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LONG-TERM INTRATHECAL BACLOFEN TREATMENT IN SUPRASPINAL SPASTICITY

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INTRODUCTION

Spasticity is defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome [3], whereby the clinical signs and symptoms vary, dependent on the localization of the upper motor neuron lesion.

In spinal spasticity tendon reflexes are exaggerated and can become oscillatory by reexcitation (clonus). Flexor spasms are commonly observed in spinal spasticity. Exaggerated flexor facilitation and extensor inhibition as a response to afferent inputs of the flexor reflex are reported to be the consequence of interrupted reticular and vestibular spinal descending moderation.

Supraspinal spasticity is the result of a mismatch of descending facilitation and inhibition secondary to damaged or disconnected cerebral structures.

The spinal cord is disinhibited consequently to interrupted cortical excitatory inputs to the medullary reticular formation. The output of this medullary reticular formation via the lateral reticulospinal tract normally inhibits antigravity spinal reflexes and promotes voluntary movements.

In man facilitated promotion of extensor reflexes via facilitatory reticulospinal and vestibulospinal pathways is less affected by cortical lesions as they are not under direct cortical control [11, 13, 14].

Patients suffering from spinal spasticity benefit only in about 75 % of oral Baclofen treatment [17], whereas in supraspinal spasticity oral antispastic treatment is less successful, probably due to the pathogenetic mechanisms mentioned above.

Persisting increased muscle tone induces joint contractures, peri-

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pheral nerve lesions secondary to compression, muscle and tendon shortening and decubitus due to complicated general care.

Baclofen (β-[4-chlorophenyl]-GABA), Lioresal®, initially introduced as an oral antispastic drug, is a gamma-amino-butyric-acid(GABA)-analogous acting selectively on the GABA-β-receptor [1].

GABA, not blood-brain barrier permeable in sufficient amounts, is therefore ineffective [5]. The muscle relaxing effect, antagonized by bicuculline, is mediated by presynaptic and probably by dendrite GABA receptors [2].

GABA-β receptors located on primary afferent neurons seem to inhibit the presynaptic Ca^{++}-ion release. The L-glutamate and L-aspartate transmitter dependant pachymyelinated primary afferences seem to be under GABA-ergic presynaptic control [30].

According to clinical observations Baclofen is effective in spinal as well as in supraspinal spasticity, obviously having more influence on mono- than polysynaptic reflexes, which probably is due to the drug's presynaptic activity [12, 20, 30]. L-Baclofen is the pharmacologically active isomer [8–10, 27]. Both isomers are components of equal parts in the commercially available drug.

MATERIAL AND METHODS

Patient inclusion criteria:

— insufficient response to physical therapy;
— inefficiency of oral antispastic drug treatment, including Baclofen;
— presence of consequences of long term spasticity (impairment of residual motor function, development of severe contractures, complicated general care)
— positive response to intrathecal Baclofen bolus application;
— patient's or relatives informed consent.

Patients with poor prognosis concerning survival as well as patients with hypoimmunity were excluded. Clinical neurological examination as well as CT-scan, EEG, SSEP, BAEP, MEP, spine and joint X-rays and in most cases MRI investigations were performed.

Prior to intrathecal Baclofen application all patients were treated with a combination of oral antispastic drugs with increased dosages up to maximal levels (Diazepam 15 mg + Tizanidine 12 mg + Baclofen 75 mg daily), mostly connected with side effects such as nystagmus or reduced consciousness. When the first signs and symptoms of side effects occurred, but no benefit of the oral antispastic treatment was observed, intrathecal Baclofen administration was initiated. After a first intrathecal bolus of 25 μg administered by lumbar puncture, the dosages were increased by steps of 25 μg/day up to a maximum of 200 μg/day, in one single case of 300 μg/day. Because of the interindividual sensitivity (fig. 1) this step by step procedure has to be used. Spasticity was rated using the Ashworth scale and reflexes using a 6 point scale (areflexia to clonus).

