Clinical relevance of pharmacological and physiological data in intrathecal baclofen therapy

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ABSTRACT

Objective: To review all pharmacological and physiological data available on intrathecal baclofen (ITB) therapy and to evaluate its use in clinical practice and future research.

Data Sources: PubMed was searched for relevant anatomic, physiological, and pharmacological data available on ITB.

Study Selection: All currently available data on ITB pharmacokinetics (PKs) and pharmacodynamics (PDs) in both human and animal studies were reviewed and combined with the anatomy and physiology of the intrathecal space and cerebrospinal fluid flow.

Data Extraction: Only 4 studies reported PK data on ITB in humans. More studies reported PD data on ITB; however, none were combined with PK data. More detailed data on PK could be gathered from studies using an animal model.

Data Synthesis: ITB does not spread equally over the intrathecal space after injection, but it diffuses according to a concentration gradient. ITB distribution can be influenced by the location of the catheter tip and by changing the infusion mode.

Conclusions: The pharmacological and physiological data on ITB can be used to support decisions in clinical practice concerning drug concentration, infusion regimens, localization of the catheter tip, and management of tolerance; however, some strategies have little evidence in humans.
INTRODUCTION

Baclofen is widely used for the treatment of spasticity. It is a muscle relaxant with its primary site of action in the spinal cord, acting as an agonist of the inhibitory gamma aminobutyric acid, type B (GABA-B) receptor. The uptake of baclofen across the blood-brain barrier is limited. Therefore, high oral doses are needed to achieve a therapeutic effect, often causing central nervous system side effects (e.g. drowsiness, sleepiness). In 1984, Penn and Kroin bypassed the blood-brain barrier in 2 patients by infusing baclofen directly into the cerebrospinal fluid (CSF) using a subcutaneously located programmable pump connected to an intrathecal lumbar drain. Intrathecal baclofen (ITB) therapy needs much lower doses (range 50 – 1000 µg/d) than oral administration (range 25 – 100 mg/d), resulting in fewer side effects. The long-term effects and safety of ITB therapy have been proven extensively in the last 2 decades. However, the pharmacologic basics of ITB therapy have not been studied extensively.

METHODS

To evaluate its use in clinical practice, PubMed was used to review all currently available pharmacokinetic (PK) and pharmacodynamic (PD) data on ITB in both human and animal studies and the physiological basics of CSF flow and intrathecal anatomy. Only 4 studies reported PK data on ITB in humans. More studies reported PD data on ITB; however, none were combined with PK data. More detailed data on PKs could be gathered from studies using an animal model. The clinical implications of these data were evaluated, especially its use to support decisions in daily practice related to drug concentration, infusion regimens, localization of the catheter tip, and treatment of tolerance.

RESULTS

Anatomy of the spinal canal and CSF flow

The spinal cord extends from the medulla oblongata to the level of the first lumbar vertebra. The human spinal cord is approximately 38±3 cm long, has a volume of 20±3 mL in adults, and is surrounded by the pia mater. The spinal canal is the compartment between the arachnoid and pia mater. The spinal canal is approximately 58±3 cm long, and it is filled with CSF surrounding the brain and spinal cord. Most of the CSF is produced by the choroid plexuses within the ventricles at a rate of about 0.35 mL/min, which makes it possible to
replace the entire CSF volume (±150 mL) 3 times a day.\textsuperscript{7,8} The spinal CSF volume is 81±13 mL, and is divided over the cervical (19±4 mL), thoracic (37±8 mL), and lumbosacral (25±7 mL) spinal canal.\textsuperscript{6}

