Title: Oral medication prescription practices of tertiary based specialists for dystonia in children with cerebral palsy

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What is already known on this topic

1. Dystonia is a movement disorder which is difficult to treat in children with cerebral palsy
2. Oral medication is often the first line medical management for children with dystonic cerebral palsy
3. There is limited evidence for the effectiveness of the common medications used to manage dystonia in children with cerebral palsy

What this paper adds

1. A range of medications are prescribed to manage dystonia in children with cerebral palsy
2. Prescribing practices vary amongst clinicians
3. Baclofen and gabapentin are the most commonly used medications at this tertiary care centre

Abstract

Aim: to examine current clinical practice for prescribing medications for children with dystonic cerebral palsy (CP) by medical doctors working at one tertiary care centre.

Methods: Rehabilitation and developmental paediatric specialists completed: 1) a custom designed online cross-sectional survey capturing their usual prescribing patterns and 2) one page questionnaires detailing medication prescription for each child with CP they started on a new medication for dystonia over a 12 month period.

Results: Eleven participating doctors ranged in experience in managing children with CP from less than 5 years to more than 20 years. The cross sectional survey showed that most doctors used more than one medication with six making choices taking into account four or more different medications. Oral Baclofen was used by all doctors and was the first choice by 10 of 11. Prospective surveys from 57 children showed that medication was prescribed mainly for children: aged 3-10 years (n=35/57), classified within Gross Motor Function Classification System levels IV and V (n=40/57) and with a mixed movement disorder (n=38/57). Gabapentin and baclofen were most frequently prescribed (n=21/57 and 19/57 respectively) with other drugs used less frequently. Dosage regimens varied between and within doctors particularly for the use of gabapentin and diazepam.

Conclusions: Oral medication prescribing practices varied among doctors managing children with dystonic CP at a tertiary care hospital, particularly with respect to dosing. There is a need for clinical guidelines for medication prescription to be developed based on best evidence and consensus by clinical experts.

Keywords: cerebral palsy, dystonia, medication

Introduction

Cerebral palsy (CP) is the most common physical disability in childhood with a prevalence in Australia of 1 in 500 children¹. The movement disorder types found in CP are spasticity, dyskinesia, ataxia and hypotonia and each child has one or more of these types. CP movement disorder type is classified according to the dominant motor pattern and the percent of children identified as having dominant dyskinetic CP is 6.4% in Australia¹. Dyskinetic CP is divided into dystonic and choreo-athetotic subgroups². Dystonia, the most common subgroup of dyskinesia, is defined as 'a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both'³. The involuntary movements cause significant pain and functional limitations for the child and have major impacts on the ability of parents to provide care.

Oral medication is often the first line medical treatment and is frequently used by paediatric physicians to manage dystonia in children with CP. However, there is limited evidence regarding the effectiveness of the common medications prescribed for children with dystonic CP and side effects are common. Most of the published studies assessing medications are small and descriptive, limiting the conclusions that can be drawn from them. Consequently, choice of medication has been largely based on clinician experience^{4,5} rather than current evidence, resulting in inconsistent management of these children across Australia and internationally. A retrospective study of 278 children with childhood dystonia, not specific to children with CP, found that the commonest drugs prescribed were baclofen, benzhexol hydrochloride, levodopa and diazepam, with 62% of children experiencing adverse drug reactions⁶. The take home messages were that there was a wide variation in drug management of childhood dystonia with absence of a clear evidence-base to guide prescription, and a rational approach to the pharmacological management is required.

For low-prevalence conditions with high complexity – such as dyskinetic CP – where randomised controlled trials are often neither feasible nor appropriate, best available evidence often involves clinically-based research where data is gathered over time, strengthened by consensus of experts in the field. The aim of this study was to examine current clinical practice for prescribing medications for children with dystonic CP by experienced medical doctors working in Developmental Medicine and Rehabilitation departments at one tertiary care centre, as an important first step to developing a best practice clinical care pathway

Materials and Methods:

Participants were rehabilitation and developmental paediatric specialists who manage children with CP at one tertiary care hospital. Eligible doctors were recruited by the first author by means of

attending staff meetings to provide information about the study or were contacted personally via email and provided with a study information statement.

Consenting doctors completed a cross-sectional survey and also prospective questionnaires.

