

TABLE 5. Total Number of Blocks/Effect of Sympathetic Blockade (over 4-week period)

No. Blocks	Group 1				Group 2			
	No. Patients	Good	Improvement	PHN	No. Patients	Good	Improvement	PHN
>31	1	0	0	1	5	0	1	4
26-30	2	0	1	1	8	0	3	5
21-25	18	12	4	2	87	68	10	9
16-20	11	8	2	1	53	42	7	4
11-15	4	4	0	0	20	15	4	1
6-10	6	3	2	1	22	12	9	1
1-5	3	3	0	0	23	20	3	0
Total	45	30	9	6	218	157	37	24

PHN = postherpetic neuralgia.

after eruption. In each series of patients suffering from postherpetic neuralgia, it is difficult to ascertain whether improvements achieved are a result of treatment received or a natural resolution of the disease process. We conclude that sympathetic blockade, even when performed in the extremely early stage, cannot always prevent the development of postherpetic neuralgia. This does not mean that sympathetic blockade therapy for postherpetic pain should be abandoned. However, we believe that the prophylactic effect of sympathetic blockade therapy in preventing postherpetic neuralgia is overemphasized. Whether it is of any prophylactic value remains to be determined in a large and/or well-controlled series. We suspect that the development of postherpetic neuralgia may be due to a yet-unknown factor, such as a special pain-provoking subtype of the virus.

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## Intrathecal Baclofen for Treatment of Tetanus-induced Spasticity

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Clinically, tetanus can be viewed as an intoxication of the central nervous system with a long-acting, strychnine-

like poison. The symptoms of tetanus depend on the pharmacodynamics and pharmacokinetics of the tetanus toxin. Spinal convulsions, often impairing respiration, are the immediate threat of tetanus. Complications and death are almost exclusively due to respiratory embarrassment and its consequent cardiovascular depression. Despite apparent progress in the intensive-care therapy of tetanus (e.g. artificial respiration, medication with suppressive and neuromuscular blocking drugs), the mortality rate of tetanus has improved very little and still ranges from 40 to 60%.<sup>1</sup> Complications from tetanus include those caused by the disease and those resulting from therapy such as prolonged mechanical ventilation.<sup>2</sup> Although the pathophysiological problems from tetanus (*i.e.*, spasms and con-

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vulsions) originate within the spinal cord, there have been only a few attempts to initiate therapy directed at the primary site of involvement. Intrathecal and intracisternal injections of tetanus antitoxin have been tried in humans with ambiguous results.<sup>3-5</sup> Present data do not allow conclusions as to how serotherapy in tetanus should be performed. Similarly, the intrathecal application of adrenal steroids has been advocated,<sup>6,7</sup> but its usefulness is unknown.

Spasticity of spinal<sup>8</sup> and cerebral<sup>9</sup> origin has been successfully treated by intrathecal baclofen, especially in cases where oral baclofen failed to produce significant relief. Apparently, the disadvantage of oral medication (the limited passage of baclofen across the blood-brain barrier<sup>10</sup>) can be overcome by applying this drug directly into the cerebrospinal fluid. Intrathecal baclofen is effective even in extreme cases of spasticity. We thought that spinal administration of this drug, which acts by mimicking the effect of spinal inhibitory transmitters, might also be useful in the treatment of tetanus.

#### METHODS

Intrathecal baclofen was tried in two patients with generalized tetanus diagnosed clinically and by electromyography and a mouse protection test.<sup>11</sup> The efficacy of the intrathecal medication was demonstrated by integrated electromyography, *i.e.*, by determination of the time-voltage integrals of the muscle action potentials.<sup>12,13</sup> Electromyographic recordings from different muscles (*m. biceps brachii*, *m. triceps brachii*, *m. quadriceps femoris*, *m. gastrocnemius*, *m. tibialis anterior*) were grouped in four combinations (right side, left side, upper extremities, and lower extremities). Each patient was subjected to 15 min of recording at rest and 30 min of recording during a series of stimuli applied in fixed succession and intervals. Recording was done before and 2 h after the intrathecal application of baclofen.

Both patients developed symptoms of tetanus after they had experienced minor lacerations (stabbing with a fork into the thenar, or extraction of the nail of the great toe).

