Pharmacokinetics and pharmacodynamics of intrathecal baclofen therapy

Heetla, Herre Wigger

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

Link to publication in University of Groningen/UMCG research database

Summary and discussion

SUMMARY OF THE THESIS

Intrathecal baclofen (ITB) therapy has been introduced by Penn and Kroin in 1984.[1] In the last three decades, ITB-therapy has been proven effective and safe for the treatment of severe spasticity in a wide ranges of diseases.[2-4] This has led to an increasing number of patients being treated with ITB-therapy. In the last three decades, research has primarily focused on the effect and safety of ITB in various indications. However, knowledge of the basics of ITB therapy, i.e. the pharmacological aspects of ITB delivery, and the use of ITB in special patient populations, is limited. As a result, the understanding and management of clinical problems associated with long-term ITB therapy is a matter of serious concern.

The research-project described in this thesis consists of two parts. The first part focuses on ITB pharmacology, including the pharmacokinetics (PK) and pharmacodynamics (PD) of ITB in adults with severe spasticity (chapters 2-5). The second part (chapter 6 and 7) is dealing with the clinical effects of ITB, focusing on measuring the effect of ITB in ambulatory patients with spasticity.

In **chapter 2** the available literature on the PK and PD of ITB is reviewed. The chapter starts with a description of the anatomical structures involved in cerebrospinal fluid (CSF) circulation, and with a survey of CSF physiology and -dynamics. Only 3 studies reported on PK data of ITB. These studies predominantly showed concentration-time curves from a single spinal location, demonstrating considerable variability in-between patients. Some studies reported PD data of ITB in humans, however without any PK data. Combining the available literature, it looks like baclofen does not spread equally in the CSF after injection into the spinal intrathecal space. Instead, most baclofen seems to remain around the location of infusion. This causes a gradient in the baclofen concentration, with a decrease in concentration correlating with the distance from the location of injection or infusion. The presence of a concentration gradient of baclofen within the spinal intradural space has also been shown after ITB infusion in pigs.

In **chapter 3** the clinical characteristics of our patient series were analyzed. A complication rate of 1 per 10.5 years of ITB treatment was found. Drug related side-effects were mostly mild and had an annual risk to occur of 13.8%. Some of our patients required increasingly higher ITB doses, in order to achieve the same therapeutic effect, indicating tolerance to ITB. Therefore, the ITB dosing data of all patients were examined, using a definition of tolerance as a minimal dose increase of 100 μg / year to keep the same clinical efficacy, after being titrated up to a clinical effective dose. This analysis of tolerance therefore started 18 months after having started ITB infusion, because our data showed that this period was needed to reach a stable ITB dose with a mean dose of about 350ug/day. The initial dose-increase

8

during these first 18 months of ITB-therapy was considered as an optimal titration period, which has also been reported by others. However, 8 patients showed a clear increase of ITB after these 18 months (22%), meeting our criteria for tolerance. This percentage was higher in comparison with the existing literature. We also analyzed the effect of different interventions to improve tolerance in this patient group. Both a drug holiday, during which the ITB infusion is completely stopped, as well as switching from continuous to pulsatile bolus infusion, was able to improve existing tolerance and to lower the daily ITB dose, while maintaining a good clinical effect.

In **chapter 4** the effect of pulsatile bolus infusion in patients showing tolerance to ITB was evaluated. During pulsatile bolus infusion the total daily ITB dose is split into a number of bolus doses, instead of continuous delivery during the day. A total of four patients with tolerance to ITB were included. These patients were switched from continuous infusion to 6 pulsatile bolus infusions per day. During the 12 months follow-up period, the daily ITB dose stabilized in three patients and dose increases were slowed down in the fourth patient, using this pulsatile ITB regimen. This was the first study showing that pulsatile bolus infusions seems to be a useful option to treat tolerance to ITB. To explain this positive effect on tolerance, one might think of resensitization of the gamma-aminobutyric acid (GABA)-ergic receptors using pulsatile infusion, or the effect of a better spreading of ITB after bolus infusion, creating a higher peak-dose, compared with continuous infusion.

