ORIGINAL ARTICLE

The incidence and management of tolerance in intrathecal baclofen therapy

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Study design: Retrospective study.

Objectives: To study the incidence and management of tolerance in patients treated with intrathecal baclofen (ITB) therapy.

Setting: Department of neurology and neurosurgery, University Medical Center Groningen, The Netherlands.

Methods: Medical records of all patients who had received an implantable ITB pump at our clinic during 1991–2005 were reviewed.

Results: A total of 37 patients (representing 116 pump years) were included. Mean follow-up time was 38 months (range 3–120 months). Baclofen dose increased in the first 18 months after implantation ($P < 0.05$), and then stabilized around a mean dose of 350 μg per day. Eight patients (22%) developed tolerance, defined as a dose increase of $> 100 \mu\text{g}$ per year. No predictive factors for development of tolerance could be determined. Three different treatment regimens for tolerant patients were analyzed. Altering the infusion mode from simple to complex continuous ($n = 6$) had no effect on the development of tolerance. Pulsatile bolus infusion ($n = 1$) and a drug holiday ($n = 2$) were both effective in reducing the daily baclofen dose. Patients who needed surgical revision of the pump system because of mechanical failures ($n = 11$) showed a significant dose decrease during the first month after revision, indicating that the preoperative dose increase most likely had been caused by the pump failure. Pump-related complications occurred once per 10.5 years of ITB treatment. Drug-related side effects had an annual risk of 13.8%. The reported events were mostly mild.

Conclusions: ITB therapy is effective and safe, also in the long term and causes tolerance in only 22% of the treated patients.

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Introduction

Spasticity is a motor disorder characterized by an increase in muscle tone, hyperactive tendon jerks and an increase in resistance to rapid muscle stretch. The resulting involuntary muscle contractions interfere with a patient's daily living and mobility. Baclofen, a GABA_B receptor agonist, is the most widely used spasmolytic agent. It is a muscle relaxant with its prime site of action in the spinal cord, where it binds to the inhibitory GABA_B receptor.¹ The uptake of baclofen across the blood–brain barrier is limited, so high oral doses are needed to achieve a therapeutic effect, causing side effects such as muscle weakness and drowsiness.² Baclofen can be infused intrathecally using a lumbar drain connected to a

subcutaneously located programmable pump. Intrathecal baclofen (ITB) therapy needs considerable lower doses as compared to oral administration, resulting in fewer side effects. First suggested by Penn and Kroin in 1984, ITB therapy has proven to be safe and successful in treating severe spasticity.^{3–5} The subcutaneous pump allows three different infusion modes: (1) simple continuous infusion at a steady rate throughout the day, (2) complex continuous infusion using 4–6 hourly blocks consisting of different doses and (3) a pulsatile bolus mode, delivering a drug bolus at a fixed interval.

The development of tolerance is one of the major concerns of ITB therapy.^{6,7} Tolerance is defined as 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.⁸ One hypothesis is that tolerance is due to a down-regulation of the number of GABA_B receptors in the spinal cord after chronic exposure.^{8–10} Development of tolerance

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has been reported extensively.^{6,7,11} This retrospective long-term follow-up study was performed to quantify tolerance in our cohort of patients and to describe our strategies to treat tolerance. Moreover the long-term drug-related side events are described.

Patients and methods

Patients

All patients treated with ITB at the departments of neurology and neurosurgery of the University Medical Center Groningen from 1991 to 2005 were screened for this study. In total 37 patients were treated (19 male, 18 female; Table 1). The indication for ITB treatment was severe spasticity due to multiple sclerosis (MS) in 14 patients, related to traumatic spinal cord injury (SCI) in 10 patients and due to miscellaneous causes in 13 patients (for details see Table 1). The patient needed at least a follow-up of 1 year to be included, with a minimum of 1 visit each 6 months, including Ashworth ratings, dosing data of baclofen and dosing data of comedication, as well as drug-related side effect reporting.

The follow-up varied between 3 and 120 months, with a mean of 38 months. Three patients died during the period of follow-up, not related to the ITB treatment.

After implantation all patients were treated with simple continuous ITB infusion. Tolerance in this study was defined as a yearly increase of at least 100 µg baclofen to maintain a stable spasmolytic effect. If patients showed tolerance they were offered three treatment options:

- Switch to complex continuous infusion
- Switch to pulsatile bolus infusion
- Drug holiday

The drug holiday always took place in the hospital. During the drug holiday, the baclofen administration was tapered off and the patients were treated with oral or intravenous clonazepam.

The effects of these treatment changes on the development of tolerance were analyzed.

