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Clinical observations
Spostrzeżenia kliniczne

Intrathecal baclofen in severe spasticity of various origin

Dokanałowy baklofen w ciężkiej spastyczności różnego pochodzenia

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SUMMARY. ***Aim.*** *To present the principles and applications of intrathecal baclofen treatment for spasticity of various origin.* ***Review.*** *Intrathecal baclofen (ITB) introduced for the first time in 1984, is widely used in the treatment of severe spasticity of various origin. Baclofen is delivered via an intrathecal catheter from an implantable pump that allows to control the dosage over many years. Numerous reports have evidenced beneficial effects of the treatment in patients with spasticity of spinal, cerebral, or mixed origin. Significantly positive treatment outcomes were noted also in patients suffering from conditions other than the classical recommendations, i.e. sclerosis multiplex, spinal cord injury, cerebral trauma, cerebral palsy, or dystonia. Neurogenic dysfunction of the urinary bladder, locomotion and mobility should be assessed both in the testing stage and over a long period of time. Undesirable side-effects are seldom reported.*

STRESZCZENIE. ***Cel.*** *Przedstawienie zasad i zastosowania leczenia dokanałowego baklofenem w spastyczności różnego pochodzenia.* ***Przegląd.*** *Dokanałowy baklofen (ITB), wprowadzony po raz pierwszy w roku 1984, jest obecnie szeroko używany w leczeniu ciężkiej spastyczności różnego pochodzenia. Baklofen jest aplikowany przez cewnik dokanałowy za pomocą implantowanego zestawu zwanego pompą, umożliwiającego kontrolę dawki przez wiele lat. Liczne doniesienia udowodniły korzystne efekty u pacjentów ze spastycznością zarówno pochodzenia rdzeniowego, mózgowego jak i mieszanego. Inne niż klasyczne wskazania, takie jak: stwardnienie rozsiane, urazy rdzenia kręgowego, urazy mózgu, dziecięce porażenie mózgowe czy dystonia również przynoszą znamienne korzyści. Dysfunkcja neurogenna pęcherza moczowego, przemieszczanie się i mobilność powinny być oceniane zarówno w fazie testowania, jak podczas obserwacji długotrwałej. Niepożądane skutki uboczne występują rzadko.*

Key words: spasticity / baclofen
Słowa kluczowe: spastyczność / baklofen

BACLOFEN

Baclofen is a selective agonist of the $GABA_B$-receptor, first discovered in 1981 after the compound had already been in use for more than 10 years as an antispastic drug. $GABA_B$-receptors are abundent in the CNS and are also found in the *substantia gelatinosa* of the spinal cord gray matter. Baclofen is a white crystalline, water soluble powder (4,3 mg/ml at pH 7,6/23°C) with a high receptor affinity (IC_{50} = 20 nmol). In implantable infusion devices baclofen solution is stable at body temperature over several months.

The continuous intrathecal infusion of baclofen does not cause morphologic changes at the spinal cord and drug-induced loca irritations or inflammations were never detected. *In vivo* and *in vitro* studies failed to show evidence for mutagenic actions. Long-term studies did not show evidence for cancerogenic actions [1, 2, 3].

Pharmacokinetics

After *oral administration* baclofen is quickly resorbed and its bioavailability in the blood is between 37% and 80% [4]. Less than 10% of the orally applied drug is degraded in the liver and excreted in metabolized form with the urine. Around 30% of baclofen is bound to plasma protein. After systemic application baclofen barely crosses the blood brain barrier. ITB circumvents the blood-brain-barrier and allows a better access to the receptors in the spinal cord. Efficient treatment of spasticity can therefore be achieved by doses 100 to 1000 times smaller than oral. A lumbar to cervical concentration gradient of 1,8 to 8,7 (mean ± SEM: 4,1 ± 1,3) has been determined. The baclofen concentration in CSF is independent of the body position, since the density of baclofen (1,003 ± 0,001 g/cm^3 at 23°C) is the same as for human CSF (1,006 to 1,008 g/cm^3).

INDICATION

The decision for intrathecal baclofen treatment has to take into account a variety of aspects such as costs, alternative treatment options and the potential functional gain for the individual patient. In all cases, the result of the intrathecal test injection is crucial for this decision since it allows both the patient and the physician to assess the result beforehand. Also, care-givers and family members have to be informed of what they can expect – and what not to expect – from the procedure well in advance. Symptoms other than spasticity will not improve using ITB. The indication criteria for ITB most frequently quoted are:

- severe, disabling spinal spasticity of spinal or supraspinal origin,
- non-responsive to standard drug treatment or such drugs not tolerated,
- known diagnosis (MS, spinal trauma, brain injury...),
- proven response to IT bolus of 50 to 100 μg.