In **chapter 5** the first pharmacokinetic-pharmacodynamic (PKPD) model for ITB in humans is presented. PK and PD data were gathered in 12 patients with severe spasticity of various origin. All patients received two external intrathecal catheters. One catheter (tip located at Th10) was used to deliver various bolus doses of ITB, while the other catheter (tip located at Th12) was used to measure the baclofen concentration in the CSF (PK) at various intervals after bolus administration. The clinical endpoint (PD) consisted of the Modified Ashworth Scale (MAS), measuring severity of spasticity, at various intervals after bolus administration. Our aim was to create a PKPD model for ITB, which could be used to predict the spinal concentrations of ITB infusion at different levels of the spinal column. However, no validated human PKPD model was available for drug delivery in the intrathecal space. Therefore, a new PK model was developed for ITB infusion, based on the anatomical characteristics of the spinal intrathecal space, with an average length of 57 cm of the spinal canal, as well as some physiological parameters of the spinal intrathecal space. The PK model consists of 57 consecutive compartments, corresponding with 1 cm of the spinal intrathecal space. The new PK model was programmed in PKPD modeling software. The clinical data (MAS scores) were used as pharmacodynamic input to create the first PKPD model for bolus infusion of ITB in humans. Using this PK model we were able to predict a steep concentration gradient

along the spinal axis. Every 6 cm further away from the infusion site, the concentration of baclofen proved to drop with about one third. This supports the existence of a concentration gradient of ITB within the human spinal canal, which was shown earlier only in pigs.

The second part of this thesis focusses on the use of ITB in ambulatory patients.

In **chapter 6** a case of a 49-years-old male with hereditary spastic paraplegia (HSP) is presented, to illustrate the beneficial effects of ITB-therapy. Due to the HSP the patient had experienced a progressive decline in his functional abilities, including impaired walking. Therefore he used a wheelchair most of the day before ITB infusion. He was offered a continuous ITB test-infusion, aiming for improvement of his functional capabilities, like walking. His ambulatory functions greatly improved after ITB infusion, showing a doubled walking speed as compared to pre-ITB infusion, and he was able again to walk 200 meters without the use of assistive devices. This case-report clearly demonstrates the positive effects of ITB in HSP, but also the benefit of using a continuous test-infusion in ambulatory patients, rather than a bolus test-infusion. The continuous test-infusion provides more time and a much better opportunity to experience the effects of ITB.

In **chapter 7** the usefulness and suitability of various tests to measure the clinical effect during a continuous ITB test-infusion were evaluated. Ten patients with spastic gait were admitted for a continuous ITB test-infusion. The outcome measures were divided over 3 domains, whereas each domain included 1 qualitative and 1 quantitative test. The 3 domains were: spasticity, strength and ambulatory function. Spasticity was measured by the MAS and the Hofmann's-reflex (H-reflex). Strength was evaluated using the Medical Research Council (MRC)-rating scale and dynamometry. Ambulatory function was assessed by the Timed Up and Go (TUG) test and knee flexion measurements. Furthermore, patients rated themselves by the patient global impression of change (PGIC). This pilot study showed that only the tests measuring spasticity (MAS and H-reflex) had a good dose-effect association, while the tests for muscle strength and functional abilities did not. The MRC grading and dynamometry only showed an effect on muscle strength in those patients having a decreased strength at baseline. The TUG actually showed a different profile, whereas a better baseline TUG score seemed to offer a higher chance to improve on the TUG. Although no final conclusions can be drawn based on this pilot study it looks like that the MAS and H-reflex both are useful to quantify spasticity, with the MAS much easier to use in daily practice, and that the TUG seems to be a suitable tool to evaluate the ambulatory function of patients with spasticity.

8

DISCUSSION AND FUTURE DIRECTIONS

The aim of this thesis was twofold. The first was to get insight in the pharmacology of ITB, by collecting human PK and PD data. The second aim was to evaluate the efficacy of ITB-therapy in ambulatory patients with spasticity, focusing on how to measure the effect on various clinical domains. The question is if we have reached our goals.

Overall, this thesis has created completely new data on the PKPD relationship of ITB, providing insight in the concentration gradient of ITB along the spinal axis, which has direct implications on the practical use of ITB. Moreover, this thesis has provided us with some useful clinical data on ambulatory patients with spasticity, showing that ITB might be very effective for this group of patients. However, a few items should be discussed in more detail.

