Chronic intrathecal baclofen administration for control of severe spasticity

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Baclofen, the most effective drug for treating spasticity, is a specific agonist of gamma-aminobutyric acid-B receptors, and is very abundant in the superficial layers of the spinal cord. Given orally, baclofen does not easily penetrate the blood-brain barrier, and is distributed equally to the brain and spinal cord. Direct intrathecal administration was given in order to change the distribution of the drug by preferentially perfusing the spinal cord. Eighteen patients presenting a severe spastic syndrome were treated with chronic intrathecal infusion of baclofen in the lumbar cerebrospinal fluid. After clinical preselection, 38 patients were implanted with a lumbar access port allowing long-term trials in order to determine the efficacy of baclofen therapy and the effective 12-hour dose. The 18 patients selected for chronic administration were implanted with a programmable pump. The pathology in these cases was: multiple sclerosis (6 cases), posttrauma spastic syndrome (eight cases), and (one case each) cerebral palsy, ischemic cerebral lesion, spinal ischemia, and transverse myelitis. The mean follow-up period was 18 months (range 4 to 43 months).

The clinical results were evaluated according to muscular hypertony on Ashworth's scale (changed for occurrence of painful spasms) and functional improvement. Results were better for spastic syndrome secondary to traumatic medullary lesion than for demyelinating disease. Hypertonia was improved in all cases as confirmed by the registration of the Hoffman (H) reflex. Painful muscular spasms disappeared in 14 of the 16 affected patients. Significant functional improvement was noted in nine patients and was considerable in three.

The risk of side effects secondary to overdose (such as excessive hypotonia or central depression) and the absence of a specific baclofen antagonist stresses the necessity for accurate determination of the efficient dose. After an initial titration period and adjustment of the therapeutic dose, the individual doses were from 21 to 500 μg/24 hrs (mean 160 μg/24 hrs). This new conservative method is very effective, perfectly reversible, and safe when administered in conditions favorable to its use.

KEY WORDS • baclofen • spasticity • intrathecal drug infusion • spinal cord disease • infusion pump

Treatment of spasticity by direct spinal intrathecal administration of a specific gamma-aminobutyric acid (GABA)-B agonist, baclofen, is a new pharmacological concept in functional neurosurgery. This method, proposed in 1984 by Penn and Kroin who conducted further experimental work on this approach, has been used and perfected by various groups working in cooperation using a multidisciplinary protocol. The number of patients treated and the follow-up period were sufficient to demonstrate the efficiency and safety of the method on the condition that the selection and prescription criteria are rigorously respected.

Now, after a period of controlled preliminary clinical trials, the third phase of development has started because of the interest attracted by the results of this therapy. The use of this mode of treatment for severe spasticity is growing. Thus, it is important to: 1) define the conditions for which it should be prescribed and the methodology used to determine an individual prescription; 2) emphasize the rules and restrictions for outpatient follow-up care; and 3) understand the limits and potential risks of this method.

Clinical Material and Methods

Since 1984, we have treated 18 patients by chronic intrathecal administration of baclofen. The patients were selected according to rigorous criteria which were defined as experience was acquired and following the protocol set up by Penn and the Food and Drug Administration. The methodology defined in this way took the form of five successive steps: clinical preselection; further selection after testing lumbar intrathecal
administration of baclofen; implantation of a drug-release system; determination of an effective daily dose; and chronic ambulatory follow-up monitoring.

Clinical Preselection

Preselection of patients for intrathecal baclofen treatment was based on the following criteria. Patients were considered if they suffered from severe debilitating spasticity secondary to a stable spinal cord lesion or cerebral lesion which was of traumatic origin (para-, tetra-, or hemiplegia), was due to a demyelinating medullary disease such as multiple sclerosis (especially in its slowly progressive medullary form), or resulted from a motor disability of cerebral origin with spastic predominance. Their spasticity must have been unresponsive to medical treatment, notably with oral baclofen (Lioresal). Oral baclofen administration must have been used long enough for its ineffectiveness to suggest direct intrathecal administration. Usually, it is the occurrence of unacceptable side effects that limits an increase in oral dose.

The patients must not exhibit contraindications for baclofen based on pharmacological, psychological, or local reasons (such as the presence of bedsores or skin lesions in the lumboabdominopelvic region which preclude the percutaneous implantation of a catheter and particularly the implantation of a drug-delivery system). Moreover, any conditions (such as limb bedsores or urinary infections) which do not directly interfere with the implantation site, but which act as an irritant aggravating the spastic syndrome must be treated before any intrathecal pharmacological trial.

Consent must be obtained from the patient who has been clearly informed as to the constraints of the method (including the necessity for regular consultations and adaptation of prescription) and the therapeutic limits. Finally, the patient must be in a favorable environment for rigorous and regular follow-up visits as an outpatient, with good family, general practitioner, and institutional support.