The tolerant patients and the nontolerant patients were correlated to the following variables: gender, nature of the underlying disease (MS/SCI/other), pump type (SynchroMed I/Ia/II/IIa), catheter tip level, concentration of baclofen, starting dose and test dose of the ITB.

Table 1 Clinical data of 37 patients with spasticity, treated with ITB therapy

Case no.	Age	Sex	Etiology	Year of implantation	Year of death
1	46	F	MS	1991	–
2	49	M	SCI	1995	–
3	53	M	Adrenomyeloneuropathy	1995	–
4	52	M	SCI	1997	–
5	53	M	Multifocal dystonia	2000	–
6	57	M	MS	2000	–
7	58	M	SCI	2001	–
8	27	M	CP	2001	–
9	68	F	MS	2001	–
10	37	F	MS	2002	2004
11	61	M	SCI	2002	–
12	37	M	SCI	2002	–
13	44	F	Subacute sclerosing panencephalitis	2002	–
14	44	M	SCI	2003	–
15	16	F	CP	2003	–
16	68	F	MS	2003	2004
17	68	M	MS	2003	2005
18	58	M	SCI	2003	–
19	17	F	CP	2004	–
20	54	M	SCI	2004	–
21	48	M	MS	2004	–
22	55	M	MS	2004	–
23	45	F	Neurosarcoidosis	2004	–
24	50	F	MS	2004	–
25	47	F	Hereditary spastic paraplegia	2004	–
26	44	M	CP	2004	–
27	41	M	MS	2005	–
28	46	M	MS	2005	–
29	44	F	MS	2005	–
30	19	F	CP	2005	–
31	47	F	MS	2005	–
32	77	F	SCI	2005	–
33	32	F	MS	2005	–
34	50	F	CP	2005	–
35	61	F	SCI	2005	–
36	60	M	Bipyramidal syndrome	2005	–
37	33	F	CP	2005	–

Abbreviations: CP, cerebral palsy; MS, multiple sclerosis; SCI, spinal cord injury.

Figure 1 Baclofen daily dose and Ashworth scale during 10-year follow-up in 37 patients.

Table 2 Significance of dose increases (repeated-measures ANOVA)

Months	P
0–6	0.024
6–12	0.043
12–18	0.048
18–24	0.873
24–30	0.194

The italic values indicate significant ($P < 0.05$) numbers.

Pump revisions were analyzed separately, with special attention to the dose–time curve in the prerevision period.

Surgical procedure

The implantation of all the pump systems was done by the same neurosurgeon (MJS) and always under general anesthesia. Preoperative antibiotic prophylaxis was applied. A one- or two-piece spinal catheter (Medtronic Inc., Minneapolis, MN, USA) was inserted in the spinal canal through a Tuohy needle after a small midline incision mostly at the mid-lumbar level. The tip was positioned at the Th-10 level. After subcutaneous tunneling the catheter was connected to the programmable pump (SynchroMed I(a) or II(a); Medtronic Inc.), placed in a subcutaneous pocket in the left lower abdominal wall. The pump was always filled with baclofen and purged before placement in the pocket. The initial daily dose was set at twice the most effective bolus dose during the test phase, which was continuously infused during the day. Postoperatively the baclofen infusion was adjusted to the patient's needs.

Statistical analysis

Data analysis was performed in SPSS (version 15). Baclofen doses were evaluated every 6 months. The Ashworth scores collected in a period of 6 months were averaged. Only the spasticity scores of the legs were assessed because ITB with the catheter tip at the lower thoracic level has its effects mainly on the legs. A repeated-measures analysis of variance (ANOVA) was used to check for significance in dose increase and to compare differences in effect between different patient groups (MS, SCI, other causes).

Because a repeated-measures ANOVA requires data during the full period of the analysis of every included patient, the ANOVA for dose increase was limited to the first 30 months after implantation. Fourteen patients with follow-up data of at least 30 months could be included in this study.

The influence of the mentioned variables on the possible development of tolerance was analyzed by a Pearson's χ^2 -test for the nominal and ordinal variables, and a Mann–Whitney U-test for the ratio variables.

Results

Effectiveness of ITB

The mean Ashworth score at baseline (before pump implantation) was 3.7 ± 1.0 s.d. Ashworth scores decreased immediately after pump implantation in all patients to a mean of 2.4 ± 1.0 s.d. after 6 months and stayed below baseline level during the whole study. Therefore, the largest decrease in spasticity took place between 0 and 6 months and stabilized afterwards (Figure 1).

