were not significant (P > 0.05, Mann–Whitney): at 15 min for comparison between flumazenil and aminophylline groups, at 20 min for comparison between aminophylline and placebo groups, and at 30 min for comparison between flumazenil and placebo groups.
DISCUSSION

The present report has demonstrated the effect of flumazenil and aminophylline in antagonizing the action of midazolam, in the absence of other possible factors that may affect the action of midazolam. Flumazenil scores for sedation, disorientation and lack of cooperation were greatest (with zero SD) 1 min after its administration. None of the patients in the flumazenil group had anxiety. This is in contrast with the study by Ricou and colleagues [8] (around 20% incidence of anxiety), in which flumazenil was used in a dose 10 times larger than that used in the present study.

In the aminophylline group, the mean sedation score at 1 min was moderate, with a large SD in comparison with that for flumazenil, indicating variation in responses to aminophylline. Subsequently, there was a gradual increase in the aminophylline score in parallel with the sedation score of placebo. This suggests that a ceiling effect of aminophylline was achieved at 1 min, and any further improvement was related probably to redistribution and metabolism of midazolam. This is in contrast with other reports. Sleigh's letter [5] suffered several limitations, of which the most important was that his patients were studied under uncontrolled conditions. Mathews and colleagues [6] reported on patients under general anaesthesia using oxygen–nitrous oxide–isoflurane. The dose of midazolam used for induction of anaesthesia was 0.3 mg kg⁻¹; this is significantly larger than the sedative dose of midazolam 0.075 mg kg⁻¹ used in our study. Aminophylline is a non-specific CNS stimulant drug and its stimulant action may not be revealed if the patient is over sedated, or other depressant drugs have been used. Aminophylline has been reported to antagonize morphine- [9] and fentanyl- [10] induced respiratory depression and to reduce the depth and duration of sedation by thiopentone [11]. However, it does not alter the anaesthetic requirement for halothane [12]. It has also been used for treatment of neonatal apnoea [13] and Cheyne–Stoke ventilation [14].

Midazolam interacts with specific high-affinity binding sites for benzodiazepines [15], and benzodiazepine derivatives potentiate the inhibitory effect of γ-aminobutyric acid (GABA) [16, 17]. In contrast, although flumazenil is an imidazodiazepine, it has no benzodiazepine action [18]. It is a specific competitive benzodiazepine antagonist [19].

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Aminophylline is a complex of theophylline and ethylenediamine. Its main action is competitive inhibition of the depressant action of endogenous adenosine [20]. In addition, ethylenediamine is known to interact with the binding of [H³] diazepam in the cerebral cortical synaptosomal membrane [21]. This may explain the moderate and non-specific effect of aminophylline in counteracting the action of midazolam.

ACKNOWLEDGEMENT

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REFERENCES

6. Mathews HML, Carlisle RJT, Fee JPH. Failure of aminophylline or doxapram to antagonize midazolam induced sedation. British Journal of Anaesthesia 1986; 58: 1333P-1334P.


