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Transdermal Clonidine Patch use in the management of childhood hypertonia – a cross-sectional UK Wide Service Evaluation

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ABSTRACT

Objectives:

Clonidine is increasingly used in the management of childhood motor disorders. Reports are limited regarding the use Transdermal Clonidine Patches (TCPs) for this indication. We aimed to explore the use of TCPs in children and young people (CAYP) across specialist movement disorder services in the UK.

Methods:

A cross-sectional service evaluation of TCP us in CAYP with motor disorders was performed. Where available, historical data on TCP use was also collected.

Results:

Data were available for 259 CAYP from 11 services,176/259 (68.0%) under active follow up. Median age at starting TCPs was 8.6 years (25^{th} to 75^{th} centile 5.2-12.0 years). GMFCS-level (or equivalent) was V for 206/253 (81.4%) CAYP. Clinically significant chorea was observed in 33/255 (12.9%), spasticity in 116/254 (45.7%) and dystonia in 234/256 (91.4%) CAYP. Commonest reasons for TCP initiation were overall dystonia severity (61/259, 23.6%) concerns about absorption of enteral medication (54/259, 20.8%), and excess sedation with enteral clonidine (46/259, 17.8%). TCP use had been discontinued by 61/259 (23.6%) CAYP, most commonly because of skin rash (24/259, 9.3%). The median time to discontinuing patches was 3.5 months. In addition to TCPs, 148/259 (57.1%) of CAYP continued with enteral clonidine. Additional tone-reducing medication use ranged from 0 to 6 additional medications (modal number of medications 3),

Conclusion:

We present the first UK based multi-centre evaluation of TCP use in CAYP with motor disorders, highlighting the complexity of the medical problems of these CAYP and their clinical management. TCPs appear generally to be tolerated by CAYP, but further work is required to establish their efficacy.

Key Messages:

- What is already known on this topic:
    - Clonidine is a centrally acting adrenergic agent which has become commonly used in the management of motor disorders in children and young people.
- What this study adds:
    - We provide details of the indications for, and complications of Transdermal Clonidine Patches in a large cohort of children and young people.
- How this study might affect research, practise or policy
    - We highlight the increasing use of transdermal clonidine patches despite the limited data to establish their efficacy, providing evidence of the need for future prospective studies.

Introduction

Clonidine is a centrally acting alpha-2 agonist which was initially developed as an anti-hypertensive treatment[1]. Uses have now expanded to include the management of peri-operative pain and anxiety[2], pre-medication use for procedures, sedation in the intensive care setting[3], ADHD[4], Sleep Disorders[5] and Tic Disorders[6]. More recently there has been interest in the use of clonidine in the management of hypertonia in childhood[7,8]. Disorders of elevated tone (most commonly dystonia and spasticity in children and young people (CAYP) can cause pain, interfere with the delivery of cares and impair participation[9]. In a cross-sectional study of 275 CAYP with CP in the UK, clonidine was the 5th most commonly used anti-tonal medication[10]. An electronic health record study including 4010 CAYP with dystonia in the USA reported that clonidine was the third most commonly used medication for dystonia (received by 26.3% of CAYP)[11]. Whilst acknowledging the low level of available evidence, the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) most recent guidance suggest the use of enteral clonidine in reducing dystonia in CAYP with CP[12].

Clonidine is considered to have a less sedating, less respiratory depressing effect in comparison to benzodiazepine class medications, with particular interest in its use in the setting of acute severe dystonia [13]. One of the potential benefits of clonidine in the management of hypertonia is that it may be delivered by the enteral, intravenous, subcutaneous and transdermal routes [14,7,15].

Transdermal Clonidine Patches (TCPs) are a transdermo-therapeutic system which releases a steady dose of clonidine for a 7 day period, avoiding the peaks and troughs seen with enteral administration[16]. A small number of reported cases have described the use of Transdermal Clonidine Patches (TCPs) in the management of severe dystonia[15,17] with greater reported experience in their use in the management of Tic disorders in childhood[16].