In some patients (n = 7) the reflexes and muscle tone were measured polymyographically, using Beckmann® surface electrodes (Mm. biceps brachii, triceps brachii, quadriceps femoris, adductores femoris, tibialis anterior, triceps surae).

Continuous monitoring in a specially equipped surveillance unit and neurological scoring was performed in intervals of 30 minutes.

In cases of a good response to intrathecal Baclofen administration the patient was considered for a DAD (drug administration device) implantation. First signs of a response to intrathecal Baclofen were observed dose-dependent after 30 to 60 minutes with a duration of the therapeutic effect for approximately 3-6 hours.

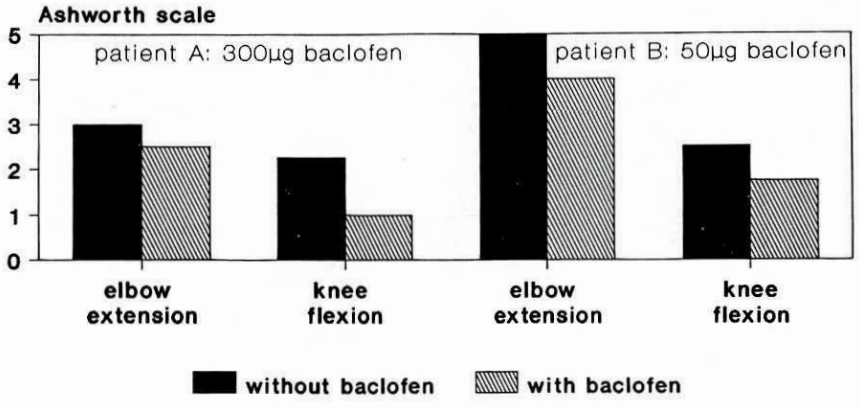

FIG. 1. — Range of interindividual sensitivity to intrathecal Baclofen bolus in supraspinal spasticity.

The implantation of the DAD[21] was performed under general anesthesia by a neurosurgeon. A 4F-Silastic catheter was introduced through a Tuohy needle between L3 and L4 and the tip pushed 20-25 cm rostrally into the subarachnoidal space, at least reaching the D8-9 level. The position of the catheter was controlled intraoperatively by fluoroscopy. Thereafter the catheter was sutured to the fascia and tunneled subcutaneously to the lateral abdominal wall, where a subcutaneous pocket for the DAD was made. The DAD was sutured to the fascia and connected to the catheter.

The DAD (SynchroMed®, Model 8611 H, Medtronic Inc., Minneapolis, USA) (fig. 2), has a drug reservoir of 20 ml volume, a lithium thionyl chloride battery powered peristaltic roller pump and an electronic circuit. Continuous infusion rates from 60 µg/day to 10.8 mg/day, bolus or bolus delay drug delivery

can be programmed by a microcomputer and can be transmitted to the implanted pump non invasively via a hand held radio frequency telemetry wand. The filled device weighs 195 g (OD 7.5 cm, thickness 2.5 cm).

Prior to implantation the device was filled with 10-12 ml of Baclofen in a low concentration (500 µg/ml, delivered by Ciba Geigy Corp., Basel, Switzerland). The flow was started slowly with about 100 µg/d and the patient's individual dosage, needed for optimal response, was determined within the next weeks. Refills were performed percutaneously through a rubber septum in the pump device with intervals ranging between 14 to 30 days. Longer lasting pump refill intervals were obtained using higher concentrations (2000 µg/ml) [25].

The battery operated pump works 3-4 years dependant on the infusion velocity.

