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# A Benefit-Risk Assessment of Baclofen in Severe Spinal Spasticity

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## Abstract

Baclofen is used for treatment of the spasticity of spinal origin that is a common sequela of spinal cord injury and multiple sclerosis; spasticity occurs in about 50% of patients affected by these disorders.

In open-label studies of oral baclofen, the drug improved spasticity in 70–87% of patients; additionally, improvement in spasms was reported in 75–96% of patients. In double-blind, crossover, placebo-controlled trials, baclofen was reported to be effective, producing statistically significant improvements in spasticity. Tizanidine is the antispasticity drug that has been most widely compared with oral baclofen; studies have generally found the two drugs to have equivalent efficacy. However, tizanidine has better tolerability, in particular weakness was reported to be occur less frequently with tizanidine than with baclofen.

The main adverse effects of oral baclofen include: sedation or somnolence, excessive weakness, vertigo and psychological disturbances. The incidence of adverse effects is reported to range from 10% to 75%. The majority of adverse

effects are not severe; most are dose related, transient and/or reversible. The main risks of oral baclofen administration are related to withdrawal: seizures, psychic symptoms and hyperthermia can occur. These symptoms improve after the reintroduction of baclofen, usually without sequelae. When not related to withdrawal; these symptoms mainly present in patients with brain damage and in the elderly. The limited data on baclofen toxicity in patients with renal disease suggest that administration of the drug in these persons may carry an unnecessarily high risk.

Intrathecal baclofen is indicated for use in patients with spasticity of spinal origin unresponsive to treatment with maximum doses of oral baclofen, tizanidine and/or dantrolene. The benefits of continuous intrathecal baclofen infusion have been demonstrated: >80% and >65% of patients have improvement in tone and spasms, respectively. The main risks of intrathecal baclofen infusion are symptoms related to overdose or withdrawal; the latter is more important because of the associated severe effects on clinical status and the possibility of death, but it is responsive to rapid treatment. Overdose primarily arises from drug test doses or human error during refill and programming of the pump, and withdrawal most commonly occurs as a result of a problem with the delivery system.

Since the adverse consequences do not exceed the benefits of oral and intrathecal baclofen for patients with spinal spasticity, the benefit/risk assessment is favourable.

Baclofen is one of the main drugs used for the treatment of spasticity.

Spinal spasticity is most commonly associated with spinal cord injury and multiple sclerosis. Spasticity occurs in approximately 50% of all spinal cord injury patients,[1-8] with reported prevalences among spinal cord injury patients ranging from 6%[5] to 72%;[7] spasticity seems to have a greater prevalence in patients with tetraplegia and in those with a complete lesion.[2] The incidence of spasticity is higher among cervical and upper thoracic than lower thoracic and lumbosacral levels of injury.[6] Spasticity has been reported to increase with time since injury.[9] Multiple sclerosis is a chronic, often progressive disease,[10] which can also produce spasticity; this disabling symptom is present in about 60% of multiple patients.[11]

Severe spasticity can be defined as considerable increase in tone with passive movement being difficult due to the rigidity in flexion or extension of the affected parts; it is usually measured by the last two scores of the Ashworth scale.[12]About 24% of the total spinal cord population are affected by severe spasticity and about 11% of patients require hospitalisation because of spasticity.[2] Twenty to sixty-five percent of spinal cord injury patients developing spasticity receive antispasticity medication.[4,6]

Along with baclofen, other drugs[13-21] can be administered for patients with spasticity. Tizanidine,[22-31] dantrolene,[16,21] diazepam,[32,33] clonidine[21] and gabapentin[16,19,21] have been reported to be effective in several studies. Botulin injection is an appropriate option for selected patients with severe localised spasticity.[14,21] In the case of failure of oral medication, intrathecal administration of baclofen should be considered.[13,14,21] Irreversible surgical procedures are indicated when severe spasticity is not responsive to oral medications and it is extensive, but limited to the region of the lower or upper limbs.[34]

The aim of this study is to evaluate the relationship between benefit and risk of the baclofen in oral and intrathecal route of administration in patients with spinal spasticity. The literature to be reviewed was obtained by searching Medline and Ingenta

**Table I.** Clinical improvement of spasticity in open-label studies of oral baclofen

| No. of patients | Pathology | Clinical improvement (%) | | Duration of study | References |
|---|---|---|---|---|---|
| | | spasticity | spasms | | |
| 72 | SCI | 87 | 96 | >6y | 40 |
| 12 | MS | | | | |
| 343 | MS | 70 | 75 | 2–30mo | 39 |
| 137 | SCI | 80 | 85 | | |
| 400 | MS | 86 | | ~4y | 38 |
| 69 | MS | 82 | 79 | >1y | 37 |

**mo** = months; **MS** = multiple sclerosis; **SCI** = spinal cord injury; **y** = years.

from 1980 to May 31 2004 using the words: spinal spasticity; baclofen; intrathecal baclofen; side effect; complication.

## 1. Oral Baclofen

Baclofen [β-(chorophenyl)-γ aminobutyric acid (GABA)] is an agonist ligand specific for bicuculline-insensitive GABA receptors (GABA-B receptors) located in the posterior dorsal horn of the medulla and in numerous other structures of the CNS.[12] The drug's action on supraspinal and spinal cord synapses is inhibitory;[35] it primarily restricts calcium influx into the presynaptic terminal thereby reducing the presynaptic neurotransmitter release in excitatory spinal pathways.[36] The postsynaptic action could be due to an increase of potassium conductance with neural activity depression.[35] The block of the release of neurotransmitters affects both monosynaptic and polysynaptic reflexes.[12]

Baclofen was introduced in clinical use in the 1960s. Administration of baclofen is primarily indicated for spasticity of spinal origin,[13] although it is also used in supraspinal spasticity.

