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Intrathecal Baclofen therapy in Germany: Proceedings of the IAB—Interdisciplinary Working Group for Movement Disorders Consensus Meeting

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Abstract Continuous intrathecal Baclofen application (ITB) through an intracorporeal pump system is widely used in adults and children with spasticity of spinal and supraspinal origin. Currently, about 1200 new ITB pump systems are implanted in Germany each year. ITB is based on an interdisciplinary approach with neurologists, rehabilitation specialists, paediatricians and neurosurgeons. We are presenting the proceedings of a consensus meeting organised by IAB—Interdisciplinary Working Group for Movement Disorders. The ITB pump system consists of the implantable pump with its drug reservoir, the refill port, an additional side port and a flexible catheter. Non-programmable pumps drive the Baclofen flow by the reservoir pressure. Programmable pumps additionally contain a radiofrequency control unit, an electrical pump and a battery. They have major advantages during the dose-finding phase. ITB doses vary widely between 10 and 2000 μg/day. For spinal spasticity, they are typically in the order of 100–300 μg/day. Hereditary spastic paraplegia seems to require particularly low doses, while dystonia and brain injury require particularly high ones. Best effects are documented for tonic paraspasticity of spinal origin and the least effects for phasic muscle hyperactivity disorders of supraspinal origin. Oral antispastics are mainly effective in mild spasticity. Botulinum toxin is most effective in focal spasticity. Myotomies and denervation operations are

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restricted to selected cases of focal spasticity. Due to its wide-spread distribution within the cerebrospinal fluid, ITB can tackle wide-spread and severe spasticity.

Keywords Intrathecal Baclofen · Pump · Continuous application · Spasticity · Consensus

Introduction

Continuous intrathecal Baclofen application through an intracorporal pump system (ITB) was first used in 1984 by Penn and Kroin (Penn and Kroin 1984) to treat adult patients with spasticity. The first child with spasticity was treated with ITB in 1985 (Dralle et al. 1985). In 1991, an extensive double-blind randomised trial demonstrated ITB efficacy and safety in children with cerebral palsy (Albright et al. 1991). In 1993, intrathecal Baclofen was registered in Germany for severe spinal or supraspinal spasticity of various aetiologies including trauma, multiple sclerosis and other processes otherwise unresponsive to oral treatment. In children, the age limit for treatment was set to 4 years of age. Since then, no new registration for ITB was pursued, although numerous additional therapeutic uses were described. Currently, about 1200 new ITB pump systems are implanted in Germany each year. Approximately 25 centres perform implantations, although only 10 of those are estimated to perform more than 30 procedures per year. Medtronic claims that 60,000 of their pumps have been implanted worldwide since 1992.

ITB is based on an interdisciplinary approach with neurologists, rehabilitation specialists, paediatricians and neurosurgeons. Additionally, with often severely affected patients involved, other physicians and health professionals are routinely involved in the patient care. For this, IAB—Interdisziplinärer Arbeitskreis Bewegungsstörungen (IAB—Interdisciplinary Working Group for Movement Disorders) developed a keen interest in ITB and organised a state-of-the art and consensual meeting which took place in Hamburg, Germany on June 20 and 21, 2014. This paper presents a literature review and a consensus of 19 experts, seven from neurorehabilitation, five from neurology, three from neurosurgery, three from neuropaediatrics and one from physiotherapy.

Baclofen

Baclofen was first synthesised in 1962 by Heinrich Keberle 1962 at Ciba-Geigy. It is a racemate of the biologically active R-(-)-enantiomer which is right configurated and left turning. The biologically inactive L-(+)-enantiomer is left configurated and right turning. After its first experimental use in the 1960s as an anticonvulsant agent, Baclofen's antispastic effects were first explored in the 1970s.

