INTRATHECAL BACLOFEN TREATMENT OF SEVERE SUPRASPINAL SPASTICITY

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Summary

Baclofen, a derivative of gamma-amino butyric acid (GABA) is widely used as an antispastic drug. Administration of elevated doses of the drug orally, used to obtain an adequate therapeutic effect, cause the presence of cerebral side effects.

Intrathecal use of baclofen is considered the treatment of choice in patients suffering from spinal spasticity who do not respond sufficiently to conventional oral antispastic medication. This approach has also been used successfully in cases with spasticity of supraspinal origin. To achieve a good therapeutic response in the latter condition the amount of intrathecal baclofen has to be at least 70% higher than is used for spinal spasticity.

We report on 18 patients affected by severe supraspinal spasticity. Intrathecal baclofen notably reduced muscle tone and reflexes in all our patients. In some cases improvement of motor performance was noted and in some improvement of bladder function. We can conclude that intrathecal baclofen is effective in cases of severe supraspinal spasticity which do not respond to oral antispastic therapy.

Introduction

Spasticity has been defined by Lance (1980) 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". The anatomical source of the disinhibition of descendent supraspinal control, or rather the disorder of the motor control system that is the cause of the spasticity, determines specific clinical patterns. Supraspinal spasticity can be divided, in animal models, into two types. Exstensive and bilateral lesions in areas 4 and 6 in the monkey produce a decortication pattern due to the interruption of premotor cortical control of the mesencephalon. In this case the predominant

disinhibition of the rubrospinal system increases the influence of the neck and vestibular stretch reflexes. The decerebration rigidity, provoked by the intercollicular section made at the vestibular nuclei, explains the increase in extensor tone with phasic and tonic components of the stretch reflex.

Classical antispatic therapy consists of drugs which have different action mechanisms. Among these baclofen (beta-4-chlorophenil-GABA), Lioresa R, initially introduced as an oral antispastic drug, is a GABA (gamma-amino-butyric acid)-analogous, that selectively acts at GABA receptors. GABA does not cross the blood-brain barrier, and is therefore ineffective. The muscle-relaxing effect is not anatagonized by bicuculline and is mediated by presynaptic GABA receptors, probably at a dentritic level. The GABA-B receptors are located on the primary neuronal afferent ways and seem to inhibit the release of Ca++ ions at a presynaptic level. L-glutamate and L-aspartate, stimulatory neurotransmitters, have more influence on mono- than on polysynaptic reflexes, which is probably due to the drug's presynaptic activity. L-baclofen is the pharmacologically active isomer.

Materials and methods

18 patients affected by serious supraspinal spasticity, who had not responded positively to oral pharmacological antispastic therapy, were studied during administration of doses of intrathecal baclofen.

Criteria of the choice of patients:

— insufficient response to physical therapy;

— ineffectivenes of oral antispastic treatment, baclofen included;

— the presence of serious side effects under oral antispastic therapy;

— a degree of spasticity such as to compromise the quality of life;

— the presence of disorders consequent to stabilised spasticity (massive contractures compromised general condition);

— positive response to baclofen dose;

— informed consent of the patient or closest relative.

The patients, mostly with brain injuries, whose prognosis considered survival improbable, were excluded, as were those who were immunodepressed. These subjects, before being given the doses by lumbar injection, were treated with oral pharmacological therapy at high dosage of diazepam (15mg/day), tizanidine (12 mg/day) and baclofen (75 mg/day). These treatments were found to be ineffective in combatting the spastic symptomatology; moreover they caused the appearance of side effects such as nystagmus, muscle weakness, decreased consciouness. All of the patients were put under various tests in order to eliminate any diagnostic doubts before using the intrathecal dose.

We carried out cerebral CT, EEG, SSEP, BAEP, MEP, MR and other radiological tests. Motor performance was assessed not only by a doctor, but also

by a physioterapist.

The initial dose was of 50 ug/day with daily increases of 50-100 ug. The maximum dose used in these cases was of 400 ug/day. After each dose the patients were monitored continuously for 12 hours in their vital functions (respiratory and heart rate, blood pressure), since baclofen may provoke respiratory depression, arterial hypothension, bradicardia. In some cases we carried out a polymiographic recording, and in others we made a video before and after any improvement. The first response for this therapy was observed about 1-2 hours after administration and the therapeutic effect persisted for 3-6 hours.