Currently there is a paucity of data available regarding the use of TCPs in the management of hypertonia in CAYP across the UK, including the number of CAYP receiving TCPs, the indications for this therapy and potential side effects. We aimed to explore the use of TCPs in CAYP across specialist paediatric movement disorder services in the UK through a cross-sectional audit.

Methods

A cross-sectional service evaluation was undertaken through the Movement Disorder Specialist Interest Group (MDSIG) of the British Paediatric Neurology Association. Members of the group, including representatives of the 25 Tertiary Paediatric Neurosciences centres in the United Kingdom, were contacted through the MDSIG membership to identify Specialist Paediatric Movement Disorder Services and invited to contribute data regarding CAYP under their care who had received, or were receiving, TCP therapy for the management of their motor disorder. Anonymised data

was collected from January to August 2024. Data included demographics (gender and age), diagnosis, Gross Motor Function Classification System (GMFCS), or equivalent level[18], age at initiation of TCP therapy, duration of TCP therapy, and details of other anti-tonal managements (medications and targeted botulinum toxin injections). Clinicians were asked to characterise hypertonia type (spasticity, dystonia and/or choreoathetosis) and subjectively grade the clinical significance based on the family and CAYP-reported interference with function, participation, delivery of daily cares and comfort[19,10]. The presence of spasticity and/or dystonia was defined as per the Hypertonia Assessment Tool (HAT)[20], whilst the definition of Choreoathetosis was taken from the Taskforce on Childhood Movement Disorders[21]

Descriptive statistical analysis was performed using IBM SPSS Statistics (Version 29).

Results:

Data were available for 259 CAYP from 11 specialist services (8 from Tertiary Paediatric Neurosciences Services, one highly specialist secondary paediatric service and one Paediatric Palliative Medicine based service) ,176/259 (68.0%) who remained under active follow up (Figure 1). A summary of clinical details is provided in Table 1. The median age at initiation of TCP therapy was 8.6 years (25^{th} to 75^{th} centile 5.2 to 12.0 years). GMFCS-level (or equivalent) was V for 206/253 (81.4%) of cases. The commonest underlying cause for hypertonia was Cerebral Palsy 125/259 (48.3%) followed by hypoxic ischaemic encephalopathy in later childhood (11/259, 4.2%), X-linked Adrenoleukodystrophy (7/259, 2.7%) and Pantothenate kinase

associated Neurodegeneration, PKAN, (7/259, 2.7%). For 23/259 (8.8%) of CAYP no unifying diagnosis had been identified. Clinically significant chorea was observed in 33/255 (12.9%) CAYP, spasticity in 116/254 (45.7%) CAYP and dystonia in 234/256 (91.4%) CAYP.

The commonest reasons for TCP initiation were overall dystonia severity (61/259, 23.6%) concerns about absorption of enteral medication (54/259, 20.8%), excess sedation with enteral clonidine (46/259, 17.8%) and “Off/on” effects with enteral clonidine (36/259, 13.9%) (Figure 2(a)). TCP use had been discontinued in 61/259 (23.6%) cases, most commonly because of skin rash (24/259, 9.3%), TCPs no longer being required (10/259, 3.9%) and a lack of perceived efficacy (8/259, 3.1%). The median time for initiation to discontinuation of TCP therapy in CAYP stopping treatment was 3.5 months. In addition to CAYP who had permanently discontinued TCP therapy, a temporary discontinuation was required in 15/259 (5.8%) CAYP due to intermittent problems with the supply of patches. Of the 83 CAYP no longer under follow up, 43 had died since initiation of TCP therapy (no deaths were related to this therapy) including 33/43 CAYP who were continuing to receive TCP therapy at the time of death. For CAYP continuing with TCP therapy, the median duration of treatment was 1.33 years (0.33 to 2.92 years 25th to 75th centile).