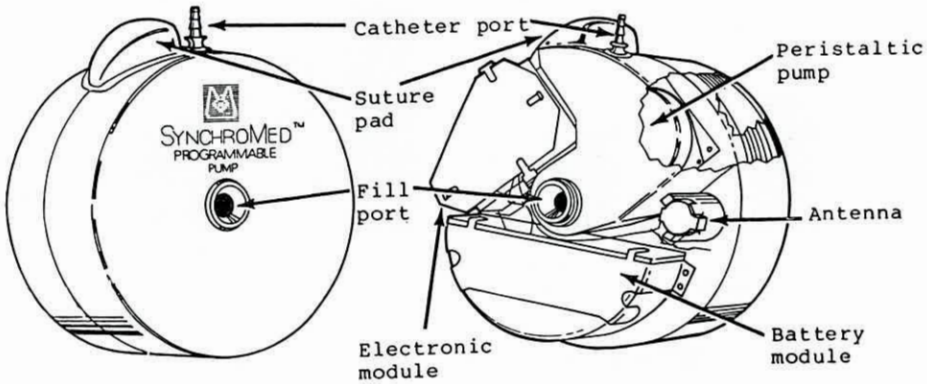

FIG. 2. Medtronic SynchroMed® pump, Model 8611H, with collapsible 18 ml drug reservoir, microprocessor-based circuitry, lithium thionyl-chloride battery, antenna acoustic transducer, peristaltic pump and a fill port with a self-sealing septum and needle stop.

Implantations of medical devices are connected with increased risks for infections, especially in apallic patients, who are immunosuppressed secondary to the chronic stress reaction [7]. Therefore most patients got prophylactically antibiotics after implantation.

All patients (n = 9) were male with a mean age of 23 years and suffered from supraspinal spasticity secondary to:

— traumatic apallic syndrome (TAS) in remission (n = 6);
— hypoxic apallic syndrome (HAS) in remission (n = 1);
— Little's disease presenting with spastic paraparesis (n = 1);
— hereditary spastic paraplegia (HSP) with spastic paraparesis (n = 1).

Spasticity was diagnosed in all patients for more than 2 months. All traumatic and the hypoxic apallic patient presented decortication patterns, resistant to conventional antispastic treatment (tab. I).

TABLE I

PATIENT CHARACTERISTICS

No	Diagnosis	Age *	Sex	Duration of disease *	Follow-up	Final dosage µg Baclofen/d
1	TAS	21	m	6¼ months	11 days **	132
2	TAS	14	m	2 months	1 month **	456
3	TAS	14	m	32 months	28 months	96 (max 170)
4	TAS	21	m	7 months	19 months	750
5	TAS	21	m	7½ months	9 months	850
6	TAS	24	m	6½ months	3 months	700
7	HAS	15	m	3 months	6 months	10000
8	Little's dis.	31	m	31 years	3 months	620
9	HSP	46	m	10 years	13 months	10000
Mean values ± SD		23 ± 10.2				623 ± 336

* At time of implantation. ** Pump explanted. TAS: Traumatic Apallic Syndrome. HAS: Hypoxic Apallic Syndrome. HSP: Hereditary Spastic Paraplegia.

RESULTS

Out of a total of 19 patients, all of them suffering from severe supraspinal spasticity and evaluated by intrathecal Baclofen boli, only 3 patients did not respond to boli up to 200 µg. In two patients with a heredodegenerative disease a marked muscular weakness occurred without effecting spasticity and in one patient with dystonic and spastic symptomatology of perinatal origin no response to intrathecal boli up to 200 µg was achieved.

All other patients responded well to intrathecal boli of 75 to 200 µg. A dose dependant response was observed. In some cases an implantation of the DAD was not possible because of either morphological (cachexia) or financial difficulties.

In all patients with implanted DAD the best dosage level was reached only after weeks or months. In apallic patients dosages of up to 1000 µg/day were needed. Compared with patients suffering from spinal spasticity our patients with supraspinal spasticity needed approximately 100 % higher dosages. However, in none of them side effects such as fatigue, reduced consciousness or nystagmus occurred. OCHS *et al.* [18], reporting on a reduced response of supraspinal spasticity to intrathecal Baclofen, may be based on insufficient dosages.

The reduction of reflexes was more pronounced than reduction of muscle tone, and both decreased more on the lower limbs in comparison to the upper limbs (fig. 3-4).

