

What is the evidence for verapamil for prevention of cluster headaches?

Prepared by UK Medicines Information ([UKMi](#)) pharmacists (or other as appropriate) for NHS healthcare professionals

Before using this Q&A, read the disclaimer at <https://www.sps.nhs.uk/articles/about-ukmi-medicines-qas/>

Date prepared: 25/09/2020

Background

A cluster headache occurs when severe or very severe unilateral pain is felt in, behind or around the eye or temple but may spread to other areas of the head (1-3). The pain during an attack is described as a sharp, boring, burning, throbbing or tightening sensation. Each attack lasts 15-180 minutes, and may occur from once every other day to 8 times daily (1-3). Attacks occur in clusters lasting for weeks or months, separated by remission periods which last months or years, although about 10% of sufferers have no remission period (1). The attacks are classified as episodic or chronic (1-3).

Each attack is associated with one or more of the following features that all affect the same side of the body: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and eyelid oedema (1-3). During an attack the person is typically restless or agitated, unable to lie down, and typically paces the floor, or may even bang their head against the wall. Attacks often occur at night, typically waking the person after 1-2 hours sleep. During a cluster period the pain almost invariably occurs on the same side and an attack can be precipitated by alcohol or other vasodilators. The onset of cluster headache is usually between 20-40 years of age. Cluster headache affects mostly men, the male to female ratio ranges from 2.5:1 to 6:1 (1, 2).

In most cases preventive treatment is required as symptomatic treatment alone will rarely achieve adequate control. The aim of preventive therapy is to suppress attacks and maintain remission with minimal side effects (1, 2).

Answer

A number of medicines have been studied as preventive treatments, for example, ergotamine tartrate, lithium carbonate, methysergide, prednisolone, verapamil, frovatriptan, pizotifen, topiramate, sodium valproate, gabapentin, carbamazepine, baclofen, clonidine, melatonin, botulinum toxin and capsaicin (1, 2, 4).

The use of calcium antagonists as preventive treatment for cluster headache was first suggested over 25 years ago. The reasoning for use of calcium antagonists is that blocking entry of calcium ions into smooth muscle will reduce blood vessel dilation which causes severe pain. Nimodipine, nifedipine and verapamil can all reduce the tone of blood vessels in the head (5). Verapamil has a number of different actions. It has an effect in the hypothalamus and blocks calcium and potassium channels. Because of the many different actions, it is impossible to single out a certain mode of action for verapamil in cluster headache (6). Verapamil is considered the drug of choice for prevention of episodic and chronic cluster headache and is unlicensed for this indication (1-4, 7). Specialist advice should be sought before initiating verapamil in primary care (3, 8). The efficacy of verapamil has been demonstrated in both non-randomised and randomised controlled trials versus placebo and other medicines used for prophylaxis (4, 9-14). Immediate or standard release preparations may be used, although some experts believe that standard release preparations are more useful than modified release formulations (2, 4).

The British Association for the Study of Headache (BASH) guidelines for the management of cluster headache acknowledge that the efficacy of preventive drug treatments is largely based on expert opinion supported by a very small number of published clinical trials. Verapamil is used as a first line

preventive treatment for both episodic and chronic cluster headache. Doses of 80mg three or four times a day may be effective, although up to 960mg per day may be required (2, 7).

The clinical effectiveness of nimodipine, nifedipine and verapamil in prophylactic treatment of migraine and cluster headaches was demonstrated in a small open non-randomised study involving 35 patients. Nimodipine 60-120mg, nifedipine 30-180mg and verapamil 240-720mg daily were found to be effective in preventing cluster headache (9).

The efficacy of verapamil for prophylaxis of cluster headache was demonstrated in a non-randomised trial. The trial included 48 patients of which 33 patients suffered with episodic cluster headaches and 15 with chronic cluster headache. Thirty three (69%) of 48 patients with cluster headache improved more than 75% during verapamil treatment. The average daily dose of verapamil in the episodic group was 354mg (range 240-600mg/day) and in the chronic group 572mg (range 120-1200mg/day). Three patients taking doses of 240mg/day discontinued treatment due to side effects (10).

A multicentre, double dummy, double blind, cross over, 23 week trial in 30 patients with chronic cluster headache compared verapamil 360mg/day with lithium carbonate 900mg/day. Both treatments were shown to be effective in preventing chronic cluster headaches and reducing analgesic consumption. Clinical improvement was noted in 50% of verapamil patients by the end of the first week compared to 37% on lithium. The incidence of side effects was reduced with verapamil compared to lithium (12% vs. 29%) (11).