1. Cross sectional survey

A custom designed online 13 item cross-sectional survey capturing usual prescribing patterns was completed on one occasion only. This was administered via the REDCap (Research Electronic Data Capture) data collection system (<https://redcap.mcri.edu.au>). Doctors were sent the link to complete the survey via email and surveys were returned with email alerts to the first author. The survey included questions on: 1) number of children with dystonic CP seen, 2) medications typically prescribed and usual dosage regimes, 3) indications for prescribing medications, 4) factors influencing choice of medication, and 5) methods for monitoring for effectiveness and adverse reactions.

2. Prospective questionnaire

One page data collection forms were completed prospectively over a 12 month period on each occasion that a doctor started a child with CP on a new medication for dystonia. Forms were provided to doctors by the first author on a weekly basis to take to their clinics and once completed placed in a marked tray in their medical department offices. This form included questions about the clinical presentation of the child, indications for medication, type and dosage of medication and methods for monitoring for effectiveness and adverse reactions.

The data from the survey and questionnaire were stored and analysed in REDCap software (redcap.mcri.edu.au). All information stored in this electronic database was encrypted, and the database password protected to further ensure security and confidentiality. Data was analysed descriptively.

Results:

Eleven doctors participated in the study. There were seven developmental paediatricians, three rehabilitation physicians and one general paediatrician. Doctors ranged in experience in managing children with CP. Three had less than five years' experience, two 5-10 years, four 11-20 years and two more than 20 years. Five doctors were currently managing more than 20 children with dystonic CP whereas six were managing less than 15 children.

Cross-sectional survey

When asked about their usual practice, most doctors reported using more than one medication with six of the 11 making choices from four or more different medications. Oral baclofen was used by all doctors and was the first choice by 10 of 11. Benzhexol hydrochloride was used by 10 of 11 doctors, diazepam by 9 of 11, gabapentin by 8 of 11, levodopa by 5 of 11 and clonazepam by 3 of 11. Doctors cited the following indications for using medication to manage dystonia in this population: pain/spasms (10/11), comfort and care (10/11), sleep disturbances (10/11), improving mobility (7/11) and improving upper limb function (7/11). Dosage regimes varied significantly amongst the group. Severity of the dystonia was the main influencing factor for decision-making around type of drug prescribed and dosage. All doctors stated that they monitored for effectiveness of the medication, however this was primarily through parent report and impairment based clinical examination in paediatrician outpatient clinics. Objective measurement tools were only used in the context of a multidisciplinary rehabilitation team. All doctors used regular clinic reviews and telephone contact as the method for monitoring adverse reactions.

Prospective survey

Over the 12 month data collection period, of the 11 doctors in the study, eight prescribed medication for a total of 57 children. Three doctors did not prescribe medication. As shown in Table 1, medication was prescribed mainly for children: aged 3-10 years (n=35/57), classified within Gross Motor Function Classification System (GMFCS)⁷ levels IV and V (n=40/57) and with a mixed movement disorder (n=38/57). Males accounted for 70% of the children. Comorbidities included 47% having feeding difficulties, 23% having seizures and 39% having an intellectual disability.

Comfort and ease of care was the main indication for use of medications (30%). Other indications were pain (18%), sleep disturbance (13%), improving upper limb function (12%), improving mobility (9%) and other (18%).

Gabapentin and baclofen were most frequently prescribed (37% and 33% respectively). Other medications were prescribed less frequently: benzhexol hydrochloride (9%), diazepam (7%), Levodopa (5%), dantrolene (5%), clonidine (2%) and orphenadrine (2%).

Most children were on more than one medication. Gabapentin was most likely to be prescribed to improve pain and comfort whereas baclofen was prescribed when multiple indications were identified.

Dosage regimes varied between and within doctors particularly for the use of gabapentin and diazepam. The most consistent dosage regime was for baclofen with doctors prescribing it for 14

children at a starting dose of 5mg daily and increasing to a maximum of 10mg three times daily, with an extra four children starting at 2.5mg daily. There was very little consistency in gabapentin prescription, however the maximum dose prescribed was 300mg three times daily (six children). Diazepam was prescribed primarily for night time use at dosages ranging from 0.5mg to 5mg (nine children). Benzhexol hydrochloride was not used frequently and dosage regimes started from 1-2mg daily increasing up to 2mg three times daily (six children).

The small sample size precluded stratification of the sample for meaningful analysis with respect to clinician experience, GMFCS level of the children, age of the children or movement disorder type (dystonia versus mixed dystonia/spasticity).