Dose titration of ITB

The mean baclofen dose at implantation was $107 \mu\text{g}$ (Figure 1). The mean dose increased significantly during the first 18 months (ANOVA, Table 2) and stabilized afterwards at $350 \mu\text{g}$. The sudden increase at 5 years and the decrease at 9 years after implantation can be explained by the loss of follow-up of two patients with a relatively low (after 5 years) and high (after 9 years) dose of baclofen.

The increases of the baclofen dose in the three different patient groups (MS, SCI and other causes) did not show any significant difference ($P = 0.558$).

Patients showing tolerance according to our definition ($N = 8$; 22%) were compared to the nontolerant patients ($N = 29$). Correlation with different variables did not provide any difference between the two groups (Table 3).

Comedication during follow-up

At the end of the study, seven patients still used oral spasmolytics: benzodiazepines ($6 \times$), tizanidine ($1 \times$) and

Table 3 Variable correlation in tolerant and nontolerant patients

Variable	P
Gender	0.931
Nature of underlying disease (MS/SCI/other)	0.208
Pump type	0.535
Catheter tip level	0.784
Concentration of baclofen	0.692
Starting dose	0.792
Test dose of baclofen	0.578

Table 4 Causes for unscheduled revisions

Cause	Number of patients
Catheter occlusion	4
Catheter disconnection	2
Catheter leakage	2
Catheter dysfunction (unknown)	2
Pump defect	1

baclofen ($1 \times$). In all cases these were continued because of remaining spasticity of the arms, not responding on ITB.

Influence of pump/catheter revisions on the dose of baclofen

Seven patients needed 11 pump/catheter revisions because of mechanical dysfunction during 116 years of ITB treatment in total, resulting in 1 revision per 10.5 years of ITB treatment, which is equivalent to an annual risk of 9.5%. The pump had to be explanted in one patient, after a meningitis preceded by wound infection after revision. In this patient the pump was reimplanted 2 years later. The causes for revision were mostly due to catheter problems (occlusion, disconnection, leakage) and once because of a pump defect (Table 4). Six patients (55%) showed a significant decrease of the dose after revision (mean $74 \mu\text{g}$ after 1 month), four patients remained at the same dose and one patient even needed an increase in dose of $10 \mu\text{g}$ per day. The baclofen dose increased almost twice as much ($55 \mu\text{g}$ per year) in the 6 months before revision as compared to the 6 months after revision ($28 \mu\text{g}$ per year). The mean decrease in dose following the 11 revisions was $47 \mu\text{g}$ after 1 month (Figure 2).

Drug-related side effects

Sixteen drug-related side effects were reported in 10 different patients during 116 ITB treatment years in total (Table 5) resulting in an annual risk of 13.8%. Drowsiness, swallowing difficulties, decubitus, urine incontinence and auditory hallucinations were reported most frequently. One patient had a baclofen overdose, which resulted in a coma.

Possible strategies to treat tolerance

In eight patients the mode of infusion was switched during follow-up. Two of these patients were not included in the analysis because post-switch data were not available.

Complex continuous infusion mode. There were six switches from simple to complex continuous infusion mode in six

Figure 2 Baclofen dose changes around pump revisions.**Table 5** Drug-related side effects reported in 37 patients with long-duration ITB

Side effect	Frequency
Drowsiness	5
Swallowing difficulties	2
Decubitus	2
Urine incontinence	2
Auditory hallucinations	2
Micturition difficulties	1
Coma after baclofen overdose	1
Speech problems	1

Figure 3 Dose change after infusion mode switch to complex continuous.

patients (Figure 3). All patients except one had an increase in total daily ITB dose after the infusion mode switch to complex continuous. The mean dose increase 3 months after the infusion mode switch to complex continuous was even larger as compared to the 3 months before. This strategy did not have a significant effect on the dose increase in most patients.

Drug holiday. Because of a continuously increasing dose after the switch to complex continuous infusion, two patients received a drug holiday. The patients were carefully

monitored in the hospital during this drug holiday, because of a potential risk on withdrawal symptoms, such as hypotension, rhabdomyolysis and even death.¹² One patient (case 1) received the 1-day drug holiday after an increase in dose from 450 to 575 µg in 6 weeks. The pump was programmed at a minimal basal rate of 2–3 µg h⁻¹ for 24 h. After restarting therapy, the dose stabilized at 300 µg, during the next 3 years. Another patient (case 8) received a partial drug holiday after an increase in dose from 315 to 345 µg, which however resulted in an increase of spasticity. The pump was switched to a simple continuous regimen of 70 µg per day for 48 h. Afterwards the therapy was restarted at 315 µg, which resulted in a satisfactory spasmolytic effect and a stable dose for the next 12 months.