Lumbar Intrathecal Baclofen Administration Testing

Testing patients for lumbar intrathecal baclofen administration is an essential step before considering chronic outpatient treatment. It is carried out in the homes of patients who satisfy the clinical criteria for inclusion. Its aim is to test individual tolerance, to judge the effectiveness of intrathecal administration, and to fix the dose of baclofen effective for 8 to 12 hours in order to rapidly optimize the prescription for chronic treatment.

We replaced the externalized lumbar subarachnoid catheter used initially by the lumbar implantation of an intrathecal system* offering a drug access site to allow prolonged testing. Regardless of the previous oral dose of baclofen, the first intrathecal dose administered must be very low in order to evaluate the individual tolerance of the patient. We usually gave a first bolus dose of 25 μg and then steadily increased the dose, generally by 25 μg/day until a dose effective for 8 to 12 hours was reached. Clinical evaluation of the results by muscular testing is gauged by systematic exploration of the Hoffman (H)-reflex (M max:H max ratio).

At the end of the trials, the lumbar intrathecal access port was left in position. This allowed subsequent sampling of the cerebrospinal fluid (CSF) not only for cytobacteriological examination but also for pharmacokinetic study (high-performance liquid assay) to check the steady state of the intrathecal concentration of chromatography baclofen. From 38 patients who underwent the trial intrathecal baclofen administration protocol, 18 were selected for chronic administration (Table 1). The exclusion factors for the 20 patients not selected were: 1) significant ineffectiveness of intrathecal administration; 2) overeffectiveness of the drug, with loss of useful spasticity of the lower limbs which enabled the patient to stand and walk to some extent and/or a decrease of the remaining motor performance of the upper limbs; 3) foreseeable difficulties in follow-up monitoring; or 4) refusal on the part of the patient.

The age of the 18 patients selected ranged from 14 to 70 years (mean 39 years); there were 12 men and six women. A summary of their clinical history is given in Table 2. Three of the first patients selected had been treated without success by chronic cervical spinal cord stimulation (Cases 1, 7, and 8).

Implantation for Chronic Intrathecal Administration

The implantable drug-release systems used changed with time. First, chronic administration was performed in six patients from the lumbar intrathecal access port used for the test. This required repeated daily injections leading to inaccuracy in the prescription and a genuine risk of infection. Because of these restrictions and risks

* Multipurpose access port or miniport manufactured by Cordis SA, Valbonne, France.
Chronic intrathecal baclofen for spasticity

**TABLE 2**
Clinical course of 18 patients treated by chronic intrathecal administration of baclofen*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Etiology</th>
<th>Previous Treatment</th>
<th>Drug-Delivery Systems</th>
<th>Intrathecal Baclofen (µg/24 hrs)</th>
<th>Follow-Up Period (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47, F</td>
<td>multiple sclerosis</td>
<td>SCS, baclofen 80 mg</td>
<td>access port</td>
<td>290, bolus</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>30, M</td>
<td>cerebral trauma</td>
<td>baclofen 100 mg</td>
<td>access port</td>
<td>45, bolus</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>70, M</td>
<td>cerebral vascular</td>
<td>baclofen 80 mg</td>
<td>access port</td>
<td>50, bolus</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>64, F</td>
<td>trauma, T-4</td>
<td>baclofen 90 mg</td>
<td>access port</td>
<td>50, bolus</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>56, M</td>
<td>trauma, C-6</td>
<td>baclofen 90 mg</td>
<td>access port</td>
<td>200, bolus</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>37, M</td>
<td>trauma, T-10</td>
<td>baclofen 90 mg</td>
<td>access port</td>
<td>210, bolus</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>29, M</td>
<td>trauma, C-5</td>
<td>SCS, baclofen 80 mg</td>
<td>Synchromed</td>
<td>500, bolus</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>27, M</td>
<td>cerebral palsy</td>
<td>SCS, baclofen 90 mg</td>
<td>Synchromed</td>
<td>100, bolus</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>56, F</td>
<td>multiple sclerosis</td>
<td>baclofen 100 mg</td>
<td>Synchromed</td>
<td>100, bolus</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>26, M</td>
<td>trauma, T-8</td>
<td>baclofen 80 mg</td>
<td>Synchromed</td>
<td>26, cont</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>27, M</td>
<td>trauma, T-4</td>
<td>baclofen 90 mg</td>
<td>Synchromed</td>
<td>210, cont</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>37, F</td>
<td>multiple sclerosis</td>
<td>baclofen 60 mg</td>
<td>Synchromed</td>
<td>180, cont</td>
<td>23</td>
</tr>
<tr>
<td>13</td>
<td>51, F</td>
<td>multiple sclerosis</td>
<td>baclofen 60 mg</td>
<td>Synchromed</td>
<td>163, cont</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>43, M</td>
<td>ischemia</td>
<td>baclofen 60 mg</td>
<td>Synchromed</td>
<td>131, cont</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>30, M</td>
<td>trauma, T-1</td>
<td>baclofen 100 mg</td>
<td>Synchromed</td>
<td>270, cont</td>
<td>14</td>
</tr>
<tr>
<td>16</td>
<td>43, F</td>
<td>multiple sclerosis</td>
<td>baclofen 80 mg</td>
<td>Synchromed</td>
<td>250, bolus</td>
<td>12</td>
</tr>
<tr>
<td>17</td>
<td>14, M</td>
<td>myelitis</td>
<td>baclofen 80 mg</td>
<td>Synchromed</td>
<td>140, cont</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>40, M</td>
<td>multiple sclerosis</td>
<td>baclofen 100 mg</td>
<td>Synchromed</td>
<td>112, cont</td>
<td>6</td>
</tr>
</tbody>
</table>