A double blind, double dummy, multicentre study comparing verapamil with placebo for prophylaxis of episodic cluster headache, randomised and followed up 30 patients. After a 5 day run in period where no prophylaxis was taken, patients were randomised to verapamil 120mg three times daily or placebo for 2 weeks. Patients were allowed to use subcutaneous sumatriptan to abort any cluster headaches that occurred. The primary endpoint of the trial was to determine if verapamil reduced attack frequency. During the first week of treatment there was no difference between the 2 groups with respect to number of attacks or the number of times sumatriptan was used. However, in the second week both the number of attacks (0.6 ± 0.88 vs. 1.65 ± 1.01 ; $p < 0.001$) and use of sumatriptan (0.5 ± 0.87 vs. 1.2 ± 1.03 ; $p < 0.004$) were lower in the verapamil arm compared to the placebo arm. Side effects were mild and did not require suspension of treatment. The most frequent side effect was constipation. There was a significant reduction in blood pressure and heart rate in patients taking verapamil although they were asymptomatic. The study concludes that the findings provide objective evidence for the effectiveness of verapamil in episodic cluster headache prophylaxis (12).

A non-randomised study to find the minimum effective dose to prevent episodic and chronic cluster headaches was conducted in 70 patients with cluster headache (52 episodic patients and 18 chronic patients). All patients were started on verapamil 40mg in the morning, 80mg in early afternoon and 80mg before going to bed. Patients were able to increase the dose by 40mg verapamil a day on alternate days depending on their attack timing, until attacks were completely suppressed. Complete relief from headaches was obtained in 49 out of 52 episodic patients (94%) and 10 out of 18 (55%) chronic patients. The majority of patients needed 200-480mg, although 9 in the episodic group and 3 in the chronic group needed 520-960mg. Ten patients, 2 in the episodic group and 8 in the chronic group experienced incomplete relief and required further therapy with ergotamine, lithium, sumatriptan or sodium valproate. One woman reduced the dose of verapamil from 240mg to 160mg because the higher dose made her too sleepy. One patient withdrew from the study because of side effects (Stevens-Johnson syndrome). The conclusion of the study is that providing the dose for each individual is adequate, verapamil is highly effective at completely preventing episodic cluster headaches, although patients with chronic cluster headache had a poorer response (13).

An abstract from a poster presentation published in *Cephalgia* (1999) gives brief details of the use of retarded verapamil in 9 patients with episodic or chronic cluster headache. The dose was 480mg to 720mg divided into 2 days' doses. Relief from attacks was achieved by 4 patients on 720mg and 3 patients on 480mg. Attacks still occurred in 2 patients with chronic headache despite treatment with 720mg (14).

Verapamil is usually well tolerated, common side effects are constipation (which can be severe) and flushing. Side effects are dose related and can include dizziness, oedema, nausea, fatigue hypotension and bradycardia. Gum bleeding may indicate gingival hyperplasia which should be confirmed by a dental practitioner. There is a high incidence of heart block and bradycardia with verapamil that can develop with initiation of therapy, increases in dose and during stable dose therapy so electrocardiograms (ECG) should be undertaken (4).

There are no standard guidelines for the frequency of ECGs. Some experts recommend an ECG before verapamil is started at a dose of 80mg three times daily and then 10 days after each dose increase of at least 80mg, paying particular attention to the PR interval (1, 4). Others suggest checking ECGs for AV-block before the dose reaches 480mg daily and then after any further dose increases (2); some recommend not monitoring until the dose exceeds 480mg, and then an ECG should be obtained after each additional 80mg increment (3). An ECG can be obtained every 3 months if the dose has not changed (4). In 2016, an international Delphi study was conducted to review cardiac monitoring of high-dose verapamil in cluster headache. Twenty two international clinical experts in cardiac rhythm disorders were interviewed to formulate ECG guidelines for the pre-treatment screening and monitoring of cluster headache patients using high-dose verapamil. The panel agreed only on performing pre-treatment ECG to screen for pre-existing cardiac arrhythmias. Pre-treatment ECG was deemed not necessary by most panel members for patients who did not have cardiac side effects during a previous period of cluster headache attacks treated with high-dose verapamil. Half the panel advised Holter ECG for patients on verapamil \geq 480 mg/day. The highest recommended daily doses varied between 240 and 960 mg (15).

In practice, drug interactions with verapamil may be an issue especially for patients with chronic cluster headache. Verapamil can inhibit the metabolism of midazolam, buspirone, simvastatin and carbamazepine. The doses of these drugs should be adjusted or alternatives used. Erythromycin and atorvastatin should not be used together with verapamil. Grapefruit juice should also be avoided as it increases the plasma levels of verapamil (6).

