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The Efficacy of Intrathecal Baclofen in Severe Tetanus

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PROTECTIVE vaccination programs and public health advances have decreased the incidence of tetanus in developed countries. Unfortunately the incidence remains significant in developing countries, with a mortality rate from tetanus of more than 50%,¹ which results in 500,000 deaths per year worldwide.² The prognosis of severe tetanus has been improved by critical care units, mechanical ventilation, and the use of neuromuscular blockade. However, this level of care is rarely available in developing countries. As deep sedation and mechanical ventilation are difficult to manage in a tropical environment, many patients die as a result of respiratory distress.

Baclofen, a γ-aminobutyric acid (GABA) receptor agonist, inhibits mono- and polysynaptic medullary reflexes,³ which results in an antispastic action. The use of baclofen has been proposed as part of the management of tetanus-induced contractures, spinal convulsions,⁴ and to limit the need for tracheal intubation⁵ in afflicted patients. It has been proven to directly stimulate postsynaptic GABA β-receptors on synapses blocked by tetanus toxin (GABergic-inhibiting synapses in the anterior cornual of the spinal cord), restoring physiologic inhibition of α motoneuron.

We report 14 cases of severe tetanus managed with intrathecal baclofen in an African sub-Saharan intensive care unit (ICU). The clinical course of a representative case is presented.

Case Report

A 35-year-old man (weight 65 kg) was admitted to our ICU with a 2-day history of severe tetanus (case #15, see table 2). He had never been immunized with tetanus toxin and had sustained a knee wound 11 days previously. Trismus and dysphagia occurred 8 days after the wound, and generalized spasms occurred 1 day later. On admission, the patient presented with complete lockjaw, neck and general contractures with frequent, severe tonic paroxysms resulting in opisthotonus. He was fully conscious, temperature was 39.3°C, heart rate (HR) was 84 beats/min, and blood pressure was 120/80 mmHg. Dakar score⁶ was 3/6 (table 1). Plasma CPK level was 1,170 U/I (normal value <100 U/I).

The knee wound was debrided. The patient was treated with tetanus antitoxin (heterologous serum 1,500 U; Serum antitétanique, Pasteur vaccins, Marne la Coquette, France), repeated on hospital days 2 and 6, intravenous ampicillin, and vaccinated with tetanus toxin (Tetavax, Merieux, Lyon, France) on days 1, 30, and 60.

Sedation was immediately achieved with intravenous diazepam. An intrathecal catheter (Epishot Minipack, Portex Ltd, UK) was inserted via the L3-L4 vertebral interspace and advanced about 3 cm cephalad. Diazepam administration was ceased, and a bolus of 750 mg baclofen (Lioresal, Giba Geigy, Rueil Malmaison, France, 500 µg/ml into saline solution) was administered intrathecally. Paroxysmal contractures disappeared within 2 h of the injection, and the patient was free of rigidity during the next 24 h. A second bolus was administered 24 h after the first. Because of mild drowsiness during the few hours after injections, a continuous infusion (1,750 µg/day) was instituted on the third day. Baclofen was continuously infused from day 3 to day 17 (mean daily dose, 1,690 µg), allowing control of muscle rigidity, although trismus persisted. Additional sedation or tracheal intubation was not required. There were no adverse effects except for well-tolerated sinus bradycardia periods (HR, 45 beats/min) from day 12 to day 16.

After 15 days of intrathecal baclofen administration, rigidity was well controlled, and the CPK normalized. The baclofen daily dosage was decreased to 1,500 µg and further to 1,000 µg on day 17. On day 18, some spasms and moderate neck rigidity reappeared, and temperature increased to 40.5°C and CPK level to 560 U/I. Cerebrospinal fluid (CSF) and blood cultures were positive for Klebsiella pneumoniae. The intrathecal catheter was removed, and ampicillin was switched to ciprofloxacin. Residual muscle rigidity was controlled with diazepam.

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Table 1. Dakar Score* of the Reported Case

<table>
<thead>
<tr>
<th>Incubation period</th>
<th>Score 1</th>
<th>Score 0</th>
<th>Patient 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 days</td>
<td></td>
<td>≥7 days or unknown</td>
<td>0</td>
</tr>
<tr>
<td>≥7 days</td>
<td></td>
<td>≥2 days or unknown</td>
<td>1</td>
</tr>
<tr>
<td>Portal of entry</td>
<td>Umbilicus, uterus, burn, open fracture, post surgery, intramuscular injection</td>
<td>Other or unknown</td>
<td>0</td>
</tr>
<tr>
<td>Paroxysm</td>
<td>Present</td>
<td>Absent</td>
<td>1</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>&gt;38.4</td>
<td>&lt;38.4</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate (bps)</td>
<td>&gt;120</td>
<td>≤120</td>
<td>0</td>
</tr>
</tbody>
</table>

* Dakar score is assessed at the 48th hour of illness.