Baclofen has direct inhibitory effects on Ia and Ib muscle and Aα cutaneous afferents in the dorsal root ganglion and laminae I and II of the dorsal horn of the spinal cord where its agonistic effects on GABA-B receptors cause presynaptic inhibition and postsynaptic hyperpolarisation, thus reducing α-motoneuron excitability within the monosynaptic spinal stretch reflex pathway (Curtis et al. 1981; Li et al. 2004, Yang et al. 2001). Direct GABA-B agonism on cortical interneurons produces anticonvulsant effects (Sato et al. 1990). Nociceptive effects are described, but mechanisms involved and target areas are unclear. Indirect antidopaminergic effects might explain possible antidystonic effects. Tardive adverse effects and parkinsonism, however, were not described. Recently, oral Baclofen generated considerable interest as an antidependency drug, especially for alcohol dependency (Müller et al. 2014). Antidepressive effects were also reported.

ITB adverse effects can be seen in overdose and withdrawal situations (Shirley et al. 2006, Watve et al. 2012). Adverse effects associated with overdose include muscle relaxation, drowsiness, constipation, circulation suppression with bradycardia and arterial hypotonia, seizures and respiratory suppression (Berger et al. 2012). Adverse effects associated with withdrawal can be life threatening when treated too late (Green and Nelson 1999). The withdrawal syndrome may include somnolence, seizures, rigidity with rhabdomyolysis, hyperthermia and circulation suppression with bradycardia. It is more common than adverse effects due to overdose.

ITB is administered into the cerebrospinal fluid volume of approximately 150 ml, of which 80 ml is spinal and 70 ml cerebral (Edsbagge et al. 2011). The entire cerebrospinal fluid volume is replaced roughly three times a day (Edsbagge et al. 2004). Due to complex pulsatile cerebrospinal fluid dynamics, lumbar Baclofen application produces a lumbocisternal concentration gradient of approximately 4:1 (Kroin and Penn 1992, Bernards 2006). Gravitation force actually lifts the hypobaric Baclofen within the cerebrospinal fluid (Heetla et al. 2014). The lesser intracisternal concentration of Baclofen constitutes the therapeutic principle of ITB, since it allows high intraspinal concentrations necessary for antispastic affects and avoids high intracisternal concentrations responsible for central nervous system adverse effects. Baclofen seems to remain in the cerebrospinal fluid within an area of a few centimetres around the catheter tip (Bernards 2006). Higher concentrations and bolus applications seem to produce wider diffusion (Bernards 2006). Intrathecal half life is 1–5 h when Baclofen is applied intrathecally (Kroin and Penn 1992). Clinically, antispastic effects of continuous intrathecal doses changes occur with a 2–4 h delay.

Table 1 Intrathecal Baclofen drugs currently available in Germany

Name	Manufacturer	Packaging concentration [μg/ml]		
		50 (ml)	500 (ml)	2000 (ml)
Lioresal®	Novartis Pharma	1	20	5
Baclofen Meduna Intrathecal®	Sinthetica	1	20	5/20
Baclofen SUN®	SUN Pharmaceuticals	1	20	5

Table 2 Intrathecal Baclofen pumps currently available in Germany

Name	Manufacturer	Features	Reservoir volume (ml)
Synchromed 2	Medtronic	programmable electrical pump	20/40
Siromedes	Tricumed	hybrid pump: programmable (can be deactivated) and reservoir pressure driven pump	20/40
IP1000 V	Tricumed	non-programmable reservoir pressure driven pump	10/12/15
IP2000 V	Tricumed	non-programmable reservoir pressure driven pump	20/35/40/60
Codmann 3000	Codman	non-programmable reservoir pressure driven pump	16/30/50

Table 1 shows the currently available Baclofen drugs registered for intrathecal use. After Novartis Pharma's patent protection expired, intrathecal Baclofen became available from several manufacturers and retail prices dropped. Different brands of Baclofen can be exchanged without recognisable differences in efficacy and adverse effects. Pump refill intervals sometimes exceed the certified drug stability of 6 months for all Baclofen drugs. However, they are applied and seem safe.