In patient no. 3 the muscle tone decreased, thus the spasticity induced dislocated shoulder and hip joint could be reduced surgically. After 4 months of therapy his finalized fine motor functions as well as his pseudobulbar paralysis improved, thus three years after the brain trauma he started to speak.

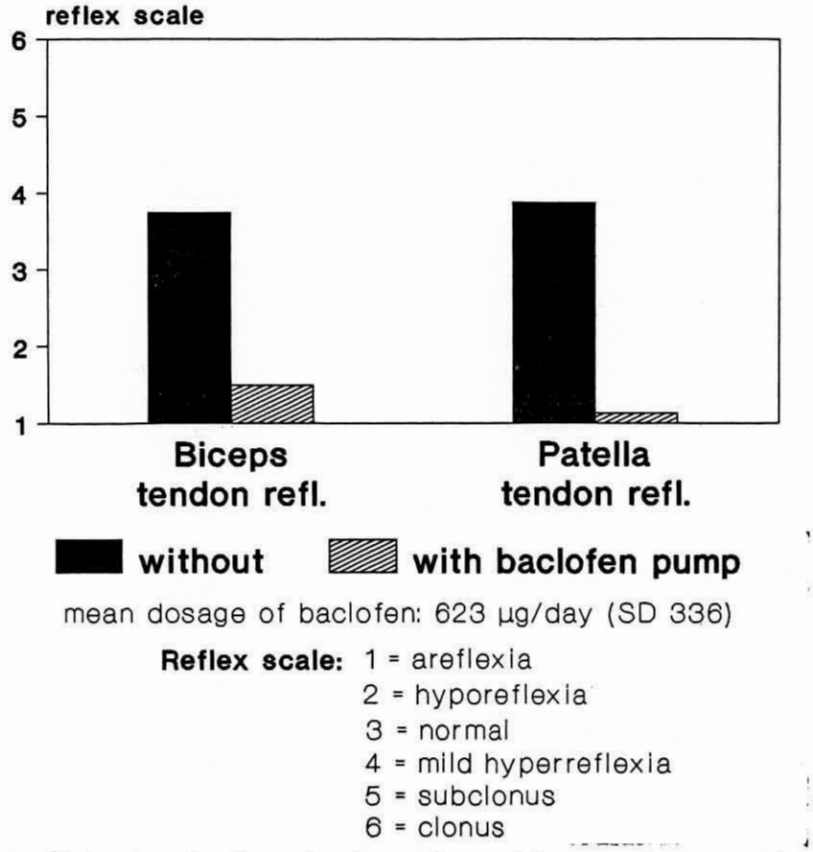

FIG. 3. — Reduction of reflexes in nine patients with supraspinal spasticity and long-term intrathecal Baclofen therapy.

In patient no. 8, suffering from a marked paraspasticity of perinatal origin, the flexion of hip and knee improved significantly under 480 µg Baclofen/day. Thereafter he was able to go up stairs, something he could not do before even with help.

At a dosage of 1000 µg/day the patient with hereditary spastic paraplegia (no. 9) improved his motor performance, although muscle tone and reflexes did not decrease to physiological levels. Nevertheless he was content with this improvement and refused a dosage increase.

Bladder function and voiding

Improved voiding due to intrathecal Baclofen application in spinal spasticity is reported [18].

The authors observed increased bladder capacity, decrease of the high bladder pressure [18, 6]. Contrary to this report, we could not observe these improvements of bladder function in spinal spasticity, confirming the observations of THALALLA *et al.* [29]. Surprisingly two patients suffering from supraspinal spasticity showed a striking improvement of micturition. Patient no. 3 was able to control his urinary incontinence due to intrathecal Baclofen application. After a pump stop he lost immediately this ability and increased spasticity returned.

