Zolmitriptan for acute migraine headaches in adults

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of the review will be to determine the efficacy and tolerability of zolmitriptan compared to placebo and other active interventions in the treatment of acute migraine headaches in adults.

BACKGROUND

Description of the condition

Migraine is a common, disabling headache disorder, affecting about 12% of Western populations, and with considerable social and economic impact. It is more prevalent in women than men (on the order of 18% versus 6% 1-year prevalence), and in the age range 30 to 50 years (Hazard 2009; Lipton 2007; Moens 2007). The International Headache Society (IHS) classifies two major subtypes. Migraine without aura is the most common, and usually more disabling, subtype. It is characterised by attacks lasting 4 to 72 hours that are typically of moderate to severe pain intensity, unilateral, pulsating, aggravated by normal physical activity and associated with nausea and/or photophobia and phonophobia. Migraine with aura is characterised by reversible focal neurological symptoms that develop over a period of 5 to 20 minutes and last for less than 60 minutes, followed by headache with the features of migraine without aura. In some cases the headache may lack migrainous features or be absent altogether (IHS 2004).

A recent large prevalence study in the US found that over half of migraineurs had severe impairment or required bed rest during attacks. Despite this high level of disability and a strong desire for successful treatment, only a proportion of migraine sufferers seek professional advice for the treatment of attacks. The majority were not taking any preventive medication, although one-third met guideline criteria for offering or considering it. Nearly

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CONTRIBUTIONS OF AUTHORS SD and RAM wrote the protocol. SD and RAM will carry out searches for studies, data extraction and analyses. HJM will act as arbitrator. All authors will be involved with writing the final review.

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DECLARATIONS OF INTEREST RAM, HJM and SD have received research support from charities, government and industry sources at various times. RAM and HJM have consulted for various pharmaceutical companies, including AstraZeneca, the manufacturers of zolmitriptan. RAM and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. AstraZeneca will not in any way be involved in carrying out this review.

all (98%) migraineurs used acute treatments for attacks, with 49% using over-the-counter (OTC) medication only, 20% using prescription medication and 29% using both. OTC medication included aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen) and paracetamol with caffeine (Bigal 2008; Diamond 2007; Lipton 2007). Similar findings have been reported from other large studies in France and Germany (Lucas 2006; Radtke 2009).

The significant impact of migraine with regard to pain, disability, social functioning, quality of relationships, emotional well-being and general health (Edmeads 1993; Osterhaus 1994; Solomon 1997) results in a huge burden for the individual, health services and society (Clarke 1996; Ferrari 1998; Hazard 2009; Hu 1999; Solomon 1997). The annual US economic burden relating to migraine, including missed days of work and lost productivity, is US\$14 billion (Hu 1999). Thus successful treatment of acute migraine attacks not only benefits patients by reducing their disability and improving health-related quality of life, but also reduces the need for healthcare resources and increases economic productivity (Jhingran 1996; Lofland 1999).

Description of the intervention

The symptomatic treatment of migraine advanced significantly with the development of the triptan class of drugs, of which sumatriptan was the first. Zolmitriptan (trade names include Zomig, Zomigon, Zomigoro, AscoTop) is a second-generation triptan, available as a standard tablet to be swallowed whole (2.5 mg), an oral disintegrating tablet (2.5 mg and 5 mg) and a nasal spray (5 mg). The disintegrating tablet contains aspartame, which can cause headache in some individuals and should be avoided by them. In England in 2009 there were 311,000 prescriptions for zolmitriptan in primary care, almost two-thirds of which were for the standard 2.5 mg tablet (PCA 2010).

In order to establish whether zolmitriptan is an effective analgesic at a specified dose in acute migraine attacks, it is necessary to study its effects in circumstances that permit detection of pain relief. Such studies are carried out in individuals with established pain of moderate to severe intensity, using single doses of the interventions. Participants who experience an inadequate response with either placebo or active treatment are permitted to use rescue medication, and the intervention is considered to have failed in those individuals. In clinical practice, however, individuals would not normally wait until pain is of at least moderate severity, and may take a second dose of medication if the first dose does not provide adequate relief. Once analgesic efficacy is established in studies using single doses in established pain, further studies may investigate different treatment strategies and patient preferences. These are likely to include treating the migraine attack early while pain is mild, and using a low dose initially, with a second dose if response is inadequate.