On day 20, the CSF was sterile, and the CPK level decreased to 143 U/L. Soon afterward the patient rapidly recovered; he was able to walk on day 22 and was discharged from the hospital on day 24.

Additional Data

The ICU is located in Bobo-Dioulasso, Burkina Faso. Mechanical ventilation and neuromuscular blockade are usable, but ventilators and monitors are scarce. Additionally, para-medical staffs are less experienced than in developed countries.

From May 1995 to August 1996, 14 patients with severe tetanus (i.e., Dakar score ≥ 2/6 and Mollaret stage II or III) were treated with intrathecal baclofen. Demographic data, main therapeutic modalities, and outcome are summarized in table 2. All patients received standard tetanus therapy with antibiotics (penicillin, ampicillin), atropin, and tetanus immunization. Baclofen administration was started as soon as possible. The dose of the first intrathecal injection was determined according to body weight (500 µg if weight ≤ 55 kg; 1,000 µg if weight > 55 kg). After administration of the first bolus, continuous intrathecal infusion of baclofen was the preferred method of administration if appropriate equipment was available (baclofen concentration in saline solution ranging from 20 to 80 µg/ml). Supplementary intravenous diazepam was used only for extra sedation in those with pain. The dose of baclofen was adjusted every 12 h to allow control of muscle rigidity without adverse effects. If consciousness decreased (Glasgow Coma Score < 15) or bradypnea (respiratory rate < 10 breaths/min) occurred, the infusion was stopped until recovery and then started again at a decreased dose. Intrathecally administered baclofen was continued until persistent resolution of muscular rigidity and then progressively decreased by steps of 500 µg every 2 days. The mean baclofen dosage was 1,225 ± 509 µg/day. Mean duration of treatment was 19 ± 8 days for survivors. When respiratory depression required tracheal intubation, a tracheotomy was performed within 24 h, although there was always an attempt to keep intrathecal baclofen as the only sedation treatment. If intrathecal baclofen failed (lack of resolution of muscle rigidity while severe side effects prohibited dosage increase or respiratory distress required mechanical ventilation), treatment was withdrawn, and general anesthesia was undertaken with mechanical ventilation.

Cerebrospinal fluid cultures were systematically performed at admiralization.

Table 2. Demographic Data, Baclofen Therapy, and Outcome

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Dakar Score</th>
<th>Portal of Entry</th>
<th>Incubation Period (days)</th>
<th>Baclofen Therapy*</th>
<th>Tracheal Intubation Outcome</th>
<th>Time in Hospital (days)</th>
<th>Time of Death (days)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>M</td>
<td>4</td>
<td>?</td>
<td>?</td>
<td>Delay 2, Duration 28</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>M</td>
<td>2</td>
<td>?</td>
<td>?</td>
<td>Delay 2, Duration 19</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>F</td>
<td>4</td>
<td>IM injection</td>
<td>8</td>
<td>Delay 1, Duration 3</td>
<td>No, Effectiveness 100</td>
<td>No</td>
<td>Death</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>M</td>
<td>3</td>
<td>Peripheral wound</td>
<td>?</td>
<td>Delay 2, Duration 34</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>F</td>
<td>3</td>
<td>Knee wound</td>
<td>17</td>
<td>Delay 1, Duration 3</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>F</td>
<td>4</td>
<td>IM injection</td>
<td>6</td>
<td>Delay 1, Duration 21</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>2</td>
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<tr>
<td>7</td>
<td>29</td>
<td>M</td>
<td>4</td>
<td>Foot wound</td>
<td>14</td>
<td>Delay 1, Duration 13</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>13</td>
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<tr>
<td>8</td>
<td>31</td>
<td>F</td>
<td>3</td>
<td>Post partum</td>
<td>7</td>
<td>Delay 1, Duration 6</td>
<td>No, Effectiveness 100</td>
<td>No</td>
<td>Death</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>M</td>
<td>3</td>
<td>Leg fracture</td>
<td>11</td>
<td>Delay 2, Duration 15</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>25</td>
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<tr>
<td>10</td>
<td>32</td>
<td>M</td>
<td>3</td>
<td>Finger wound</td>
<td>10</td>
<td>Delay 3, Duration 8</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>F</td>
<td>3</td>
<td>Cutaneous infection</td>
<td>7</td>
<td>Delay 4, Duration 13</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>M</td>
<td>5</td>
<td>Hand wound</td>
<td>6</td>
<td>Delay 1, Duration 3</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>35</td>
<td>M</td>
<td>3</td>
<td>Knee wound</td>
<td>8</td>
<td>Delay 2, Duration 17</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>15</td>
<td>M</td>
<td>5</td>
<td>Arm fracture</td>
<td>6</td>
<td>Delay 3, Duration 16</td>
<td>Yes, Effectiveness 100</td>
<td>No</td>
<td>Survival</td>
<td>2</td>
</tr>
</tbody>
</table>

