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Placebo controlled utility and feasibility study of the H-reflex and flexor reflex in spastic children treated with intrathecal baclofen

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Abstract

Objective: To evaluate feasibility and utility of the soleus H-reflex and tibialis anterior flexor reflex (FR) in identifying spinal cord neuronal response to intrathecal baclofen (ITB) in children with severe spastic cerebral palsy.

Methods: During a randomized, double-blind, placebo-controlled dose-escalation test treatment, maximum *H* amplitude/maximum *M* amplitude (*H*/*M* ratio) and FR parameters were bilaterally recorded at baseline and 2–3 h after intrathecal bolus administration of placebo and increasing doses of baclofen until both an improvement in the individual treatment goal(s) and a one-point reduction on the Ashworth scale were observed.

Results: Electrophysiological data of 14 children were studied. The H-reflex was feasible in 13 children, the FR threshold area in 9 and the FR, elicited with supramaximal stimulation, in only one child. After ITB, the *H*/*M* ratio significantly decreased (left: 0.67 ± 0.47 to 0.15 ± 0.18, $P = 0.005$; right: 0.55 ± 0.32 to 0.14 ± 0.19, $P = 0.002$) without placebo effect. FR threshold area after ITB, only decreased significantly in children not taking oral baclofen (left: 146 ± 53 to 41 ± 54 mV ms, $P = 0.000$; right: 156 ± 80 to 66 ± 48 mV ms, $P = 0.002$).

Conclusions: This is the first randomized, double-blind, placebo-controlled dose-escalation study in spastic children demonstrating the soleus H-reflex to be a feasible and objective measure to quantify the decreasing motoneuron excitability in response to ITB bolus administration. Only in children not taking oral baclofen, FR threshold area can also be used as an objective outcome measure, yet feasibility is limited.

Significance: We suggest introducing the H-reflex as the electrophysiological gold standard for the evaluation of the effect of ITB in spastic children.

Keywords: H-reflex; Flexor reflex; Spasticity; Outcome measure; Intrathecal injection; Baclofen

1. Introduction

Cerebral palsy is the most common cause of severe physical disability in childhood (Kuban and Leviton, 1994). It is a term for a heterogeneous collection of clinical syndromes that are characterized by abnormal motor actions and postural mechanisms, and that are due to non-progressive abnormalities of the developing brain (Miller, 1998). Two thirds of the individuals with cerebral palsy suffer from mild to severe spasticity (Kuban and Leviton, 1994). Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with

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exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex (Lance, 1980). An effective treatment option for otherwise untreatable spasticity is the continuous delivery of intrathecal baclofen (ITB) (Albright et al., 2003; Campbell et al., 2002; Gilmartin et al., 2000).

In daily clinical practice, there has been no objective outcome measure yet to evaluate the effect of ITB in spastic children. In spite of its clear limitations, the standard clinical scale for measuring spasticity is the Ashworth scale (Ashworth, 1964; Damiano et al., 2002). The Ashworth scale is a score for grading muscle tone and does not exclusively quantify spasticity. It lacks sensitivity for the detection of small changes in muscle tone, there is no consensus on the exact scoring procedure and the test requires some cooperation of the patient, which is often limited in children or patients with cognitive deficits (Damiano et al., 2002). The Ashworth scale should therefore not be used as the gold standard for measuring spasticity (Levin, 2005).

From a pathophysiological point of view, both the soleus H-reflex and the flexor reflex (FR) could be useful and sensitive objective outcome measures for the spinal cord neuronal response to ITB administration. Baclofen is a selective agonist for gamma-aminobutyric acid (GABA)-B receptors (Bowery and Pratt, 1992). As baclofen influences both monosynaptic and polysynaptic reflexes, both the H-reflex and the FR have been previously considered as suitable, objective outcome measures in the evaluation of ITB treatment (Parise et al., 1997; Stokic et al., 2005; Yablon and Stokic, 2004).

The normal FR, elicited at supramaximal electrical stimulation of the tibial nerve behind the ankle, is a two-component exteroceptive reflex (Fisher et al., 1979; Hallett et al., 1994; Shahani and Young, 1971). Both components are changed by supraspinal influences and it is the second component, which is associated with the withdrawal response (Shahani and Young, 1971). In patients with supratentorial lesions, the FR mostly appears as a single component response of prolonged latency and duration (Fisher et al., 1979; Shahani and Young, 1971). Flexor spasms are the clinical counterpart of hyperactive flexor withdrawal reflexes (Shahani and Young, 1971). The FR threshold is often decreased in spasticity and tends to normalize with oral baclofen (Milanov, 1992; Shahani and Young, 1973).

The H-reflex can be used as a tool to measure the excitability of the neural components of the stretch reflex arc, bypassing the effects of gamma motoneurons and of muscle spindle discharges (Misiaszek, 2003; Schieppati, 1987; Zehr, 2002). The ratio of the peak-to-peak maximal *H*-amplitude to maximal *M* amplitude (*H*/*M*) indicates the part of motoneurons within the pool that can be recruited reflexively and is therefore, a measure of motoneuron pool excitability (Fisher, 2002). Since the 1960s, the *H*/*M* ratio has been considered as an index for spasticity, as it is increased in the majority of patients with spasticity (Angel and Hofmann, 1963; Bakheit et al., 2003; Katz et al., 1992; Levin and Hui-Chan, 1993; Macdonell et al., 1989; Matthews, 1966; Orsnes et al., 2000). Nevertheless, the H-reflex has never been introduced in daily clinical practice. One explanation for this could be the large range of variation of the *H*/*M* ratio in spastic and healthy people, limiting the diagnostic value of the *H*/*M* ratio (Angel and Hofmann, 1963; Bakheit et al., 2003). A second reason could be the lack of strong correlation between the *H*/*M* ratio and clinical assessment scales of muscle tone, such as the Ashworth scale (Bakheit et al., 2003; Katz et al., 1992; Levin and Hui-Chan, 1993; Pisano et al., 2000; Stokic et al., 2005). However, we would like to refute these argumentations. First, we believe the *H*/*M* ratio can still be useful for evaluating changes in motoneuron excitability in response to ITB administration in single patients, as the reproducibility of the *H*/*M* ratio is good (Delwaide, 1993; Levin and Hui-Chan, 1993; Stokic et al., 2001). Secondly, it is not very useful to compare the H-reflex with the Ashworth scale, as the latter is no valid test for measuring spasticity.

This is the first report on a randomized, double-blind, placebo-controlled dose-escalation study evaluating the utility and feasibility of the H-reflex and FR as objective outcome measures of the effect of ITB bolus administration in a relatively large group of severely spastic children with cerebral palsy.

2. Methods

2.1. Patients

Children aged between 4 and 16 years, with a spastic diplegia or tetraplegia as part of cerebral palsy, who insufficiently responded to oral spasticity reducing medications, were included. Magnetic resonance imaging of the brain was mandatory to rule out progressive causes of spasticity. Exclusion criteria were hypersensitivity to baclofen, contraindications for general anaesthesia, intractable epileptic seizures, an infection of the lumbar skin and a systemic infection. Eligible children from all parts of the Netherlands were referred to the University Hospital of Maastricht.

2.2. General study design

The study was designed as a randomized, double-blind, placebo-controlled dose-escalation test treatment during which the effects of intrathecal bolus injections with increasing doses of baclofen versus placebo were studied. All study phases, including the selection of referred children and hospitalization, took place at the University Hospital of Maastricht. After admission, the neurosurgeon inserted an external lumbar catheter under general anaesthesia. The next morning, the first bolus with study medication was administered intrathecally via the catheter. The test regimen