Baclofen administration is indicated when spasticity produces a clinical disability.[13] The general goal of treatment is to promote tone reduction, to improve the range of motion and to facilitate rehabilitative procedures. However, the functional objectives – improving gait, daily living activities, ease of care – should also be kept in mind as the purpose of treatment. The intervention should be timed in the early stages to prevent permanent contractures or deformities.[13]After determination of its optimal dosage in patients by careful titration,[14] baclofen administration must be continued long term.

### 1.1 Benefit Evaluation

In open-label studies of oral administration of baclofen (table I), the drug was demonstrated to improve spasticity in 70–87% of patients; additionally, improvement in spasms was reported in the 75–96% of patients.[37-40] However, it should be noted that the measures of symptom improvement used differed between the studies. Spasticity and spasms following spinal cord injury seem to show better clinical improvement with baclofen treatment than multiple sclerosis-associated symptoms.[39] Despite the reported symptomatic improvements, baclofen has not yet been clearly shown to produce long-term functional improvement measured by appropriate scale.[39]

In double-blind crossover placebo-controlled trials,[41-44] baclofen was reported to be an effective drug that produced a statistically significant improvement in symptoms (table II). However, in five patients with traumatic spinal cord injuries the quantitative effects of baclofen versus placebo treatment failed to provide a convincing effect of spasticity reduction;[45] of interest, baclofen did appear to have anxiolytic effects in these patients.[46] The administration of oral baclofen demonstrated an improvement in gait in patients with spasticity and an improvement in vertical unsteadiness in patients with multiple sclerosis; however, this study only lasted 11 days.[47]

However, it should be noted that the clinical measure of improvement was not homogeneous between the placebo-controlled studies. In particular

**Table II.** Clinical improvement of spasticity in placebo-controlled studies of oral baclofen lasting ≥2 weeks

| No. of patients | Pathology | Clinical improvement (%) | | | | Duration of study (wk) | Statistical significance | References |
|---|---|---|---|---|---|---|---|---|
| | | spasticity | | spasms | | | | |
| | | baclofen | placebo | baclofen | placebo | | | |
| 11[a] | SCI | 55 | 5 | 72 | 11 | 4 | $p < 0.01$ | 42 |
| 11[a] | MS | | | | | | | |
| 23[a] | MS | 65 | 17 | 40 | 4 | 4 | $p < 0.05$ | 41 |
| 13 | MS | 84 | 29 | | | 5 | $p < 0.001$ | 48 |
| 6 | SCI | | | | | | | |
| 21[a] | MS | 72 | 0 | | | 3 | $p < 0.001$ | 44 |
| 38[a] | MS | 30 | 20 | | | 2 | $p < 0.05$ | 33 |

a Crossover study.

**MS** = multiple sclerosis; **SCI** = spinal cord injury.

the study of Basmajian et al.[49] did not report the outcomes measured. The methodology for quantifying spasticity was electromyography in some reports.[48,49] Recently, a paper regarding patients with minimal to moderate spasticity demonstrated significant correlation between the Cybex II isokinetic unit and Ashworth scale as methods of measuring improvement of the spasticity in patients with multiple sclerosis.[50]

The effective and well-tolerated dosage of oral baclofen lies in the range of 30–80mg daily,[39] but in multiple sclerosis patients high-dose administration has been suggested.[51] The cost-effectiveness of managing spasticity using baclofen was calculated as £10.50 per successfully treated day (year 2000 values) in one economic analysis.[22] There are currently no other studies into the economic impact of oral baclofen in the treatment of spasticity.

#### *1.1.1 Comparison with Alternative Agents*

Baclofen is not unique in the treatment of the spasticity: other drugs have been suggested, the most common of which is tizanidine for the treatment of spinal spastic symptoms in both multiple sclerosis[26-29] and spinal cord injury.[20,52] The antispastic effects of baclofen and tizanidine were found to be equivalent in several studies[26-28,30,31] (table III); the dose ratios on a milligram for milligram basis were generally 2 : 1 for baclofen versus tizanidine. As for baclofen oral administration, tizanidine failed to demonstrate a long-term functional benefit for patients.[39]

The tolerability of both drugs seems to be not statistically different,[39] but baclofen is reported to cause more weakness than tizanidine[14,26,27,30,31] (table III). The economic impact of tizanidine is equivalent to baclofen.[22]

The efficacy of diazepam has been demonstrated in the reduction of spasticity.[13] In studies with comparison between baclofen and diazepam[32,33,53] there was no significant difference in preference for one or other drug (table III); the major disadvantage of diazepam is its tendency to produce sedation when compared with baclofen.[32,33,53]

Dantrolene does not exert an antispastic effect through the CNS but has an effect on skeletal muscle; however, there has been little use of dantrolene in spinal cord injury and this drug has been used in multiple sclerosis patients with mixed results.[16] Again, long-term functional improvement has not been documented for dantrolene.[13] For gabapentin the results of a few placebo-controlled studies have recently documented a good effect on spasticity,[13] based on the Ashworth scale. There are very few controlled studies on the other drugs.[13,16,21]

In a recent meta-analysis, tizanidine, baclofen and diazepam were equally effective in decreasing excessive muscle tone in patients with multiple sclerosis or cerebrovascular lesions.[23]

### 1.2 Risk Evaluation

#### *1.2.1 Overview*

The tolerability of baclofen is generally considered to be good;[39-41,43] the adverse effects of oral