Tolerance

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.[5] The problem with this definition is that tolerance is defined purely based on clinical symptoms, which might have alternative explanations. We faced this problem in chapter 3, because we tried to delineate optimal dosing from tolerance. All patients showed an increase of the dose during the first 1.5 years of ITB treatment, apparently belonging to the normal optimization of the ITB dose. But nobody is able to rule out tolerance as a possible explanation for the dose increase during this initial period of ITB infusion, because no data are available about pharmacodynamic processes like GABA-ergic receptor desensitization and / or a reduction in the total number of GABA-ergic receptors, during this period.[6] This GABA-ergic receptor desensitization would have been supported by changes in the levels of secondary messengers or via a reduction of neuronal firing rates at the same spinal concentration of ITB in these patients.[7] However, these data have not been collected and are difficult to collect in our patient group. Moreover, also changes in pharmacokinetic parameters could be an explanation for tolerance, like changes in the activity of metabolic enzymes, like the cytochrome oxidases, or changes in the absorption from the spinal CSF into the myelum. Unfortunately, no data are available in our study to rule out an influence of these factors on the clinical observations in our patients. Furthermore, also progression of the underlying disease may mimic tolerance, which further complicates the diagnosis of tolerance.

So, we tried to overcome this lack of basic pathophysiological data on tolerance by using a clinical definition: "an unexplained dose increase of more than 100 μg / year, after at least 18 months of ITB therapy". This was a very practical definition, based on long-term observations in our patients, at least showing unexplained dose-increases in some patients versus the others. Using this definition, the incidence of tolerance in our population was 21%, which

is relatively high if compared to the incidence in the literature (1-20%).[3, 8-10] No clinical risk factors were identified, correlating with tolerance, but as said before, no pathophysiological data were included in this analysis.

In conclusion, many uncertainties remain around the phenomenon of tolerance in ITB. Partially, because tolerance is a diagnosis by exclusion of other known causes (e.g. pump- or catheter problems, and anatomical anomalies). This may result in a rest-group, polluted by non-tolerant patients with an incomplete or sloppy work-up. Future work should include also pathophysiological parameters to delineate real tolerance phenomena from other causes of unexplained dose-increases.

Management of tolerance in ITB

The possible treatment of tolerance is discussed in chapter 4. The proposed therapy of pulsatile ITB infusion was mainly focused on the mechanism of receptor desensitization. The pilot data shown in this chapter are really encouraging, because the infusion of 6 boluses per day stopped the dose-increase, and in some patients even reduced the daily dose. The fluctuations in baclofen concentrations due to bolus infusions might have caused resensitization of baclofen receptors in between boluses, because the interval of 4 hours in between boluses corresponds with about 0.8 – 4 elimination half-lives of ITB (1 – 5 hours in CSF).[27] This interval will result in a significant reduction of the CSF levels of ITB with at least 50% during each cycle, but without complete elimination of ITB.

Using a pulsatile schedule with larger intervals theoretically should improve the resensitization of GABA-receptors. However, the ITB concentration should not drop below the minimal effective CSF concentration, with the risk of losing clinical effect. Therefore, the optimal number of boluses remains to be established, and might be different in between patients.

An alternative explanation for the improved efficacy at lower doses of ITB, not related to tolerance, may be the better spreading of ITB, causing higher peak-concentrations of ITB in the CSF after bolus infusion.[11]

An interesting question is if pulsatile infusion of ITB is able to prevent patients from becoming tolerant to baclofen? This thesis cannot answer this question, which needs a prospective trial comparing different infusion regimens on the long term.

8

Dosing of ITB

Our data show a long period of about 18 months to reach a stable infusion regimen in the majority of patients. Why should this period be so long? It may indicate that the starting dose of ITB therapy is too conservative, caused by a fear for side effects and ignorance of the full potential of ITB therapy.

On the other hand follow-up intervals are mostly related to refilling of the pump, generally after several months. So, to titrate patients quickly to an adequate dose the initial follow-up intervals should be much shorter, f.i. weeks instead of months. Less conservative dosing might lead to an earlier optimal effect of ITB, whereas also the possibility of starting patients on pulsatile bolus infusions might improve the overall long-duration efficacy of ITB.

