Flumazenil in Mixed Benzodiazepine/Tricyclic Antidepressant Overdose: A Placebo-Controlled Study in the Dog

PHILIPPE LHEUREUX, MD,*† MARC VRANCKX, MD,* DIMITRI LEDUC, MD,t† ROBERT ASKENASI, MD, PhD*†

This study evaluates the cardiac and neurologic risks associated with the antagonization of the benzodiazepine component of mixed drug overdoses, when cyclic antidepressants are also implicated. Twenty-four mongrel dogs were anesthetized and ventilated. Electroencephalogram, electrocardiogram, and tidal carbon dioxide and arterial pressure were continuously recorded. Amitriptyline (1 mg/kg/min) associated with midazolam (1 mg/kg + 1 mg/kg/h) was infused in 12 of the dogs. Midazolam was replaced by saline in the other 12. Drug administration was continued until signs of cardiotoxicity (QRS prolongation >120 milliseconds or sustained arrhythmias) occurred. At that moment, midazolam effects were suddenly reversed by administration of flumazenil 0.2 mg/kg in six dogs out of each group. Placebo was administered in the others. Reactions were observed for the next 120 minutes. Midazolam-induced sedation efficiently protects (P < .02) against seizures due to amitriptyline. These were observed for the next 120 minutes. Midazolam-induced sedation efficiently protects (P < .02) against seizures due to amitriptyline toxicity. This protective effect is counteracted by flumazenil. Midazolam has limited influence on the cardiac toxic effects of amitriptyline. The bolus of flumazenil is, however, associated with a significant worsening of electrocardiogram disturbances, and two sudden deaths were recorded. The mechanism of this effect remains unclear, as it could be unrelated to the antagonization of midazolam sedation. Given the problem of extrapolating animal data to humans, these results suggest that bolus administration of high doses of flumazenil in mixed intoxication implicating benzodiazepine and cyclic antidepressants has the potential to precipitate convulsions and/or arrhythmias. A slowly titrated administration of the antidote, as usually recommended, could prevent these effects. (Am J Emerg Med 1992;10:184-188. Copyright © 1992 by W.B. Saunders Company)

Benzodiazepines (BZD) and cyclic antidepressants (TCA) are psychotropic drugs often ingested simultaneously in self-poisonings. Flumazenil, a specific antagonist which acts by competitive interaction at the central BZD receptor, has been recently introduced to reverse BZD sedation. When this antidote is used in pure BZD overdose, side effects are mild and can usually be avoided by slow administration and with close observation of the patient’s reactions. However, adverse events, possibly related to flumazenil administration, have been reported to be twice more frequent in mixed drug overdoses than in pure BZD intoxication, particularly when TCAs have been ingested. Seizures have been attributed to the unmasking of the proconvulsant effect of antidepressants. The relationship between cardiac rhythm disturbances and flumazenil administration, suggested in two reports, is less clear. Nevertheless, a previous preliminary study of mixed intoxication in an animal model has suggested that fatal arrhythmias could occur when flumazenil is given for this condition.

The purpose of this placebo-controlled study was to evaluate the protective effect of midazolam sedation on amitriptyline (AMI)-induced seizures or cardiotoxicity, and to verify if the administration of flumazenil is associated with a risk of neurologic or cardiac adverse events.

MATERIALS AND METHODS

Twenty-four mongrel dogs of either sex weighing 9 to 15 kg were anesthetized with a bolus of 5 mg/kg propofol, followed by continuous infusion of 10 mg/kg/h, and paralyzed with pancuronium sulfate (0.2 mg/kg). They were mechanically ventilated by a cuffed endotracheal tube with room air. The tidal volume (15-20 mL/kg) was adjusted to maintain an arterial PCO₂ between 30 and 35 mmHg at a frequency of 20/min (Servo-ventilator 900B, Siemens Elema, Solna, Sweden). Arterial pressure was measured in the aorta through a fluid-filled 16G8 teflon catheter (B-D IV Cath, Becton Dickinson & Co. Mountain View, CA) inserted by direct puncture of the femoral artery. A large peripheral venous line (Abbocath 14G, Abbo, Belgium) was introduced into a posterior limb for the continuous infusion of saline (4 mL/kg/h) and drug administration. Electroencephalogram (EEG, Sirecust 400 Siemens, “EEG + TEMP” module—two epicranial electrodes in temporal regions, one neutral midfrontal electrode); electrocardiogram (ECG) (standard limb lead DII—subdermal needle electrodes in the extremities); end tidal carbon dioxide, (Capnometer 47210A, Helwett Packard) at a rate of 5 mm/min. Faster tracing was obtained for reading of pressure values at end expiration. Electrocardiograph 3-lead tracings (DI, DII, DIII) were serially recorded at a rate of 25 and 50 mm/sec for rhythm, PR, QRS, and QT interval measurements. Mean arterial pressure was calculated as systolic pressure + 2 × diastolic pressure/3.