Spasticity was evaluated using the Ashworth scale for muscle tone and a scale of 6 for reflexes.

In the cases in which there was a satisfactory response for Baclofen, we considered the possibility of a DAD (Drug administation device) implant. The implant of the above mentioned pump was carried out by a neurosurgeon under general anaesthetic. A spinal catheter of the 4F-Silastic type was introduced with a Tuohy needle into the L3-L4 space and the point was pushed for about 20-25 cm in a rostral direction in the subarachnoid space, at least as far as D8-D9.

The position of the catheter was controlled during the operation by fluoroscopy. Then the catheter was sutured to the support tissue and subcutaneousely passed to the lateral abdomen wall, where a subcutaneous pouch was prepared. At this point the DAD was sutured to the support tissue and connected to the catheter. The DAD (Synchromed R, model 8611H, Medtronic Inc. Minneapolis, USA) has a volumetric capacity of 20 ml, works with a lithium thiouyl chloride battery, with a peristaltic rotation pump and an electronic circuit.

Doses from 60 ug/day to 10-8 mg/day of the drug can be programmed by a microcomputer and can be transmitted, non-invasively, to the implanted pump via a telemetric antenna at radio frequency. The entire system weighs 195 g, has a diameter of 1-5 cm and a thickness of 2-5 cm. In one patient, who dislpayed signs of significant malnutrition after cerebral hypoxy, and whose abdominal space was therefore insufficient for a normal pump, we implanted a smaller pump with a reserve of 10 ml.

Before the implant the pump was filled with baclofen (14 ml) at low concentration (500 ug/ml), supplied by Ciba Geigy Corp, Basel, Switzerland. The initial flow was decided depending on the patient: those with spinal spasticity received initially 25-50 ug/day of baclofen, those with supraspinal spasticity 50-100 ug/day. Dose-adjustment was planned for the following days and weeks, observing the reduction in spasticity obtained daily.

The refilling processes were carried out after variable intervals depending on the optimal dose for each patient. In order to achieve a longer interval

between one refilling and the next, the concentration of the drug was changed, using the highest available concentrate at 2000 ug/ml (21,22).

The battery lasts for about 3-4 years and depends on infusion velocity. The pump implants can be affected by infections, especially in apallic patients, who are immunodepressed following a chronic reaction to stress. All patients received prophylactic antibiotic therapy after the operation.

15 of the patients were male and 3 female with an average age of 28.6 years (table I):

post-traumatic apallic syndrome in remission (n=9);

hypoxic apallic syndrome in remission (n=3);

Little's disease with spastic paraparesis (n=1);

Familiar spastic paraparesis (n=3);

oligodendrioglioblastoma with serious spastic paraparesis (n=1);

serious spastic tetraparesis, as a consequence of aneurismatic rupture from artero-venous malformation (n=1).

In all of these patients spasticity had been diagnosed at least two months previously (table I). All traumatic and hypoxic patients displayed decerebration patterns, untreatable with conventional antispastic therapy.

Results

Out of 23 patients, affected by serious supraspinal spasticity and administered doses of baclofen, only 5 did not respond to elevated intrathecal doses. In two patients with heredo-degenerative disease we observed marked muscle weakness without any improvement of the spastic symptomatology. This was also the case in two patients with spasticity of a traumatic origin, already stabilised for a couple of years. In one patient with spastic and distonic patology of a perinatal origin we observed no improvement in spasticity althought doses of more than 200 ug were used. All the remaining patients all responded to baclofen doses between 75 and 400 ug. In some cases the implant of the pump was ruled out due to the high cost of the system, unfortunately not always within the family's means, or due to lack of interest. In all 18 patients in which we performed a DAD implant, the optimal dose was achieved after weeks or months. In some apallic patients doses of baclofen higher than 1000 ug/day were necessary (table I).