**Table III.** Comparison between oral baclofen (BAC) and other antispastic drugs

| Pathology | No. of patients | Drug and dosage (mg/day) | | Clinical results | Duration of study (wk) | Reference |
|---|---|---|---|---|---|---|
| | | BAC | comparator | | | |
| **Comparisons with TIZ** | | | | | | |
| MS | 40 | BAC 60 | TIZ 24 | No difference | 6 | 28 |
| MS | 16 | BAC 15–60 | TIZ 12–24 | No difference<br>Weakness greater with BAC | 7 | 26 |
| MS | 100 | BAC 60 | TIZ 24 | No difference<br>Weakness greater with BAC | 8 | 31 |
| MS | 66 | BAC 40–60 | TIZ 24–36 | No difference<br>Weakness greater with BAC | 8 | 27 |
| MS and brain injury | 53 | BAC 60 | TIZ 24–36 | No difference<br>Weakness greater with BAC | 6–8 | 30 |
| **Comparisons with DIA** | | | | | | |
| MS | 40 | BAC 60 | DIA 10–40 | No difference<br>Sedation greater with DIA | 4 | 53 |
| MS | 17 | BAC 60 | DIA 15–40 | No difference<br>Sedation greater with DIA | 4 | 32 |
| MS and spinal cord injury | 13 | BAC 25–60 | TIZ 12–40 | No difference<br>Sedation greater with DIA | 5 | 33 |

**DIA** = diazepam; **MS** = multiple sclerosis; **TIZ** = tizanidine.

baclofen administration in reported studies is shown in table IV. When given orally, the incidence of adverse effects with baclofen is reported to range from 10%[39] to 75%.[43] The most common adverse effects include sedation or somnolence, excessive weakness, vertigo and psychological disturbances. Symptoms are rarely severe and frequently subside or disappear with continued therapy. The majority of adverse effects are reversible (table IV).

Adverse effects appear to be dose related and may be minimised by initiating treatment at a low dose and gradually titrating upward.[54]Adverse effects usually appear at dosages >60 mg/day.[40,44] The rate of treatment discontinuation due to intolerable adverse effects has generally been in 4–11% in studies,[31,39,40,51] although some studies have reported higher rates (16%,[27] 27%[53]). The dosage of baclofen was reduced, with subsequent improvement or disappearance of adverse effects, in 12–20% of patients in some studies,[29,40,44] and 63%[27] in another study.

Oral baclofen in clinical studies does not exert an untoward influence on blood parameters,[27,29,39-44] liver[27,29,39-44] or renal function[27,29,39-44] or on the gastrointestinal tract.[41,42] In some patients a fall in systolic blood pressure can occur, but without clinical signs or symptoms of hypotension.[29,39] In a double-blind comparative trial[29] an increase in serum creatinine level and a decrease of erythrocyte sedimentation rate and fasting blood glucose level was observed but was not considered clinically relevant. In general, the ECG revealed no changes with baclofen treatment.[28,29]

Sinus bradycardia with delayed arousal has been reported in a patient with a spinal cord injury taking oral baclofen 25mg three times daily.[55]

Acute intestinal pseudo-obstruction was observed in a 75-year-old man during treatment with baclofen 20mg daily. After discontinuation of

**Table IV.** Adverse effects of oral baclofen administration for treatment of spasticity (percentage of patients)

| Weakness | Somnolence | Vertigo | Headache | Nausea | Vomiting | Depression | Asthenia | Diarrhoea | Confusion | Hypotension | Dry mouth | Constipation | Bladder symptoms | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 68.7 | 25 | 12.5 | 6.2 | 18.7 | | 6.2 | | 25 | | | 12.5 | | 11.5 | 26 |
| 35 | 19 | 11.2 | 8 | 9.6 | 6.4 | | | | | | | 0 | 11.2 | 27 |
| 13.1 | | | | | | | | | | | | | | 28 |
| 14.2 | | | | 4.7 | | | | | | | 4.7 | | | 29 |
| | 7.6 | | | 7.6 | | | | | | | | | 7.6 | 33 |
| | ~10 | ~7.5 | ~1.5 | ~10 | ~7 | ~2 | ~2.7 | ~2.5 | | | | | | 39 |
| 0.8 | 7 | | 1.7 | 1.7 | | 1.7 | | | 1.7 | | | | | 40 |
| | 17.3 | 8.6 | | | | | | | | | 21.7 | 13 | | 41 |
| 9 | 13.6 | 4.5 | | 22.7 | 4.5 | | | | | 4.5 | | | | 42 |
| 24 | 70 | 13 | 17 | 15 | 2 | 4 | | | | | | 9 | | 43 |
| 14 | 29 | 10 | 14 | 24 | 10 | 19 | | 5 | | 5 | | | | 44 |

baclofen he recovered completely. No other cause of intestinal obstruction could be demonstrated.[56]

#### *1.2.2 Neurological and Psychic Adverse Effects*

Deterioration on EEG was observed with baclofen treatment in two patients with epilepsy.[39] Although baclofen does not generally appear to have a deleterious effect in patients with epilepsy,[57] reported effects on seizure activity have been inconsistent; there have been reports of increased, decreased, or no changes in seizure activity.[54,57] Changes in seizure activity are mainly described after baclofen withdrawal;[58-61] this adverse effect seems to be more frequent in patients with spasticity from brain damage.[58,60] A case of neonatal convulsions after baclofen withdrawal has been reported. In this case, the mother had been taking baclofen 20mg four times daily during her pregnancy.[62] Baclofen has also been reported to have antiepileptic action; *in vitro* studies suggest that it can attenuate epileptiform bursting by altering potassium conductance and therefore variation of interstitial brain potassium levels can reduce the antiepileptic potency of the drug.[63] Baclofen is an inhibitor of substance P and through this mechanism can inhibit the dopamine neurons of the corpus striatum and mesolimbic areas.[64]

The adverse effects of baclofen of psychic origin, such as paranoia and hallucinations, could be due to excessive stimulation of the dopamine neuron areas of chronic inhibition after abrupt withdrawal of the medication.[58,61,65-69] In these cases the onset of withdrawal symptoms generally occurs within 12–38 hours and last for 1–2 days. Restitution of baclofen therapy restores baseline neurological status within a few days. These effects are considerably less common in patients who have had the dosage gradually tapered.[61] However, a case of acute psychosis that developed years after gradually tapered discontinuation of baclofen has been described.[61] Of note, an operation with postoperative adynamic ileus can lead to withdrawal symptoms, because intestinal baclofen absorption can be disturbed.[61]

Psychic symptoms have also been described after oral administration of baclofen without sudden withdrawal.[70-75] In these cases of baclofen therapy

for spinal spasticity, the dosage of medication was 70–80 mg/day and the symptoms improved within 24–72 hours after reduction of the baclofen dosage.