Exact ITB dosing requires maximal safety precautions since drug reservoir doses are large and ITB is directly applied to the central nervous system. Antidotes are not available. 50 μg/ml concentrations are used for bolus testing; 500 and 2000 μg/ml concentrations for filling of the pump system. 2000 μg/ml is the standard concentration. It allows extended refill intervals. Higher concentrations would bear the risk of Baclofen precipitation at the catheter tip. Concentrations of 500 μg/ml are used when very low Baclofen doses are requested to maintain minimal pump flow rates. In those cases, further dilution is possible. Consensus strongly suggests better marking and differentiating the different units, and better warning of users of the potential dangers and risks associated with confusing them.

ITB doses vary widely between 10 and 2000 μg/day. ITB doses for spinal spasticity are typically in the order of 100–300 μg/day. Hereditary spastic paraplegia (HSP) seems to require particularly low doses, while dystonia and brain injury require particularly high doses, sometimes up to 1500 μg/day. In children, there is no clear age or body weight correlation of ITB doses used (Voss et al. 2009).

Pump systems

Over the years several different pump systems have been developed. These were usually designed and manufactured by small specialised companies. Early on, Anschütz developed its IP15.1 which was refined by Tricumed and later became Medtronic Isomed. Tricumed then designed its Archimedes pump which was acquired by Codman. Tricumed also developed its IP2000 and IP 3000. Therex and Fresenius also designed and distributed pumps under the names of Arrow and VIP30, respectively.

The ITB pump system consists of the implantable pump with the drug reservoir, the refill port and a flexible catheter. An additional side port allows direct access to the catheter. The side port can be used to apply boluses and contrast medium to better identify the catheter on X-ray examinations. Obviously, every effort has to be undertaken to differentiate the refill port and the side port, as drugs injected into the side port directly, immediately and completely reach the cerebrospinal fluid where they can cause life-threatening adverse effects. Generally, pumps are capsuled in titanium containers. Non-polished surfaces seem to prevent seromas. Plastic outer materials did not succeed. Most pumps have grommets to fix them to the abdominal fasciae. Design quality, manufacturing precision, corrosion resistance and robustness are key features for ITB pumps. Pumps can be distinguished by their control mechanism (programmable, non-programmable), the power supply that produces the drug flow (pump, reservoir filling pressure with butane gas compression and/or spring load) and their reservoir volume. Table 2 shows the ITB pump systems currently available in Germany.

Non-programmable pumps drive the Baclofen flow by the reservoir pressure which is stored by gas compression or spring load. With a pre-set constant drug flow, the Baclofen dose can only be changed by variations of the drug concentration. During the dose-finding phase, this procedure requires frequent complete refills with wasting of considerable amounts of Baclofen. Risks of miscalculations of the drug concentration have to be born in mind. Additional time, effort and money necessary may prevent dose optimisation in difficult cases. With flow rates depending on the pressure within the drug reservoir, the accuracy of drug delivery may vary with temperature, air pressure and filling level of the reservoir. Non-programmable pumps are cheaper, mechanically more robust and require no pump exchange for a prolonged period of time. Due to the lack of a control unit, an electrical pump and its power supply, their volume is smaller as compared to programmable pumps.

Programmable pumps additionally contain a radiofrequency receiver, a control unit controlling the flow rate of the pump and a battery powering the pump and the control unit. Programmable pumps have major advantages during the dose-finding phase. Costs of the pump are 50–100 % higher as compared to non-programmable pumps. Savings of drug costs, however, have to be counterbalanced. Battery exhaustion after 4–6 years requires replacement of the entire pump system and generates extra costs and an additional invasive procedure. Drug delivery as such seems to be equally robust as with non-programmable pumps. Flow rate seems to vary less as compared to non-programmable pumps. The option to programme diurnal profiles is felt to be less important for ITB.