**Patient 1.** This patient (male, 50 yr of age) was admitted to the hospital after an incubation period of 7 days and presented with early symptoms of tetanus (*i.e.*, trismus and risus sardonicus). Electromyography demonstrated spontaneous discharge of the *m. orbicularis oris* and permanent activity (without silent periods) in the *mm. orbicularis oculi* and *masseter*. Tracheostomy and wound excision were done immediately after admission. At the same time, serotherapy (tetanus hyperimmunoglobulin for 6 days) and antibiotic therapy (penicillin for 9 days) were started. Within 4 days, during which the patient was kept under close supervision in our intensive care unit, he developed opisthotonos and general spasms. Intravenous diazepam infusion (5–15 mg/h) during controlled ventilation could only partly suppress rigidity and spasms. Restricted efficacy was especially evident in spasticity evoked by manipulation of the patient. Therefore, after 3 days, we decided to implant an intrathecal catheter, tunneled to a subcutaneous

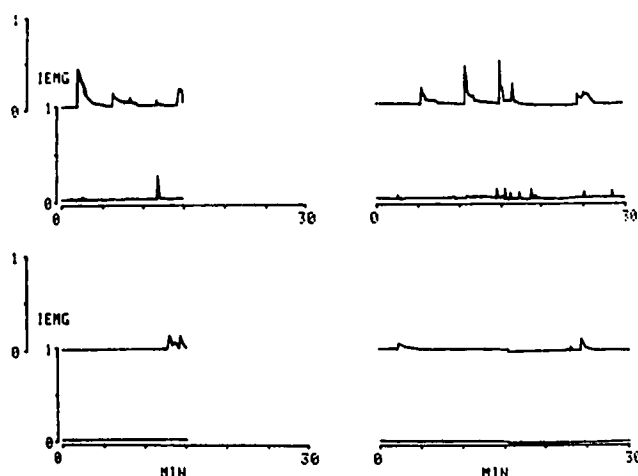


FIG. 1. Case 1. Continuous recording of integrated electromyographic activity of right and left side at rest (15 min) and during stimulation (30 min) before (upper) and 2 h after (lower) intrathecal application of 600 µg baclofen in generalized tetanus. The unit 1 corresponds to an integral, which results from a voltage of 100 µV at a frequency of 100 Hz.

port in the abdomen, for application of baclofen. Immediately after implant the diazepam infusion was stopped. The first intrathecal bolus application of baclofen (600 µg) led to a complete disappearance of all neurologic symptoms of tetanus within 2 h. This effect lasted for approximately 24 h. Integrated electromyography demonstrated a decrease in motor activity (fig. 1), although the initial conditions before intrathecal baclofen appeared to be influenced by prolonged diazepam sedation. During the next day, a continuous intrathecal infusion of the same dose of baclofen was started using an external battery-driven pump. As no spasms or convulsions reappeared, controlled ventilation was gradually terminated. He recovered rapidly without neurologic deficits. Withdrawal of spinal medication was first attempted 9 days after the onset of spasms (4 days after the start of continuous infusion of intrathecal baclofen with the portable pump). Twelve hours later, rigidity and spasms recurred. Immediately, baclofen infusion was started again (after a preceding bolus injection), this time using a daily infused dosage of 1.0 mg/24 h. During the second period of intrathecal infusion, which once again led to a complete suppression of spasticity, the trachea was extubated. Apparently, continuous baclofen infusion, even in the relatively high dosage of 1 mg/24 h, had no evident influence on the patient's mobility and vigilance (as shown by electroencephalographic recording). A second withdrawal trial after another 7 days was successful, and the patient could be discharged from the intensive care unit after the port and catheter had been removed. The duration of clinical care was 34 days (24 days in the intensive care unit and 10 days on the general ward).

**Patient 2.** This patient (male, 61 yr of age) was admitted with the symptoms of full tetanus (trismus, risus sardonicus, opisthotonos, rigidity, and general convulsions). The incubation period was approximately 5 days, the period of onset approximately 2 days. Convulsions were accompanied by short-lasting periods of hyperthermia (up to 39° C). Electromyography demonstrated general muscular hypertonia and additional massive discharge during spasms. Excised material from the wound was contaminated with *Clostridium tetani*. The patient was immediately started on controlled ventilation after tracheostomy. Sedation with iv diazepam infusion (10–20 mg/h) had little effect on the frequency of convulsions, especially those elicited by manipulation. Conventional therapy also included penicillin and hyperimmunoglobulin

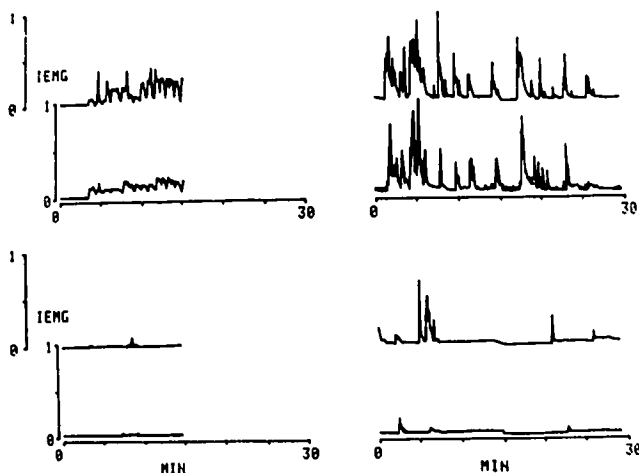


FIG. 2. Case 2. Continuous recording of integrated electromyographic activity of right and left side at rest (15 min) and during stimulation (30 min) before (upper) and 2 h after (lower) intrathecal application of 1 mg baclofen in generalized tetanus. The unit 1 corresponds to an integral, which results from a voltage of 100  $\mu$ V at a frequency of 100 Hz.