*SCS = cervical spinal cord stimulation; cont = continuous infusion. Follow-up period as of April, 1989.

we now use only implantable programmable drug-release systems that allow accurate administration of the individual dose of baclofen. Thus, the last 12 patients benefited from the implantation of a Synchromed system† which has a reloadable storage volume of 18 ml and which specifically allows delivery of repeated bolus doses, continuous perfusion, or complex administration cycles with all the required dosing accuracy. During the changeover period, two patients were implanted with a mechanical Secor pump‡ giving repeated bolus doses of 0.1 ml as required. Lack of sufficient accuracy in this system of delivery led us to replace the mechanical release systems in these two patients by a Synchromed system with the required flexibility.

The implantation technique is simple and can be performed percutaneously under local anesthesia; however, in certain patients implantation was carried out under general anesthesia either at their own request or in the presence of excessive muscular spasm inflexion. The simplicity of the surgical technique of implantation does not, however, mean that technical precautions can be ignored, especially those concerning the positioning of the subarachnoid catheter. Puncture of the interspinous space usually in the abdominal wall but occasionally in a laterothoracic location.

Determination of Effective Daily Dose

Selection of the daily dose suitable for each individual is the most delicate and the most important phase of the treatment. Immediately after implantation, for reasons of safety, the initial dose administered was twice the effective 8-hour dose determined during the intrathecal selection test. Baclofen, supplied as a solution administrable intrathecally, was used at 2 concentrations, either 50 µg/ml (during the test period) or 500 µg/ml (during the period of titration and chronic administration).

During the first weeks a steady increase in the dose was made, depending on the clinical and electrophysiological H-reflex effectiveness, in steps of 10% to 20% of the daily dose. After the initial efficient daily dose has been determined and stabilized, adjustments must be made periodically depending on the clinical evolution and development of side effects.

Chronic Ambulatory Follow-Up Monitoring

Monitoring is an essential step. Rigorous organization is required in order to adapt the dose and also to be ready to counteract possible side effects. A pharmacist in our team (B.S.C.) is responsible for maintaining a constant link between our laboratory and the patients, their family, and their medical environment. The 18 patients came in for regular consultations, either pre-
planned or instigated by the alarm beep informing them that the pump reserve was low and that it had to be filled within a week. The residual volume that sets off the alarm system is fixed according to the daily consumption of the individual patient. At each consultation, a clinical and functional check-up was made after which adjustments of the therapeutic dose were sometimes required.

The patients were informed of the risks of side effects and especially of overdose. Owing to the absence of known antagonists specific for baclofen, it is essential that the patients know the first signs of overdose, namely excessive salivation, dizziness, nausea and/or vomiting, too high and excessive increases in muscular hypotonia especially spreading to the upper limbs, progressive difficulty in concentrating, and a state of somnolence. Respiratory depression and coma are the symptoms of a large overdose of baclofen. Apart from a mechanical problem with the drug-delivery system giving a sudden increase in delivery, overdose phenomena (when they do occur) are slow to become manifest, taking several hours or even days. If the distance from the hospital is not too great, there is enough time for a forewarned patient and an informed family to reach the hospital so the prescription can be checked and, if necessary, the pump stopped and the reserve emptied.

**Results**

The 18 patients selected and implanted for chronic intrathecal administration were treated during the period from May, 1984, to December, 1988. In April, 1989, the mean follow-up time was 18 months (range 4 to 43 months) for an overall total follow-up period of 24 years.

**Evaluation of Results**

The patients' clinical course was followed by assessing as objectively as possible both the spasticity and functional improvement. Spasticity was evaluated by scoring muscular rigidity on the Ashworth scale (Table 3).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Degree of Muscle Tone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no increase in tone</td>
</tr>
<tr>
<td>2</td>
<td>slight increase in tone, giving a &quot;catch&quot; when affected part is moved in flexion or extension</td>
</tr>
<tr>
<td>3</td>
<td>more marked increase in tone but affected part easily flexed</td>
</tr>
<tr>
<td>4</td>
<td>considerable increase in tone; passive movement difficult</td>
</tr>
<tr>
<td>5</td>
<td>affected part rigid in flexion or extension</td>
</tr>
</tbody>
</table>

This evaluation is sometimes made more difficult by the occurrence of tendon retraction. At clinical examination, the painful spasms were quantified according to their frequency of occurrence, and osteotendinous hyperflexia and the plantar reflex were also rated.