A case of baclofen-induced dyskinesia in a 75-year-old man with spasticity of spinal origin has been described.[76] In this person, the adverse effect appeared when baclofen was first initiated but the patient's history included a basal ganglia stoke; the suspension of medication resolved the symptom. Another case of orofacial dyskinesia in a patient with hypothyroidism has been reported.[77] Those neurological symptoms that are not related to baclofen withdrawal usually develop after long-term treatment[65] and in the elderly; however, neurological symptoms developing after a few days of receiving low-dosage baclofen have been reported.[78] Recently a case of *jamais vu* episodes (a sense of unfamiliarity in a familiar situation) in a patient receiving baclofen for cervical spasm pain has been reported.[79] Low-dosage baclofen can also cause encephalopathy with mental confusion.[80,81] Cases of baclofen-induced akinetic mutism,[82] catatonia[83] and generalised nonconvulsive status epilepticus[84] have also been described.

Baclofen withdrawal can cause a rebound increase in spasticity,[39] which may be associated with hyperthermia as reported in a case of spasticity from craniospinal trauma.[85]A clinically significant neuroleptic malignant-like syndrome involving disorientation, signs of autonomic dysfunction, rigidity and a raised total creatine kinase level has been reported after abruptly stopping baclofen administration.[86] In this case, the patient improved markedly after the reintroduction of baclofen.

#### *1.2.3 Pharmacokinetic and Pharmacodynamic Factors*

An important point to be considered is baclofen toxicity in patients with subclinical[87] or clinical renal insufficiency[88-93] resulting from renal disease or from nephrotoxicity of other medication.[94] In 17 such reported cases, the main symptoms described were altered consciousness with abdominal pain.[88] The time from the start of baclofen therapy to the onset of clinical toxicity ranged from 1 hour to 10 days, and was <3 days in 11 patients. The total dose of baclofen taken among these patients ranged from 12.5–70mg in total. Patients who were given concomitant CNS depressants developed toxicity more rapidly than those who were not. Total recovery of consciousness generally required more than one session of haemodialysis. The number of these patients being treated for spinal spasticity was not clearly reported.[88]

It is important to keep in mind that the pharmacokinetics of high-dose baclofen may vary from those described for standard therapy (50–70 mg/day). Baclofen blood levels were observed to rise gradually over time in some patients on a stable dosage regimen, probably as a result of impaired renal clearance.[95] These findings may indicate that a change in pattern of prescription is warranted and that a reliable and practical measurement of systemic baclofen levels could have a useful role in clinical practice, particularly for the patient with neurogenic bladder and potential renal insufficiency.

In the literature there are reports of clinical situations that can interact with oral baclofen: in patients with asthma,[96] in patients with obstructive sleep apnoea and spinal cord injury,[97] and when tricyclic antidepressants are administrated at the same time.[98,99] In the first case, the reported baclofen-induced bronchospasm or increased bronchial reactivity seems to be a paradoxical response that may be related to the reduction in airway responsiveness to various bronchoconstricting agents that has been shown with the GABA-agonist baclofen in animal studies.[96] In the second instance, the combined presence of obstructive sleep apnoea and spinal cord injury may create additional risk due to decreased oropharyngeal muscle tone.[97] In relation to the third point, a patient receiving baclofen experienced a clinically important increased muscle relaxant effect when given two different tricyclic drugs;[98] another patient receiving baclofen had exacerbation of spasticity after administration of fluoxetine and trazodone.[99]

#### *1.2.4 Overdosage*

The complications of oral baclofen overdosage[100] are usually due to error of administration,[101]

attempted suicide[102] or to drug experimentation.[103]

Effects of baclofen overdose are well defined and include hypotonia, respiratory depression, coma, seizures, cardiac conduction abnormalities,[104,105] and EEG abnormalities.[106] In patients receiving previous long-term administration of baclofen, an overdose can cause prolonged severe withdrawal symptoms.[107]

#### 1.2.5 Comparison with Alternative Therapies

Alternative drugs to baclofen for treatment of spasticity are mainly tizanidine, diazepam and dantrolene. Tizanidine, when compared with baclofen, demonstrated similar efficacy and better tolerability;[21] in particular, weakness was reported to occur less frequently with tizanidine than with baclofen.[27] Adverse effects of tizanidine include somnolence/drowsiness (54%), dry mouth (45%), visual hallucinations (3%) and elevated liver function tests (5%). Global tolerability was assessed as good to excellent in 44–100% of patients receiving tizanidine, compared with 38–90% of baclofen and 20–54% of diazepam recipients.[108]

Diazepam can cause excessive sedation and cognitive impairment. Moreover, it can cause physiological addiction.[54] Withdrawal syndromes are associated with benzodiazepines including diazepam and abrupt cessation of diazepam has been associated with seizures.[21] Moreover, withdrawal symptoms may occur in patients receiving recommended doses and/or short-term therapy.[54]

Chemical evidence of liver dysfunction may occur in 0.7–1% of patients on long-term treatment with dantrolene, with symptomatic hepatitis in 0.35–0.5% and fatal hepatitis in 0.1–0.2%.[109] The most common adverse effects associated with dantrolene are transient drowsiness, dizziness, weakness, general malaise, fatigue and diarrhoea at the start of therapy. Muscle weakness may be the principal limiting adverse effect in ambulant patients, particularly in those with multiple sclerosis. Moreover, administration could be hazardous in patients with pre-existing bulbar or respiratory weakness. The dosage of dantrolene has been fixed in most controlled trials, although long-term studies have indicated the need for individualisation of dosage.[110]

### 1.3 Benefit-Risk Evaluation

Oral baclofen appears to be effective in the treatment of spasticity. With regards to increased tone and spasms, the drug is effective in 55–96% of patients (section 1.1); however, the long-term functional benefit for patients is not yet certain. Considering the seriousness of the diseases affecting these patients (mainly spinal cord injury or multiple sclerosis) and their clinical status, this result is favourable.