PKPD data and catheter tip placement

The PKPD model as described in this thesis can be used to predict the spreading of an ITB bolus after injection into the CSF. The model predicts a strong spinal concentration gradient of baclofen along the spinal axis, whereas most baclofen seems to remain around the catheter tip after injection. The concentration of baclofen is reduced by a third, every six centimeters further apart from the catheter tip. These findings have important clinical consequences.

Twenty years ago, it was already shown that the baclofen concentration in the lumbar CSF, after lumbar infusion, was 4.1 times higher as compared to the baclofen concentration in the CSF at the level of the cisterna magna.[12] The existence of a spinal gradient after ITB infusion has been replicated in pigs as well.[11] However, no data have been published so far on the spinal gradient of ITB in humans, probably due to the difficulties related to repetitive CSF sampling.

The spinal gradient predicted by our model explains why ITB does provide a much better spasmolysis compared to oral baclofen, with minimal CNS (central nervous system) side effects. The high spinal gradient of ITB means that the efficacy of ITB is directly related to the level of infusion, without any significant spreading of ITB.

So, the placement of the catheter tip is very important. The tip should be placed as close as possible to the targeted spinal segments. To treat spasticity of the lower extremities, ITB should be administered at the level of Th10, near the lumbar enlargement (Th8 – Th12) of the spinal cord, which contains the spinal segments of the lower extremities. However, to treat spasticity of the upper extremities, ITB should be infused ideally at the cervical spinal segments (C5 – Th1). The question is if patients with spasticity of upper and lower extremities can be treated with ITB infusion at one spinal level. A few studies have addressed this issue

and found that positioning of the catheter tip at a cervical (C5 – C7) or thoracic (Th6) level can be effective for all extremities, also in children.[13, 14] Future studies should compare both strategies, looking at practical consequences and differences in dosing, efficacy and safety.

Intraventricular Baclofen

The last few years, intraventricular baclofen (IVB) infusion has been proposed as an alternative for ITB infusion.[15, 16] IVB infusion was first used in patients suffering from dystonia, because baclofen is thought to achieve its effect on dystonia by acting on the (pre)motor cortex.[17] Baclofen being infused into the 3rd ventricle, diffuses through the aqueduct and is thought to cause a higher concentration at the cerebral convexities as compared to spinal infusion.[16]

IVB is interesting, because one would expect that high cerebral concentrations of baclofen are associated with CNS side-effects. However, IVB has shown to be safe and successful in treating dystonia as well as spasticity, although dose-dependent lethargy was reported, which disappeared after dose reduction.[16] No other adverse events like seizures or coma were reported.[16]

It is interesting that patients with dystonia seem to require lower doses of IVB as compared to patients with spasticity (300 vs 550 µg/day), while in ITB therapy this is the other way around.[15, 16, 18] This might be explained by the fact that the target location for ITB is the spinal cord, which is at distance from the intraventricular infusion site.

Further research should analyze the possible role of IVB in spasticity. Probably IVB is more suitable to treat patients with dystonia, who need adequate cerebral concentrations of baclofen.

Pros and cons of the human PKPD model

Our PKPD model for ITB in humans is based on only 12 patients with ITB bolus infusion. Future research should try to validate our findings in much bigger cohorts.

The most important weakness of our model is that just one sampling location, apart from the infusion location, was used to build the model. So, the predicted CSF concentrations at the different spinal levels are extrapolations of the findings at this single sampling site. The use of multiple sample locations would greatly increase the model's validity, although this will be very difficult to realize in humans. As an alternative radiolabeled baclofen could be an option to study the PK and PD of ITB, which would bypass the practical difficulties of multiple CSF sampling sites.

8

Furthermore, our PK data showed a large inter-patient heterogeneity, also reported previously.[19] This heterogeneity might be explained by variables such as the underlying disease or anatomical characteristics. For instance, patients with spinal cord injury may develop anatomical changes, such as syringes, which might have a large impact on the CSF flow and spreading of ITB.