Functional improvement resulting from improvement of the spastic syndrome was evaluated on a scale scoring the different motor performances. The scale used was derived from that proposed by Davis and Gray for evaluation of motor performances of patients suffering motor deficits associated with cerebral palsy. We have previously used this scoring system in similar patients, and, in applying it to the present series of patients, we found it useful to divide it into three classes: large improvement (greater than +3), moderate improvement (between 1 and 3) and no improvement (nil).

The modifications of hypertonia in these patients were correlated to the neurophysiological assessment of the H-reflex (M max:H max ratio) which was carried out using different protocols at different stages of their course. During the test period, the H-reflex was measured before and after a bolus intrathecal injection of baclofen. After implantation of the drug-delivery system and during titration of the therapeutic dose, the H-reflex was monitored semicontinuously while the drug was administered by either rapid or slow perfusion of the effective therapeutic dose. The H-reflex correlated with the clinical modifications of spasticity (Fig. 1). Finally, during the out-patient follow-up period, frequent isolated measurements of the H-reflex were carried out in order to bring the M max:H max ratio to normal levels (value ≤ 50%) depending on the individual functional target.

**Results of a Single Intrathecal Bolus of Baclofen**

During the test period, 38 patients received a single bolus of intrathecal baclofen in the lumbar region. The delay before any clinical effect was seen was relatively long (on the order of 1 hour) after a single lumbar intrathecal bolus. The lower limbs were affected first, then the effect spread rapidly (over about 15 minutes). First, muscular hypertonia decreased, then the tonus progressively disappeared with a parallel but later decrease of the osteotendinous reflexes. Babinski's sign (or the plantar reflex in extension) was the last to reappear.

**TABLE 3**

<table>
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</tr>
<tr>
<td>4</td>
<td>considerable increase in tone; passive movement difficult</td>
</tr>
<tr>
<td>5</td>
<td>affected part rigid in flexion or extension</td>
</tr>
</tbody>
</table>

**FIG. 1.** Progressive normalization and complete inhibition of the Hoffman reflex (H max:M max ratio) after intrathecal bolus of 100 µg of baclofen.
Chronic intrathecal baclofen for spasticity

disappear. The intensity, the metameric topographic extension, and the duration of the clinical effect depended on the dose administered and on the patient involved. The effectiveness of any individual dose depended on the clinical state of the patient considered since, in some cases, it was necessary to avoid full rigidity of the lower limbs in order to maintain “useful spasticity” of the extensor muscles.

Results of Chronic Baclofen Administration

In all 18 patients receiving chronic baclofen infusion, muscular spasticity improved significantly (Table 4). All of the patients selected exhibited Stage 4 (five patients) or Stage 5 (13 patients) spasticity on the Ashworth scale. After treatment, muscular hypertonia was reduced for various periods of time in all cases: to Stage 1 in four patients, to Stage 2 in 12, and to Stage 3 in two. Improvement in spasticity began at the titration period and remained stable from then on. Of 16 patients presenting painful muscle spasms, an improvement was seen in 14 cases.

Functional improvement varied greatly between patients, depending on both the clinical stage and the etiology. Three patients (Cases 10, 16, and 17) showed a good and lasting functional improvement. Improvement was moderate in nine other patients (Cases 1 to 5, 8, 11, 14, and 15); however, in three of these improvement was considered important. The last six patients (Cases 6, 7, 9, 12, 13, and 18) showed no functional improvement. They were all severely disabled, were bedridden, and presented tendon retraction. What improvement they showed essentially affected nursing quality. Four of the patients (Cases 9, 12, 13, and 18) were completely paraplegic secondary to multiple sclerosis.

Etiology of Spastic Syndrome and Results

The most frequent etiology among the patients selected for chronic intrathecal baclofen administration was spasticity of medullary origin either secondary to spinal trauma (seven patients) or secondary to degenerative myelopathy through multiple sclerosis (six patients). Comparing the results obtained in these two subgroups of patients, it was observed that the most significant and the most stable improvements are found in spasticity of posttraumatic origin, especially in the case of incomplete paraplegia. Here the improvement not only involved the spasticity but also resulted in functional gain.