The CSF moves from the lateral ventricles, through the third and fourth ventricle, and into the subarachnoid space around the brain and spinal cord. The CSF does not move in a 1-directional manner (e.g. blood) but is moved in a pulsatile pattern, synchronous with the contractions of the heart. During each systole, blood is pumped into the cerebral arteries causing an increase of the intracranial volume. Because both blood and brain are less compressible, some CSF will be forced in a caudal direction into the spinal canal, which is expandable because it is not constricted by the skull. During the diastole, the CSF flow reverses in a rostral way. In a recent human physiological model, it has been calculated that because of this process only 0.5 to 2 mL of CSF is displaced with every heartbeat.\textsuperscript{9} At the spinal level, pulsations from the spinal arteries contribute to these pulsatile waves as well.\textsuperscript{10}Because the driving force of these pulsatile movements starts in the skull, its effect decreases caudally, resulting in a limited CSF flow at the lumbar/low thoracic level. When injected at this level, most of the drug remains around the injection site, creating a higher drug concentration gradient along the spinal cord than the high thoracic level injections.\textsuperscript{11} This concentration gradient is important to understand the variation in clinical effect of ITB.

CSF absorption takes place by a 1-way flow through the arachnoid villi in the dura of the superior sagittal sinus. However, animal data suggest that CSF absorption also takes place at the spinal level because arachnoid villi have been found along the nerve roots in the spinal cord in various animals, where they account for up to 25% to 50% of the total clearance from the intrathecal space.\textsuperscript{12,13}

Drug distribution depends not only on CSF flow but also on baricity. Baricity refers to the density of a fluid (i.e. baclofen) compared with the density of another fluid (e.g. human CSF). The density of baclofen ranges from 0.99836 mg/mL (1000 µg/mL) to 0.99971 mg/mL (2000 µg/mL), which is lower than the CSF density (1.00049 - 1.0007 mg/mL).\textsuperscript{14} Therefore, baclofen behaves like a hypobaric compound causing distribution against gravity.

**Pharmacology of ITB**

The pathophysiology of spasticity and dystonia is complex and caused by alterations to various spinal mechanisms. One of these is the loss of inhibitory mechanisms, which can cause a hyperexcitability of the stretch reflex because of increased sensory neuron and motoneuron excitability.\textsuperscript{15}
Baclofen is a potent GABA-B agonist and binds to the inhibitory GABA-B receptor. During ITB therapy, baclofen is infused directly into the CSF where it binds to GABA-B receptors in the dorsal root ganglion and spinal gray matter, especially in lamina I and II of the dorsal horn of the spinal cord. It is believed that baclofen achieves its antispastic effect by presynaptic inhibition and postsynaptic hyperpolarization of the dorsal horn neurons, which causes an inhibition of neurotransmitter release and a reduction in motoneuron excitability, leading to a reduction of the stretch reflex in patients with spasticity. Baclofen exists as a racemic mixture, but the therapeutic effect is mostly attributed to the L-enantiomer. There are no major differences in PKs between both enantiomers.

**PK data**

All PK data on ITB in humans are derived from 4 studies. The reported PK parameters have been summarized in table 1. All studies used different doses of ITB and sampled CSF at varying distances from the infusion location causing a large variability of the reported PK data. The most important conclusions with respect to the PK data in table 1 are as follows: 1) The intrathecal half-life of ITB ranges from 1 to 5 hours, roughly the same as the plasma half-life of baclofen (3 – 4 h); 2) CSF clearance is thought to take place by bulk flow of the CSF and its constituents through the arachnoid villi. As in animal models, spinal clearance (6.6 – 13.8 mL/h) accounts for up to 25% to 50% of the total CSF clearance (22 mL/h). However, the reported baclofen clearance rates (29.9 – 41 mL/h) are higher, suggesting an additional clearance route. It might be possible that some baclofen is cleared from the spinal tissue via the blood and/or lymphatic system; 3) The distribution volume (the apparent volume of the theoretical compartment in which baclofen is dissolved) is higher than the spinal CSF volume, indicating distribution into spinal tissue as well, which seems logical because its receptors are located within the myelum. Baclofen is a slightly hydrophilic compound (partition coefficient octanol/water 0.1); therefore, it has difficulties passing the lipophilic membranes of the cells aligning the spinal canal. Therefore, most baclofen will remain in the CSF. The total spinal CSF volume is 81 mL, from which 62 mL is found at the thoracic and lumbosacral levels, where baclofen is mostly injected. Two studies reported the distribution volume of ITB as ranging from 85 to 119 mL (see table 1).
Figure 1. ITB concentration time curves from 3 ITB PK studies: (A and C) ITB concentration at the infusion location after different boluses of ITB; (B) ITB concentration 0 to 4 vertebral levels below the infusion location of 4 different boluses in 4 different patients. Data from Muller, Sallerin-Caute, and Kroin.20-22
Table 1. Summary of intrathecal baclofen pharmacokinetic studies in humans