After ensuring steady state conditions for 10 minutes, an imals were randomized. Group AMI/MID received a bolus of 1 mg/kg midazolam, followed by 1 mg/kg/min AMI and 1 mg/kg/h midazolam, administered by constant infusion pumps. In group AMI/PLA, AMI was administered at the

From the *Emergency Department and †Clinical Toxicology Unit, Erasme University Hospital, Brussels, Belgium. Manuscript received February 13, 1991; revision accepted October 30, 1991.

Supported by grants from Roche Research Department, Basel, Switzerland), and Roche S. A. (Belgium).

Address reprint requests to Dr P. Lheureux, Emergency Department, Erasme Hospital, 808, route de Lennik, B-1070 Brussels, Belgium.

Key Words: Benzodiazepine, antidepressants, flumazenil, antidote, convulsions, cardiac arrhythmias, drug poisoning. Copyright © 1992 by W.B. Saunders Company 0735-6757/92/1003-0002$5.00/0
same rate, but midazolam was replaced by an equivalent volume of saline. Drug infusions were stopped with onset of cardiovascular toxicity from tricyclics (intraventricular conduction abnormality with QRS > 120 milliseconds or ventricular tachycardia with at least five beats). At that moment, blood samples were taken for determination of amitriptyline and midazolam plasma levels. An intravenous bolus of flumazenil (0.2 mg/kg) was randomly administered to six dogs out of each group (subgroups AMI/MID/FLU and AMI/PLA/FLU) with the intention of producing sudden and complete reversal of midazolam effects. Other animals received an equivalent volume of saline (subgroups AMI/MID/PLA and AMI/PLA/PLA). The complete design of the study is summarized in Figure 1. Progress was observed during a total time of 120 minutes or until spontaneous death. Occurrence of convulsions or dysrhythmias were recorded and severity of disturbances were scored as follows:

**EEG**
- No convulsion, 0; convulsions, 1

**ECG: conduction disturbances:**
- Sinus rhythm, 0; 1st degree atrioventricular block, 1; 2nd degree atrioventricular block, 2; nodal rhythm, 3; ventricular rhythm, 4; asystole, 10

**ECG: Arrhythmias**
- No (premature ventricular breaks [PVB]), 0; isolated PVB, 1; frequent PVB, 2; repeated PVB < 5, 3; multifocal PVB, 4; ventricular tachycardia, 5; ventricular fibrillation, 10

Ten was the maximal ECG score.

Amitriptyline (Redomex Labaz-Sanofi) and midazolam (Dormicum Roche, Basel, Switzerland) were used as solutions available for human use. Flumazenil was prepared as a sterile 0.2 mg/mL aqueous solution. Determination of plasma levels of AMI and midazolam were performed by high-pressure liquid chromatography.

**Statistics**

Differences between cumulated doses of TCA and plasma levels were statistically evaluated by unpaired Student’s t-test. The comparison between groups AMI/MID and AMI/PLA for cardiotoxicity and neurotoxicity occurrence (effect of midazolam) was achieved by χ² test with Yates correction or by Fisher exact test. Electrocardiogram scores before flumazenil administration were compared by Mann-Whitney U-test.

Evolution of ECG score in each subgroup was evaluated by Wilcoxon signed rank test. Evolution of QRS duration was analyzed by paired t-test.

**RESULTS**

Initial trial groups (AMI/MID and AMI/PLA) were similar in weight. Although there were more male dogs in the AMI/PLA group, the sex ratio did not differ significantly (Table 1).

**Effect of Midazolam on Amitriptyline Toxicity**

**Cardiac Toxicity**

As the appearance of cardiotoxicity was used as criteria to determine the duration of TCA infusion, the mean cumulated dose and the mean plasma level of AMI could be considered as markers of the cardiac sensitivity to this drug. The mean doses of AMI were almost identical in both groups. Although a larger variability was observed in the AMI/MID group, the mean AMI levels at the end of the TCA infusion were also similar (Table 2). The mean plasma midazolam level at the end of the infusion was 0.92 ± 0.31 μg/mL in the AMI/MID group.