In the six patients presenting medullary spasticity secondary to multiple sclerosis, the results were less favorable. Spasticity was reduced in all cases and in some even completely suppressed; however, the actual functional improvement remained poor (good in one case, moderate in one case, and nil in four cases) owing to the severity of the initial state and/or the absence of residual movement. Moreover, although the selection criteria used required a stable demyelinizing disease, there was always a potential for evolution of the disease; the medullary deficit was very often associated with an extraspinal deficit such as a cerebellum syndrome aggravating the handicap. Also, these patients were gen-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Spasticity</th>
<th>Muscle Spasms</th>
<th>Functional Improvement</th>
<th>Complications</th>
<th>Therapy Status†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>1</td>
<td>++ 0</td>
<td>+2</td>
<td>overdose; catheter displacement, evolutional multiple sclerosis stopped</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>3</td>
<td>+ 0</td>
<td>+2</td>
<td>catheter displacement, local sepsis stopped</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1</td>
<td>++ 0</td>
<td>+3</td>
<td>catheter displacement + hypotonia stopped</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>++ ++</td>
<td>+3</td>
<td>none stopped</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2</td>
<td>++ 0</td>
<td>+3</td>
<td>sepsis, meningitis stopped</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>++ 0</td>
<td>0</td>
<td>sepsis, Huntington’s disease stopped</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>2</td>
<td>++ 0</td>
<td>0</td>
<td>respiratory infection stopped</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>2</td>
<td>++ 0</td>
<td>+2</td>
<td>overdose; pump failure stopped</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>3</td>
<td>++ 0</td>
<td>0</td>
<td>sepsis, meningitis stopped</td>
</tr>
<tr>
<td>10</td>
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<td>2</td>
<td>+ 0</td>
<td>+2</td>
<td>none cont</td>
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<tr>
<td>12</td>
<td>5</td>
<td>2</td>
<td>++ +</td>
<td>0</td>
<td>none cont</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>2</td>
<td>++ 0</td>
<td>0</td>
<td>none cont</td>
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<td>0 0</td>
<td>+1</td>
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<td>+4</td>
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<td>0 0</td>
<td>+4</td>
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</tr>
<tr>
<td>18</td>
<td>5</td>
<td>2</td>
<td>+ 0</td>
<td>0</td>
<td>none cont</td>
</tr>
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</table>

* Spasticity was measured using the Ashworth scale (Table 3); functional improvement was measured using the system of Davis and Gray.†

Muscle spasms were graded from ++ (very painful) to 0 (no pain).

† Status as of April, 1989. Cont = baclofen infusion continued at that time.
Complications

Complications were of technical, neurological and pharmacological origin and represent a potential risk for this type of therapy (Table 4). Rigorous efforts to control these problems and careful follow-up monitoring are required.

Technical Problems. The technical complications included displacement of the catheter from the subarachnoid space toward the epidural or extrarachidian space in three patients. One patient (Case 8), the only individual in this series suffering from cerebral palsy, received an overdose causing severe side effects (respiratory depression and temporary coma). This problem was due to the pump developing a defect. The pump, which was removed in an emergency procedure, was an implantable programmable first-generation device implanted in September, 1984, which had operated perfectly for more than 1 year.

Infections and Neurological Complications. The series included four cases of local sepsis around the subcutaneously implanted drug-delivery systems and three cases of temporary meningitis. No transitory or permanent neurological complications occurred. Purulent meningitis was observed in three patients and was treated by both local (via the access port) and systemic (intravenous) antibiotic administration. In two of the patients (Cases 9 and 14), the meningitis was established during the initial trial with the access port and was isolated without subcutaneous sepsis; after recovery, treatment by intrathecal administration was continued either temporarily (Case 9) or permanently (Case 14) via an implanted Synchromed pump. The third patient (Case 5) developed purulent meningitis at the same time as subcutaneous sepsis. Recovery was only attained after explantation of the access port. Since the therapy was particularly effective in this patient, it is planned to implant a programmable pump as soon as we are positive of the sterility of the CSF.

All complications due to infection, whether local or meningeal, were observed in patients treated via access ports. This risk arising from daily percutaneous injections in immunosuppressed patients led us to abandon this administration technique in favor of the now routine use of implantable programmable pumps.

Pharmacological Complications. The fundamental risk involved with this method relates to pharmacological problems. These arise from either overefficacy, an overdose, or a loss of effectiveness due to acquired tolerance.

The occurrence of detrimental transitory muscular hypotonia was one of the most frequent therapeutic reasons for nonselection during the initial trial period. Some patients were rejected from the chronic treatment protocol because baclofen administered intrathecally removed useful spasticity in the lower limbs and/or reduced the motor performances of the arms.

During the period of chronic treatment in the initial titration phase, muscular hypotonia was also noted in five patients. Case 10 was particularly sensitive to the antispastic effects of intrathecally administered baclofen; the daily dose was stabilized at 26 \( \mu \text{g} \)/24 hrs at the time of writing this paper. This stresses the necessity for a very exact individual dose level and an accuracy which can only be reached using programmable implantable pumps.

An incident of minor overdose causing diffuse muscular hypotonia and a state of temporary drowsiness was observed in four patients, three of whom were being treated via an access port. In all cases, this was due to an overdose during the titration period and was not repeated during the outpatient follow-up period after determination of the efficient daily therapeutic dose.