<table>
<thead>
<tr>
<th>Study</th>
<th>Infusion (mode)</th>
<th>N</th>
<th>Dose (μg)</th>
<th>V_d (ml)</th>
<th>CL (ml/h)</th>
<th>T½ (min)</th>
<th>C_SS (ng/ml)</th>
<th>Delivery (spinal level)</th>
<th>Sampling (spinal level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>continuous</td>
<td>8</td>
<td>50 – 1200 / 24h.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>130 - 950</td>
<td>Pump*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>bolus</td>
<td>3</td>
<td>200 – 600</td>
<td>NA</td>
<td>NA</td>
<td>270†</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sallerin-Caute et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>bolus</td>
<td>4</td>
<td>75 – 140</td>
<td>119</td>
<td>36</td>
<td>54-300</td>
<td>NA</td>
<td>T6 – T11</td>
<td>T10 – L3</td>
</tr>
<tr>
<td>Kroin et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>bolus</td>
<td>2</td>
<td>50</td>
<td>85</td>
<td>35</td>
<td>101</td>
<td>NA</td>
<td>T12 – L2</td>
<td>T12 – L2</td>
</tr>
<tr>
<td></td>
<td>bolus</td>
<td>5</td>
<td>100</td>
<td>86</td>
<td>41</td>
<td>82</td>
<td>NA</td>
<td>T12 – L2</td>
<td>T12 – L2</td>
</tr>
<tr>
<td></td>
<td>continuous</td>
<td>10</td>
<td>96 – 600 / 24h.</td>
<td>NA</td>
<td>29.9</td>
<td>NA</td>
<td>76 – 1240</td>
<td>pump*</td>
<td>side-port*</td>
</tr>
<tr>
<td>Albright et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>continuous</td>
<td>43</td>
<td>70 – 1395 / 24h.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>200 – 20,000</td>
<td>pump*</td>
<td>side-port*</td>
</tr>
</tbody>
</table>

Abbreviations: CL, clearance; C_max, maximum concentration; C_SS, lumbar steady-state concentration; NA, not applicable; Tmax, time of maximum concentration; T½, half-life; V_d, volume of distribution.

* Delivery and sampling happened using the pump, whereas the catheter tip level is unknown.
† Calculated from the graph.
Only 3 studies have reported detailed time-concentration data after bolus infusion of ITB (figure 1).\textsuperscript{20-22} Two of these studies (see figure 1A and C) used the same catheter for both infusion and sampling, which may have caused error in the sample data. These time-concentration curves represent the disappearance of ITB as measured at the catheter tip, which explains why the upswing of the curves is missing. The peak concentration of baclofen (1.5 – 107 µg/mL) shows a large variation.\textsuperscript{20,21} None of the studies attempted to fit their data in a PK model. However, the biphasic elimination of most curves (fast concentration drop in the beginning, slower drop at the end) suggests that a multicomartment model could be helpful to describe the time-concentration profiles of baclofen.