* Delay of baclofen therapy: delay between first symptoms and start of baclofen; effectiveness of baclofen therapy: no need of general anesthesia with mechanical ventilation, nor death because of spasms.
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sion and twice a week and additionally when temperature increased to
more than 58.5°C. The catheter was removed when a meningeal
infection was diagnosed, and baclofen was administered via daily
lumbar punctures.

In 12 patients, intrathecal baclofen was effective as antispastic treat-
ment with resolution of generalized muscle rigidity and spasm, al-
though dysphagia and trismus most often persisted. However, two
patients (17.3%) had to be intubated because of tracheal obstruction
and laryngeal spasm (table 2). Overall mortality rate was 5 of 14
(35.7%).

Discussion

These results can be compared with those of the previous 11 patients admitted in our ICU for severe tetanus before the use of intrathecal baclofen. Despite demographic data and severity scores similar to the baclofen-treated patients, 45.5% of these previous patients were intubated, requiring deep sedation in each case. Overall mortality rate was 9 of 11 (81.8%), reaching 100% for intubated patients. These mortality rates are higher than in developed countries (now between 20%8,9 and
50%,8,10 depending on age and severity of illness). However,
mortality is commonly more than 50% in developing countries (up to 74% in Gabon11). In such countries, facilities for specialized cares with respect to equipment, medications, and qualified staff are more limited. Although comparison with retrospective controls is difficult, it is our impression that patient outcome is better since the introduction of intrathecal baclofen.

To our knowledge, 26 adults with severe tetanus treated by intrathecal baclofen have been reported to date,12-22 including 11 cases in Africa. Our series is the largest reported in the literature. Our results agree with the literature, showing efficacy of intrathecal baclofen in controlling muscle rigidity. They also suggest a decreased need for tracheal intubation or deep anesthesia. These findings are important for developing countries wherein intensive care facilities are scarce.

Because of slight liposolubility, baclofen does not easily cross the blood brain barrier. Therefore local administration yields to higher concentration on effect site, with fewer adverse systemic effects. After intrathecal injection, the effect of baclofen begins within 1 or 2 h and persists 12-48 h.5,12 Baclofen elimination half-life in CSF has been found to range from 0.9 to 5 h.23 After lumbar intrathecal administration, cervical-to-lumbar concentration ratio is 1:4.24 This distribution probably explains the cephalic progression of hypotonia and the higher posology necessary to relax trismus than legs, which is reported by every author.

The major adverse effect of baclofen is depressed level of consciousness (LOC) and respiratory compromise.5,25 These potentially deleterious effects can develop at any dose and can develop before resolution of tetanus spasms.22,26

Seven of our patients developed decreased LOC or respiratory depression that was readily reversed by decreasing the baclofen dose. This side effect seems more closely related to overdose than to accumulation because it is more often reported after first injections5 or during bolus administration.27

Three cases of sinus bradycardia were noted, but two of them did not seem to be related to dosage nor to timing of baclofen injection.

Infection of the intrathecal catheter is another serious adverse effect of intrathecal baclofen administration. Meningitis occurred in three patients in our series (patients 2, 13, and 14 on days 5, 8, and 16). However, recovery without sequelae was obtained after withdrawal of the catheter and antibiotic therapy. To avoid these risks, administration by repeated lumbar punctures has been proposed.15 However, this technique is uncomfortable and also creates the risks of overdose and inability to titrate effect, resulting in consciousness disorders.

Consequently these inherent adverse effects preclude use of this treatment for moderate tetanus that can be managed with benzodiazepine alone without need of tracheal intubation. Nor is intrathecal baclofen appropriate for the most severe forms that need deep sedation and even muscular blockade.

Conclusion

In our 14 patients with severe tetanus, intrathecal baclofen was an efficient treatment allowing effective control of muscle rigidity and spasms in 12 patients and reduced the need for deep sedation in the remaining 2 who required tracheal intubation. These results, which appear to represent an improvement compared with our previous experience and which agree with those previously reported, argue in favor of use of intrathecal baclofen for severe tetanus, especially in developing countries where respiratory resuscitation techniques are seldom available. Further prospective studies comparing intrathecal baclofen with conventional treatment in regard to overall mortality rate, cost, and length of hospital stay are needed.

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References