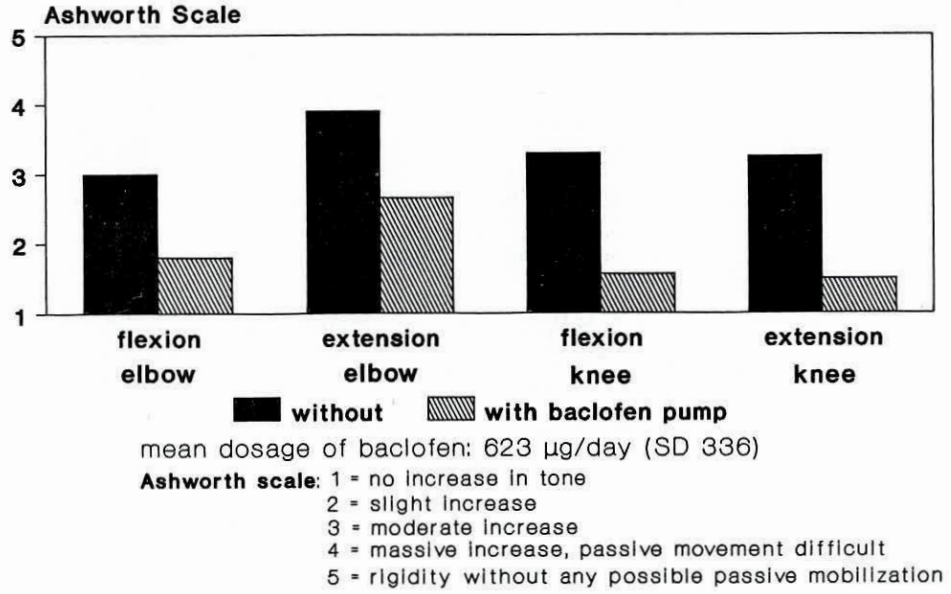

FIG. 4. — Reduction of muscle tone in nine patients with supraspinal spasticity and long-term intrathecal Baclofen therapy.

Patient no. 8, dependant on CIC (clean intermittent catheterism) for 3 years, complicated by sphincter spasms, was able to micturate spontaneously without residual urine under a 280 µg/day dosage. This clinically observed improvement could be demonstrated dramatically by urodynamic investigations (fig. 8, 9).

Complications

Infections: One DAD had to be explanted due to an infection of the subcutaneous pocket. Contrary to other authors [15] observations, meningitis or secondary infections due to refilling were not observed.

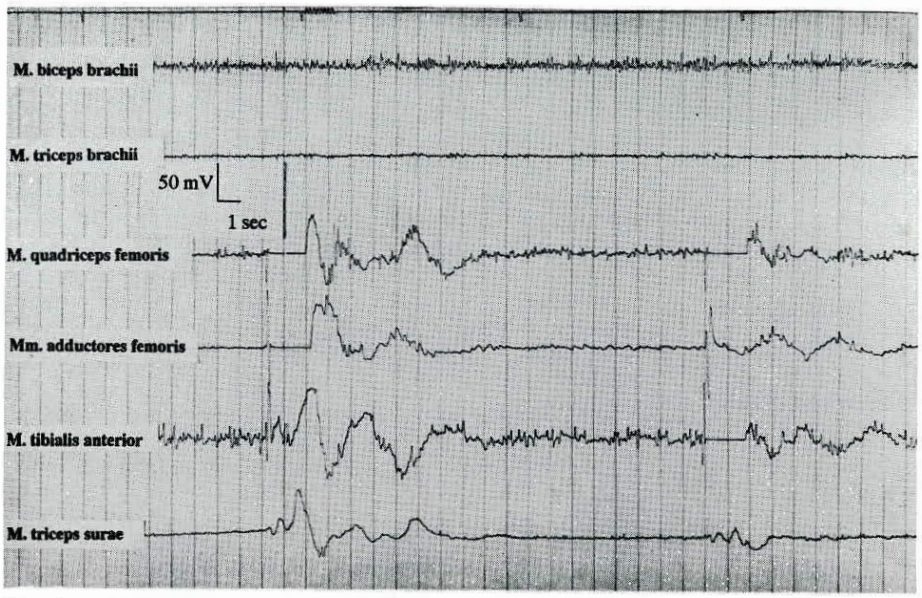

FIG. 5. — Polymyographic recording of the right side extremities, after T-reflex (right patella) without intrathecal Baclofen.

