Flumazenil Counteracts Intrathecal Baclofen-induced Central Nervous System Depression in Tetanus

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Tetanus, provoked by an infection due to Clostridium tetani (a gram-positive bacillus), is characterized by severe muscular contractures and convulsions. Death can occur through respiratory muscle contracture. These symptoms are due to the action of tetanospasmin, a neurotoxin produced by the bacterium. At the level of γ-aminobutyric acid (GABA) and glycine synapses, the toxin acts through a presynaptic blockade of motoneuron inhibition by Renshaw cells and Ia fibers of reciprocal innervation.1 Tetanus has become rare in industrialized societies but is still frequent in Third-world countries.5 And despite the availability of artificial ventilation, benzodiazepines, and neuromuscular relaxants, the disease is often lethal.2 Baclofen (β-[4-chlorophenyl] γ-aminobutyric acid) inhibits polysynaptic nociceptive reflexes through an action on GABA_B medullary interneurons.4 Although baclofen can cross the blood–brain barrier and can exert its antispasticity effect by a systemic route, the dose required to manage severe spasticity may result in significant side effects, such as somnolence and respiratory depression. To diminish these side effects and to obtain high concentra-

REFERENCES

Anesthesiology
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tions of the drug at its target site in the spinal cord, the agent may be administered intrathecally. According to Muller et al., who demonstrated that baclofen is active on tonic tetanic contractions and convulsions when administered intrathecally, intrathecal administration, leading to a dose-dependent muscular hypotonia, has been used to treat severe spasticity. However, side effects may develop because of an action on supraspinal receptors: these may include central depression with sedation, occasional coma, bradypnea, bradycardia, and hypotension. These central effects are potentiated by benzodiazepines.

We report here a baclofen-induced central nervous system depression which was successfully counteracted with the competitive benzodiazepine antagonist flumazenil in two patients with tetanus. Because baclofen is approved for clinical use in Sénégal, informed consent of the patients was not obtained before the intrathecal administration of baclofen, as this product has been proven effective.

CASE REPORTS

Case 1. The patient was a 24-year-old woman. After a therapeutic abortion, she developed generalized tetanus with trismus, dysphagia, contractures, and tonic muscular paroxysms. Upon admission to the intensive care unit, the patient was conscious (Glasgow score = 15); rectal temperature was 38°C, heart rate (HR) 110 beats/min, blood pressure (BP) 120/70 mmHg, PaO₂ 109 mmHg, PaCO₂ 33 mmHg, and hemoglobin oxygen saturation (SpO₂) 99%. Tetanus antitoxin and antibiotics were administered. One hour after intrathecal administration of baclofen (1,000 μg), contractures and paroxysms had ceased, but dysphagia persisted. Hemodynamic (HR 80 beats/min, BP 110/80 mmHg) and respiratory (SpO₂ 99%) variables and consciousness (Glasgow score = 15) remained stable.

Because of the recurrence of paroxysms, a second intrathecal injection of 1,000 μg baclofen was given 22 h later. Within 8 h, general hypotonia with coma (Glasgow score = 7) and bradypnea (10 breaths/min) developed. SpO₂ decreased to 58%; PaO₂ decreased to 39 mmHg; and PaCO₂ reached 61 mmHg. HR (88 beats/min) and BP (110/80 mmHg) were preserved. A benzodiazepine antagonist, flumazenil, was injected intravenously (0.5 mg) and immediately improved the patient’s state of consciousness and ventilation (table 1). No paroxysm occurred. Flumazenil then was infused intravenously (0.1 mg·h⁻¹). Within 4 h, blood gases (during nasal administration of 3 l oxygen) returned to normal values (PaO₂ 145 mmHg, PaCO₂ 40 mmHg). The patient was then conscious, without any contracture or paroxysm.

However, while flumazenil was still infused, tonic paroxysms reappeared 13 h later, with a rapid deterioration of arterial blood gases (PaO₂ 59 mmHg, PaCO₂ 58 mmHg) and sympathetic hyperactivity (HR 180 beats/min, BP 200/120 mmHg). At this stage, flumazenil infusion was stopped. Baclofen was not administered because of the sympathetic hyperactivity. Tracheal intubation and assisted ventilation were undertaken. The patient died 8 days later after left ventricular failure probably due to tetanus-induced myocarditis.

Case 2. A 60-year-old man was admitted to the hospital because of Fournier’s gangrene (perineal necrosis with an anaerobic infection). Eight days after surgery, he was transferred to the intensive care unit because of the occurrence of tetanus with general contractures, trismus, dysphagia, and tonic paroxysms resulting in opisthotonus. The patient was conscious (Glasgow score = 15), with rectal temperature 37.4°C, HR 98 beats/min, BP 140/80 mmHg, PaO₂ 90 mmHg, and PaCO₂ 58 mmHg. SpO₂ (99%) was not altered during paroxysms.

