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European Journal of Physical and Rehabilitation Medicine 2023 Sep 21
DOI: 10.23736/S1973-9087.23.07960-1

Intrathecal baclofen as an effective treatment for generalized dystonia in Wilson's disease

Intrathecal baclofen (ITB) is a well-established treatment for adults' with generalized spasticity.[1]

While in children with dystonic cerebral palsy (CP) ITB has shown to be superior to placebo,[2] in adults with generalized dystonia there is contrasting evidence that ITB can be used as an effective treatment, since the available data are based mainly on non-controlled studies[3, 4] except for a small placebo-controlled study in patients with secondary dystonia.[5] ITB has also been advocated for the treatment of dystonic storm in generalized dystonia and Wilson's disease (WD).[6] Even if WD is a known cause of secondary generalized dystonia (sometimes accompanied by spasticity), at present time there are no available outcome descriptions for patients with WD treated with ITB.[7] In this paper, we report the case of a patient successfully tested and treated with ITB for generalized dystonia in WD.

The patient is a 36-year old Caucasian male, suffering from generalized dystonia and a parkinsonism that progressively appeared from the age of 21 years. He was diagnosed with WD at the age of 25, but unfortunately, he received no treatment due to limited access to specialized care, until he moved as a refugee to Switzerland in 2014.

He was then treated with d-penicillamine that allowed a satisfactory control of blood copper levels. Nevertheless, due to severe dysphagia and recurrent aspiration pneumonia, the patient underwent a percutaneous gastrostomy in 2015.

He was referred to rehabilitation unit for the treatment of a severe motor disability associated to his generalized dystonia. Along with adaptation of aids (wheelchair, bathroom at home), stretching and exercise, the patient underwent a treatment with oral baclofen (up to 100 mg/day), and subsequently with tryhexiphenidyl (12 mg/day), which were both unsuccessful. We decided then to treat dystonia at upper and lower extremities with onabotulinumtoxinA (Botox®). We injected wrist flexors to improve hand grasp (with the goal of improving his capacity to hold a walker or a bar) and either hip adductors and triceps surae to improve gait, characterized by scissoring and equinus foot. On the whole he was treated with 400 UI, without any satisfactory outcome.

Faced to these multiple failures, we discussed with our Hospital's neurosurgeons about the possibility for him to undergo the implantation of bilateral deep brain stimulation. Due to the presence of extensive basal ganglia lesions and atrophy at brain MRI the patient was not considered eligible for this treatment, we then considered the use of ITB.

From a functional point of view, the patient was able to do transfers (from his wheelchair, from the bed, to the toilet) only with total assistance. He was able to walk for about 20 meters with an ante-brachial walker and assistance of one person. During transfers, standing position and assisted gait, the patient showed a severe dystonia at upper limbs, with a pattern of flexed elbow and flexed wrist. During gait, also lower limbs had a severe dystonia, with a bilateral talipes equinus foot (in association with a sustained plantar flexors' clonus), flexed knee and adducted thighs, and moreover, during gait, a severe forward trunk lean.

The patient also needed physical assistance for all the activities of daily living.

Due to the severe generalized dystonia, the absence of literature supporting its use in patients with WD and considering the difficulty to predict the possible functional outcome, we proposed to undergo a continuous ITB test using an external pump, connected to an intrathecal catheter.

In our service, for all patients undergoing an ITB test before pump implantation, we evaluate the attainment of client's (patient and/or caregiver) relevant goals based on the GAS method[8] and using a SMART approach.[9]

The identified goals were: 1) improvement of transfers' speed (at least of 25%) and in particular bed to wheelchair transfers; 2) decrease of the physical assistance during transfers (at least 2 points in a 0 to 10 scale basing on care-giver's difficulty in transfers assistance); 3) improvement of gait speed (at least 25%, and assessed with the 10 meters walking test, evaluating both the comfortable gait speed and the maximum gait speed). Each evaluation was assessed before the ITB test (T0), and after each ITB dose modification (T1 to T6). Along with the goals, we also evaluated the modifications in muscle hypertonia, before (T0) and at the end of the ITB test (T6) with the Modified Ashworth Scale (MAS). For the ITB test, we utilised an external MICREL Rythmic © pump (MicrelMedical Devices SA, Koropi, Athens, 19441, Karella Industrial Area Greece).

After sedation with propofol, the patient had the implantation of an intrathecal catheter (Bbraun Perifix® - B. Braun Medical, Sempach, 6207, Switzerland). The catheter was implanted at T6 level with a sterile, fluoroscopic-guided procedure (the catheter tip level is confirmed by injection of radio-opaque contrast, Iopamiro® 200 mg/mL, Bracco Suisse SA, Cadempino, 6814, Switzerland). Then, the catheter was tunneled under the skin, secured to the skin with a suture and connected to the pump after having placed a 0.2 μm antibacterial filter. Baclofen was diluted at 10 mcg/mL. We started the test with a priming bolus of 50 μg, followed by a continuous infusion of 72 μg/day. During the following days the dose was progressively titrated up to 216 μg/day. The test ended after 5 days.

