Pharmacokinetics and pharmacodynamics of intrathecal baclofen therapy
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General introduction and outline
INTRODUCTION

Spasticity is derived from the Greek word spasticos (σπαστικός) and spaon (σπάω, to draw out, stretch).1 The term was first used by Good in 1829 to describe excessive muscular action.1 However, the most commonly used definition of spasticity is from Lance:

“Spasticity is a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron syndrome.”2

This definition describes spasticity as one of the symptoms of the upper motor neuron (UMN) syndrome. The UMN syndrome is caused by a disruption of the descending motor pathways (the UMN) between the motor cortex and the spinal cord. These pathways control the spinal reflexes, which become hyperactive after a lesion to the UMN.3 The UMN syndrome results in negative and positive symptoms. The negative symptoms are characterized by muscle weakness (paresis), loss of dexterity, and fatigability.4 The positive symptoms are characterized by spasticity, hyperactive tendon reflexes, clonus and flexor spasms.4 The symptoms do not always occur in combination and depend on the site and nature of the lesion.

Recently the definition by Lance has been criticized, being too narrow and it was suggested that spasticity should be used as an umbrella term for all positive symptoms of the UMN syndrome.5 In this thesis however, the classical definition of Lance is used.

Pathophysiology of spasticity

A spinal reflex is the interaction between an afferent sensory neuron to an efferent motor neuron within the spinal cord. The sensory neurons detect change (e.g. in muscle length) and transmit this signal to the motor neurons, which respond with muscle contraction. Spinal reflexes are under supraspinal control by the pre- and primary motor cortex, by means of the pyramidal and parapyramidal fibers. The pyramidal fibers (the corticospinal tract) are involved in voluntary movement. The parapyramidal fibers have an inhibitory and excitatory control on spinal reflexes. The main inhibitory tract is the dorsal reticulospinal tract, which is under facilitary control from the motor cortex. The main excitatory tract is the medial reticulospinal tract.3

The UMN syndrome results from lesions to pyramidal and especially parapyramidal fibers. Isolated lesions to the pyramidal tract do not often result in spasticity, but only in a reduction in muscle tone and reflexes.3 Spasticity arises when the parapyramidal fibers of the inhibitory system are interrupted either by damage to the pre- and primary motor
cortex, or to the dorsal reticulospinal tract in the spinal cord. The loss of inhibitory control leads to hyperactive spinal reflexes, accounting for most of the positive UMN symptoms. After the loss of supraspinal control, secondary changes at cellular level in the spinal cord below the lesion further contribute to hyperactivity of the spinal reflexes. The hyperactive reflexes are the result of (a) an increased gain in the stretch reflex networks (i.e. from a given sensory input, the motor response is greater), and (b) a decreased threshold in the stretch receptors (i.e. the stretch reflex can be triggered with a smaller stimulus).

Symptoms of upper motor neuron pathology

The symptoms and severity of the UMN syndrome depend on both the site and the nature of the lesion. In the next paragraph spasticity and other positive symptoms of the UMN syndrome will be reviewed.

Spasticity is a form of hypertonia. Hypertonia is defined as an abnormally increased resistance to muscle stretch. Spasticity is characterized by a velocity dependent hypertonia. This means the hypertonia increases with the speed of movement, which is the result of the hyper-excitability of the stretch reflex. It should be distinguished from hypertonia due to dystonia and rigidity, which are not velocity dependent and are caused by lesions of the basal ganglia. During physical examination of patients with spasticity, there is a direct relationship between the speed of stretching the muscle and the magnitude of resistance. Spasticity causes invalidating movements, especially if spasticity occurs in combination with other UMN symptoms, like muscle weakness. Spasticity may also result in a continued shortened position of muscles, which in turn may result into secondary soft tissue changes and contractures. Spasticity can be painful, especially if it results in a permanent state of flexion, which may give rise to contractures.

Disinhibition of existing spinal reflexes causes flexor- and extensor spasms, which are disinhibited normal reflexes, like the withdrawal reflex after painful stimuli. However, in patients with an UMN syndrome, very small stimuli (e.g. passive movements or touching the skin) may already cause these spasms. Damage of the UMN may also result in primitive reflexes. These primitive reflexes (such as the Babinski sign) normally disappear during the first year of life, but may return, for instance as a symptom of lesions in the UMN.

Another phenomenon belonging to UMN pathology is clonus. Clonus consists of a series of involuntary rhythmic muscular contractions and relaxations, mostly seen in the ankle, which is also caused by disinhibition of spinal reflexes.
The *clasp knife phenomenon* is a clinical sign which appears if spastic muscles are being stretched. It is characterized by an increased muscle tone in either flexion or extension, with sudden relaxation as the muscle continues to be stretched repetitively. This phenomenon is based on the fact that spasticity is not only velocity dependent, but also length dependent.\(^6\) The initial hypertonia slows down the movement. Due to the slowing movement and the lengthening of the muscles, hypertonia may disappear suddenly.