Antibiotics were given along with tetanus antitoxin. The paroxysms disappeared 1 h after an intrathecal administration of 800 μg baclofen. Trismus was attenuated but persisted, as did dysphagia. Consciousness, SpO₂, and BP remained unchanged. Three days later, a second baclofen injection (500 μg) proved effective and was well tolerated.

However, on the 5th day, 6 h after a third baclofen injection (400 μg), a hypotonic comatose state developed (Glasgow score = 7), with bradypnea (12 breaths/min), PaO₂ 88 mmHg, PaCO₂ 48 mmHg, and SpO₂ 95% but stable hemodynamics (HR 80 beats/min, BP 140/80 mmHg). Flumazenil (0.5 mg) was injected intravenously (table 1) and caused an immediate awakening without any recurrence of paroxysms. Flumazenil infusion (0.1 mg·h⁻¹) was administered for 18 h. On the 6th day of the disease, 30 h after the previous intrathecal injection, baclofen (200 μg) was administered again. The state of consciousness did not change, and respiratory depression did not occur.

The patient left the intensive care unit after 30 days, during which he had received nine intrathecal injections of baclofen for a total dosage of 3,300 μg. There had been no need for intubation or ventilatory assistance.

DISCUSSION

Supraspinal effects of intrathecally administered baclofen are well documented. Of their 30 patients treated for spinal and supraspinal spasticity, Muller et al. observed mild sedation in 10 and bradycardia and hypotension in 7. However, severe intolerance is rare (1 case of bradypnea with bradycardia and hypotension in Muller et al.’s series), and 1 case of coma, with quadriplegia and bradypnea has been reported by Romijn et al. These events have been attributed to an overdose or to the intracranial migration of a baclofen bolus.

The supraspinal effects of baclofen are similar to those

<table>
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<th>Variable</th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tr>
<td></td>
<td>0 min</td>
<td>5 min</td>
</tr>
<tr>
<td>Glasgow score (3–15)</td>
<td>7</td>
<td>15</td>
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<tr>
<td>Respiratory rate (breaths/min)</td>
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<td>PaO₂ (mmHg)</td>
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<td>59</td>
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<td>PaCO₂ (mmHg)</td>
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<td>Heart rate (beats/min)</td>
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<td>Blood pressure (mmHg, systolic/diastolic)</td>
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<td>120/80</td>
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<td>Tetanus paroxysms</td>
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of opioids and are attributed to an action on brain GABA receptors, especially in the hippocampus. Such receptors are also present in brainstem areas involved in the control of respiratory and cardiovascular functions. In animals, GABA agonists such as baclofen can provoke bradycardia and hypotension. However, in humans, intrathecally administered baclofen has been reported essentially to reduce consciousness and induce respiratory depression, although cardiovascular complications have been observed. This depression is not likely to be due to a direct effect of baclofen on GABA brainstem receptors present in the fourth ventricle. However, such a mechanism could be invoked regarding brainstem ventral surface GABA receptors, which are in direct contact with the cerebrospinal fluid.

Adverse effects of baclofen were first treated with naloxone because of the similarity between baclofen and morphine intraspinal overdose (respiratory depression). However, naloxone treatment was unsuccessful, because baclofen does not act on central opioid receptors. Physostigmine (2 mg intravenous), which antagonizes the benzodiazepine-induced anticholinergic syndrome, was shown to reverse coma and other baclofen overdose symptoms within 2 min. In our observations, the favorable action of flumazenil can be related to that of physostigmine. Flumazenil acts as a specific antagonist of the binding of benzodiazepine to the GABA complex (GABA$_A$). It therefore antagonizes the inhibition resulting from the binding of benzodiazepines to their central receptors. Flumazenil counteracts coma and respiratory depression (supraspinal action) without a spinal action. This suggests that baclofen (or one of its isomers: L, GABA$_B$ agonist; D, weak antagonist) is not a supraspinal agonist of GABA$_B$ receptors but may act through binding to either the central benzodiazepine receptor inside the GABA complex or specific receptors.

In conclusion, in these two cases of tetanus treated with baclofen, flumazenil seemed to counteract selectively the central effects of baclofen, preserving its spinal action. However, before making any general recommendation for the treatment of other rigidity states, further pharmacologic and electrophysiologic studies must be undertaken to elucidate the mechanism of action of flumazenil.

REFERENCES