Another limitation of our PKPD model is that the model can only be used to predict bolus infusions of ITB. Sampling data gathered from patients receiving continuous ITB therapy are needed to predict the baclofen concentration gradient after continuous infusion. However, it is expected that during continuous infusion, even more baclofen will be found around the infusion site, due to the very low infusion rates of continuous infusion. If a patient is prescribed f.i. 300 μg ITB per day, with a concentration of the ITB solution of 1500 μg/ml, this means that overall just 0.2 ml ITB per day is released at the infusion site. A previous study in pigs confirmed that bolus infusions resulted in a better spreading of ITB as compared to continuous infusions.[11]

Finally, the clinical effect on spasticity was assessed using the MAS, which is used all over the world. However, recently its validity and reliability for measuring spasticity have been criticized, as the MAS measures resistance to passive movement, which is also influenced by non-neural mechanical factors such as contractures, and because the MAS was unable to detect slight changes.[20, 21] More sophisticated neurophysiological tests, provide more objective measurements, but are also much more complicated to perform. Furthermore, the changes in spasticity after ITB are quite significant, which means that the MAS can be considered as the preferred clinical scale to monitor spasticity, as confirmed by our study described in chapter 7.

ITB in ambulatory patients

Studies on the effect of ITB on ambulatory function show mixed results. Some studies reported functional improvement with ITB-therapy due to a reduction in spasticity.[22, 23] Other studies reported a functional deterioration, caused by a reduction in spasticity, probably related to pre-existing extensor hypertonia, supporting transfers, standing and even walking.[24] The question is how to use ITB optimally in ambulatory patients with spasticity.

First of all, ambulatory patients with spasticity should be offered a continuous test-infusion instead of a bolus test-infusion. A continuous ITB test infusion, as described in chapter 6 and 7, provides the opportunity to titrate gradually, being able to balance pros and cons at

steady state concentrations of ITB. Another benefit of continuous infusion for the patient is the extra time to experience the effects of ITB on spasticity, strength and functional abilities.[23]

Secondly, the timing of ITB therapy in the course of spasticity should be improved. Currently ITB is considered only if other treatments (e.g. oral baclofen, botox) have been tried for years, irrespective the size of effect. Most patients suffering from progressive UMN damage (i.e. HSP, MS) are only referred for ITB, if the ambulatory function is (almost) lost. Earlier intervention with ITB-therapy may prevent the negative effects of chronic spasticity, such as contractures. Moreover, patients with better baseline walking capabilities seem to respond better to ITB therapy.[25]

Another problem is how to select proper patients for ITB infusion. So far no reliable selection criteria have been found.[26] Our pilot study described in chapter 7 unfortunately was too small to produce reliable selection criteria. However, the analysis of the data gave us some new insights. In daily practice ambulatory patients with a marginal strength of their quadriceps generally are not advised to start with ITB. Actually, most patients in our study did not show worsening of their muscle strength during ITB infusion, except from 2 patients with a low strength at baseline. The TUG also showed that patients with a good baseline score performed better after ITB, compared to patients with a low baseline score. This suggests that ITB infusion should not be postponed too long, which needs confirmation in larger prospective trials.

Finally, it should be stressed that adequate spasmolysis by ITB may not only improve ambulatory function, but may also cause more relaxed limbs, less discomfort, less pain and a decreased risk of long-term adverse effects due to spasticity. This is supported by the results from the patient's global impression of change (PGIC) after ITB (chapter 7). These data show that patients may rate their overall condition as improved, even when their functional abilities have worsened.

In conclusion, ITB should be offered to patients with spasticity in a timely fashion, not only focusing on motor function, but also on non-motor domains.

8

REFERENCES

1. Penn RD, Kroin JS. Intrathecal baclofen alleviates spinal cord spasticity. Lancet. 1984 May 12;1(8385):1078.

2. Middel B, Kuipers-Upmeijer H, Bouma J, Staal M, Oenema D, Postma T, et al. Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. J Neurol Neurosurg Psychiatry. 1997 Aug;63(2):204-9.

3. 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 Feb;78(2):226-32.

4. Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke B, et al. Intrathecal baclofen for severe spinal spasticity. N Engl J Med. 1989 Jun 8;320(23):1517-21.

5. 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 Jul;250(1):1-8.

6. Wetherington JP, Lambert NA. GABA(B) receptor activation desensitizes postsynaptic GABA(B) and A(1) adenosine responses in rat hippocampal neurones. J Physiol. 2002 Oct 15;544(Pt 2):459-67.