**Epidemiology of spasticity**

Spasticity is related to disorders affecting the (para)pyramidal system. The damage may be acute, due to stroke, spinal cord injury (SCI), traumatic brain injury (TBI) or cerebral palsy (CP), or may be progressive over a number of years, like multiple sclerosis (MS) or hereditary spasticity. The incidence of spasticity in these various disorders is variable. Spasticity appears in more than 34-80% of all patients with MS\(^9,10\), in 65-78% of patients with SCI\(^11\), and in 20-38% of patients suffering from a stroke.\(^12,13\)

**The burden for the patient**

The different symptoms of spasticity may cause a wide range of functional problems, which may have a negative influence on the various activities of daily living.\(^12\) Spasticity of the lower extremities has a large impact on mobility, such as walking and making transfers.\(^4\) Spasticity of the upper extremities may cause difficulties with feeding and self-care. Inactivity due to spasticity may lead to decubitus and or contractures. Involuntary movements, spasms and hypertonia might disturb sleep, or might cause pain and difficulties in daily care. Adductor spasms f.i. frequently cause problems with the handling of urinary catheters and may prevent putting on pants.\(^4\)

**Treatment of spasticity**

It is important to pay attention to the prevention of trigger factors for spasticity (f.i. pain, infections and constipation) in all patients with spasticity.\(^9\) Other non-pharmacological treatments consist of physical therapy, such as stretching, and repetitive transcranial magnetic stimulation, a non-invasive therapy stimulating the cerebral cortex by means of electromagnetic induction.\(^14\) Stretching of affected muscles is thought to prevent contractures, although its effect has been questioned with respect to the long term consequences.\(^15,16\)

Pharmacological treatments can be categorized in central and local acting agents. Central acting agents consist of different oral spasmolytics, mostly used for generalized spasticity. Oral baclofen was the first effective drug for spasticity and still is the most widely used treatment option, followed by tizanidine and gabapentin.\(^9\)
Local acting agents can be injected into isolated muscles or nerves, to achieve a local effect. The most commonly used agent is Botulinum toxin, a reversible treatment, with a duration of effect of several weeks to months. Phenol or alcohol injections, leading to axonal damage, and surgical interventions are other less frequently used focal therapies.

**Intrathecal baclofen therapy**

Baclofen is a potent gamma-aminobutyric acid (GABA)-B agonist and binds to the GABA-B receptors in the dorsal root ganglion and the spinal grey matter. Baclofen seems to achieve its effect by the increase of GABA activity, leading to a reduction of the stretch reflex in patients with spasticity. Although baclofen acts on the central nervous system (CNS), its concentration in the cerebrospinal fluid (CSF) after oral administration is very low, because baclofen does not cross the blood-brain barrier effectively. In 1984, Penn and Kroin bypassed the blood-brain barrier by injecting baclofen directly into the CSF, using a subcutaneous programmable pump connected to an intrathecal lumbar drain. This intrathecal baclofen (ITB) therapy resulted in an improved effect and much higher baclofen concentrations in the CSF, as compared to oral baclofen therapy (25 – 100 mg), with a fraction of the oral dose (50 – 1000 µg). ITB is a local therapy and has less side-effects as compared to (systemic) oral baclofen, which may induce drowsiness and sleepiness, related to its inhibitory effects on the CNS. Since its introduction in 1984, ITB has shown good efficacy in patients with spasticity.

**Indications for ITB therapy**

In the past three decades, ITB therapy has shown to be effective for spasticity of both spinal and cerebral origin, not responding to oral spasmolytics. A survey of more than 1000 ITB pump implantations showed the following underlying diseases: CP 44%, SCI 22%, TBI 9%, anoxic brain injury 3% and other pathologies, including MS, 22%. ITB has also shown to be effective in treating generalized dystonia, hereditary spasticity and spasticity due to stroke.

Candidates for ITB therapy can be divided into ambulatory and non-ambulatory patients. Ambulatory patients still have the ability to walk (with or without assistive devices). Non-ambulatory patients lost the functional ability of their legs and are often bedridden or confined to a wheelchair. In both groups a reduction of spasticity is the main goal of ITB therapy. In the ambulatory patient group ITB therapy may also result in functional improvement.
ITB test-infusion

ITB therapy is considered if oral spasmyotics have limited efficacy and/or too much side effects. The implantation of an ITB pump for spasticity and the related hospitalization is costly, but has proven to be cost-effective in patients who do not respond to less invasive treatments. It is recommended that possible candidates initially receive a test-infusion prior to implantation, to evaluate the effect and tolerability of ITB. A test-infusion can also help to manage expectations of the patient and their caregivers.

The ITB test-infusion is performed during a hospital admission of several days, using an external intrathecal catheter to administer test doses of baclofen. Clinical effects and possible adverse events are closely monitored during this period. ITB is mostly administered as a 25 – 100 µg bolus, which provides an effect for several hours. Continuous test-infusion can be used to titrate the optimal dose more precisely, for instance in ambulatory patients with a narrow therapeutic window in between a decrease of muscle tone and functional gain.