Comparing the average of these doses with those of our spinal patients, it turns out to be about 70% higher. However, in none of our patients did we observe the appearance of side effects such as tiredness, reduction of consciousness or nystagmus.

Ochs et al., in describing an inadequate response to the administration of intrathecal baclofen in a case of supraspinal spasticity, probably used insufficient doses. The reduction of the reflexes was greater than that of the muscle tone and both

were more evident in the lower limbs than in the upper limbs.

In patient no.3 the muscle tone was reduced to such an extent that it provoked dislocation of the shoulder which was repositioned surgically. In the same patient, three years after the trauma and four months after continued intrathecal therapy with baclofen, we observed finalized movements of the upper limbs and an improvement of the pseudobulbar symtomatology, so that verbal comunication was possible for the first time since the trauma. In patient no.8, affected by a serious spastic paraparesis of perinatal origin, the flexion of the hip and knee was notably improved under daily intrathecal doses of baclofen of 480 ug. This subject was able to climb stairs, whereas this had been possible previously only with help. Patient no.12, after 8 months of continuous intrathecal baclofen therapy at doses of 1200 ug/day, was able to stand up and make a few steps. This had been not possible before the implant of the baclofen pump; in fact, despite intense physiotherapy, it had not been possible to reduce hypertone in this patient, in particular the excessive of the thigh on the hip and of the lower leg on the thigh.

Also patient no.18, affected by serious spasticity with notable spasms during flexion of the lower limbs, significantly benefitted from intrathecal baclofen treatment, in the sense that only 2 weeks after the implant and with a daily dose of 600 ug, he managed to sit upright and stand erect.

A significant result obtained with the use of intrathecal baclofen in patients with supraspinal spasticity is the improvement in bladder function observed in two of the reported cases. The improvement in bladder evacuation after the administration of intrathecal baclofen in spinal spasticity has been elsewhere reported. Some authors have observed an increase in capacity and decrease in high bladder pressure. Patient no.3 regained bladder control after intrathecal baclofen treatment. After the pump was stopped, he immediately became incontinent and spasticity notably increased. Patient no.8 who had made intermittent use of catheters daily and who displayed excessive sphincter spasms, menaged to urinate spontaneously without leaving bladder residue on a daily dose of baclofen of 280 ug. These clinical improvement were further demonstrated by urodynamic tests.

Three pumps had to be explanted becouse of an infection of the subcutaneous pocket in the abdominal wall. Another pump was removed because of loosening of the suture at the surgical wound.

No case of meningitis or secondary infections subsequent to refilling of the pump were noted, contrary to the findings of other authors. In none of the 18 supraspinal patients was there catheter displacement. Two patients developed focal, and subsequently general, epileptic seizures.

Discussion

The administration of intrathecal baclofen in spinal spasticity is widely accepted, whereas its use in supraspinal spasticity is controversial.

Since 80% of the substance remains in the lumbar region and the pathogenetic mechanism of spinal and supraspinal spasticity differ, the inefficiency of lumbar administration in supraspinal spasticity is under discussion. Low doses, analogous to those used in spinal spasticity were also initially used in patients with supraspinal spasticity. Our experience with supraspinal patients has shown that in such cases doses at least 70% higher are required than those used for patients with spinal spasticity. This could be due, in patients suffering from brain injury, to the heterogeneous influences of the multifocal supraspinal traumatic lesions on the control motor circuits employed for posture regulation; spinal damage is more localized and usually consists of a more segmental hyperexcitability. Another explanation could be the different location of the GABA-B receptors involved or in the probably different response of the various subtypes of receptors.

In some patients the decrease in muscle tone and spasms caused an improvement in motor functions, in one patient the pseudobulbar paralysis was reduced with a recovery of verbal capacity. The improvement in bladder function, linked to a decrease in sphinteric disinergy, in two of the 18 supraspinal patients, suggests a potential effect of baclofen on the pontine centre of the micturition, as has been observed in rats. The epileptic fits observed in two cases could be caused by post-traumatic cerebral scars, even though the close relation indicates a connection with the intrathecal administration of baclofen.

Meningitis and local infections are generally avoidable by maintainig absolute sterility, especially in the process of refilling the pump.