7. Kanaide M, Uezono Y, Matsumoto M, Hojo M, Ando Y, Sudo Y, et al. Desensitization of GABA(B) receptor signaling by formation of protein complexes of GABA(B2) subunit with GRK4 or GRK5. J Cell Physiol. 2007 Jan;210(1):237-45.

8. 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 Dec;48(4):177-81.

9. Akman MN, Loubser PG, Donovan WH, O'Neill ME, Rossi CD. Intrathecal baclofen: Does tolerance occur? Paraplegia. 1993 Aug;31(8):516-20.

10. Koulousakis A, Kuchta J. Intrathecal antispastic drug application with implantable pumps: Results of a 10 year follow-up study. Acta Neurochir Suppl. 2007;97(Pt 1):181-4.

11. Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusion in pigs. Anesthesiology. 2006 Jul;105(1):169-78.

12. Kroin JS, Penn RD. Cerebrospinal fluid pharmacokinetics of lumbar intrathecal baclofen. In: Lakke JPWF, Delhaas EM, Rutgers AWF, editors. Parenteral drug therapy in spasticity and Parkinson's disease. Casterton Hall, Carnforth: The Parthenon Publishing Group Limited; 1992. p. 67-78.

13. Grabb PA, Guin-Renfroe S, Meythaler JM. Midthoracic catheter tip placement for intrathecal baclofen administration in children with quadriparetic spasticity. Neurosurgery. 1999 Oct;45(4):833,6; discussion 836-7.

14. McCall TD, MacDonald JD. Cervical catheter tip placement for intrathecal baclofen administration. Neurosurgery. 2006 Sep;59(3):634,40; discussion 634-40.

15. Turner M, Nguyen HS, Cohen-Gadol AA. Intraventricular baclofen as an alternative to intrathecal baclofen for intractable spasticity or dystonia: Outcomes and technical considerations. J Neurosurg Pediatr. 2012 Oct;10(4):315-9.

16. Albright AL, Ferson SS. Intraventricular baclofen for dystonia: Techniques and outcomes. clinical article. J Neurosurg Pediatr. 2009 Jan;3(1):11-4.

17. Siebner HR, Dressnandt J, Auer C, Conrad B. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve. 1998 Sep;21(9):1209-12.

18. Albright AL, Barry MJ, Shafton DH, Ferson SS. Intrathecal baclofen for generalized dystonia. Dev Med Child Neurol. 2001 Oct;43(10):652-7.

19. Albright AL, Shultz BL. Plasma baclofen levels in children receiving continuous intrathecal baclofen infusion. J Child Neurol. 1999 Jun;14(6):408-9.

20. Fleuren JF, Voerman GE, Erren-Wolters CV, Snoek GJ, Rietman JS, Hermens HJ, et al. Stop using the ashworth scale for the assessment of spasticity. J Neurol Neurosurg Psychiatry. 2010 Jan;81(1):46-52.

21. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the ashworth and modified ashworth scales as measures of spasticity. Clin Rehabil. 1999 Oct;13(5):373-83.

22. Francisco GE, Boake C. Improvement in walking speed in poststroke spastic hemiplegia after intrathecal baclofen therapy: A preliminary study. Arch Phys Med Rehabil. 2003 Aug;84(8):1194-9.

23. Phillips MM, Miljkovic N, Ramos-Lamboy M, Moossy JJ, Horton J, Buhari AM, et al. Clinical experience with continuous intrathecal baclofen trials prior to pump implantation. PM R. 2015 Oct;7(10):1052-8.

24. Kofler M, Quirbach E, Schauer R, Singer M, Saltuari L. Limitations of intrathecal baclofen for spastic hemiparesis following stroke. Neurorehabil Neural Repair. 2009 Jan;23(1):26-31.

25. Horn TS, Yablon SA, Stokic DS. Effect of intrathecal baclofen bolus injection on temporospatial gait characteristics in patients with acquired brain injury. Arch Phys Med Rehabil. 2005 Jun;86(6):1127-33.

26. Klebe S, Stolze H, Kopper F, Lorenz D, Wenzelburger R, Deuschl G, et al. Objective assessment of gait after intrathecal baclofen in hereditary spastic paraplegia. J Neurol. 2005 Aug;252(8):991-3.

27. 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: 363–5.

8