**Concentration gradient of ITB**

The pulsatile flow of CSF causes a concentration gradient of all its constituents along the spinal canal. Unfortunately, very little data on this concentration gradient of ITB are published. The only human data show a mean lumbar to cisternal drug ratio of 4.1:1 (range, 2 – 8.7) after 48 hours of continuous ITB infusion.\textsuperscript{22} These data suggest a decrease in baclofen concentration of 50% to 89% along the total spinal canal (58±3 cm), which is a decrease in ITB concentration of about 0.9% to 1.5% per centimeter. Detailed examination of the spinal ITB concentration gradient has only been performed in a pig model.\textsuperscript{11} The spinal canal of the pig is comparable with the human spinal canal with regard to the anatomy and dimensions and CSF formation rate. If a pig is placed in an upright position, the results from this animal model can possibly be comparable with the ITB distribution in humans. Figure 2 shows the ITB concentration gradients along the pig spinal canal after 8 hours of infusion at 3 different ITB regimens: a 40 µg/h and 2000 µg/h continuous infusion regimen and a 2000 µg/h bolus infusion regimen.\textsuperscript{11} During both continuous infusion regimens, most baclofen remains around the catheter tip in pigs, especially in the 40 µg/h group, which is most similar to the infusion delivery rate in humans (4 – 20µg/h). In this group, no baclofen could be measured at 5 cm above the catheter tip. Comparing the two 2000 µg/h infusion regimens, the bolus infusion demonstrated an increased distribution compared with a continuous infusion. After bolus infusion, baclofen was detected in 52% of the CSF samples at a distance of 10 cm from the tip, whereas this was the case in only 14% of the samples after continuous infusion at 10 cm from the tip. Peak concentrations were also higher at 5- and 10-cm distance from the catheter tip during bolus infusions (see figure 2).
Figure 2. Comparison of rostral CSF peak concentrations after 3 different ITB infusion regimens in pigs. The concentration at the injection location is set at 100%.

**PD data**

Several methods are described to monitor the PDs of ITB. The most widely used method to assess spasticity is the Modified Ashworth Scale (MAS). It grades muscle tone on a scale from 0 to 5 and has been proven to be a good indicator of effectiveness of ITB. However, recently, the MAS has been criticized for its reliability and validity in measuring spasticity because it is unable to detect slight changes in spasticity. Other clinical tests, such as the Penn Spasm Frequency Scale (measures the number of spontaneous spasms) and Reflex Scale (measures reflex intensity), are less often used and suffer from the same disadvantages as the MAS. More advanced neurophysiological tests (e.g. H-reflex and fiberglass casts) to measure spasticity are used only in research methodologies because of their complexity.

