BACD British Academy of Childhood Disability

BPNA British Paediatric Neurology Association

Association for Paediatric Palliative Medicine

NPPG Neonatal & Paediatric Pharmacy Group

Position statement

Safe Use of Transdermal Clonidine Patches in the Management of Childhood Motor and Movement Disorders

Background

Clonidine is a centrally-acting alpha-2 adrenergic agonist. Originally developed as an anti-hypertensive, clonidine is increasingly used off-label as an anti-dystonia medication in children with movement disorders[1,2]. Although most commonly given enterally for this indication, transdermal delivery from a patch is also used[3,4]. Transdermal administration is likely to provide more consistent levels of clonidine in the blood, minimising breakthrough symptoms and/or side effects associated with the plasma level peaks and troughs that arise with enteral dosing.

Whilst undoubtedly many children have benefitted from the delivery of clonidine via this route, the limited evidence-base and absence of nationally-agreed guidance for their use is of concern. Anecdotally, the lack of consensus has led to unnecessary use of these products, variation in practice and medication safety incidents. Failure to consistently train and support parents/carers in the use of transdermal clonidine patches may further compound the potential for error.

Clonidine patches are not licensed in the UK, but are available as imported medicines. The supply chain for transdermal clonidine patches in the UK has been relatively unstable in recent years, and there have been a number of instances where shortages of patches have necessitated the urgent conversion of children back to enteral preparations. Such conversions are high risk and associated with both loss of symptom control and adverse drug effects; therefore, advanced planning for such eventualities is key.

This position statement aims to provide healthcare professionals with pragmatic guidance on the use of transdermal clonidine in children with movement and motor disorders. This includes providing recommendations on when it is appropriate to consider initiation of transdermal patches; monitoring and advice to be provided to families and carers; and conversion back to enteral dosing.

Practicalities of Dosing and Administration

- There is some variation between the different brands available for import, although in general:
  - Patches are available in three strengths, providing either 100, 200 or 300 micrograms/day of clonidine.
  - Each patch contains 7 days' worth of drug, and so patches should be removed and replaced weekly.
- Clonidine patches must always be prescribed in terms of the number of micrograms/day of clonidine required. The total quantity of clonidine in each patch should not be included on the prescription, as this can vary between brands, even for patches delivering the same number of micrograms/day. An illustrative example of this is given in Table 1.

Table 1: Comparison of contents of two clonidine patch brands (note other brands are also available).

Drug Delivery (micrograms/day)	Total Drug Content of Catapres-TTS patch (mg)	Total Drug Content of Maynepharma patch (mg)
100	2.5	3.09
200	5	6.19
300	7.5	9.28

- The imported products are not all labelled in English, leading to incidents where a non-drug-containing adhesive, protective cover has been mistaken for the drug-containing patch. Such products should be over-labelled in English and a translated manufacturer's patient information leaflet provided wherever feasible, but either way, Pharmacy teams should ensure that patients/carers are clear how to use the product supplied.
- After the initial application of a transdermal clonidine patch, it can take 2-3 days to achieve therapeutic plasma levels[5,6]. Similarly, due to clonidine saturation within the skin, therapeutic plasma levels can persist for some time after a patch is removed, before slowly declining over several days.