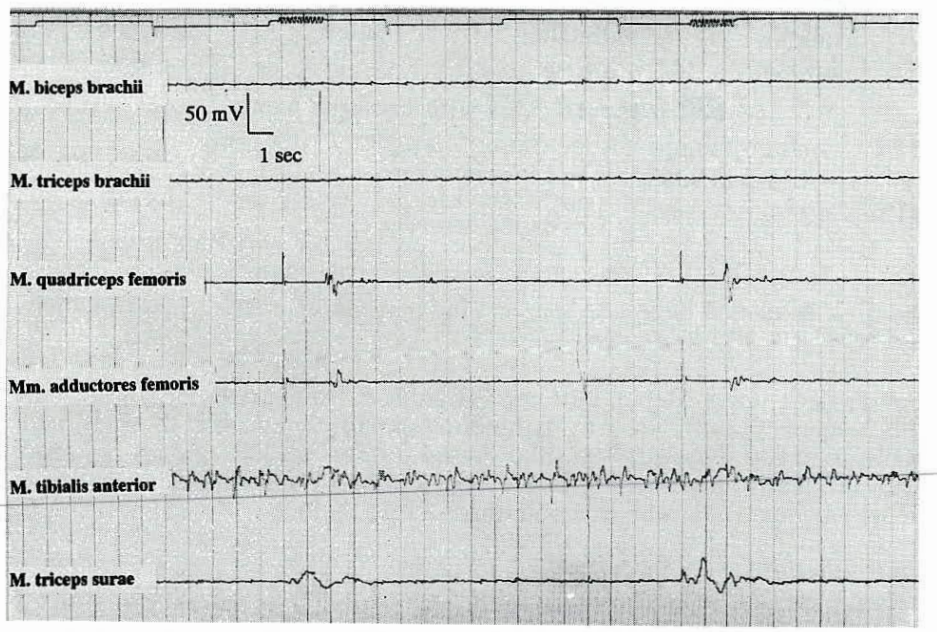

FIG. 6. — Polymyographic recording of T-reflex (right patella) after intrathecal bolus application of 25 µg Baclofen.

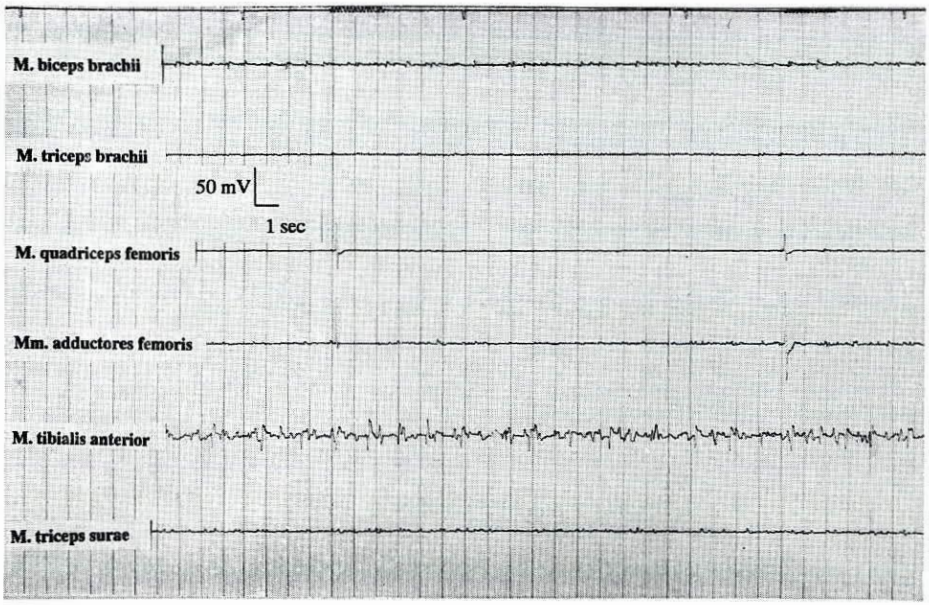

FIG. 7. — Polymyographic recording of T-reflex (right patella) after intrathecal bolus application of 50 µg Baclofen.