Table 2 summarizes the human PD data of ITB. All data were assessed after lumbar bolus injections and showed the latency of effect to be between 30 and 120 minutes. The maximal clinical effect of an ITB bolus demonstrated great variability, averaging between 4 and 6 hours. The duration of the effect varied from 6 to 8 hours after single boluses delivered in the lumbar area. During continuous ITB therapy, the baclofen is infused at a much slower rate, resulting in a longer latency of onset (6 – 8h) and a later maximum effect (12 – 24h).
Table 2. Summary of intrathecal baclofen pharmacodynamic studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cause</th>
<th>Delivery (mode)</th>
<th>N</th>
<th>Dose (μg)</th>
<th>Measurement</th>
<th>Latency of onset (hours)</th>
<th>Maximum Effect (hours)</th>
<th>Duration of effect (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn et al(^2)</td>
<td>SCI</td>
<td>bolus</td>
<td>2</td>
<td>5 – 50</td>
<td>MAS</td>
<td>&lt;1</td>
<td>1 – 7</td>
<td>6 – 8</td>
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<tr>
<td>Muller et al(^3)</td>
<td>various</td>
<td>bolus</td>
<td>30</td>
<td>50 – 500</td>
<td>SFS / MAS</td>
<td>1</td>
<td>1 – 12</td>
<td>8 – 48</td>
</tr>
<tr>
<td></td>
<td>continuous</td>
<td>25</td>
<td>Various</td>
<td>SFS / MAS</td>
<td>6 – 8</td>
<td>12 – 24</td>
<td>NA</td>
<td></td>
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<tr>
<td>Zierski et al(^2)</td>
<td>various</td>
<td>bolus</td>
<td>44</td>
<td>10 – 300</td>
<td>SFS / MAS</td>
<td>1 – 2</td>
<td>NA</td>
<td>4 – 24</td>
</tr>
<tr>
<td>Albright et al(^4)</td>
<td>CP</td>
<td>bolus</td>
<td>23</td>
<td>25 – 100</td>
<td>MAS</td>
<td>&lt;2</td>
<td>4</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>various</td>
<td>bolus</td>
<td>6</td>
<td>25</td>
<td>MAS</td>
<td>&lt;2</td>
<td>4</td>
<td>&gt;8</td>
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<td></td>
<td></td>
<td></td>
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<td>50</td>
<td>MAS</td>
<td>&lt;2</td>
<td>8</td>
<td>&gt;8</td>
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<td></td>
<td></td>
<td></td>
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<td>100</td>
<td>MAS</td>
<td>&lt;2</td>
<td>4</td>
<td>&gt;8</td>
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<tr>
<td>Sallerin-Caute et al(^3)</td>
<td>various</td>
<td>bolus</td>
<td>4</td>
<td>75 – 136</td>
<td>MAS</td>
<td>1</td>
<td>NA</td>
<td>9 – 16</td>
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<tr>
<td>Meythaler et al(^4)</td>
<td>traumatic brain injury</td>
<td>bolus</td>
<td>11</td>
<td>50</td>
<td>MAS</td>
<td>&lt;1</td>
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<td>6</td>
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<tr>
<td>Meythaler et al(^3)</td>
<td>stroke</td>
<td>bolus</td>
<td>22</td>
<td>50</td>
<td>MAS</td>
<td>&lt;1</td>
<td>6</td>
<td>&gt;6</td>
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<td></td>
<td></td>
<td></td>
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<td>4</td>
<td>&gt;6</td>
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<td></td>
<td></td>
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<tr>
<td>Scheinberg et al(^3)</td>
<td>CP</td>
<td>bolus</td>
<td>1</td>
<td>50</td>
<td>MAS</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<td></td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pohl et al(^3)</td>
<td>CP</td>
<td>bolus</td>
<td>13</td>
<td>100</td>
<td>Fibreglass cast / MAS</td>
<td>0.5 – 1</td>
<td>3.5 – 4.5</td>
<td>2 – 8.5</td>
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Abbreviations: CP, cerebral palsy; MAS, Modified Ashworth Scale; NA, not applicable; RS, Reflex Scale; SCI, spinal cord injury; SFS, Penn Spasm Frequency Scale; TBI, traumatic brain injury
PK-PD modeling
An interesting approach to predict the clinical effect after ITB infusion is PKPD modeling. PKPD models connect drug concentrations to a particular clinical effect. A well-designed model is able to predict the time-effect profile after drug administration. However, because of the lack of adequate PKPD data on ITB, these models are not yet available.

DISCUSSION

Location of the catheter tip
An important clinical issue is the location of the catheter tip because it determines the center of the concentration gradient. The pig model demonstrated that continuous infusion at a low speed (40 µg/h) will spread no baclofen beyond a 5-cm distance of the catheter tip. Irrespective of this concentration gradient, it is clear that the highest concentration of ITB is found around the tip. Therefore, the tip of the catheter should ideally be located as close as possible to the targeted spinal cord level. Theoretically, it should be placed near the lumbar enlargement (Th11 – L1) for spasticity in the lower extremities and around the cervical enlargement (C3 – Th2) for spasticity in the upper extremities. There has been discussion about the optimal catheter tip location in patients who experience both upper- and lower-extremity spasticity. One study reported that increasing baclofen dosages infused from a lower position of the catheter tip (Th10) to provide an effect on spastic upper extremities, resulted in hypotonia of the lower extremities.