The following patient grouping can be made:

1. Patients with residual force in lower limbs, partly able to walk or stand (e.g. incomplete spinal lesion), but suffering from muscle spasms, pain and/or exaggerated muscle tone interfering with mobility (about 10% in our series).
2. No residual or weak motor activity (i.e. complete spinal transsection, spastic paraplegia), suffering most from disabling muscle spasms, pain, and/or tremendously exaggerated muscle tone leaving the patient unable to use a wheelchair and significantly reducing their quality of life (about 80% of our patients).
3. Para- or tetraplegic individuals in late stage of chronic illness (multiple sclerosis) or generalised cerebral deficits (head-trauma, intracerebral haemorrhage (10% of our patients).

Patients in categories (1) and (2) have the most favourable functional outcome. They can gain a greater degree of mobility and independence in daily life. Many of the patients that we have followed for years were able to re-establish some of their professional activities and former social life. Patients in category (1), however, were somewhat more difficult to dose-titrate. A few of those patients choosed not to proceed with implantation after the ITB trial because it resulted in loss of residual force or stance stability. A longer trial phase may be necessary for many of these patients to determine whether they will be earn functional improvement.

In our experience, patients in third category (3) usually only benefit in terms of nursing care and by avoiding some of the complications secondary to spasticity, such as pressure sores or contractures. Any major impact on their general performance of life was missed. This holds true for apallic patients or patients with other serious brain damage. Furthermore, the effective baclofen dose is usually higher for these patients than for spinal cord patients, which increases the risk of unwanted side effects of the drug

while providing only a modest effect on muscle tone. The reason for this might be, that the muscle tone is affected by supraspinal lesions. Central dysregulation of muscle tone like rigitidy or posture abnormalities contribute to the clinical picture in addition.

All symptoms directly related to spasticity such as hyperreflexia, muscle tone, clonus, spasms, and some bladder disturbances, show improvement or complete alleviation.

Muscle tone

All our patients experienced a significant reduction of muscle tone with ITB. The average spasticity score remained stable at more than 2 steps below the initial on the Ashworth scale through several years.

Hyperreflexia

In parallel to the relaxation of muscle tone, spontaneous spasms diminish. Spasms, however, are not a consistant clinical feature in all patients. It was the most refractory complaint and responded usually with higher dosage. In a number of cases, spontaneous spasms re-occurred even after long periods of therapy. These were sometimes due to bladder infections or other concommitant illness and were usually manifest much earlier than the increase in muscle tone. The reduction of spasticity coincided with a complete relief of muscle pain (i.e. spastic pain), although deafferentation pain due to spinal cord lesions, if present, remained unaffected.

Dosage

In order to maintain the effect of ITB the daily dose had to be increased from 107 ± 45 µg/day in the first week to $192 \pm \pm 131$ µg/day after six months of treatment (data from 48 patients). Approximately 5% of the patients developed signs of tolerance within the first 3–4 months with escalating dose requirements of more than 1000 µg/day (range: 500 to 1250 µg/day). In case of sudden withdrawal of ITB, even after years of treatment, spastic symptoms reoccurred and the patients experienced rebound spasticity for several days together with autonomic dysfunction [5].

Mobility

Under stable reduction of muscle tone, the physical therapy is facilitated, leading to a significant functional improvement and gain in the residual muscle strength. Many patients suffering from contractures, ankylosis, or tendon shortenings due to the long-lasting spasticity can be re-mobilised. This brings many patients to a better state of mobility. Among 38 of our patients preferentially bedridden before the procedure was initiated, 12 were able to abandon the bed and to use wheelchairs after 6 months. The residual muscle force, which had previously been insufficient to overcome the tremendous spastic muscle tone, could be activated.

Functional benefits

The functional status showed significant improvements regarding dressing activities, eating or other self controlled activities. Prior to treatment, 73% of our patients needed major help or were completely dependent on help for dressing, whereas only 36% did so after 6 months of ITB treatment [1, 2, 3].

Physician's and patient's global assessment

Both physicians and patients judged the outcome as excellent in 60 to 70% of cases, and as good or excellent in 85 to 90%. Neither group rated an outcome as poor.

Complications

Complications were related either to the drug, the drug pump or the catheter. Complications never resulted in permanent discontinuation of the therapy, and adverse symptoms and signs were always reversible. Two out of 61 multiple sclerosis patients died from their underlying diseases during this follow-up time (14 months and 21 months after pump implant), unrelated to the ITB treatment [1, 2, 3, 4, 5, 6, 7].

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