Recently, a hybrid pump was introduced under the name of Siromedes (Tricumed, Kiel, Germany). It uses the reservoir filling pressure to generate the drug flow and a small battery to drive the valve-operated control unit. During the dose-finding phase, the pump is programmable. Once the dose finding is accomplished, the control unit is deactivated to safe battery power and the pump essentially runs as a non-programmable pump.

Another integral part of the pump system is the catheter. It is manufactured from flexible silicone or Polytetrafluorethylene-containing composite plastic materials. It is inserted by a special Tuohy cannula. It is the most vulnerable part of the pump system. It can be damaged by surgical sutures, cuts and by body tissues; it can be compressed between the spinal processes and—most of all—its tip can dislocate. Dislocation may produce kinking and bending resulting in partial or complete lack of Baclofen propagation and subsequent undersupply. Catheter connections may become disconnected. Recently, a metal coil reinforced catheter (Surestream, Codman) and a multilayer catheter (Ascenda, Medtronics) became available. The standard catheter tip position is mid-thoracic. More cranial positioning is believed to increase effects in the arms without increasing central nervous system adverse effects (McCall and MacDonald 2006).

Programmable pumps require a control unit to set the pump controller to the required data. Data traffic is performed by wireless electromagnetic transmission. Control units should be easy and safe to handle. Modern non-programmable as well as programmable pumps withstand magnetic resonance imaging with magnetic fields of up to 3 Tesla (Shellock et al. 2008). Function control afterwards is recommended in programmable pumps.

Refill sets

Refill sets are built around the special punctuation needle necessary to penetrate the silicone refill membrane (port) without damaging it. With the appropriate needle the port is claimed to withstand 500 penetrations without losing its sealing properties. Mechanical stability of the needle is important to avoid deformations when the needle is advanced too far into the pump. Surecan needles (B. Braun Melsungen) seem to be particularly robust. All other items in the refill set are standard items. Depending on the manufacturer they contain two syringes for emptying and refilling of the pump reservoir, a sterile drape to cover the area around the punctuation site, a plastic tube to connect the punctuation needle with the syringes and a bacterial filter to avoid bacterial contamination of the injected Baclofen. The necessity of the bacterial filter has been questioned.

Indications for intrathecal Baclofen therapy

ITB is registered to treat severe and otherwise unresponsive spasticity of spinal and supraspinal origin (Pin et al. 2011). Spasticity may be due to stroke (Francisco 2001), traumatic brain injury (Ordia et al. 2002), multiple sclerosis (Dario & Tomei 2007) and cerebral palsy regardless of age (Hoving et al. 2007, Tassëel Ponche et al. 2010). It may be used in symptomatic or idiopathic dystonia (Albright et al. 2001), in dystonic storm (Allen et al. 2014), in stiff person syndrome (Newton et al. 2013), in tetanus (Santos et al. 2004) and in hereditary spastic paraparesis (Bushman et al. 1993). Experimental uses include hiccups, spinal myoclonus, post-traumatic hemiballism, dystonic cramps in parkinsonian syndromes, Tourette syndrome, neuropathic pain, complex regional pain syndrome, cluster headache, hyperthermia and severe autonomic failure. Future uses may include modified application sites including the ventricles (Turner et al. 2012), multi-catheter devices and exploration of drug delivery profiles.

Exclusion criteria and precautions

Exclusion criteria for intrathecal Baclofen therapy are few. They include untreatable seizures, infections at the time of implantation, history of hypersensitivity to Baclofen, insufficient body size to accommodate the pump bulk and weight, and lack of compliance for the dose-finding process, the system maintenance and its timely refills. Precautions should be used in patients with spinal abnormalities, respiratory insufficiency and urinary retention. There are insufficient data on Baclofen during pregnancy and lactation. Participation in road traffic and control over machinery may be reduced. The recommended minimum age for pump implantation is around 4 years, although patients with 1.5 years of age and a body weight of 9.5 kg have received an ITB pump (Voss et al. 2009).