Another option is to place the catheter tip at a midthoracic (Th6) level, which effectively decreased the upper-extremity spasticity without loss of effect on the lower extremities in patients with spasticity of both cerebral and spinal origin. Only 1 study directly compared midthoracic (Th6 – 7) with lowthoracic (Th12) localization of the catheter tip placement and found a greater relief of spasticity of the upper extremities in patients with a midthoracic catheter tip without a loss of effect on the lower extremities. Midthoracic-infused baclofen seems to achieve its effects on the lower extremities by reaching a sufficient concentration at the lower spinal levels. The alternative explanation might be a local inhibiting effect on the GABA-B receptors on the descending pyramidal axons. The concentration gradient of ITB is influenced by the pulsatile CSF movements, which are stronger at the rostral/midthoracic area than the caudal area of the spinal canal. Baclofen injected at a rostral level may therefore show an increased distribution compared with an injection at the lumbar level, possibly explaining the sufficient lumbar concentrations after midthoracic ITB infusion. Theoretically, this may also increase cerebral baclofen concentrations and associated side effects after midthoracic and lower cervical infusion of ITB; however, this has not been reported so far.
It would be an interesting option to infuse baclofen at both the cervical and caudal enlargement using 2 catheters or a double lumen catheter; however, this is not possible with the currently available catheters.

Considering the importance of the catheter tip location on the effect of ITB, migration of the catheter tip should be ruled out in a patient demonstrating a sudden drop in clinical effect. Another concern is the formation of catheter tip granulomas in patients receiving chronic intrathecal infusions, especially opioids. This occurs less frequently in patients who receive baclofen; however, a few cases have been reported in the literature. Because the formation of a mass around the catheter tip can alter the local CSF flow and drug distribution, this complication should also be considered if there is a sudden drop of response to ITB therapy. Furthermore, there have been no studies on the potential influence of other anatomic variations (e.g., those because of postinfectious, posttraumatic, or postsurgery changes) that could affect the flow and concentration gradient of baclofen in the spinal canal.

Recently, intraventricular baclofen (IVB) infusion has been suggested as an alternative delivery route. In small case series, IVB appears to be as effective and to have similar complications as ITB. It has been suggested that baclofen can increase GABA-B-mediated inhibition at the premotor and supplementary motor cortex in patients with dystonia. IVB might also play a role in the treatment of patients who suffered from multiple revisions. However, caution is needed because high cerebral concentrations of ITB might be associated with increased side effects. Furthermore, obstruction of CSF flow might induce regional toxic effects of ITB. Therefore, the role of IVB needs to be clarified in larger prospective studies, especially because long term effects and safety are unknown.

**Infusion mode**

Altering the mode of infusion is perhaps the most important tool for clinicians to influence the distribution of ITB in spinal CSF. Most implantable ITB pumps offer the following three infusion modes.

**Continuous infusion**

The baclofen is infused at a constant speed. This is the initial infusion mode in most ITB patients. It takes about 5 times the half-life for a drug’s concentration to reach a steady state after infusion is started, which is approximately 24 hours for baclofen. Evaluation of dose changes should take place after steady-state concentrations have been reached. Although the steady-state concentration shows a positive correlation with daily ITB dose (figure 3), the strength of the correlation varies considerably between studies. One study in
children was not able to demonstrate a correlation between the steady-state concentration and dose after long-term ITB. However, in this study, CSF was sampled from the infusion catheter, which is likely to influence the samples with baclofen from this catheter.

Figure 3. Results of 2 studies which measured the correlation between the daily continuous ITB dose and steady-state baclofen concentrations in the lumbar CSF after at least 24 hours of infusion.

**Flex-mode infusion**

The baclofen is infused continuously but with varying speeds over the day, resulting in higher and lower dose periods. Flex mode is often used to tailor the ITB dose to periods of higher and lower spasticity during the day. However, one should bear in mind that switching between different infusion speeds will take several hours to reach a new steady-state concentration of ITB. This relatively long adaptation period limits the practical use of flex-mode infusion. Flex-mode infusion cannot be used effectively to lower daily ITB dose in tolerant patients (as subsequently shown).