Discussion

The results of this small but representative sample of paediatricians who manage children with CP showed that a range of medications are prescribed to manage dystonia in children with CP and prescribing practices vary amongst clinicians. The first line medication for the majority of clinicians was baclofen. Baclofen and gabapentin were the most commonly used medications, alone and in combination. Other medications were used infrequently. The cross-sectional survey results indicated that baclofen was the first line medication, however the prospective questionnaires indicated that gabapentin was prescribed more frequently. This can be explained by the likely scenario that the majority of children were already on baclofen when prescribed gabapentin.

Baclofen is a gamma-aminobutyric acid (GABA) B receptor agonist, used in the management of hypertonia, however evidence to support the use of oral baclofen in childhood dystonia is limited, despite widespread use⁴.

In this study, gabapentin was prescribed primarily to improve pain and comfort. Although used commonly by clinicians, there is very limited evidence for its effectiveness in the CP population. It was originally designed to be used as an anticonvulsant but gained popularity for neuropathic pain and has the advantages of a low side effect profile, few interactions with other drugs and effectiveness even at low doses in children⁸. Recently a retrospective observational study reported on the use of gabapentin for severe dystonia in 69 children, 25 of them with CP⁹. While there was a significant decrease in the severity of dystonia and significant improvements in sleep quality, sleep amount, mood and agreeableness, pain, general muscle tone, involuntary muscle contractions and seating tolerance, the results of the CP group were not reported separately, therefore it is unclear how that group responded. A major limitation of prescribing gabapentin for pain in children with CP is that in Australia this indication is considered 'off label' and the Pharmaceutical Benefits Scheme

does not fund it. This means that the price of gabapentin is at the discretion of the pharmacy from where it is purchased, which may create a large financial burden to families and patients, thus reducing their access to a potentially effective medication.

Benzhexol hydrochloride is an anticholinergic drug and is one medication that has some evidence in dystonic CP. Three main studies reported variable response and side effects were common in all three¹⁰⁻¹². Consequently there remains uncertainty about the benefits of using this drug for treating dystonia in children with CP. Despite most doctors in this study stating in the cross-sectional survey that they use benzhexol hydrochloride, the results of the prospective survey showed that in reality this medication was used far less frequently and in only a small number of children. This may be due to the side effects often observed with this medication and poor tolerance by many children.

Many factors can influence medication prescription by doctors. For example, often a specific dose is aimed for, but either not achieved fully or medication is ceased due to intolerable side effects. When evidence is lacking, clinician preference and experience are used to assist decision making. The variation in medication prescription found in this study, particularly the dosage regimes, reflects this. There are treatment guidelines available for managing spasticity in children with CP as determined by a systematic review of the evidence of efficacy and safety of pharmacologic treatments for childhood spasticity due to CP¹³. Similar guidelines are lacking for managing dystonia in children with CP. With little evidence available for the effectiveness of medications commonly used in dystonic CP it is not possible to have evidence based prescription guidelines. Dosage guidelines need to be developed but in the short term these will be based on clinical expertise and consensus rather than strong evidence.

This study is limited by the small sample size of participating doctors who were from one tertiary care centre only. The results can therefore only be generalised to that centre. Another limitation is that the data collected focused on new medications started and not medications the children were already taking. Therefore, complete information about the various combinations of medications used in this sample is lacking. In addition, the study did not collect information on previously trialled medications for the children and why they were ceased. Despite these limitations, it is a first step towards gathering expert opinion, in the absence of evidence, on the path to reaching a consensus around best care prescription practice for managing dystonia in children with CP. The next steps are to 1) conduct a longitudinal national surveillance study involving doctors from around Australia to gather clinical expertise on prescribing patterns, including combinations of medications and from this 2) create consensus amongst leading clinical experts using a Delphi process.

In conclusion, despite baclofen and gabapentin commonly used by most doctors managing children with dystonic CP at a tertiary care hospital, oral medication prescribing practices varied, particularly with respect to dosing. In the absence of strong evidence, there is a need for clinical guidelines to be developed based on consensus by clinical experts.

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Table 1. Characteristics of the children included in the prospective surveys

	n (%)
Total	57 (100)
Age (years)	
0-2	4 (7)
3-5	12 (21)
6-10	22 (39)
11-14	12 (21)
15-18	7 (12)
GMFCS level	
I-II	4 (7)
III	13 (23)
IV-V	40 (70)
Topography	
Hemiplegia	2 (4)
Diplegia	7 (12)
Quadriplegia	48 (84)
Movement disorder type	
Predominant dystonia	14 (24)
Predominant spasticity	5 (9)
Mixed spasticity/dystonia	38 (67)

GMFCS; Gross Motor Function Classification System

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