Testing for intrathecal Baclofen therapy

Before a pump system is implanted, test boluses of Baclofen can be applied intrathecally. Bolus tests may be used to predict the general responsiveness of the patient's symptomatology, to test for intolerability, to roughly predict the continuous doses necessary in the particular patient and to convince the patient, the caregiver and the reimbursement authority about the efficacy of the proposed intrathecal Baclofen therapy. Since the test boluses are applied by single or repeated lumbar punctures, the dose range is restricted and long-term ITB effects can not be judged. To avoid these shortcomings, continuous Baclofen application through an extracorporal pump has been suggested. However, since sterility of the extracorporeal pump system is limited to 1 or 3 weeks and application of the temporary catheter is already an invasive procedure, its value has been challenged. Typically, test bolus doses for adults are 50, 75, 100 and 125 μg of intrathecal Baclofen 50 μg/ml and 25, 50 and 75 μg of intrathecal Baclofen 50 μg/ml for children. Depending on the goals defined, the test parameter, the starting dose and the dose escalation varies. Bolus effects in temporal and dose-related order include tendon reflex level decrease, muscle tone decrease, increase of passive range of motion, muscle weakness, and cardiovascular and respiratory adverse effects. Since the effect of the test bolus starts after 1–2 h and lasts for 12–24 h, the testing can be escalated, if necessary, every third day. In adult patients with spinal spasticity, testing may be waived, as negative test results are rare.

Dose adaptation

After implantation of the pump system in a neurosurgical department, the patient is usually referred back to the neurologist. The pump is filled and—based on the response to the test bolus—an initial dose is set. The initial dose adaptation should be performed in a hospital. Baclofen doses may be increased by up to 30 % every second day in spinal spasticity and by up to 15 % every second day in supraspinal spasticity. In case of adverse reactions, dose reductions should be performed in a similar way. Dose adaptation can be continued on an outpatient basis. Then dose adaptation should be performed more slowly. In accordance with the pre-defined treatment goals, optimal reduction of the muscle tone and the spasm frequency without induction of paresis and reduction of stabilising muscle tone is aimed for.

Complications

Perioperative complications

General perioperative complications include local infection, meningoencephalitis, cerebrospinal fluid leak with cerebrospinal fluid low pressure syndrome, haemorrhages and bruising. Prophylactic antibiosis reduces the risk of infection. Perioperative complications concerning the catheter include problems with insertion and advancing of the catheter, correct placement of the catheter tip, avoidance of blocking the catheter lumen between the spinal processes, avoidance of tension on the catheter through the body movements and correct connection of the catheter with the connector. Perioperative complications concerning the pump include incorrect placement over bones, under pressure of garment, non-sterility and inadequate fixation so that pumps become mobile and rotate making refilling impossible. A special problem is implantation of pumps with incorrect reservoir size. In small children, pumps with smaller reservoir sizes are used because of lack of implantation volume and often low Baclofen dose requirements. In adult patients, large reservoir sizes are preferable, especially in patients with severe spasticity and in bed-ridden patients where transport logistics become a problem when very short refill intervals are necessary.

Postoperative complications

Most postoperative complications are due to catheter problems including catheter tip displacement, kinking, breaking and disconnection. Occasionally, catheter tips become occluded by granulomas. These granulomas may also affect the spinal cord and produce paraparesis. Pumps may rotate within their pouch so that refill becomes impossible. Refill complications include delayed patient presentation. Patients or their caregivers need to be informed about the absolute necessity for timely refills to avoid life-threatening withdrawal reactions. Programmable pumps include an acoustic alarm function which sets off

few days before pump reservoirs are empty. Again, patients and caregivers have to be informed about the importance of the alarm signal. Other refill complications include wrong calculations of the Baclofen concentration in non-programmable pumps. In programmable pumps, the refilled reservoir volume has to be reset after each refill. Also in programmable pumps, the concentration filled in and the concentration to which the pump is set have to match to avoid severe overdose or withdrawal reactions.