Catheter displacement: In spinal spasticity catheter displacement could be observed in several cases [15] probably as the consequence of repeated pronounced anteflexion during positioning. In none of our patients suffering from supraspinal spasticity this complication occurred.

Wound-healing impairment: One DAD had to be explanted because of a suture dehiscence.

CSF leakage: As a consequence of the Tuohy needle gauge a long duration CSF leakage with the typical symptoms of CSF loss was seen. In these cases local autologous blood injection is effective.

Intoxications: Generally, boli or continuously applicated high dosages of Baclofen are affected with the risk of intoxication. Nevertheless highest dosages of intrathecal Baclofen up to 10 mg can be survived without any sequela as reported previously [24], intensive care monitoring, artificial ventilation and CSF exchange provided. Physostigmine as antidote [15] is ineffective in severe intoxications [24].

Seizures: During severe intoxication generalized seizures had to be observed [23]. Contrary to DRALLE *et al.* [4] increased seizure frequency occurred in 4 patients, all of them treated within a therapeutical range.

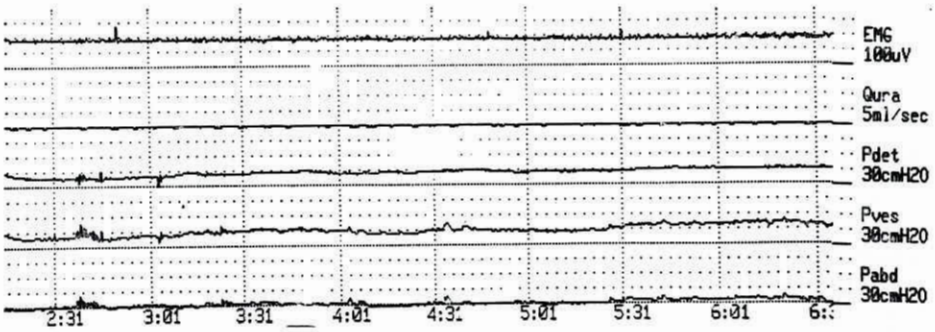

FIG. 8. — Patient No. 8: Urodynamic investigation without Baclofen. Filling volume 323 cc, dullpain in the bladder area; no detrusor contraction; no micturition; patient remains on CIC (Clean Intermittent Catheterism). *Legend*: EMG: random EMG from the pelvic floor muscles; Qura: flow; Pdet: detrusor pressure (subtraction of intravesical minus intrarectal); Pves: intravesical pressure; Pabd: intra(rectal) abdominal pressure.