In two patients, a serious overdose accident occurred causing progressive respiratory depression and transient coma. In one of the patients (Case 8), this accident arose from malfunction of the pump which supplied more than the required amount of drug. The coma and respiratory depression (slowing down of respiration without complete stoppage) were progressively corrected by respiratory resuscitation with intubation, repeated lumbar puncture, and intravenous hyperhydration to increase the renal elimination of baclofen. The pump was stopped and explanted in an emergency procedure and this treatment was permanently discontinued in this patient. In another patient (Case 1), who was suffering from advanced multiple sclerosis, the overdose occurred after a bolus administration of 200 \( \mu \text{g} \) baclofen into the access port. Respiratory depression and coma, which were both much more moderate than in Case 8, reversed spontaneously without the need for respiratory resuscitation in intensive care. Any similar accident would now be easily avoided by interruption of intrathecal administration and the intravenous injection of physostigmine.

Acquired Tolerance to Intrathecal Baclofen. After the titration period, the baclofen doses were usually adjusted progressively each 24 hours. As shown in Fig. 2, the increases involved varied greatly from one patient to another. From the 3rd month of treatment, the effective doses were stabilized. In our clinical experience, we have not observed a genuine case of pharmacological tolerance.

It should be noted that all patients receiving chronic intrathecal administration through repeated injections of baclofen via an access port had to stop treatment after various periods of time. The risks of infection, inaccuracy of dosage, and the restrictions of using an intrathecal lumbar access port in this type of treatment have led us to implant programmable pumps.

Y. Lazorthes, et al.
Chronic intrathecal baclofen for spasticity

Discussion

Bowery, et al., showed that the main site of action of baclofen (beta-(4-chlorophenyl)-GABA) is at the presynaptic level in the medulla. Baclofen is an agonist ligand specific for bicuculine-insensitive GABA receptors called GABA-B receptors. Price, et al., demonstrated by autoradiographic studies that the GABA-B binding sites are present at high concentrations in the posterior dorsal horn and also in numerous structures of the central nervous system (CNS), especially the thalamus.

Baclofen (Lioresal) has, for the last 20 years, been the most widely used antispastic drug, as it is most effective in the treatment of motor and spastic syndromes, notably those of medulla origin. Its effect on muscle tonus and spinal neuron hyperexcitability is mainly attributed to its powerful inhibiting action on medulla synaptic transmission, at the presynaptic level, by blocking the release of neurotransmitters. It has been demonstrated that baclofen depresses both monosynaptic and polysynaptic spinal reflexes. When given orally, large doses of baclofen are required since the drug crosses the blood-brain barrier only with great difficulty, so a very low concentration is found in the CNS and CSF. Moreover, oral baclofen is evenly distributed between the spinal and supraspinal levels, giving rise to side effects (notably somnolence) when therapeutic doses are reached. It was with the aim of activating the GABA-B receptors directly and modifying the kinetic distribution of the drug by preferential perfusion in the spinal cord that Penn and Kroin proposed, in 1984, the direct intrathecal administration of baclofen for the treatment of spasticity.

The present study confirms the effectiveness of intrathecal administration in patients suffering from a disabling spastic syndrome intractable to long-term oral antispastic therapy. In all of our patients, high doses of baclofen (60 to 100 mg/24 hrs) were given orally in association with sodium dantrolene and also very often diazepam. In all of these patients, this treatment had become ineffective and/or had brought about side effects such as somnolence.

Variability of Individual Doses

The phenomenon of pharmacological tolerance observed on oral administration was counteracted by the administration of very low doses of baclofen intrathecally. After the titration period, a therapeutic effect was obtained with an average dose of 90 μg. There was a very large variation in the threshold of effective dosage between patients, with a range of 15 to 250 μg.

The duration of the effect was variable and dose-dependent, and the reappearance of symptoms could occur in the reverse order and just as rapidly on withholding the drug. The therapeutic effect could be perfectly reinstated by another administration. These facts, already reported after the first trials of Penn and Kroin and confirmed by various other authors, are at the basis of the concept of chronic intrathecal administration via implantable systems.

In the present series of 18 cases, the follow-up period (on average 18 months) and the long-term results were significant enough to confirm the maintenance of stable clinical effects without secondary occurrence of acquired tolerance on intrathecal administration. In all of our patients, the 24-hour doses had to be steadily increased over the first months of treatment and then they became stabilized (Fig. 2). The average effective dose rose by 90 to 150 μg to give a range of individual values between 26 and 500 μg/24 hrs. These results are comparable to those of Penn and Kroin who found that, in a series of 16 patients, the initial average effective dose increased from 150 to 350 μg (range 20 to 600 μg). Müller, et al., in a series of 25 patients with an average follow-up period of 2 years, reported an increase of the average daily dose from 234 to 294 μg.