The main risks of oral baclofen administration are related to withdrawal (i.e. seizures, psychic symptoms and hyperthermia) [section 1.2]. These symptoms have been reported to improve after the reintroduction of baclofen therapy, usually without sequelae. When these symptoms are not related to drug withdrawal, they present mainly only in patients with brain damage and in the elderly. The limited data available on baclofen toxicity in patients with renal disease suggest that administration of the drug in these persons may carry an unnecessarily high risk. The interactions between tricyclic drugs and baclofen are not clearly defined, so the contemporaneous administration of the two drugs should be cautiously performed.

Because the adverse consequences do not exceed the benefits of oral baclofen for the treatment of patients with spinal spasticity the benefit-risk assessment is favourable. Nevertheless, the treatment of spasticity with tizanidine might avoid the withdrawal danger and the renal toxicity.

## 2. Intrathecal Baclofen

The parenteral form of baclofen is indicated for intrathecal delivery, that is, injection or infusion to the intrathecal space (the area surrounding the spinal cord that contains cerebrospinal fluid).[34] The use of intrathecal baclofen is based on pharmacokinetic principles: if baclofen acts at GABA-B receptors in superficial layers of the spinal cord and orally administered baclofen crosses the blood-barrier poor-

ly, then intrathecally administered baclofen would be more effective.[111]

Baclofen injection was first approved in the US in 1992 for managing spinal origin spasticity and in 1996 for cerebral origin spasticity. Intrathecal baclofen is delivered continuously via a programmable pump and catheter directly into the cerebrospinal fluid, and can be considered for long-term therapy.

To date, over 15 000 patients worldwide have been treated with intrathecal baclofen. The indication for intrathecal use is patients with spasticity of spinal origin unresponsive to oral antispasmodics, patients with unacceptable adverse effects at effective doses of other agents and patients with a positive response to the intrathecal baclofen screening test. An alternative surgical therapy available for the same indication is a neuroablative procedure that destroys the nerves or a portion of the spinal cord.[34]

### 2.1 Benefit Evaluation

Although the majority of patients with spasticity are managed conservatively with oral medication and/or physiotherapy, 25–35% of patients will developed unacceptable adverse effects or fail to respond to maximum doses of oral baclofen, tizanidine and dantrolene.[112] For these patients, baclofen intrathecal infusion is an important adjunct in the management of spasticity.

The purpose of the intrathecal infusion is to reduce or abolish intractable spasticity and/or spasms, as well as possibly preventing decubital ulcers, respiratory or urinary infections. Continuous intrathecal baclofen infusion is an effective treatment, with a decrease in spasticity and spasms as measured by the by Ashworth Scale and Spasm Frequency Scale (SFS) reported in the majority of patients.[113] This finding may be in part attributable to the screening test; as continuous intrathecal infusion is provided only to patients who are responsive to the screening test, this is likely to limit the occurrence of poor long-term results.

Studies of intrathecal baclofen[109,114-137] have reported very good (>85%)[122] improvement in spasticity, while the spasms have been reported improved by 66% (table V); yet few papers have described improvement according to functional scales[121,130,133,135,138] or measures of health-related quality of life.[131,132] The systematic review of Beard et al.[139] showed there is good evidence that intrathecal baclofen is effective in reducing spasticity with functional benefit. The analysis of Campbell et al.[140] suggests that ~66% of patients can expect improved function as a result of decreased spasticity.

The QOL were observed to be improved by the studies of Middel et al.[131] and of Gianino et al.[132] The study of Middel et al.[131] of intrathecal baclofen in patients with severe spasticity reported such clinical outcome measures as Ashworth scale, spasm score, self reported pain score as well as health-related functional status on the sickness impact profile (SIP). Perceived physical and mental health and depression according to the Hopkins symptoms check list (HSCL) was also considered. One year after implantation of the programmable pump, the intrathecal baclofen and the placebo groups did not differ significantly in the SIP psychosocial dimension and HSCL mental health scores; however, for the other items on the SIP and HSCL scales, and for the Ashworth scale, spasm score and self reported pain score, the difference was statistically significantly in favour of baclofen. Gianino et al.[132] did not report improvement in total Quality of Live Index (QLI) after 12 months of treatment with intrathecal baclofen while the SIP revealed signifcant positive changes in the total scores as well as the physical and psychosocial subscales. It is possible that some of the scales used to measure quality of life with intrathecal baclofen treatment were not appropriate to detect an improvement.

There are only a few double-blind, placebo-controlled studies of intrathecal baclofen infusion in the treatment of spasticity.[114-118,120] The follow-up in these studies has generally been rather short, mainly being 12 months after implant of the pump. Moreover, the methods of spasticity evaluation differ between the studies.[140] Differences of results between complete and partial cord injury[134] and between