The signs of cardiotoxicity at the end of TCA infusions (QRS > 120 milliseconds or ventricular arrhythmias) were almost identical in both groups. However, the mean maximal ECG score which was reached during the TCA infusion was slightly lower in the AMI/MID group (3.1 ± 2.4 versus 4.8 ± 2.4; Mann-Whitney U-test P < .05) because of lower incidence of atrioventricular conduction disturbances and lesser severity of ventricular arrhythmias in this group (Table 3).

At the end of AMI infusion, mean arterial pressure was slightly lower in the AMI/MID group than in the AMI/PLA group (65.4 ± 14 versus 82.4 ± 28 mmHg; P < .03).

**TABLE 1. Comparison of Trial Groups**

<table>
<thead>
<tr>
<th></th>
<th>AMI/MID</th>
<th>AMI/PLA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>11.5 ± 1.7</td>
<td>10.6 ± 1.5</td>
<td>t-test NS</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>7/5</td>
<td>9/3</td>
<td>χ² NS</td>
</tr>
</tbody>
</table>

**TABLE 2. Cardiac Tolerance to Amitriptyline Infusion**

<table>
<thead>
<tr>
<th></th>
<th>AMI/MID</th>
<th>AMI/PLA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Dose of amitriptyline (mg/kg)</td>
<td>31 ± 13</td>
<td>36 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Amitriptyline level (μg/mL)</td>
<td>8.63 ± 3.25</td>
<td>8.03 ± 7.19</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: values are mean ± SD.
Neurologic Events

The influence of midazolam administration on the arrhythmogenic effect of AMI is less clear. The total dose of AMI tolerated by the dogs or their plasma levels are almost identical in AMI/MID and AMI/PLA groups. Occurrences of QRS prolongation or ventricular arrhythmias are also similarly recorded. Slightly lower mean ECG score and arterial pressure are, however, observed in the AMI/MID group. Although significant, these differences could be due to redundant statistical comparisons.

The antagonization of BZD-induced sedation in animals previously intoxicated with AMI is clearly associated with a risk to precipitate convulsions. Although seizures related to TCA toxicity are usually attributed to their central anticholinergic effects and to the blockade of norepinephrine re-uptake in the brain, a GABA-antagonistic activity has been suggested as another possible mechanism. Benzodiazepine possesses potent anticonvulsant properties related to the stimulation of the GABA-dependent chloride influx and is usually recommended as a first-line agent to interrupt TCA-induced seizures. Reversal of its pharmacologic effects sometimes triggered convulsions in our animal model, as previously reported. The absence of seizures reported in

<table>
<thead>
<tr>
<th>TABLE 3. Signs of Cardiotoxicity at the End of Cyclic Antidepressant Infusion</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>QRS &gt;120 milliseconds</td>
</tr>
<tr>
<td>QRS &lt;120 milliseconds</td>
</tr>
<tr>
<td>Arrhythmias</td>
</tr>
<tr>
<td>No arrhythmias</td>
</tr>
<tr>
<td>Mean ECG score</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
</tr>
</tbody>
</table>

* Values are mean ± SD.

Seizures

Electroencephalogram recordings did not disclose any seizures in the AMI/MID group, whereas five dogs developed convulsive activity during AMI infusion in the AMI/PLA group (Fisher exact test P < .02; Table 4).

Events Associated with Flumazenil Administration

Cardiovascular Events

Rhythm disturbances. A significant worsening of the mean maximal ECG score was observed in the two subgroups receiving flumazenil (7.0 ± 3.3 versus 2.2 ± 2.3; P = .04 and 7.2 ± 1.6 versus 3.8 ± 2.8; P < .05 in AMI/MID/FLU and AMI/PLA/FLU groups, respectively) (Wilcoxon rank-sum test for paired data). Such evolution was not observed in the placebo subgroups (Table 5).

QRS duration. Flumazenil administration was associated with a slight reduction of QRS duration in the AMI/PLA/FLU subgroup (paired t-test P < .03; Table 5). No significant change was observed in other subgroups.

Deaths. Two deaths were observed. In the AMI/MID/FLU subgroup, a dog developed sudden ventricular tachycardia and fibrillation 7 minutes after the administration of flumazenil. In the AMI/PLA/FLU group, another dog developed slow idioventricular rhythm and asystole 9 minutes after the administration of flumazenil. The maximal ECG score of these animals was never observed in the AMUMIDiPLA subgroup (Fisher exact test).