There are no firm guidelines to indicate how long prophylaxis should be given for. Patients with chronic cluster headache may require indefinite prophylaxis. For episodic cluster headaches prophylaxis is usually continued for 1-2 months after a patient becomes asymptomatic and then stops. However, the exact length of prophylaxis depends on the length of previous clusters (16).

Summary

- A cluster headache consists of attacks of severe unilateral pain that is felt in, behind or around the eye or temple but may spread to other areas of the head.
- Attacks can be classified as episodic or chronic depending on frequency and remission periods.
- Preventive treatment is required as symptomatic treatment alone will rarely achieve adequate control.
- Calcium antagonists block entry of calcium ions into smooth muscle. This reduces blood vessel dilation which is responsible for the severe pain.
- Verapamil is considered the current drug of choice for prevention of episodic and chronic cluster headache. A dose of 360mg daily has been shown to be efficacious in some studies, although sometimes doses of up to 960mg daily is required. Standard release preparations are believed to be more useful than modified release formulations.

- There is a high incidence of heart block and bradycardia with verapamil that can develop with initiation of therapy, increases in dose and during stable dose therapy so electrocardiograms (ECG) should be undertaken
- The efficacy of verapamil in preventing cluster headaches has been demonstrated in both non-randomised and randomised controlled trials versus placebo and other medicines used for prophylaxis.
- Verapamil is highly effective at preventing episodic cluster headaches, although patients with chronic cluster headache have a poorer response.
- Patients with chronic cluster headache may require indefinite prophylaxis. The length of prophylaxis for episodic cluster headache depends on the length of the cluster.

Limitations

This answer is specific to use of verapamil for prevention of cluster headache, it does not apply to other calcium channel blockers.

This Q&A does not consider the use of verapamil in children aged 12 and under.

References

1. Nesbitt AD, Goadsby PJ. Cluster headache. *British Medical Journal* 2012; 344: e2407.
2. MacGregor EA, Steiner TJ et al. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type headache, cluster headache and medication-overuse headache. British Association for the Study of Headache. 3rd edition (1st revision); September 2010. http://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf
3. National Institute for Health and Care Excellence. Headaches – diagnosis and management of headaches in young people and adults. Clinical Guideline 150. September 2012. Last updated November 2015. <https://www.nice.org.uk/guidance/cg150/>
4. Weaver-Agostoni J. Cluster headache. *American Family Physician* 2013; 88 (2): 122-128.
5. Meyer JS. Calcium channel blockers in the prophylactic treatment of vascular headache. *Annals of Internal Medicine* 1985; 102 (3): 395-397.
6. Tfelt-Hansen P, Tfelt-Hansen J. Verapamil for cluster headache. *Clinical pharmacology and possible mode of action. Headache* 2009; 49: 117-125.
7. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press; September 2020. Accessed 17/09/2020 <https://bnf.nice.org.uk/>
8. Clinical Knowledge Summaries. Headache – cluster. Last updated November 2017. <https://cks.nice.org.uk/topics/headache-cluster/>
9. Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. *Headache* 1983; 23: 266-277.
10. Gabai IJ, Spierings ELH. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989; 29: 167-168.
11. Bussone G, Leone M et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; 30: 411-7.
12. Leone M, D'Amico D et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000; 54: 1382-1385.
13. Blau JN, Engel HO. Individualizing treatment with verapamil for cluster headache patients. *Headache* 2004; 44: 1013-1018.
14. Gobel H, Holzgreve H et al. Retarded verapamil for cluster headache prophylaxis. *Cephalalgia* 1999; 19: 458-459.
15. Koppen H, Stolwijk J, Wilms E, van Driel V, Ferrari M, Haan J. Cardiac monitoring of high-dose verapamil in cluster headache: An international Delphi study. *Cephalalgia*. 2016;36(14):1385-1388.
16. Becker WJ. Cluster Headache: Conventional Pharmacological Management. *Headache* 2013; 53 (7): 1191-1196.

Quality Assurance

Prepared by

Marianne Eve, East Anglia Medicines Information Service

Available through Specialist Pharmacy Service at www.sps.nhs.uk

Date Prepared

25th September 2020

Checked by

Ms Iram Husain, London Medicines Information Service (Northwick Park)

Date of check

13th October 2020

Search strategy

1. Embase [exp VERAPAMIL/dt [dt=Drug Therapy] AND exp CLUSTER HEADACHE/pc [pc=Prevention] [Limit to: Human and English Language and Publication Year 2014-Current]
2. Medline [exp VERAPAMIL AND exp CLUSTER HEADACHE] [Limit to: English Language and Humans and Publication Year 2014-Current]
3. In-house database/ resources including BNF, Martindale, AHFS, Drugdex, Clinical Knowledge Summaries, UpToDate, NICE.
4. Internet Search BASH (British Association for the study of headaches)