**Table V.** Clinical results of continuous baclofen intrathecal infusion for treatment of spasticity

| No. of patients | Pathology | Clinical result | | Trial | p-Value/significance | Duration of follow-up | Reference |
|---|---|---|---|---|---|---|---|
| | | impairments | functional | | | | |
| 5<br>4<br>5 | SCI<br>MS<br>Other | Decrease on SFS: 85%<br>Pain free: 90% | | Open, prospective, uncontrolled | | 11mo | 109 |
| 47<br>27 | SCI<br>MS | Decrease on AS and SFS | | Open label, longitudinal | | Median 19mo | 114 |
| 2<br>4<br>3 | SCI<br>MS<br>Other | Decrease on AS and in pain | | Double-blind, placebo controlled | <0.005 | | 115 |
| 4<br>2 | SCI<br>MS | Decrease on AS and SFS: 100% | 5 ADL improvement | Double-blind, placebo controlled | <0.05 | 30d | 116 |
| 9 | SCI | Decrease on AS | 42% increase bladder capacity | Double-blind, placebo controlled | <0.001 | 3–22mo | 117 |
| 5<br>1<br>4 | SCI<br>MS<br>Other | | 72% increase bladder capacity | Double-blind, placebo controlled | NS | 6–12mo | 118 |
| 32<br>33 | SCI<br>MS | Decrease on AS and SFS: 97% | | Open, prospective, uncontrolled | | Median 30mo | 119 |
| 5<br>1<br>4 | SCI<br>MS<br>Other | Decrease on AS and SFS | Improvement of walking | Double-blind, placebo controlled | <0.0001 | 1y | 120 |
| 4<br>4 | SCI<br>MS | Decrease on AS and SFS: 100% | PECS improvement | Open | | 6mo | 121 |
| 4<br>2 | SCI<br>MS | Decrease on SFS: 66% | Improved sleep | Double-blind, placebo controlled | NS | 2 nights | 122 |
| 10<br>12<br>6 | SCI<br>MS<br>Other | Decrease on AS and SFS | Dressing, hygiene voiding facilitated | Open, prospective, uncontrolled | | 2y | 123 |
| 5<br>4 | SCI<br>Other | Decrease on AS and SFS | | Open, prospective, uncontrolled | <0.0001 | Median 15mo | 124 |
| 2<br>3<br>1 | SCI<br>MS<br>Other | Decrease on AS and SFS | ADL improvement | Open, prospective, uncontrolled | | 12–36mo | 125 |
| 5<br>6<br>9 | SCI<br>MS<br>Other | Decrease on AS | Hygiene and bathing facilitated | Open, prospective, uncontrolled | | 2–24mo | 126 |

*Continued next page*

**Table V.** Contd

| No. of patients | Pathology | Clinical result: impairments | Clinical result: functional | Trial | p-Value/significance | Duration of follow-up | Reference |
|---|---|---|---|---|---|---|---|
| 15<br>4 | SCI<br>MS | Decrease on AS and SFS | | Open | | 2–34mo | 127 |
| 9<br>2<br>4 | SCI<br>MS<br>Other | Decrease on AS and SFS | GHS 86% improvement | Open, prospective, uncontrolled | | 1–42mo | 12 |
| 5<br>2 | SCI<br>MS | Decrease on AS and SFS | ADL improvement | Double-blind, placebo controlled | <0.005 | 24–41mo | 128 |
| 2<br>6<br>1 | SCI<br>MS<br>Other | Decrease on AS | Improvement sitting, personal care | Open, prospective, uncontrolled | | 13–34mo | 129 |
| 12<br>4<br>2 | SCI<br>MS<br>Other | Decrease on AS and SFS | FIM improvement | Prospective | <0.001 | 9–72mo | 130 |
| 9<br>13 | SCI<br>MS | Decrease on AS and SFS and SRP | SIP and HSLC improvement | Double-blind, randomised | <0.01 | 12mo | 131 |
| 7<br>15<br>3 | SCI<br>MS<br>Other | Decrease on AS and SFS | QLI no significant change; SIP significant improvement | Prospective | <0.05 | 12mo | 132 |
| 17<br>31<br>12 | SCI<br>MS<br>Other | Decrease on AS and SFS: 100% | Functional improvement variable | Prospective, uncontrolled | | 4–43mo | 133 |
| 40<br>5<br>19 | SCI<br>MS<br>Other | Decrease on AS and SFS | ADL improvement | Prospective | <0.001 | 36mo | 134 |
| 4<br>13<br>3 | SCI<br>MS<br>Other | Decrease on AS and SFS and in SRP | FIM improvement | Retrospective | <0.01 | 12–36mo | 135 |
| 53<br>63<br>15 | SCI<br>MS<br>Other | Decrease on AS and SFS | | Open, prospective, uncontrolled | <0.0005 | 2–137mo | 136 |
| 12 | SCI | Decrease on AS and SFS | QOL improvement | Retrospective | <0.05 | 12mo | 137 |
| 4<br>8 | MS<br>Other | Decrease on AS and 100% on SFS | | Prospective, longitudinal, uncontrolled | | 9mo | 141 |
| 15<br>6 | MS<br>Other | Decrease on AS 76% and 85% on SFS | | Prospective, longitudinal, uncontrolled | | 9–79mo | 142 |

**ADL** = activities of daily living; **AS** = Ashworth scale; **d** = days; **FIM** = functional independence measure; **GHS** = global handicap score; **HSLC** = Hopkins symptom checklist; **mo** = months; **MS** = multiple sclerosis; **NS** = not significant; **PECS** = patient evaluation conference system; **QLI** = quality of life index; **QOL** = quality of life; **SCI** = spinal cord injury; **SFS** = spasm frequency scale; **SIP** = sickness impact profile; **SRP** = self reported pain; **y** = years.

spinal cord injury and multiple sclerosis[133] have been described, and also functional improvement has been reported to be variable.[133] Changes in neurogenic bladder dysfunction have been evaluated and shown a decrease of detrusor hypertonia and hyperactivity in 50% of patients,[143] with an increase of 72% in functional bladder capacity also reported.[118] However, long-term effects are still not fully known, as few studies have reported follow-up after 10 years.