Arterial pH remained within the normal range (7.35-7.45) throughout the experiment in all dogs, except when they were dying.

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DISCUSSION

Most of the data which are found in the literature report a synergistic effect between BZD and TCA toxicities, suggesting the possibility of a beneficial action of flumazenil in mixed overdoses. In a group of patients who died from AMI overdose, King observed lower lethal levels of AMI in poisonings also involving BZD. Limbitrol (Roche chlor Diazepoxide and AMI) overdose is associated with unexpectedly severe central nervous system depression. In a recent retrospective series of TCA poisoning, Kresse-Hermendorf and Muller-Oerlinghausen report a higher percentage of patients suffering ECG changes and respiratory depression when other drugs (mainly BZD and ethanol) are involved. Conversely, Boehnert and Lovejoy have reported no difference in the occurrence of seizures and ventricular arrhythmias in TCA single or multiple-drug overdoses. Although BZD was probably often implicated, details about associated drugs are not given in this series. Finally, in the study by Storm et al., a lower incidence of seizure and ECG abnormalities is reported in mixed-overdoses (including 10% associations with BZD). Respiratory and circulatory failure are, however, more often observed in this group.

The results of the present study show that midazolam effectively protects against the development of the convulsions associated with severe AMI toxicity, which were observed in about one half of the dogs in the AMI/PLA group. The influence of midazolam administration on the arrhythmogenic effect of AMI is less clear. The total dose of AMI tolerated by the dogs or their plasma levels are almost identical in AMI/MID and AMI/PLA groups. Occurrences of QRS prolongation or ventricular arrhythmias are also similarly recorded. Slightly lower mean ECG score and arterial pressure are, however, observed in the AMI/MID group. Although significant, these differences could be due to redundant statistical comparisons.

The antagonization of BZD-induced sedation in animals previously intoxicated with AMI is clearly associated with a risk to precipitate convulsions. Although seizures related to TCA toxicity are usually attributed to their central anticholinergic effects and to the blockade of norepinephrine re-uptake in the brain, a GABA-antagonistic activity has been suggested as another possible mechanism. Benzodiazepine possesses potent anticonvulsant properties related to the stimulation of the GABA-dependent chloride influx and is usually recommended as a first-line agent to interrupt TCA-induced seizures. Reversal of its pharmacologic effects sometimes triggered convulsions in our animal model, as previously reported. The absence of seizures reported in

| TABLE 4. Effect of Midazolam on Amitryptiline-Induced Seizures |
|---------------------------|-----------|-----------|
| No.                       | 12        | 12        |
| Seizure activity          | 0         | 5         |
| No seizure                | 12        | 7         |

* Values are mean ± SD.
two other recent animal studies, 15,16 is probably due to the slight anticonvulsant effect of flumazenil itself 17-19 when higher amounts (5 mg/kg in these studies) are given. With the dose we used (0.2 mg/kg), such an anticonvulsant effect is less likely.

As was suggested in our preliminary study, 5 worsening of cardiac dysrhythmias also occurs after flumazenil administration, and two sudden deaths were observed. Initially, we thought that these arrhythmias might be related either to the suppression of a central protective effect of BZD on TCA-induced rhythm disturbances (as has been suggested in chloroquine intoxication, 20,21 or to acute neurovegetative changes associated with the sudden reversal of BZD-induced sedation. Indeed, occurrences of PVB have been sporadically observed after the use of flumazenil in pure BZD overdoses, 22 and multifocal PVBs and ventricular tachycardia have been reported after administration of flumazenil 0.5 mg in a deliberate overdose, implicating oxazepam and chloral hydrate, 23 a compound sensitizing the heart to the arrhythmogenic effects of catecholamines. However, the results of the present study suggest that the worsening of dysrhythmias may not only be related to the reversal of midazolam-induced sedation. Indeed, a similar evolution of ECG score and one death are observed when flumazenil is administered in "midazolam-free" dogs. Although our results do not strictly exclude this hypothesis, an intrinsic arrhythmogenic effect of flumazenil is very unlikely and not suggested by the large experience already obtained with this compound, including intravenous administration of very large doses in human volunteers. The antagonization of a putative endogenous ligand with protective effect could be an alternate hypothesis.

Although the mechanism remains unclear, electrophysiological side effects are observed after rapid administration of flumazenil at much higher doses than usually recommended to treat BZD overdose. In a recent Scandinavian series, 24 10 patients with mixed TCA/BZD overdoses received slow flumazenil administration in standard doses (1 mg). Three of them presented wide QRS complex. Neither seizures nor arrhythmias were reported, but flumazenil administration was associated with an acute fall in blood pressure in a patient intoxicated by maprotiline, lorazepam, and alprazolam. Such changes in blood pressure were not observed in our animal studies.