Additional tone-reducing medication use ranged from 0 to 6 additional medications (modal number of medications 3). In addition to receiving clonidine via the transdermal route, 148/259 (57.1%) CAYP continued with enteral clonidine. It was not possible to say for all CAYP whether enteral clonidine use was as a regular or as required medication. The commonest enteral medications after clonidine were

gabapentin 147/259 (56.8%) and chloral hydrate 128/259 (49.4%). It was not possible to differentiate regular from as required use of chloral hydrate.

The Median absolute daily clonidine dose delivered by TCP was 300 micrograms (range 50 to 2700 micrograms). This equated to a median dosage of 0.51 mcg/kg/hour (range 0.05 to 4.75 mcg/kg/hour) delivered via TCP. TCP dose differed by GMFCS (or equivalent) level (Independent-Samples Median Test, $P<0.001$, Figure 3). For 18/259 CAYP (6.9%) of CAYP, the dose of clonidine delivered by TCP therapy alone was > 2mcg/kg/hour.

Discussion

We present the first national service evaluation of CAYP receiving TCP therapy in the UK, describing the clinical features of 259 CAYP from 11 specialist movement disorder services. CAYP receiving TCP therapy typically exhibited significant motor disability (GMFCS level V in 81.4%), almost all of whom experienced dystonia and less commonly spasticity and choreoathetosis. Use of additional tone reducing medications was frequent, with additional regular clonidine the most common enteral medication.

At present the evidence base to support decision making around the choice of tone reducing medications in CAYP is limited. The most recent AACPDM guidelines on the management of dystonia in CP found insufficient evidence upon which to make “recommendations” and was subsequently limited to “suggestions” for choice of medications[12]. Which medication should be used and in what sequence in the

management of hypertonia in CAYP was recently identified as one of the top 10 research priorities for interventions in Childhood Neurological Disorders[22].
Whilst an increasing number of studies have described patterns of medication prescription in CAYP with hypertonia, an understanding of the factors influencing clinician decision making is currently limited[23].

Our study adds to the observational data of the use of clonidine in the management of elevated tone, and in particular dystonia. The choice of clonidine, particularly in the context of an acute dystonia exacerbation, is likely influenced by its lesser respiratory depressant effect compared to other commonly used sedative medications such as the benzodiazepines and chloral hydrate[13,15]. The delivery of clonidine via the transdermal route offers in principle a number of potential benefits, in keeping with the reasons for initiating TCP therapy identified by our study. In the severally motor disabled population, GI dysmotility and inconsistent absorption are commonly observed concerns which are avoided with delivery via a transdermal delivery route. At the most severe gut dysmotility in this population may result in what has become termed “GI Dystonia” [24]. Clonidine, particularly via the transdermal route, has been recommended in recent consensus guidance on the symptomatic management of GI dystonia[24].

Drug delivery via transdermo-therapeutic systems provides steady state dosing. This avoids both the peaks and troughs of plasma drug levels observed with enteral medication delivery. With enteral clonidine “Off” effects may be observed in terms of a re-emergence of hypertonia/agitation, and “On” effects excess sedation coinciding with peak plasma levels. One common indication observed for initiation of TCP

therapy was ease of administration. TCPs are typically replaced every 7 days (though anecdotally some services reported changing patches every 5-6 days for some CAYP) and require no adjustments/maintenance between replacements. For most parents and carers this is likely more convenient than multiple daily enteral dosing. Transdermal clonidine patch use is unlicenced in the UK, as is clonidine use in <18 year old by any formulation.

The majority of CAYP receiving TCP therapy were also receiving additional enteral tone reducing medications, most commonly additional enteral clonidine. It is important to note the risk of polypharmacy in CAYP with complex medical problems receiving medications for tone management, with some CAYP receiving TCPs also receiving in addition 6 different enteral tone reducing medications. Whilst TCP therapy provides a steady-state background of clonidine, additional as required enteral dosing typically targets more troublesome or problematic times of the day, or periods when more intrusive symptoms arise (e.g. during periods of acute illness). Additional enteral doses at night may help with sleep initiation and consolidation, through a greater sedative effect which may not be tolerated during the daytime, when CAYP and their parents/carers are likely to wish to promote wakefulness.