Intrathecal baclofen origin has been proven to have efficacy in upper extremity hypertonia in tetraplegia of spinal origin,[144] as well as in vasomotor disorders in the lower limbs in a patient with spastic paraplegia.[145]

The possibility of a lasting reduction in severe spasticity after ending chronic intrathecal treatment has been reported, as has the possibility of reducing the dose of chronic infusion.[146]

Costs of continuous intrathecal baclofen administration have been analysed.[147] The most important cost can be attributed to the pump implantation but improved quality of life justifies these costs.[147] The cost/benefit ratio compared with other interventions is acceptable.[148]

The alternative surgical therapies to intrathecal baclofen infusion are neuroablative techniques (peripheral neurotomies, dorsal rhizotomies, microsurgical destruction of the dorsal root entry zone) and neuromodulative techniques (cervical spinal cord, deep brain, cerebellar cortex neurostimulation).[34] The clinical improvement with neurostimulation is reported to be very limited, whereas the neuroablative procedures produce an improvement in spasticity of 76–82%.[34] There are a number of notable differences between these procedures and intrathecal baclofen. First of all, the neuroablative procedures are ablative and irreversible, whereas intrathecal baclofen is conservative and reversible. Second, the tonus modulation is topographic with the dorsal root entry zone destruction, whereas it is quantitative in baclofen infusion. Lastly, dorsal root entry zone destruction is indicated in regional spasticity of lower or upper limbs with no useful mobility, whereas baclofen infusion is indicated in diffuse spasticity with useful mobility because the dose can be finely modulated in order to preserve useful spasticity.[34]

## 2.2 Risk Evaluation

### *2.2.1 Overview*

Intrathecal baclofen has been demonstrated to lack significant toxicity at concentrations up to 2000 μg/mL in the dog model.[149] The tolerability of continuous intrathecal baclofen infusion is reported to be good, with adverse effects being tolerable in most cases and rarely severe.[123,134] The adverse effects of intrathecal baclofen usually are transient and/or resolved with a reduction in baclofen dosage (table VI). Fatigue, sleepiness, weakness are reversible symptoms observed mainly after the bolus test or in the beginning of therapy.

Penn et al.[119] reported transient adverse effects in 50% of patients treated with intrathecal baclofen for spasticity: the only treatment required was lowering the dosage. Adverse effects reported included: drowsiness (35.4%); dizziness (16.1%); blurred vision (16.1%); slurred speech (9.6%). Episodes of nausea, orthostatic hypotension, urinary retention, nystagmus, confusion, memory decrease, dry mouth, or dysmetria were reported with an incidence <4%. Coffey et al.[114] described a total inci-

**Table VI.** Adverse effects of intrathecal baclofen administration (percentage of patients)

| Drowsiness | Dizziness | Blurred vision | Slurred speech | Nausea | Confusion | Memory decrease | Ejaculation impairment | Constipation | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 35.4 | 16.1 | 16.1 | 9.6 | | | | | | 119 |
| | | | | <4 | <4 | <4 | | | 114 |
| 2.2 | | | | 2.6 | | | 0.8 | 2.9 | 113 |
| 5.4 | | | | 0.7 | | | 1.5 | 9.1 | 136 |
| 13.2 | | | | | | | | | 133 |

dence of adverse effects of 12% in a series of 74 patients treated with intrathecal baclofen.

An important adverse effect of baclofen infusion is impairment of erection and ejaculation.[118,150] This inhibitory effect is reversible and none of the affected patients in clinical trials[118] asked for treatment interruption. Intrathecal baclofen infusion can deteriorate intestinal function. This adverse effect has been reported in two patients with spasticity of spinal origin by Kofler et al.[151] and in six by Ordia et al.[136] The effect can be related to a central site in the brainstem or in the brain.

One case of deep vein thrombosis as result of hypotonia secondary to intrathecal baclofen infusion for spinal spasticity was recorded by Ochs et al.,[123] while another case was reported in a patient with cerebral palsy treated with intrathecal baclofen.[152] As for oral baclofen, increased dystonia after treatment with intrathecal baclofen was reported in one case.[153] In the series of Ochs et al.,[123] a case of renal insufficiency associated with baclofen toxicity after administration of 80–100mg of oral baclofen in addition to intrathecal baclofen has been reported. A case of febrile reaction to intrathecal baclofen administration has been reported;[154] the genesis of fever could be spread of baclofen within cerebrospinal fluid to higher rostral centres. In fact baclofen has been observed to cause marked increase of body temperature in the rat when injected into cerebral ventricles.[154]

Administration of general anaesthesia in patients treated with intrathecal baclofen can cause cardiovascular adverse effects.[155]

In three pregnant woman[156-158] treated with baclofen infusion there was no toxicity for the fetus.

#### 2.2.2 Tolerance

Tolerance is defined as a phenomenon manifested by an escalation of the dose required to produce a previously obtained effect or by the decrement of the effect produced by a given dose of drug with continued administration.[159] The first effect appears to be common with continuous intrathecal baclofen administration; it is estimated to occur in about 15–20% of patients and is usually only observed within the first 12 months after pump implantation.[133,160] The second effect requires a 'drug holiday' to restore full effectiveness, and has been reported to occur in 3.5–15% of patients.[114,123,127] The mechanism by which tolerance develops is thought to involve a decrease in the number of receptors after repeated drug infusion, causing the loss of baclofen efficacy.[161] When a 'drug holiday' is required, usually intrathecal morphine is administered for 1 or 2 months; sometimes the treatment with morphine becomes definitive.[162]

#### 2.2.3 Overdose and Withdrawal Symptoms

The important adverse effects of intrathecal administration of baclofen are similar to those following oral administration of this drug (see section 1.2)[163] and can be due to overdose or to withdrawal. These events can occur after the screening test with intrathecal baclofen or after long-term continuous intrathecal infusion. In the first case, the symptomatology is typical for drug overdose:[164] sedation or coma, hypotonia, respiratory depression, hyporeflexia. The incidence of overdose-type symptoms after an intrathecal baclofen test has been reported to be ≤7%,[12,114,127] with some series reporting an incidence of 0%.[123,133] The symptoms were transitory in all patients. Other cases in patients with different causes of spasticity, such as tetanus,[165] have also been described.