Pulsatile bolus infusion mode. After an increase of more than 100 µg baclofen per day (from 470 to 590 µg) during 1 month, one patient (case 20) was switched to a pulsatile bolus infusion mode. This resulted in a decrease of spasticity and a drop in daily dose to 440 µg baclofen for at least 6 months (end of study follow-up).

Discussion

According to the findings in this study, ITB therapy is very effective in reducing spasticity, as shown by the mean Ashworth scores, remaining below the baseline score of 3.68 during the total follow-up of 120 months.

The mean therapeutic dose of baclofen significantly increased during the first 18 months after pump implantation ($P < 0.05$). The dose stabilized after this period and during the rest of the treatment (± 350 µg). This initial increase represents the period to optimize the dose and is not related to tolerance.

Other studies reported similar periods of increasing doses after having started ITB therapy, varying from 3 to 18 months.^{5–7,10,13} Some studies however reported even titration phases of up to 3 years.^{3,11}

These long titration phases again emphasize the importance of long-term follow-up. Furthermore, this provides us with data to inform our patients properly, resulting in reasonable expectations.

However, tolerance did occur in later stages in 22% of the patients in this study. Analysis of different variables did not provide any clue to predict the occurrence of tolerance. The numbers reported in other studies vary from 1 to 20%.^{5,11,14} Because there is no clear definition of tolerance in most studies, the numbers mentioned depend on the judgments of the different investigators.

Although the underlying mechanisms of tolerance development are not clear, studies on rats report a decrease in the number of GABA_B receptors following chronic baclofen infusion (33% less receptors after 7 days).⁹ Furthermore, studies on intrathecal morphine treatment provide data suggesting that the development of tolerance is caused by mechanisms on a cellular level within the receptor.¹⁵ The same changes within GABA_B receptors could be responsible for the tolerance to baclofen. Stopping or diminishing the

baclofen infusion possibly may reverse these mechanisms. These so-called 'drug holidays' have proven to be successful in the past and seem to be an excellent instrument in the treatment of tolerance.^{16,17} However, drug holidays are not without any risk because they may cause a 'baclofen withdrawal syndrome' with serious symptoms, such as hyperthermia, altered mental status and hypotension.^{12,18,19} Therefore, patients on a drug holiday should be treated with alternative muscle relaxants, such as clonazepam. GABA_A binding drugs are preferable because they have a spasmolytic effect without binding to the GABA_B receptor.

At this moment it is not clear why particular patients are more susceptible to tolerance than others. This study at least did not show any correlation with the cause of the disease.

In contrast to our findings, Nielsen *et al.*¹⁰ reported that both MS and non-MS patients increased in dose the first 1.5 years of the study. Thereafter the non-MS patients stabilized, whereas the MS patients further increased their baclofen doses. A possible explanation for these different findings could be that Nielsen's MS patients were treated in a later stage of the disease, needing a higher dose of baclofen.

This study has also shown the importance of considering pump failure as an alternative explanation for unexpected dose increases, so the pump should always get a status check in case of an unexpected dose increase.

Six patients with tolerance were treated with a different infusion regimen, providing us some pilot data. These data suggest that switching a patient from simple to complex continuous infusion does not have an effect on tolerance. Probably this is due to a too short low-dose period within the complex continuous regimen, which is supported by the intrathecal half-life of baclofen (4–5 h).²⁰ So even if the low dose period has been 4–5 h, the level of baclofen is not even reduced below 50%.

Two patients (cases 1 and 8) received a drug holiday during complex continuous infusion. This resulted in a dose decrease and stabilization afterwards in both cases. A drug holiday therefore seems to be a potent measure to reverse tolerance phenomena. In spinal cord-injured patients with severe spasticity, who become tolerant to ITB, treatment with intrathecal morphine may be another useful treatment modality, which however was not practiced in our patients.²¹

The only experience with pulsatile bolus infusion in this study was promising, and reflects probably a clinical relevant mode of infusion in patients showing tolerance. A prospective follow-up study is being planned.

The risk on a pump-related complication was 9.5% per year of treatment. This is at the lower end of the range of complication rates reported by others, varying between 7 and 20%.^{10,11,22} The drug-related side effects were mostly mild and the annual risk of 13.8% per year of treatment was also within the range reported by others.^{3,11}

Conclusions

ITB is an effective and safe therapy and does not induce tolerance in the long term in most patients. Dose increases

are seen during the first 18 months of ITB therapy and stabilize afterwards.