When used in the management of Tic disorders, TCP therapy dosages have typically ranged from 100mcg to 200mcg daily[25]. This is lower than the 300mcg median dose reported in our study, and considerably lower than the peak reported dose of 2700mcg. Peak combined enteral and TCP therapy clonidine dose was reported at 4.75mcg/kg/hour. High dose clonidine via a variety of routes has previously been described, including a peak dosage of 9mcg/kg/hour[15], but further work is required to

establish the effective dose range, and side effect profile, of clonidine in the treatment of dystonia via any route.

TCP therapy had been discontinued in 61/259 (23.6%) CAYP. It should be noted that the cross-sectional and retrospective nature of our study design carries a greater risk of missing CAYP no longer receiving TCP therapy compared to those continuing to actively receive therapy. Consequently, the proportion of CAYP discontinuing therapy may be higher. The commonest reason for discontinuing TCP therapy was a significant skin rash (and example of which is shown in Figure 2(c)). Significant skin rashes were reported in 24/259 (9.3%) of CAYP. Significant skin rashes with transdermal systems may arise due to an irritant contact dermatitis caused by the adhesive of the patch, the active medication or excipients. Allergic Contact dermatitis may also emerge after a period of use[26]. Contact dermatitis is well described with longer term use of transdermal clonidine patches, and is most likely irritant in nature[27]. Changing brand of patch does not seem to be helpful in reducing skin reaction. In a large RCT including 488 participants with Tic disorders, skin conditions at the patch site were observed in 7.9% of participants (with a higher proportion seen in the placebo group)[25]. The second commonest reason for discontinuation of TCP therapy reported was that therapy was no longer required (10/246, 10.1%). The retrospective nature of our data capture precludes a more detailed exploration the reasons why therapy was no longer required, though this may represent a temporary need for increased therapy during a period of dystonia exacerbation, or the resolution of a period of poor enteral absorption.

A major limitation to our presented study is that the efficacy of TCP therapy cannot be determined. TCP therapy was noted to have been discontinued due to a perceived lack of efficacy in 8/259 (3.1%) of CAYP, and due to a paradoxical worsening in 4/259 (1.5%) of CAYP. The continuation of TCP therapy in 198/259 (76.5%) of CAYP may infer that a perception of benefit was seen, but significant further work is required to established this. The median duration of TCP use of > 1 year may be taken as a potential proxy indicator of efficacy. Other limitations include motor disorder phenotype characterisation, and clinical significance of this, being based on reporting by individual clinicians, with no measure of reliability or reproducibility. Data was available for 11/25 Neuroscience centres in the UK. For centres not contributing data we cannot say for all cases whether this was due to a lack of prescription of TCPs in the centre, or for other reasons.

A further limitation is the lack of data regarding the experiences of CAYP who had been on TCP therapy and their families / carers. The authors recognise that while most existent evidence is based on reporting of efficacy and safety from a clinician perspective, the experience of the CAYP and families should form a key factor in shared decision making and counselling. Such conversations should include the setting of shared goals for tone management; an important area which is not covered in our study.

Future prospective studies are required to address the limitations acknowledged for our study. Such studies will require a thoughtful trial design, ensuring that recruitment is able to encompass the range of CAYP we have demonstrated to be currently receiving TCP therapy and the inherent complexity of their medical

problems and co-morbidities. Outcome measures will need to reflect the varying indications for TCP use, and it is unlikely that a single “one size fits all” measure will be suitable, particularly considering the age range over which TCP patch use currently ranges.