for 5 days. Similar to the first patient, intrathecal baclofen injections (via implanted port and catheter) were started after 3 days. Intrathecal bolus application of 1 mg of baclofen was necessary to abolish completely spasms for 24 h without systemic diazepam infusion. Integrated electromyography revealed a significant decrease in the overall motor activity (fig. 2). Although general convulsions no longer occurred, the intrathecal dosage of baclofen during continuous infusion had to be increased (maximal dosage: 2 mg/24 h) to depress completely residual rigidity (especially in the upper extremities and the face). After 2 days with an obvious hangover due to previous diazepam sedation, the patient regained consciousness and could be weaned from the respirator. The first withdrawal trial 5 days after the start of continuous infusion (12 days after the onset of convulsions) was followed by reappearance of rigidity and spasms. A second trial after another 5 days of intrathecal baclofen (dosage: 1–1.5 mg/24 h) was successful. During this second period of intrathecal infusion the trachea was extubated. Discharge from the hospital was possible after 32 days (21 days in the intensive care unit and 11 days in a general ward). The port and intrathecal catheter were removed 3 days before discharge from the hospital.

## DISCUSSION

Baclofen [ $\beta$ -(p-chlorophenyl)-aminobutyric acid] reduces polysynaptic nociceptive reflexes in animals after systemic<sup>14</sup> or intrathecal administration.<sup>15</sup> In addition, monosynaptic tendon reflexes are decreased.<sup>16</sup> The action on spinal reflexes is accompanied by dose-dependent muscular hypotonia, *i.e.*, flaccidity.<sup>15</sup> Besides its spinal activity, baclofen induces cerebral depression, *i.e.*, sedation (or even coma in case of intoxication), bradycardia, and hypotension.<sup>17</sup> Due to its analgetic properties in animal experiences (which have not been confirmed definitely in humans) baclofen was originally assumed to act as an opiate agonist. Nevertheless, its effects could not be antagonized with naloxone, and no cross-tolerance to opiates

could be demonstrated.<sup>18</sup> As a gamma-aminobutyric acid (GABA) derivative, baclofen is commonly considered a GABA-agonist<sup>19</sup> or, more precisely, the prototype of a GABA<sub>B</sub>-selective agonist.<sup>20</sup> Dependent or independent of its GABA activity, baclofen was assumed to antagonize excitatory transmitters like acetylcholine,<sup>21</sup> substance P,<sup>22</sup> and, most probably, glutamate<sup>23,24</sup> within the spinal cord.

Baclofen is the most frequently used drug for the treatment of rigidity and spasms following lesions of the central nervous system.<sup>25</sup> Recent clinical research has pointed out that intrathecal baclofen is approximately 600 times more potent than orally administered baclofen.<sup>26</sup>

Clinical symptoms of tetanus are induced by blocking transmission at inhibitory spinal synapses by presynaptic inhibition of transmitter release,<sup>27–30</sup> causing disinhibition of appertaining motoneurons. According to its pharmacologic action, baclofen possesses many properties of the ideal drug in tetanus. Nevertheless, the authors are not aware of any detailed clinical trial of baclofen (as well as of other centrally acting antispastic agents) in tetanus, probably because baclofen has so far been available only for oral administration. Because of the poor passage of baclofen across the blood–brain barrier, oral administration (at least in a dosage usually recommended, *i.e.*, approximately 25–100 mg/24 h in adults) may not have any significant effect against tetanus-induced spasms.

There are also few animal experiments in which topically applied inhibitory transmitters or transmitter agonists have been used to antagonize the action of the tetanus toxin. The synaptic blockade of Renshaw cells by tetanus toxin can be reversed by electrophoretically administered glycine.<sup>27</sup> (So far, there are no drugs available that act as glycine agonists.) Topical application of GABA onto a cortical focus induced by topical application of tetanus toxin completely suppresses electroencephalographic “tetanus spikes” in animals.<sup>31</sup>

Local spinal application of baclofen (and, similarly, of other inhibitory transmitter agonists) may prove to be an advance in the treatment of tetanus. The implantation of a subcutaneously tunneled intrathecal catheter in connection with a port may help to reduce hygienic risks. Under certain conditions, *e.g.*, in developing countries, a simple externalized catheter may do as well, and bolus application can be used instead of continuous infusion with a pump. Long-term sedation and respirator therapy (which are often not available in developing countries) as well as their complications can be avoided. Further clinical studies, especially in areas with a high tetanus morbidity rate, are needed to prove the effectiveness of intrathecal baclofen administration.

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