Role of intrathecal Baclofen for treatment of spasticity

Spasticity can be treated with different treatment methods. Table 3 gives an overview about the treatment methods used for spasticity. Oral antispastics are mainly effective in mild spasticity regardless of focality. Especially, oral Baclofen has sedative adverse effects. Mucosa-absorbable THC + CBD (Sativex®, Almiral) is also mainly effective in mild spasticity. German registration only allows its application in patients with spasticity due to multiple sclerosis. Botulinum toxin therapy is a local antispastic drug. Therefore, it is most effective in focal spasticity. Due to its strong effects it can target mild, moderate and severe spasticity. In more wide-spread forms, it can be used when selected target muscles can be identified. Similar to botulinum toxin therapy, surgical approaches including myotomies and denervation operations are restricted to focal spasticity of moderate and severe severity. With its wide-spread distribution within the cerebrospinal fluid, ITB can tackle wide-spread spasticity. Use in focal spasticity is currently been investigated. Negative effects on the non-affected contralateral limb may occur. Strongest effects seem to occur in the spinal cord under the catheter tip. Placement of the catheter tip in relationship to the spinal cord can therefore be used to focus the ITB effect (Hugenholtz et al. 1993). Whether also ventral or dorsal catheter positions modulate the antispastic effects is unclear (Flack and Bernards 2010).

Best effects are documented for tonic paraspasticity of spinal origin and the least effects for phasic muscle hyperactivity disorders of central nervous system origin.

Table 3 Overview over the role of intrathecal Baclofen therapy for treatment of spasticity

Severity	Location	Treatment method				
		OAS	CBN	BTT	CHX	ITB
Mild	Focal	+	+	+		
	Wide-spread	+	+			
Moderate	Focal			+	+	
	Wide-spread					+
Severe	Focal			+	+	
	Wide-spread					+

BTT Botulinum toxin therapy, *CBN* Cannabinoides (THC + CBD), *CHX* Surgical interventions, *ITB* Intrathecal Baclofen, *OAS* Oral antispastics

Interdisciplinary framework for ITB

As discussed above, treatment of spasticity as a chronic and often severe condition requires an interdisciplinary approach which in Germany most likely will be coordinated by a neurologist or a paediatrician ideally knowing the patient for a prolonged period of time. This remains true when treatment of spasticity requires ITB. When oral antispastic treatment is not effective or intolerable and when botulinum toxin therapy can not sufficiently addresses all muscles relevant for goal attainment, ITB is indicated provided all logistic requirements are given and no contraindications can be detected. ITB testing requires hospitalisation and can either be performed by the neurologist, the paediatrician or the neurosurgeon. After positive testing and after reconfirmation of the ITB indication by the neurosurgeon, the pump system is implanted in a neurosurgical unit. The pump system is then filled with Baclofen and set to a minimal dose. The patient is then transferred back to the neurologist who performs the dose adaptation. Supported by physiotherapists and occupational therapists, the pre-set treatment goals are followed. Depending on disease severity, additional orthoses, specialised nursing, speech therapy, urological care, gastrointestinal expertise and reconstructive surgery may become necessary. A combination with botulinum toxin therapy is possible. In the absence of long-term outpatient rehabilitation in Germany, coordinating all these treatment efforts on an outpatient basis remains a major challenge. IAB is prepared to facilitate this interdisciplinary approach by education and communication (Adib Saberi and Dressler 2013).

Outlook

ITB is a safe and effective method to treat severe and otherwise therapy refractory spasticity. After its introduction in 1984, other interesting indications were explored. However, scientific interest seems to have stalled in the meantime. Clinical standards for its safe application do not seem to be uniformly maintained. Investment to build multidisciplinary teams as organised by IAB—Interdisciplinary Working group for Movement Disorders may be helpful.

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