Conclusion:

We present the first national multi-centre audit of TCP use in children with motor disorders, highlighting the clinical complexity of the medical problems these CAYP and their clinical management. Use was most commonly described in CAYP with CP and severe motor disorders. This population exhibits significant medical comorbidities, as evidenced by the significant mortality rate of CAYP initiated on TCPs (noting importantly that no deaths were felt to be related to TCP use). TCPs appear generally to be tolerated by CAYP with motor disorders, but further work is required to establish their efficacy. Clinicians perceived the main advantages of TCP to be related to reliable dose absorption, which in turn reduces unwanted sedation and on/off effect.

Data Availability Statement

Data are available on reasonable request to the corresponding author

Contributors: DEL designed the study, performed data collection and the first draft of the manuscript. RL advised on study design and reviewed early drafts of the manuscript. All authors collected and submitted data, reviewed and agreed on the final manuscript.

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Figure Legends

Figure 1: (a) Map of the UK demonstrating location of services providing data (NB two services reported data from London), (b) GMFCS-level (or equivalent) for CAYP included in the data collection, and (c) Motor Phenotype of CAYP included in the data collection.

Figure 2: (a) Sankey chart indicating reasons for initiating and discontinuing TCP therapy, and (b) and example of a significant skin reaction to TCP therapy resulting in a discontinuation in patch therapy.

Figure 3: Box and whisker plot illustrating TCP dosage (in mcg/kg/hour) on the y-axis by GMFCS (or equivalent) level on the x-axis. A significantly higher median TCP dosage was seen with greater GMFCS (or equivalent) level (Independent-Samples Median test, $P<0.001$)

Clinical Feature	
Number CAYP actively receiving TCP/Number CAYP reported	166/246
Age at TCP Initiation (Median, Range)	9.1 years (1 month to 21 years)
Diagnosis of Cerebral Palsy (% of whole cohort)	121/246 (49.2%)
Number CAYP discontinuing TCPs	61/246 (24.8%)
Died since initiating TCP	40/246 (16.3%)

Motor Phenotype (Clinically Significant)	Dystonia	221/243 (90.9%)
	Spasticity	103/241 (42.7%)
	Choreoathetosis	32/242 (13.2%)
GMFCS (or equivalent) Level	I	1/240 (0.4%)
	II	5/240 (2.1%)
	III	10/240 (41.7%)
	IV	29/240 (12.1%)
	V	195/240 (81.3%)
Commonest Reasons for initiating TCP therapy	Concerns about enteral absorption of clonidine	54/246 (22.0%)
	Excess Sedation with enteral clonidine	46/246 (18.7%)
	"Off/On" effects with enteral clonidine	36/246 (14.6%)
	Ease of administration	14/246 (5.7%)
	Step down from IV clonidine	7/246 (2.8%)
Commonest Reasons for discontinuing TCP therapy	Skin Rash	24/246 (9.8%)
	No longer required	10/246 (4.1%)
	Lack of efficacy	8/246 (3.3%)
	Worsening dystonia	4/246 (1.6%)
Number of Anti-tonal Medications	0	41/246 (16.7%)
	1	50/246 (20.3%)
	2	61/246 (24.8%)
	3	61/246 (24.8%)
	4	19/246 (7.7%)
	5	10/246 (4.1%)
	6	4/246 (1.6%)
Commonest Medications Used for tone	Gabapentin	135/246 (54.9%)
	Chloral Hydrate	117/246 (47.6%)
	Baclofen	81/246 (32.9%)
	Diazepam	71/246 (28.9%)
	Trihexyphenidyl	41/246 (16.7%)

Table 1 – Clinical Details of CYP receiving Transdermal Clonidine Patch therapy. Abbreviations used "CAYP" – Children and Young People, "GMFCS" – Gross Motor Function Classification, "TCP" – Transdermal Clonidine Patch. NB – the denominator varies for clinical characteristics with respect to Clinical Motor Phenotype and "GMFCS or equivalent" where data is missing