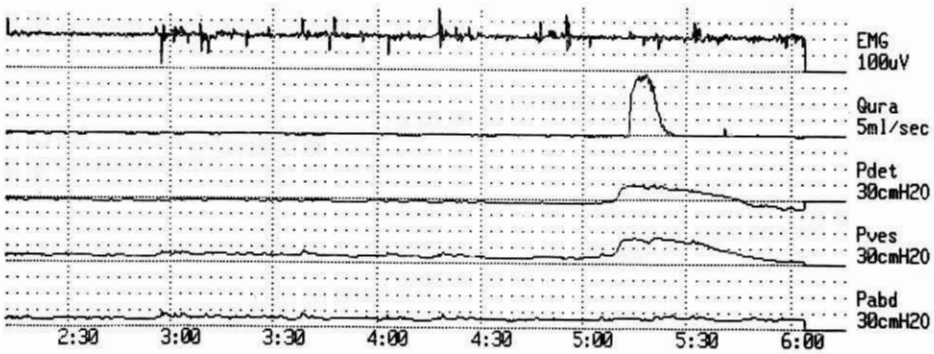

FIG. 9. — No: 8: Urodynamic investigation with 600 µg intrathecal Baclofen/d. Filling volume 150 cc micturition on command resulting in a good detrusor contratcion, with intravesical pressure up to 50 cm H_2O with excellent flow and without residual urine. *Legend*: EMG: random EMG from the pelvic floor muscles; Qura: flow; Pdet: detrusor pressure (subtraction of intravesical minus intrarectal); Pves: intravesical pressure; Pabd: Intra(rectal) abdominal pressure.

DISCUSSION

Intrathecal Baclofen administration in spinal spasticity is already generally established [19, 22, 28]. The application of Baclofen in supraspinal spasticity is controversially discussed [18, 26, 4]. As 80 % of the substance remains in the lumbar region and the pathogenetic mechanism of supraspinal and spinal spasticity differs an inefficiency of lumbar application in supraspinal spasticity is discussed [18]. Low dosages analogous to those used in spinal spasticity were initially also applied in supraspinal spasticity. According to our observations supraspinal spasticity requires high dosages of intrathecal Baclofen. A reduction of muscle tone but also an amelioration of voluntary motor

performance as well as an improvement of a pseudobulbar paralysis induced disturbance of speech can be achieved, as mentioned above. The improvement of bladder control in two patients with supraspinal spasticity indicates a supraspinal action of the substance at the pontine micturition center.

Nevertheless not all patients presenting with supraspinal spasticity responded to intrathecal Baclofen application, as especially observed in heredodegenerative diseases. Supraspinal spasticity has to be considered as a comprehensive conception with several subgroups clinically not to be differentiated and not responding equally to intrathecal Baclofen.

Therefore the application of test boli is unavoidable in cases of supraspinal spasticity.

The risk of intoxication especially during the phase of evaluation by bolus application necessitates a special surveillance unit for these patients.

According to the observations mentioned above, intrathecal Baclofen treatment is an effective method to be used in patients suffering from supraspinal spasticity, not responding to conventional oral pharmacological and physicotherapeutical treatment. Despite the risks connected with this method it has to be considered as treatment of choice in cases of severe supraspinal spasticity as the patients benefit not only of the reduced muscle tone but in some cases also improve motor functions and/or bladder control.

SUMMARY

Baclofen, a derivate of gamma-amino butyric acid (GABA), is known to be a useful drug in spasticity treatment. To achieve a good therapeutic response higher oral dosages have to be administered related with central side effects. Intrathecal application of Baclofen in µg range dosages is proved to be effective in spinal spasticity. The efficiency of intrathecal Baclofen in patients suffering from supraspinal spasticity is discussed controversially.

We report on 9 patients with long-term intrathecal Baclofen treatment, all of them responding well presenting a marked reduced muscle tone. In most cases an improvement of motor performance and in two cases improved bladder function was observed. The therapeutical dosages administered to patients with supraspinal spasticity exceed those administered to patients with spinal spasticity for approximately 100 % without provoking central side effects.

Despite the risks connected with this method it has to be considered as treatment of choice in cases of severe supraspinal spasticity.

RIASSUNTO

Il trattamento della spasticità sopraspinale è stato preso in considerazione alla luce delle difficoltà esistenti con le terapie convenzionali. Il Baclofen, derivato dell'acido gamma amino butirrico (GABA), è uno dei farmaci normalmente utilizzato, ma a causa delle alte dosi impiegate per os, sono frequenti gli effetti collaterali che costringono alla sospensione. La somministrazione

per via intratecale di basse dosi del farmaco ha consentito di valutare in nove soggetti una marcata riduzione del tono muscolare, con un miglioramento nella maggior parte delle prestazioni motorie ed in due casi della funzione vescicale. Nonostante i rischi connessi a tale metodo esso può essere considerato come trattamento di scelta in casi di severa spasticità sopraspinale.

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