Practicalities of Dosing and Administration continued

- In practice, transdermal clonidine is usually bioequivalent to enteral and intravenous clonidine, and so the ***total daily*** dose ordinarily remains the same when converting between routes. However, given that the full effects of a patch may not be seen for 2-3 days after application, transition to transdermal clonidine is usually achieved in a step-wise fashion over several days. Conversion from enteral to transdermal clonidine should be undertaken in an inpatient setting, except in exceptional circumstances such as end of life care.
- Example protocols for conversion between transdermal and/or enteral/intravenous clonidine are provided in Appendix 1. These are intended to be illustrative rather than instructive; a bespoke plan is required for each patient, and this remains the responsibility of the initiating specialist. It is possible that the plan may need to be adjusted mid-conversion according to patient response.
- It is not uncommon for patients to need the use of two or more patches to deliver the required dose.
- Ideally, for each child only one strength of transdermal patch (i.e. 100 microgram/day, 200 microgram/day or 300 microgram /day) should be used. The use of multiple transdermal patch strengths in the same patient should be avoided wherever possible as it likely to increase the risk of administration error, however this may not always be achievable due to the need to "fine tune" dosing.
- Where a patient is on more than one patch at a time, staggering the days on which the patches are changed may be helpful in reducing potential for "end of patch" tailing off clinical effect. It also reduces the risk of worsened dystonia if a patch is inadvertently not changed on time. Where patch changes are staggered:
  - Each patch should be clearly labelled as to which day it should be changed.
  - It is not normally necessary to change each individual patch on a different day, so for example in a patient needing four patches, they could be changed two at a time on two different days of the week rather than each being changed on a separate day.
- In some cases, changing patches more frequently than once weekly, e.g. every 5 days may be beneficial, however this has the potential to increase confusion/administration error and so patient/family circumstances should be considered carefully before this approach is adopted.

Initiation of Patches

- Transdermal clonidine should only be initiated by a Tertiary Consultant Paediatrician with expertise in management of movement/motor disorders and/or palliative care, and experience in use of this therapy.
- Transdermal clonidine should generally not be initiated without a prior trial of enteral clonidine, although direct conversion from intravenous/subcutaneous clonidine may be appropriate in some instances.
- The main indications for initiating transdermal clonidine are:
  - Significant "Off-On" effects with regular enteral dosing.
  - Concerns about unpredictable/irregular absorption of clonidine delivered by the enteral route.
- All efforts should be made to ensure enteral clonidine has been given an appropriate trial (including reduced doses at more frequent intervals, e.g. 3-4 hourly) before consideration of transdermal patches. High frequency of enteral dosing alone should not be an indication for transdermal clonidine.
- When clonidine patches are introduced, clear therapeutic goals should be set. Failure to meet these goals after 6 months of treatment should result in treatment discontinuation. During this 6-month trial period, responsibility for prescribing and review should remain with the initiating specialist.
- Where a 6-month trial of clonidine patches has been successful and it is decided to continue with treatment, the responsibility for prescribing and ongoing review can be delegated to an appropriate consultant paediatrician (see *Ongoing Management* below). Prescribing should remain within Secondary Care, however the patient's GP should also be informed of:
  - The fact that clonidine patches have been initiated, and the intended therapeutic goals.
  - Which specialist team to contact in case of any queries.
- At initiation, parents/carers should be provided with a documented plan as to how, for example due to patch unavailability, transdermal clonidine could be converted back to the enteral route . However, parents/carers should not initiate conversion without talking to the team responsible for prescribing the patient's clonidine. The initiating clinical team must also disseminate the plan to other health care professionals involved in the care of the child. This plan must also be updated should the patient's clonidine dose change during treatment.
- At initiation of transdermal clonidine, parents/carers should be provided with clear guidance for contacting the initiating team (both in and out of office hours).
- In most cases, initiation of transdermal clonidine should occur in an inpatient setting. Where multiple patches are needed to deliver the required dose, initiation is usually achieved over a period of at least 5-7 days. Where the patient is stable following the first few days of treatment, they may be discharged to complete the initiation process in the community.
- A clear plan for monitoring blood pressure, heart rate and state of consciousness must be in place during patch initiation. Monitoring should be performed at a frequency in line with local practice and patient need; but in general no less frequently than 4 times daily, especially during the first 2-3 days of treatment.
- Initiation of clonidine patches entirely in the community setting should only be undertaken in exceptional circumstances and where "in-house" support from an appropriate team, such as hospice outreach professionals, can be provided. Where this is considered necessary and appropriate, parents/carers should be provided with support throughout the process, including face to face training on the practicalities of patch use.