**Bolus infusion**

The baclofen dose is divided in a number of bolus doses, which are administered during the day. Because the ITB pump cannot be stopped completely, there is always a low basal rate of continuous infusion between the boluses. Based on the previously referred pig study, bolus infusion seems to achieve a better ITB distribution in the CSF of the spinal canal. This may be a result of the increased speed of injection during bolus infusion. The increased
distribution may deliver the ITB more effectively, leading to a lower daily ITB dose. The optimal number of boluses per day has not been established so far. Four patients were previously described with tolerance to ITB and were switched to a 6 times per day bolus infusion regimen. The pump was programmed to deliver the lowest continuous dose possible in between boluses (minimal infusion rate, 72 µg/d). The bolus dose was calculated as follows:

\[
\text{bolus dose} = \frac{(\text{total daily dose} - 10\%) - \text{minimal infusion rate}}{6}
\]

The total continuous daily dose was lowered by 10% to avoid high peak concentrations. Using this regimen, the ITB dose was stabilized in all 4 patients. Another study effectively switched patients to a bolus regimen of 4 times per day (every 6h; basal rate, 4.6 µg/h) after they had shown a lack of response. With the currently available data, bolus infusion regimens seem to offer the best chance to reduce tolerance.

Finally, it is important to gradually alter a daily ITB dose independent of the ITB infusion regimen. ITB therapy can trigger seizures, especially during the ITB test infusion. Seizures have been associated with rapid dose changes, overdose, and withdrawal. Patients with structural brain disease or multiple sclerosis seem to be more susceptible.

**Concentration and infusion speed**

ITB concentration varies between 500 and 3000 µg/mL. Using higher concentrations is not recommended because pharmacy compounded baclofen at a concentration of 4000 µg/mL has been shown to cause catheter tip masses caused by precipitation of baclofen. However, ITB concentrations also determine the speed of infusion. For some spinal anaesthetics it was demonstrated that a faster injection provided a better distribution. Although there is no evidence that this is true for ITB, this could be because of the greater kinetic energy imparted to the infusate, causing it to spread further away from the injection site. Because the CSF volume at the level of injection consists of only a few milliliters, a small volume of the drug might already create local CSF flow. This theory might explain why bolus infusion achieves better distribution. The infusion speed has a negative correlation with concentration if the same dose is administered. This implies that adjusting the concentration of ITB in the pump might change the clinical effect. A more variable infusion speed in future pumps could offer the clinician more control over ITB kinetics by increasing the distribution of a lower concentration of baclofen when the catheter tip is not located...
immediately adjacent to the targeted spinal cord level. However, the limited volumes of the current ITB pumps (20 – 40 mL) would lead to shorter times between refills if lower concentrations of ITB are used. However, no published data support these hypotheses.

**Baricity**

Baclofen behaves as a hypobaric compound when infused into the CSF, causing it to distribute against gravity.\(^1\) Changing the baricity theoretically could offer a tool to influence baclofen distribution. It has been tried in a pig model, where baclofen was mixed in saline containing 7.5% dextrose, making it hyperbaric to pig CSF.\(^5\) By using this hyperbaric drug solution, caudal drug distribution was increased and rostral distribution decreased in pigs that were placed in an upright position.\(^5\) This study supports the idea that drug distribution might be either increased or decreased by the use of a hyperbaric solution, depending on the position of the subject. However, the possible influence of baricity is not used in humans so far.