Goal progression related to ITB doses is reported in Table I, II.

The patient did not show any side effect during the whole test. Patient's maximal gait speed improved along with the increase of baclofen dose, mainly due to an increase of step cadence. On the other hand, comfortable gait speed did not improve, even if the gait quality did (pointed out by a resolution of plantar flexors clonus

TABLE I.—*Goal Attainment Scaling of patient's objectives of treatment and clinical evaluation before the ITB test (T0) and after each dose increase (T1 to T6).*

Patient's goal	SMART goal	Weight	Baseline	Achieved
Reduce the time from sit to stand	Reducing of at least 25% the time needed for transfer from sit to stand (with 1 person)	3x2	-1	0
Reduce the help of the mother during transfers	Reducing caregiver perceived difficulty during transfers of at least 2 points (0-10 scale)	3x3	-1	0
Walking faster	A) Increase of at least 25% comfortable gait speed	1x3	-1	-2
	B) Increase of at least 25% fast gait speed	1x3	-1	2
T-score			Baseline: 35.8	Achieved: 50

TABLE II.—*Goal Attainment Scaling of patient's objectives of treatment and clinical evaluation before the ITB test (T0) and after each dose increase (T1 to T7).*

	T0	T1 (day 1)	T2 (day 2)	T3 (day 3)	T4 (day 3)	T5 (day 4)	T6 (day 5)	T7
ITB daily dose (µg/day)	0	72	96	120	144	192	216	216
ITB daily flow (mL/h)	0	0.3	0.4	0.5	0.6	0.8	0.9	
10 mWT (comfortable gait speed, m/s)	0.15	-	0.19	0.12	0.13	0.12	0.14	0.13
10 mWT (maximal gait speed, m/s)	0.32	-	-	-	0.59	0.79	1.17	1
Time of bed-wheelchair transfer (s)	49	-	26	-	24	37	18	22
Caregiver's perceived difficulty (0-10)	6	-	4	-	4	4	3	3

T7: after definitive ITB pump implantation
ITB: intrathecal baclofen; 10 mWT: 10-meter Walking Test.

during contact phase and by a reduction in equinus foot). Results also showed a reduction in time needed to transfer from bed to wheelchair as well as the subjective ease for both the patient and the caregiver for doing this task.

In conclusion, the functional goals identified before ITB test were achieved, and patient accepted the definitive pump implantation (Synchromed II®, Medtronic Inc., Minneapolis, USA). The latter was done few months later, and the infusion of the definitive pump was set at the same rate at which the patient obtained the best results during the test phase. The post-surgical phase did not show any complications and no side effects of the treatment were noted. The functional goals achieved with the external pump have been attained after the definitive pump implantation, particularly concerning transfer ability as well as gait and transfer speed. At present time, 5 months after the implantation of the definitive pump, the patient still shows the same efficacy of the drug, without side effects.

Literature shows that approximately 11 to 65% of patients with WD may develop dystonia,[10] which can be focal, segmental, multifocal, or generalized. Possible treatments of dystonia in patients with WD are botulinum toxin injections, deep brain stimulation, or oral treatments as baclofen or tryhexiphenidyl.[11]

ITB is an effective treatment for diffuse spasticity in adult patients, but could also be utilized for generalized dystonia,[12] even if, compared to patients with CP, solid evidences are still lacking. Intrathecal administration, compared to the oral route, minimize cognitive side effects,[13] and improve the biodisponibility of baclofen due to his poor capacity to pass the blood-brain barrier. The first authors reporting the use of ITB in the treatment of generalized dystonia were Narayan *et al.*[14] Subsequently, other authors showed that ITB could be considered a possible treatment for similar patients, non-responding to oral treatments,[13, 15] as in our case.

However, up to date, there is no published description of the positive effects of ITB in a patient with generalized dystonia in WD.

In conclusion, this report shows that ITB, tested before by a continuous intrathecal infusion, can be considered as a safe and effective treatment for generalized dystonia in adults with WD.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
All authors read and approved the final version of the manuscript.

History
Article first published online: September 21, 2023. - Manuscript accepted: September 4, 2023. - Manuscript revised: July 10, 2023. - Manuscript received: March 7, 2023.

(*Cite this article as:* Grana E, Peschi L, Carda S. Intrathecal baclofen as an effective treatment for generalized dystonia in Wilson's disease. Eur J Phys Rehabil Med 2023 Sep 21. DOI: 10.23736/S1973-9087.23.07960-1)