Ongoing Management

- Ongoing use of transdermal clonidine should remain under the supervision of a Tertiary Paediatric Consultant with expertise in the management of movement/motor disorder and/or palliative care.
- Prescribing of transdermal clonidine must be retained in secondary care and should never be undertaken via shared care with primary care
- Where it is not feasible for the supervising tertiary clinician oversee the ongoing prescribing and supply of clonidine patches, this can be delegated to an alternative named paediatric consultant by mutual agreement. Where this is necessary:
    - A clear, shared plan for regular review and monitoring should be in place. This plan should be reviewed and updated annually as a minimum, and accessible to all professionals involved in the patient's care.
    - Patients and carers should be provided with contact details for both teams, and have a clear written plan for escalation should any concerns arise.
    - It may be necessary to submit a formulary application for use of clonidine patches if the consultant to whom responsibility is being delegated is working in a Trust where the patches are not routinely used. This is likely to result in a delay to the handover of care, and the initiating centre should continue to supply until all the necessary local arrangements are in place.
- Use of transdermal clonidine should be reviewed at least on a 6-monthly basis to ensure that the patient is still benefitting from treatment. Where the benefits are lost, or patches are no longer required, transdermal clonidine should be discontinued.
- Each time the dose of transdermal clonidine is adjusted, the written plan for conversion to enteral clonidine should be updated.
- For young people transitioning to adult services, discussions on ongoing prescription of clonidine patches should be initiated with the relevant adult team well in advance of the date for transition.
- Parents/carers should continue to be educated and supported on the safe use of clonidine patches. Key points are provided in the *Key Messages which must be provided to patients/carers* section of this document.

Discontinuation of Transdermal clonidine

- The decision to discontinue transdermal clonidine should be made with input from the initiating/supervising Tertiary Consultant.
- Assuming that the patient is to be converted to enteral clonidine, the written conversion plan provided to the patient/carers should be followed, after ensuring the plan reflects the patient's current transdermal dose.
- If the plan is not to convert to enteral clonidine, a separate management plan should be developed.
- 6 weeks following discontinuation of clonidine patches, a review appointment (virtual or in person) should be arranged to ensure that there has not been a significant worsening or rebound of dystonia symptoms.

Key Messages which must be provided to Patients/Carers

- There are two different components included in the box: patches and adhesive, proetective covers. The patch contains clonidine; the adhesive plaster does not contain drug.
- As the patches are imported from outside the UK, the boxes, patches and adhesive covers may not always be labelled in English. Patients/carers should contact their specialist team if unsure that they have the correct medicine or unclear as to which component is the drug-containing patch and which the adhesive cover.
- The patch should be applied to the skin first, then covered with the adhesive cover to ensure good adhesion.
- The patches should be changed weekly. The site of application should be changed from week to week in order to minimise the risk of skin irritation.
- Each patch/adhesive cover should be a labelled with the day it is due to be changed so that this information is visible to all carers and professionals involved in the patient's care.
- Where a patch becomes detached prematurely (i.e. before it has been on for 7 days) it should be replaced as soon as possible, but the replacement patch should be changed on the day the original patch would have been changed. For example, if a patch due for change on a Saturday needs to be replaced early on Wednesday, the replacement patch should be changed on Saturday, rather than the following Wednesday.
- A daily check must be performed to ensure that each patch remains in place, in addition to also checking after bathing, swimming or showering.
- Redness/irritation of the skin can occur at the patch application site. If this occurs, the team responsible for prescribing clonidine patches should be consulted. Regular rotation of application site may help reduce symptoms. There are anecdotal reports that off-label topical application of beclomethasone to the patch site using a metered dose inhaler before applying the patch may reduce symptoms without affecting patch adhesion. However, is not known if this practice adversely affects clonidine absorption, and so caution is needed. If symptoms do not resolve, transdermal clonidine should be discontinued.
- A Medicines for Children leaflet is available here to support safe and effective use of clonidine patches.

Supporting Information

Dystonia can be described as involuntary sustained or intermittent muscle contractions. Such contractions can cause abnormal, often repetitive movements, postures or both. Acute worsening of dystonia in children is distressing, painful and can progress to life-threatening status dystonicus[3].