CONCLUSION

This study suggests that midazolam-induced sedation protects efficiently against seizures, but has few effects on rhythm or conduction disturbances due to TCA toxicity. The antagonization of midazolam by flumazenil may unmask the underlying convulsive activity. Although the mechanism remains unexplained, bolus administration of high doses of flumazenil also precipitates severe rhythm disturbances in some dogs.

Given the problem of extrapolating animal data to humans, multicenter trials in human mixed drug overdoses are needed to confirm the potential risks associated with flumazenil administration. Our results suggest, however, that a risk/benefit ratio should be carefully evaluated before flumazenil is used in mixed drug overdoses implicating TCA (and probably other drugs decreasing the seizure or arrhythmia threshold). If the decision has been made to administer the

TABLE 5. Cardiac Events Associated With Flumazenil Administration

<table>
<thead>
<tr>
<th>Subgroup number</th>
<th>AMI/MID FLU 12</th>
<th>PLA 0</th>
<th>AMI/PLA FLU 0</th>
<th>PLA 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal ECG score</td>
<td>Before FMZ 2.2 ± 2.3</td>
<td>4.0 ± 1.8</td>
<td>3.8 ± 2.3</td>
<td>5.7 ± 0.9</td>
</tr>
<tr>
<td>After FMZ 7.0 ± 3.6</td>
<td>5.0 ± 2.8</td>
<td>7.2 ± 1.7</td>
<td>4.3 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Wilcoxon signed rank test</td>
<td>P = .04</td>
<td>NS</td>
<td>P &lt; .05</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of QRS (milliseconds)</td>
<td>Before FMZ 128 ± 16</td>
<td>113 ± 12</td>
<td>125 ± 12</td>
<td>105 ± 16</td>
</tr>
<tr>
<td>After FMZ 140 ± 62</td>
<td>110 ± 17</td>
<td>105 ± 18</td>
<td>112 ± 10</td>
<td></td>
</tr>
<tr>
<td>Paired t-test</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; .03</td>
<td>NS</td>
</tr>
<tr>
<td>Deaths</td>
<td>1*</td>
<td>0</td>
<td>1†</td>
<td>0</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>Before FMZ 57 ± 8</td>
<td>73 ± 15</td>
<td>77 ± 12</td>
<td>87 ± 33</td>
</tr>
<tr>
<td>After FMZ 64 ± 15</td>
<td>81 ± 21</td>
<td>88 ± 14</td>
<td>113 ± 24</td>
<td></td>
</tr>
<tr>
<td>Paired t-test</td>
<td>NS</td>
<td>NS</td>
<td>P = .05</td>
<td>P &lt; .03</td>
</tr>
</tbody>
</table>

ABBREVIATION: FMZ, flumazenil.

* Death due to ventricular fibrillation.
† Death due to asystole.

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TABLE 6. Neurologic Effects Associated With Flumazenil Administration

<table>
<thead>
<tr>
<th>Subgroup number</th>
<th>AMI/MID FMZ 12</th>
<th>PLA 6</th>
<th>AMI/PLA FMZ 6</th>
<th>PLA 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs already seizing when FMZ was administered</td>
<td>0/6</td>
<td>0/6</td>
<td>1/6</td>
<td>4/6</td>
</tr>
<tr>
<td>Dogs seizing during the 5 minutes after FMZ administration</td>
<td>4/6</td>
<td>0/6</td>
<td>1/6</td>
<td>4/6</td>
</tr>
</tbody>
</table>

NOTE: Fisher exact test P = .03.
antidote, it should be carefully titrated under close observation of the patient’s reactions, of ECG, and possibly of EEG monitoring.

Roche Research Department (Basel, Switzerland) and Roche S. A. (Belgium) are gratefully acknowledged for their generous gift of flumazenil and midazolam. The authors also thank the Pharmacy Department, Erasme Hospital for preparing injectable solutions of flumazenil, Dr D. Ganji (Department of Clinical Pharmacology, Erasme Hospital) for performing the high-pressure liquid chromatometry dosage of amitriptyline and midazolam, and Dr C. Melot (Intensive Care Unit, Erasme Hospital) for skilful advice in statistical analysis. L. Edwards is acknowledged for reviewing the manuscript.

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