**Tolerance**

The development of tolerance is a problem during long-term ITB therapy.\(^5\) Although definitions of tolerance vary between studies, it is reported to occur in 1% to 20% of all ITB patients.\(^3\,4\,7\,5\,5\) Tolerance is defined as an escalation of the dose required to produce a previously obtained effect or by a decreasing effect produced by the same given dose of the drug.\(^6\) It is associated with a return of spasticity and increased side effects. Increases in the ITB dose during the first 12 to 18 months of ITB therapy should be considered a result of careful individual dose titration, associated in part to a reduction of other oral antispasticity medications. This should not be diagnosed as tolerance.\(^4\,5\,7\,5\,9\) Tolerance in ITB therapy is thought to be induced by a reduction in the total number of GABA-B-receptors\(^6\) and by pre- and postsynaptic desensitization of the remaining GABA-B receptors after prolonged ITB administration.\(^6\) It has been demonstrated that the G-protein coupled kinases 4 and 5 desensitize GABA-B-receptor mediated responses by forming protein complexes with one of the two GABA-B-receptor subunits (type 1) and the plasma membranes.\(^6\)

Tolerance should be considered after exclusion of other causes of reduced drug effectiveness, such as technical problems with the delivery system (pump, catheter), improper drug composition, and progression of the underlying disease. Tolerance in ITB therapy has been treated by drug holidays. During these drug holidays, varying from a few days up to 2 months, ITB therapy was lowered or stopped. The patient was then treated with another antispasticity medication, usually intrathecal morphine (0.25 – 2 mg/d).\(^3\,5\,6\,6\) Although the exact mechanism is unclear, the GABA-B-receptors are thought to resensitize during the absence of baclofen. As a result, ITB therapy may be restarted at a lower (30% - 80%) dose than
before the drug holiday; however, a dose increase may reappear because of new receptor desensitization.\textsuperscript{3,56,65,66} During a drug holiday, the patient has to be monitored carefully because abrupt withdrawal of baclofen may cause a baclofen withdrawal syndrome with serious complications, which make drug holidays not the preferred therapy for the treatment of tolerance.\textsuperscript{67} In patients with baclofen withdrawal syndrome it is essential to restore GABA-mimetic drugs, either by restoring ITB administration or by infusion of benzodiazepines.\textsuperscript{67} Treatment with oral cyproheptadine, a serotonin antagonist, has been shown to be a useful adjunct in the management of baclofen withdrawal syndrome, possibly because baclofen withdrawal syndrome shows similarities with acute serotonin syndrome.\textsuperscript{68} As previously discussed, switching the pump from continuous to bolus infusion mode appears to be a promising method to treat ITB tolerance.\textsuperscript{48} Although switching a patient from continuous to bolus infusion has not been reported to cause baclofen withdrawal syndrome so far, it remains important to monitor the patient carefully.

**Study limitations**

This article reviews all available PK and PD data on ITB. However, the number of studies is limited, especially on human ITB PK data. Furthermore, most studies have considerable differences in study protocols, which make it difficult to compare the studies. Animal studies can be used to fill this gap of knowledge, especially because of the practical and ethical limitations related to CSF sampling in humans. Animal studies need to be considered with care because they cannot be directly compared with humans because of differences in anatomy and physiology. Hopefully, a radiotracer with ITB will be developed in the near future, which would offer clinicians a safer and easier tool to gather in vivo information about ITB distribution in humans.

**Conclusion**

In the 2 decades after the introduction of ITB therapy, most of the research has focused on its efficacy and safety in multiple indications. With an increasing number of patients being treated with ITB therapy, research needs to deepen our basic understanding of this effective therapy. Future research should produce more human PKPD data on ITB and a better understanding of normative ITB distribution and its spinal concentration gradient. The hardware of ITB pumps should be improved, focusing on a higher degree of customization (e.g. with a variable bolus infusion rate). Furthermore, double lumen catheters with the possibility to deliver ITB at different spinal levels would be an interesting tool as well. Improved insight into the basics of ITB therapy, especially the relation between PK and PD of ITB, would also improve the short- and long-term outcomes of ITB treatment. Future
research should also focus on the promising effects of bolus infusion of ITB. It would be interesting to compare bolus infusions with continuous infusion in a randomized controlled trial, looking for differences in the incidence of tolerance between these 2 regimens.

Overall, ITB has been proven to be efficacious in the treatment of severe spasticity. More insight into the PKs and PDs of ITB is necessary to improve its applicability in clinical practice.
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