A range of medicines have been employed in the treatment of dystonia, with the aims of reducing pain and distress; supporting independent function and participation; improving quality of life; and preventing progression to status dystonicus[2]. Clonidine has been increasingly used for this indication, principally via the enteral route. It has been shown to be both effective and well-tolerated and may be preferred to alternative agents such as benzodiazepines as its use is not associated respiratory depression[1,3].

Clonidine was developed and is marketed as a centrally-acting antihypertensive agent. Acting as an alpha-2 agonist, clonidine reduces sympathetic outflow from the central nervous system and thus lowers peripheral vascular resistance, renal vascular resistance, heart rate, blood pressure and skeletal muscle tone[5]. Clonidine is readily absorbed following enteral administration, with bioavailability in the range 75-100%[5,6]. It can also be administered via the transdermal route, with quoted bioavailability of 60%[5,6]. Published bioavailability data is however based on adult studies, and in paediatric practice the enteral and transdermal routes are often considered to be broadly bioequivalent. However, inter-patient variability can be significant, and therefore close observation (usually in an inpatient setting) is advised during patch initiation.

The reservoir design of clonidine patches means that they should not be cut to achieve "part patch" dosing. It is rarely necessary to dose in part patches, although some centres have achieved this effect by only partially removing the plastic backing on the patch or partially occluding the underside of the patch with an adhesive dressing. Where it is felt that part patch dosing is clinically necessary, this should be undertaken as part of a written patient-specific plan, and clear training and support processes should be in place locally.

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Disclaimer

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Appendix 1- Example Protocols for Conversion between Transdermal and Enteral/Intravenous Clonidine

The follow examples are intended as guidance only, and an individualised plan should be developed for each patient by the responsible clinical team. Recommendations on oral/iv to patch conversions are also provided in the *Association for Paediatric Palliative Care Medicine (APPM) Formulary*. The recommendations differ subtly, with the APPM recommending a slightly quicker conversion. Irrespective of the plan developed for an individual patient, it should be recognised that the plan may need to be adapted during the initiation process, slowing down or speeding up according to patient response.

a) *A patient receiving 150 micrograms four times daily via the **enteral** route may be converted **to** an equivalent **transdermal** dose as follows:*

Day	Enteral Clonidine Dose	Transdermal Clonidine Dose
1	Keep unchanged at 150 micrograms four times daily (600 micrograms daily).	Apply 1 x 300 microgram/day patch.
2	Reduce **daily** dose by 150 micrograms (i.e. to 112.5 micrograms four times daily).	No change.
3	Reduce **daily** dose by 150 micrograms.	Apply second 300 microgram/day patch (leave first patch in place).
4	Reduce **daily** dose by 150 micrograms.	No change.
5	Stop	No change.

b) *A patient receiving 600 micrograms per day via the **intravenous** route may be converted **to** an equivalent **transdermal** dose as follows:*

Day	Intravenous Clonidine Dose	Transdermal Clonidine Dose
1	Keep unchanged at 600 micrograms daily.	Apply 1 x 300 microgram/day patch.
2	Reduce **daily** dose by 150 micrograms.	No change.
3	Reduce **daily** dose by 150 micrograms.	Apply second 300 microgram/day patch (**leave** first patch in place).
4	Reduce **daily** dose by 150 micrograms.	No change.
5	Stop	No change.

c) *A patient receiving 600 micrograms per day (as 2 x 300 microgram/day patches) via the **transdermal** route may be converted **to** an equivalent **enteral** dose as follows:*

Day	Transdermal Clonidine Dose	Enteral Clonidine Dose
1	Remove one 300 microgram/day patch, leaving the other in place.	Start at 150microgram/**day**
2	No change.	Increase to 300microgram/**day** (in 3-4 divided doses).
3	Remove the second 300 microgram/day patch, leaving no patches in place.	Increase to 450microgram/**day** (in 3-4 divided doses).
4	No change.	Increase to 600microgram/**day**
5	No change.	No change.