As in our study, authors have found great variability in the effective individual therapeutic dose. In our series it was on the order of 1 to 20, in the study by Penn and Kroin it was 1 to 30, and in the series of Müller, et al., it was 1 to 80 (10 to 800 μg). This variability can be explained by enzyme-mediated metabolism, by local clearance by recirculation, and by the very different medullary lesions from one patient to another. This stresses the importance of very accurate dose titration, perfectly modulated in accordance with the therapeutic aim which itself differs in each patient depending on the stage of the disease and on whether the desired effect is total antispasticity (in patients who have lost all motor activity) or partial antispasticity aiming at the conservation of a certain degree of useful spasticity (in patients who have retained a functional motor activity).

The M max:H max ratio, established at clinical consultations, is an index of drug effectiveness which must also be considered in the light of the therapeutic aims. The very high efficacy of intrathecal baclofen admin-
istration is confirmed by the fact that not only can the ratio be normalized but it can also be reduced to zero with complete disappearance of the H-reflex (Fig. 1). This situation is, of course, not to be sought when useful spasticity is to be maintained in a patient; in this case the M max:H max ratio should be maintained in a range between 50% (normal) and 30%.

Our experience and that of others\textsuperscript{19,20,26} stress the advantages of continuous intrathecal administration compared to administration by repeated injections. Of the nine patients in our series who are still under chronic treatment with the Synchronomed system, only one (Case 16) showed a better clinical response to daily bolus administration at a fixed time (9:00 a.m.). The other eight patients showed a better balance of the spastic and motor syndrome with continuous perfusion.

**Variability in Function With Etiology**

Analysis of the results shows that the efficacy depends on the etiology and the clinical deficits. From the clinical selection criteria and the temporary intrathecal administration trials using repeated bolus doses, we found, as did the other authors, higher effectiveness in cases of spasticity of medulla origin whether it was of posttraumatic origin or secondary to demyelinating disease. If we consider the two subpopulations separately, the effect of treatment on spasticity and painful muscular spasm was more or less identical. However, functional improvement was greater in traumatic cases presenting medullary lesions, stabilized neurological lesions, and an essentially sublesional deficit, whereas in patients with multiple sclerosis the progressive character and the associated supraspinal lesions worsened the handicap and limited functional improvement. This difference is correlated with the gravity of the clinical stage. Initially, this therapy was restricted to patients with advanced clinical forms of disease which are very disabling, to bedridden patients, or to patients with very little independence. In these clinical forms, the sublesional motor deficit is total, there are often already irreversible musculotendinous retractive, and the only functional benefit is restricted to nursing comfort and suppression of painful muscle spasms. This was the case for seven patients in our series, of whom two were suffering from posttraumatic cervical or cerebral lesions (Cases 1 and 7) and five had multiple sclerosis (Cases 1, 9, 12, 13, and 18).

Later, patients for whom independence of movement and motor performance were reduced owing to the intractable nature of the spastic syndrome were selected for treatment. In this class of patients, therapy was aimed at improving not only comfort but also the degree of autonomy. The goal of treatment included the achievement of independence in a wheelchair, and sometimes even a real functional improvement in the motor performance of the arms or, when useful spasticity and partial movement of the lower limbs existed, walking once more with the aid of a frame. This was the situation for eight of our patients, four of whom were suffering from thoracic medullary posttraumatic lesions (Cases 4, 6, 10, and 11).

Future applications of this mode of intrathecal baclofen administration will probably be extended to minor clinical forms in independent ambulatory patients presenting disabling spasticity during effort, disturbance of ambulation, and sometimes painful spasms (especially at night). It is difficult to modulate the optimal dose accurately enough to normalize muscle tone without creating iatrogenic hypotony, thus conserving perfect motor function. It is possible to use a complex perfusion cycle allowing administration of higher doses at night, especially to counteract painful spasm, without interfering with the motor function during the day. However, the spastic syndrome is not stable over time and numerous intrinsic factors (such as infections or asthenia) or extrinsic factors (such as changes in the weather, temperature, atmospheric pressure, or activities) can aggravate the situation and bring about the need for temporary adjustments of the intrathecal baclofen administration.