The causative factors in the development of tolerance, as well as the most optimal strategy to treat this tolerance, are still unknown. This study suggests that two strategies might be helpful: a drug holiday of at least 24 h or switching to a pulsatile bolus infusion mode.

References

- Wallace M, Yaksh TL. Long-term spinal analgesic delivery: a review of the preclinical and clinical literature. *Reg Anesth Pain Med* 2000; **25**: 117–157.
- Deguchi Y, Inabe K, Tomiyasu K, Nozawa K, Yamada S, Kimura R. Study on brain interstitial fluid distribution and blood-brain barrier transport of baclofen in rats by microdialysis. *Pharm Res* 1995; **12**: 1838–1844.
- Albright AL, Gilmartin R, Swift D, Krach LE, Ivanhoe CB, McLaughlin JF. Long-term intrathecal baclofen therapy for severe spasticity of cerebral origin. *J Neurosurg* 2003; **98**: 291–295.
- Penn RD. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. *J Neurosurg* 1992; **77**: 236–240.
- Koulousakis A, Kuchta J. Intrathecal antispastic drug application with implantable pumps: results of a 10 year follow-up study. *Acta Neurochir Suppl* 2007; **97**: 181–184.
- Akman MN, Loubser PG, Donovan WH, O'Neill ME, Rossi CD. Intrathecal baclofen: does tolerance occur? *Paraplegia* 1993; **31**: 516–520.
- Penn RD, Kroin JS. Long-term intrathecal baclofen infusion for treatment of spasticity. *J Neurosurg* 1987; **66**: 181–185.
- Stevens CW, Yaksh TL. Potency of infused spinal antinociceptive agents is inversely related to magnitude of tolerance after continuous infusion. *J Pharmacol Exp Ther* 1989; **250**: 1–8.
- Kroin JS, Bianchi GD, Penn RD. Intrathecal baclofen down-regulates GABAB receptors in the rat substantia gelatinosa. *J Neurosurg* 1993; **79**: 544–549.
- Nielsen JF, Hansen HJ, Sunde N, Christensen JJ. Evidence of tolerance to baclofen in treatment of severe spasticity with intrathecal baclofen. *Clin Neurol Neurosurg* 2002; **104**: 142–145.
- Coffey JR, Cahill D, Steers W, Park TS, Ordia J, Meythaler J *et al*. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. *J Neurosurg* 1993; **78**: 226–232.
- Coffey RJ, Edgar TS, Francisco GE, Graziani V, Meythaler JM, Ridgely PM *et al*. Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life-threatening syndrome. *Arch Phys Med Rehabil* 2002; **83**: 735–741.
- Meythaler JM, Steers WD, Tuel SM, Cross LL, Haworth CS. Continuous intrathecal baclofen in spinal cord spasticity. A prospective study. *Am J Phys Med Rehabil* 1992; **71**: 321–327.
- Dario A, Scamoni C, Picano M, Casagrande F, Tomei G. Pharmacological complications of the chronic baclofen infusion in the severe spinal spasticity. Personal experience and review of the literature. *J Neurosurg Sci* 2004; **48**: 177–181.
- Taylor DA, Fleming WW. Unifying perspectives of the mechanisms underlying the development of tolerance and physical dependence to opioids. *J Pharmacol Exp Ther* 2001; **297**: 11–18.
- Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. *J Neurosurg* 1996; **85**: 452–457.
- Vidal J, Gregori P, Guevara D, Portell E, Valles M. Efficacy of intrathecal morphine in the treatment of baclofen tolerance in a patient on intrathecal baclofen therapy (ITB). *Spinal Cord* 2004; **42**: 50–51.
- Zuckerbraun NS, Ferson SS, Albright AL, Vogeley E. Intrathecal baclofen withdrawal: emergent recognition and management. *Pediatr Emerg Care* 2004; **20**: 759–764.
- Leo RJ, Baer D. Delirium associated with baclofen withdrawal: a review of common presentations and management strategies. *Psychosomatics* 2005; **46**: 503–507.
- Sallerin-Caute B, Lazorthes Y, Monsarrat B, Cros J, Bastide R. CSF baclofen levels after intrathecal administration in severe spasticity. *Eur J Clin Pharmacol* 1991; **40**: 363–365.
- Soni BM, Mani RM, Oo T, Vaidyanathan S. Treatment of spasticity in a spinal cord-injured patient with intrathecal morphine due to intrathecal baclofen tolerance—a case report and review of literature. *Spinal Cord* 2003; **41**: 586–589.
- Fluckiger B, Knecht H, Grossmann S, Felleiter P. Device-related complications of long-term intrathecal drug therapy via implanted pumps. *Spinal Cord* 2008; **46**: 639–643.