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Original article

Long-term use of botulinum toxin type A in children with cerebral palsy: Treatment consistency

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ABSTRACT

At the University Hospital of Pellenberg (Belgium), more than 1000 patients have been treated with Botulinum toxin type A (BTX-A) over the last decade. Ten percent of these patients ($n = 106$) received multiple (at least four times), multi-level, high-dosage treatments. The aim of this study was to evaluate the stability of dosage and treatment intervals in long-term, multi-level, high-dosage treated children with cerebral palsy and to evaluate the evidence for a safe and stable response to this treatment. Data on disease, age, dosage and target muscles were extracted for each treatment session of 106 patients who received multiple BTX-A treatment sessions. Patients had a follow-up of 4 y 6 mo (range 1 y 8 mo–8 y 9 mo) on average and received 4 to 12 BTX-A treatments within the period of January 1996 and December 2005. Patients received a mean dosage of 23.5 ± 5.2 U/kg bw at first treatment with stable subsequent values. Mean dosages for children with diplegia, hemiplegia and quadriplegia were 24.5 ± 4.7 U/kg bw, 15.9 ± 3.7 U/kg bw and 22.0 ± 4.8 U/kg bw, respectively. Mean age at first treatment was 4 y 6 mo (range 1 y 11 mo–18 y 10 mo) with a majority of patients (76.4%) first treated within 2 and 4 y of age. Treatment intervals of approximately 1 y remained stable within four, five and six subsequent treatments. Long-term, high-dosage, multi-level BTX-A applications can be considered as a safe and stable treatment option for children with cerebral palsy and the formation of antibodies, responsible for secondary non-response, can be indirectly precluded.

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1. Introduction

Botulinum toxin type A (BTX-A) is a local, reversible and commonly used and accepted treatment option for spasticity in children with cerebral palsy.[1–5] The toxin produces, to some extent, dose-related and reversible chemodenervation of agonist muscles by impairing the release of acetylcholine at the neuromuscular junction. Molenaers et al.[6] investigated the influence of multi-level, high-dosage botulinum toxin type A on the prevalence, frequency and timing of orthopaedic surgical procedures of 424 children with cerebral palsy at the University Hospital of Pellenberg (Leuven, Belgium). Their outcomes suggest that BTX-A treatment decreases the frequency and delays the need for orthopaedic surgical procedures until gait is mature when carefully applied to conscientiously selected patients.

A multitude of BTX-A studies has been published in the last decade. Most of them, however, focus on single, one-level BTX-A treatment in cerebral palsy.[7–19] A few studies, though, highlight the need and overall better response of multi-level injections.[20–23] As several muscles are injected simultaneously within one treatment session, multi-level treatments may request a higher total dosage when compared to single-level treatments to achieve optimal treatment outcomes.[24,25]

Nevertheless, it is generally accepted that for repeated injections of multi-level, high-dosage BTX-A, there may be a risk of the development of neutralizing antibodies. Evidence of developing antibodies was mainly investigated in long-term studies on cervical dystonia by performing a mouse neutralisation bioassay.[26–29] In cerebral palsy studies, little evidence for the development of antibodies following repeated, high-dosage, multi-level injections was found.[30,31] There are, however, many differing opinions about treatment strategies, extent of dosage and treatment intervals in cerebral palsy studies.[7–20,25] Additional information on long-term efficacy and safety of high-dosage, multi-level BTX-A is required in order to expand the current knowledge of BTX-A treatment in cerebral palsy.

This study investigates a long-term strategy of multi-level, high-dosage BTX-A treatments in children with cerebral palsy, thereby focusing on safety data and excluding the formation of antibodies that interfered with clinical response. The standard examination of antibodies by mouse neutralisation bioassay, as performed by several investigators, is an expensive and complex venture. Therefore it was decided to consider an alternative approach to antibody formation by evaluating the consistency of dosage and treatment intervals over a long-term follow-up period.

We hereby partly followed the approach of Brashear et al.[32] who investigated the dose consistency and treatment intervals over a period of 3 y in cervical dystonia patients to eliminate the formation of antibodies as an alternative to the mouse neutralisation bioassay.

Antibody formation was correlated with secondary non-response in former studies[27,31] and discovered that risk factors for secondary non-response were high dosages of BTX-A per treatment session and frequent injection intervals.[26,28,31,33] The long-term stability of dosage and treatment intervals can therefore be considered as an indirect indication that the patient is continuing to respond to BTX-A treatment, thereby excluding the formation of antibodies. Although response to BTX-A treatments was not specifically examined in the study of Brashear et al.[32] treatment efficacy and safety were supported by stable intervals, dosages and the patient's returning for subsequent treatments. Adult cervical dystonia patients, however, generally receive low-dosage treatment over a longer time period and within shorter treatment intervals[26–29,32] which is different to the treatment of children with cerebral palsy. BTX-A in the latter patients is usually a treatment option together with conservative treatment at an early age (<5 y) and may require higher dosages and longer treatment intervals when compared to cervical dystonia treatment.[6,34] These different approaches can therefore not be directly compared which deepens the need for long-term safety and efficacy data in patients with cerebral palsy.

In former studies at Pellenberg Hospital,[6,35] efficacy data of high-dosage, multi-level BTX-A treatment of children with cerebral palsy have already partly been investigated.

The purpose of this study is to evaluate the stability of dosages and intervals between treatment sessions, in order to evaluate the safety of repeated multi-level, high-dosage BTX-A injections to children with cerebral palsy. It is hypothesised that (i) the mean total BTX-A dosage does not increase and (ii) the mean intervals between treatments do not decrease within the longitudinal follow-up.

2. Materials and methods

2.1. *Patients and treatment concept*

For this retrospective study, adequate patients have been selected from the general patient database and the database of the Clinical Motion Analysis Laboratory at Pellenberg University Hospital.

The following inclusion criteria were established: the diagnosis of predominantly spastic cerebral palsy and at least four treatments with BTX-A from January 1996 to December 2005. The Surveillance of Cerebral Palsy in Europe (SCPE) describes spastic cerebral palsy as one of the subtypes of cerebral palsy.[36] The spastic subtype is further divided by the SCPE into a unilateral (limbs on one side of the body are involved, hemiplegia) and a bilateral (limbs on both sides of the body are involved) type. In this study, the spastic bilateral type was further subdivided into diplegia and quadriplegia.

Patients were excluded when having received BTX-A treatment only of the upper limbs and when having been treated with a combination of surgery and BTX-A in the same session, for reasons of biased dosage and interval measures.

The patients with spastic cerebral palsy received an integrated approach of BTX-A, as formerly described by Molenaers et al.[37] According to this approach, the reduction in muscle tone, induced by BTX-A injections, was intended to provide an opportunity to optimise the effects of casting and orthotic management and enhance both motor ability and functional skills.

Three-dimensional gait analysis including kinetics, kinematics and electromyography (EMG) was performed before and after each treatment with BTX-A to detect abnormal