**Pharmacological Complications and Risks**

Pharmacological complications are the only real potential risks, involved with this method and can reduce its usefulness. Baclofen administered orally becomes evenly distributed in the brain and spinal cord even though its antispastic action is preferentially medullar. An increase in dosage when delivered by the systemic route causes central side effects like drowsiness or confusion. Local intrathecal administration modifies the distribution of the drug by direct and therefore preferential perfusion of the spinal cord. However, the subarachnoid CSF compartments are in continuity, and the same central side effects can also occur. A pharmacokinetic study of baclofen in the CSF showed that its half-life was about 4 to 5 hours.\textsuperscript{23,28} In the event of an overdose, it is possible to withdraw 30 to 40 ml of CSF by lumbar puncture or via the access port to reduce the side effects more rapidly. Although it is not a specific antagonist of baclofen, physostigmine, administered intravenously at 1 to 2 mg over 5 minutes, can counteract the central effects of baclofen, notably drowsiness and respiratory depression.\textsuperscript{21} It is therefore an effective antidote, improving the safety of intrathecal baclofen use. However, it must be noted that physostigmine has a very short half-life in the CSF and it may be necessary to repeat a 1-mg intravenous injection every 30 to 60 minutes. Recently, a group of investigators has described a specific baclofen antagonist, phaclofen,\textsuperscript{12} which is reported to act both peripherally and centrally, and another group has reported the existence of the antagonist action of delta-amino-valoric acid\textsuperscript{21} in the CNS. The availability of specific antagonists for baclofen will make its use that much safer.

**Alternatives to Intrathecal Baclofen**

Whether administered intrathecally or systemically, baclofen is the most effective antispastic drug described
Chronic intrathecal baclofen for spasticity

to date. We made a comparative evaluation, during both the percutaneous trial period (in five patients) and the chronic administration period (in three patients), of the efficacy of two other antispastic drugs: morphine and midazolam. The intrathecal administration of morphine in the control of spasticity was proposed by Erickson, et al. With a follow-up period of 1 to 7 months, significant results were reported for spasticity of posttraumatic origin. Morphine is a nonspecific opiate agonist of the mu receptors; its action is dose-dependent, selective, and affects nociception and polysynaptic reflexes (A Struppler: unpublished data). Administered intrathecally, it does not cause any objective modification of the motor function or of gamma monosynaptic reflexes, as demonstrated by Willer and Busse in voluntary paraplegics. In our series, there was an overall decrease of spasticity but it was quite moderate compared to the effect of baclofen.

Midazolam is a water-soluble benzodiazepine that can be administered intrathecally; it has also been used in cases of spasticity. The clinical effect is moderate and limited, since the biological half-life is very short (about 2 hours). High doses give no additional therapeutic effect and lead to somnolence.

How should the use of intrathecal baclofen administration in the treatment of spasticity be considered today? Controversy still surrounds the surgical treatment of spasticity. Chronic electrical neurostimulation of the spinal cord has been used in the treatment of spasticity of posttraumatic origin or arising from demyelinating disease, and stimulation of the anterior cerebellum has been applied in spastic and motor syndromes of motor deficits of cerebral origin. The advantages of neurostimulation of the spinal cord or cerebellum include the facts that it is only slightly invasive, is totally reversible, and is based on basic neurophysiological processes. However, its immediate effectiveness is moderate, without significant clinical or neurophysiological modifications, and it does not offer appreciable long-term functional improvement. The very limited effect of electric neurostimulation led us to abandon it for treatment of intractable spasticity in favor of intrathecal baclofen administration.

The history of functional neurosurgery for spasticity started as early as 1908 with the technique of posterior radiculotomy performed by Foerster. Since then, numerous techniques involving interruption of the spinal reflex pathways have been proposed, whether by longitudinal myelotomy or stereotactic operations such as cerebellum dentatec tomoy or thalamotomy. Apart from chemical or surgical partial peripheral neurotomy, which is of doubtful value when a single muscle group is involved, only posterior radiculotomy has remained a relevant technique. This procedure is not the classical general radiculotomy involving all the posterior radicles but selective radiculectomy at the point of posterior spinal-root junction, as proposed in 1974 by Sindou, et al. The use of this technique is currently questioned for cases of spasticity with limited topography involving the territory of two or three roots at most; this is especially the case for spastic syndromes of the arm in the motor disability of brachial diplegia secondary to cerebral palsy.

Conclusions

The present experience is sufficiently large to confirm the advantages of lumbar intrathecal administration of baclofen over oral administration and even over destructive techniques in the treatment of severe widespread disabling spasticity of medulla origin. Its remarkable effectiveness makes the use of double-blind testing superfluous. The advantages of the method arise from the fact that it is conservative, noninvasive, reversible, and selective in that it can suppress muscular hypertony and inhibit the mono- and polysynaptic reflexes without modifying the residual voluntary movement. The disadvantages in its use stem from the variability of the effect in each patient and the necessity to determine the individual effective doses with accuracy. Administration by continuous microperfusion gives better results than a repeat bolus. The development of implantable programmable pumps with a sufficiently large reservoir, totally reliable function, and at an acceptable cost, as well as better understanding of baclofen pharmacokinetics and the development of specific antagonists, should confirm an important role for this new technique in the treatment of intractable spasticity.

Longer clinical trials are still necessary to judge the possible long-term occurrence of tolerance to the drug and also to accurately modulate the optimal effective dose in ambulatory patients for whom detrimental spasticity must be suppressed without interfering with motor function.

References

2. Bowery NG: Baclofen 10 years on. TIPS: 400–403, 1982

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