Usually high baclofen levels can be tolerated when the dosage is gradually increased, so rapid increases in the dose of baclofen intrathecally administered should be avoided.[166] Overdose of intrathecal baclofen is usually due to human error of pump programming or of pump refill.[119,127,133,167] Series have reported incidences of such events to generally be between 0% and 5%,[90,114,123,127,133] although some higher rates have been reported (14.2%[128]). The reported symptoms were reversible without definitive damage. In cases of severe overdose a lumbar puncture to evacuate cerebrospinal fluid and to exchange it with artificial fluid is advised.[168]

Overdose can also cause seizures,[169] this event was reported in cases of patients with brain damage.[170,171] EEG changes can be associated to seizures in baclofen overdose.[172] The mechanism

could be a suppression of recurrent inhibition in the dentate gyrus, possibly through an action on the inhibitory interneurons;[12] in this case, the alterations are reversible. A case of seizures without overdose was reported in a 55-year-old woman with multiple sclerosis in progression.[114]

The withdrawal of intrathecal baclofen can be due to a failure of the infusion system or more simply it can be due to the pump reservoir in the infusion system being empty. Coffey et al.[173] found ten cases of intrathecal baclofen withdrawal syndrome previously reported in the literature and reported six new cases.[168,174-181] Other cases have also been described.[182-186] Spasticity was of spinal origin in 16 patients (11 with cervical cord injury level and five with thoracic level).[166,168,173-179,185,187] The duration of intrathecal baclofen administration exposure before drug withdrawal varied from 7 to 78 months, with a mean of 37.6 months. The mean baclofen dosage at onset of symptoms was 696.2 (range 100–1200) μg/day in the ten cases for which dosage was known. Severe symptoms began within 1 or 2 days after cessation of intrathecal administration in the cases in which data about onset of the symptoms were described. The causes of withdrawal were: empty pump reservoir (n = 2); break or displacement of the catheter (n = 5); end of battery life (n = 2); pump malfunction (n = 2); removal for system infection (n = 2); pump inversion (n = 1); syringopleural shunt (n = 1); and a suspected error refill-programming (n = 1). Six patients with spinal spasticity died after onset of symptoms of baclofen withdrawal.[173]

The symptoms of withdrawal of intrathecal baclofen are most often limited to return of the patient's baseline spasticity and rigidity.[173] Abrupt withdrawal of intrathecal baclofen may cause the symptoms as described for oral baclofen (see section 1.2). In a few reported cases, intrathecal baclofen withdrawal has caused rebound spasticity, muscle rigidity, fever, seizures, labile blood pressure or hypotension, and lowering of consciousness. If not treated promptly the syndrome can progress over 24–72 hours towards rhabdomyolysis with elevated plasma creatine kinase levels, elevated transaminase levels, renal and hepatic failure, disseminated intravascular coagulation and sometimes death.[168,173-178] Therefore, withdrawal from intrathecal baclofen appears to be much more problematic than withdrawal from oral baclofen.[173,178] When the drug is restarted, symptoms resolve within 24–72 hours.[176] According to Meythaler et al.,[187] the administration of cyproheptadine may be a useful adjunct to baclofen and benzodiazepines in the management of baclofen withdrawal syndrome.

The probable pathogenesis of the baclofen withdrawal syndrome is related to the release of excitatory neurotransmitters that occur when the inhibiting influence of baclofen is abruptly removed. Patients with a T6 or higher spinal cord lesion, the same patients that are at risk for episodic autonomic dysreflexia, may be vulnerable to the more severe manifestations of intrathecal baclofen withdrawal.[173]

### 2.3 Comparison with Alternative Therapies

The only intrathecal therapy for spasticity that can be compared to baclofen is the infusion of morphine; however, the efficacy of intrathecal morphine is inferior to baclofen and morphine causes adverse effects such as vomiting, mental confusion, somnolence, urinary dysfunction and pruritus.[34] However, morphine can be used temporarily for a 'drug holiday' (see also section 2.2.2).[127] There is not an intrathecal formulation of tizanidine. Neuroablative surgical procedures are irreversible and deficits in sensitivity or movement impairment can arise in the postoperative period.

### 2.4 Benefit-Risk Evaluation

The benefits of continuous intrathecal baclofen infusion have been demonstrated. More than 80% of patients have improvement in tone and >65% in spasms. There is evidence of improvement in functional abilities and in sphincter disorders. However, it should be kept in mind that this therapy is carried out when the oral administration of drugs fails.

The main risks of intrathecal baclofen infusion are symptoms arising from overdose or withdrawal. Overdose usually arises from drug administration for testing or from human error during refill and

programming of the pump. More important in terms of the severity of clinical status and the possibility of death is the withdrawal of baclofen. To date there have been reported 34 cases of withdrawal-related events temporally related to abrupt discontinuation of intrathecal baclofen therapy, including seven fatalities.[188] Abrupt withdrawal most commonly occurs as a result of a problem with the delivery system. Although dangerous, a clinically threatening intrathecal baclofen withdrawal syndrome has been experienced by very few patients when this event is related to the total number of patients with implanted baclofen pumps. Nevertheless, physicians should be alert to the danger of abrupt withdrawal of intrathecal baclofen and should be prepared to treat the patient immediately.

Since the adverse consequences of intrathecal baclofen infusion do not exceed the benefits in patients with intractable spasticity, the benefit/risk assessment is favourable.

## 3. Conclusions

The benefit-risk assessment of baclofen in severe spinal spasticity is favourable for oral administration as well as for intrathecal infusion. Oral administration shows reversible adverse effects, but careful attention is required for patients with renal diseases, brain damage and in the elderly. The abrupt discontinuation of therapy can cause risk of withdrawal symptoms, and patients should be carefully instructed to avoid this happening. The possibility of death after abrupt withdrawal of intrathecal baclofen can be eliminated by immediate diagnosis and treatment.

The evaluation of functional results in intrathecal infusion should be standardised to obtain the best results possible with this expensive treatment.

Future research, mainly for intrathecal infusion, should be orientated to emphasise the relationship between long-term administration of baclofen and drugs such as corticosteroids or interferon in patients with multiple sclerosis. Also neuropsychological and psychic perception studies after intrathecal baclofen pump implant should be carried out.

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