ITB pump implantation

A successful test-infusion normally leads to implantation of a permanent subcutaneous ITB pump-system. Surgery is performed under general anesthesia. During surgery a one- or two-piece spinal catheter is introduced in the spinal canal via a Tuohy-needle, usually at mid lumbar level, in the midline. The tip of the infusion catheter is usually positioned near the 10th thoracic vertebra (Th10), close to the spinal cord segments of the lower limbs. The distal end of the catheter is subcutaneously connected to a programmable pump, which is positioned in a subcutaneous pocket in the abdominal wall. Postoperative complications can be divided into wound-related and device-related complications. Wound infections occur with a frequency varying from 3 to 41% and occur more frequently in children as compared to adults. Catheter complications (dislocation, fracture, disconnection) are the most common device-related complications with an incidence of 10 – 40%.

After ITB pump implantation the patient will be controlled with regular intervals, mostly once every 3 months, to evaluate the effect of ITB and to check and/or adapt the pump settings. The initial ITB infusion rate per day is based on the optimal dose determined during test-infusion. Dose alterations can be made using a Personal Digital Assistant (PDA) with a wireless connection to the implanted ITB pump. Every 2-3 months the pump needs to be refilled with baclofen using a special sterile needle. The average life time of the pump battery is 4-5 years, after which the device needs to be replaced.
Unsolved problems and unmet needs

Since its introduction in 1984, ITB has proven to be a potent and effective therapy, able to treat severe spasticity from various causes. A number of studies has shown its indications, clinical effect and safety.24-26 Over the years an increasing number of patients with severe spasticity, dependent from ITB, have shown an increasing amount of clinical problems, especially related to maintaining the beneficial effect on the long-term.

One of these problems is the unexplained ITB dose increase over time in some patients. Most patients show a gradual increase of the ITB dose over the year(s) after pump implantation, before finally reaching a stable level of infusion.46 However, some patients show a very rapid increase of the baclofen dose, to maintain a satisfactory clinical response.47 This phenomenon is known as tolerance.48 Although tolerance has been described previously in ITB, its etiology and management has not been studied in more detail so far. In clinical practice, ITB infusion regimens are just adapted based on clinical experience. Until now, there is no evidence-based pharmacological guideline to structure the infusion regimens of ITB infusion.49

Irrespective the known efficacy, little is known about the mechanism of action, the pharmacokinetics (PK; how is baclofen spread over the body) and the pharmacodynamics (PD; how does the body react to baclofen) of ITB therapy. The general lack of pharmacokinetic-pharmacodynamic (PKPD) data of ITB therapy is caused by the difficulty of collecting CSF samples with baclofen in humans. A better knowledge of the PKPD of ITB would improve the understanding and management of dosing problems with ITB, including the issues of drug tolerance.

Finally, another important puzzle is the application of ITB in ambulatory patients. Studies on the effect of ITB on ambulatory function in patients with spasticity, still able to walk, showed mixed results.33, 40, 50, 51 These variable data have restricted the use of ITB in ambulatory patients with spasticity, which could be a missed opportunity to improve functional abilities in these patients.40, 51 Therefore, more data are needed to get a better understanding of the effect of ITB in ambulatory patients.
AIMS AND OUTLINE OF THE THESIS

The primary aim of this thesis is to investigate and describe the pharmacology of ITB, collecting human pharmacokinetic (PK) and pharmacodynamic (PD) data.

The secondary aim is to evaluate the efficacy of ITB in ambulatory patients, focusing on how to measure the effect on various clinical domains, like spasticity, strength and ambulatory function.

The current state of knowledge on the pharmacology of ITB therapy is reviewed in chapter 2. Since there were no data on the incidence of tolerance in the ITB population, the medical records of all patients treated with ITB therapy between 1991-2005 in the University Medical Center Groningen (UMCG) were reviewed. The results of this review are reported in chapter 3, addressing both the details about tolerance, and the different regimens that were used to overcome baclofen tolerance. The hypothesis that pulsatile bolus infusion could be effective in lowering the daily ITB dose in patients with tolerance was studied and presented in chapter 4. In chapter 5 the sampling of PK and PD data after an ITB test-infusion is described. These data were used to develop the first PKPD model for intrathecal baclofen in humans. In chapter 6 the possible benefit of ITB in ambulatory patients is illustrated, as we describe the effect of ITB-therapy on gait performance during the test-infusion and after pump-implantation in a patient with hereditary spasticity. The objective of the study presented in chapter 7 was to determine which qualitative and quantitative tests on the domains of spasticity, strength, ambulatory function and the patient’s personal impression are useful in measuring the effect of a continuous ITB test-infusion in ambulatory patients with spasticity. In chapter 8 the thesis is summarized and discussed.
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