The risk of intoxication is especially present in the intrathecal administration of the doses. Close observation of the patient by expert personnel is necessary after the administration of the dose or during the "adjustment" of the daily dose, especially when increases are made which are more than 30% higher than the base dose. In any case, of fundamental importance is the evaluation phase with doses of the drug to better predict the long-term effectiveness of the therapy on the improvement in motor function and in the quality of life of the patient.

Despite the risks connected with this method, our results indicate that continued intrathecal baclofen treatment can be considered the therapy of choice in serious spasticity which does not respond to normal oral antispastic therapy. The use of a telemetrically programmable pump is especially useful.

Table 1: characteristics of the patients affected by supraspinal spasticity

No	Diagnosis	Age*	Sex	Duration**	Follow-up***	Final doses ug/day
1	PTAS	21	M	6.25	0.35	132
2	PTAS	14	M	2	1	456
3	PTAS	14	M	32	46	190
4	PTAS	21	M	7	48	750
5	PTAS	21	M	7.5	26	820
6	PTAS	24	M	6.5	5	700
7	PTAS	15	M	3	6	800
8	M.Little	31	M	372	20	700
9	FSP	46	M	120	30	330C
10	AVM	17	F	55	15	120
11	PTAS	27	M	12	14	700
12	PTAS	17	M	8	11	1200
13	FSP	46	M	144	10	70
14	FSP	49	F	468	73	70
15	HAS	48	F	5	0.35	400
16	PTAS	37	M	22	3	300
17	HAS	30	M	4	2	1100
18	ODGB	37	M	84	1	800

Mean doses: 535.44
SD: 343.09
* At the moment of the pump implant; in years.
** Of disease at the moment of the pump implant; in months.
*** In months.

SAPT: post-traumatic apallic syndrome.
SAIP: hypoxic apallic syndrome.
PPSF: familiar spastic paraparesis.
MAV: artero-venous malformation.
ODGB: oligodendroglioblastom.
C: complex (doses differentiated over 24 hours).

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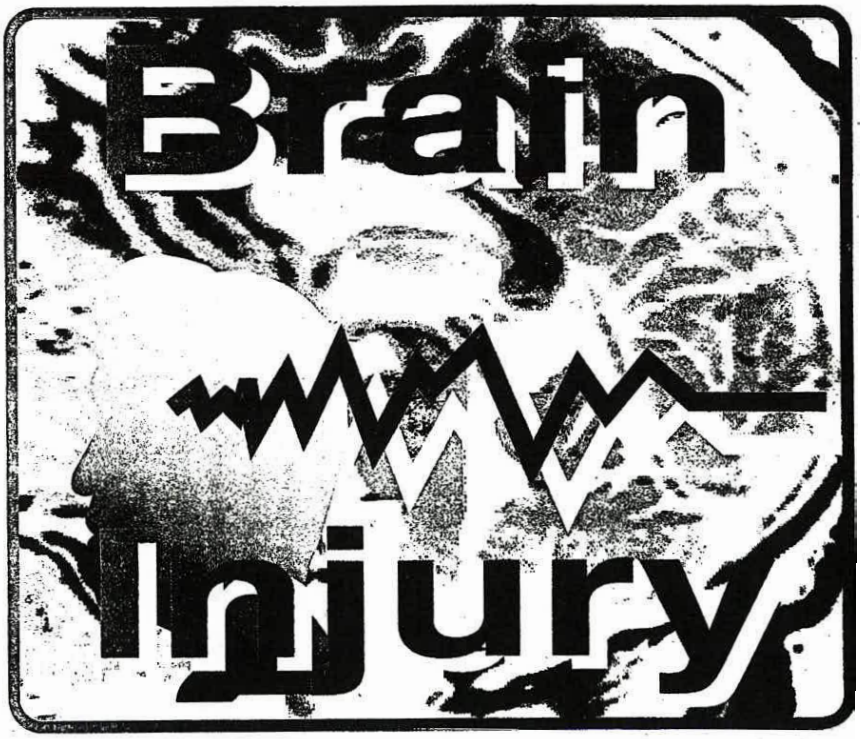

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