How the intervention might work

Zolmitriptan is a 5-HT₁ agonist, mainly targeting the 5-HT (serotonin) 1B and 1D receptors. It has three putative mechanisms of therapeutic action (Ferrari 2002; Goadsby 2007):

- vasoconstriction of dilated meningeal blood vessels;

- inhibition of the release of vasoactive neuropeptides from perivascular trigeminal sensory neurons;
- reduction of pain signal transmission in the trigeminal dorsal horn.

It is used for acute treatment, having no efficacy in preventing future attacks.

Why it is important to do this review

There are now a number of studies investigating the efficacy and tolerability of zolmitriptan for the treatment of acute migraine attacks, but no Cochrane review of these studies. Several treatment options are available to treat acute migraine headaches, including triptans and common OTC analgesics such as aspirin, ibuprofen and paracetamol. This is one of a series of reviews planned for acute treatments for migraine attacks.

OBJECTIVES

The objective of the review will be to determine the efficacy and tolerability of zolmitriptan compared to placebo and other active interventions in the treatment of acute migraine headaches in adults.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised, double-blind, placebo- and active-controlled studies using zolmitriptan to treat a discrete migraine headache episode will be included. Studies must have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. Studies reporting treatment of consecutive headache episodes will be accepted if outcomes for the first, or each, episode are reported separately. Cross-over studies will be accepted if there is adequate washout (48 hours) between treatments.

Types of participants—Studies must include adults (at least 18 years of age) with migraine. The diagnosis of migraine specified by the International Headache Society (IHS 1988; IHS 2004) will be used, although other definitions will be considered if they conform in general to IHS diagnostic criteria. There will be no restrictions on migraine frequency, duration or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency will be accepted; details on the prophylactic therapy prescribed or allowed will be provided in the ‘Characteristics of included studies’ table.

Types of interventions—Included studies must use either a single dose of zolmitriptan to treat a discrete migraine headache episode when pain is of moderate to severe intensity, or investigate different dosing strategies and/or timing of the first dose in relation to headache intensity. There will be no restriction on dose, or route of administration, provided the medication is self-administered.

A placebo comparator is essential to demonstrate that zolmitriptan is effective in this condition. Active-controlled trials without a placebo will be considered as secondary

evidence. Studies to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches will not be included.

Types of outcome measures

Primary outcomes: The choice of main outcome measures for this review was made by taking into consideration scientific rigour, availability of data and patient preferences (Lipton 1999). Patients with acute migraine headaches have rated complete pain relief, no headache recurrence, rapid onset of pain relief and no side effects as the four most important outcomes (Lipton 1999).

In view of these patient preferences, and in line with the guidelines for controlled trials of drugs in migraine issued by the IHS (IHS 2000), the main outcomes to be considered will be:

- Pain-free at 2 hours, without the use of rescue medication;
- Reduction in headache pain ('headache relief') at 1 and 2 hours (pain reduced from moderate or severe to none or mild without the use of rescue medication);
- Sustained pain-free over 24 hours (pain-free within 2 hours, with no use of rescue medication or recurrence within 24 hours);
- Sustained pain reduction over 24 hours (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication).

Pain intensity or pain relief should be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes will be:

- Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm VAS;
- Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

In the full review, we will report the pain measures used in the included studies and be as explicit as possible about how we 'mapped' data from the various scales to the dichotomous outcomes specified above if they differ.

Only data obtained directly from the patient will be considered.

Secondary outcomes: Secondary outcomes considered will include:

- Participants with any adverse event over 24 hours post dose;
- Participants with particular adverse events over 24 hours post dose;
- Withdrawals due to adverse events over 24 hours post dose;
- Relief of headache-associated symptoms;
- Functional disability.

Search methods for identification of studies

Electronic searches—The following databases will be searched:

- Cochrane CENTRAL;
- MEDLINE (via OVID);
- EMBASE (via OVID);
- Oxford Pain Relief Database (Jadad 1996a).

See Appendix 1 for the search strategy for MEDLINE (via OVID). This will be modified for searching the other databases. There will be no language restrictions.

Searching other resources—Reference lists of retrieved studies and review articles will be searched for additional studies. Grey literature and abstracts will not be searched. The authors will make a written request for information about both published and unpublished data from the manufacturer of zolmitriptan (AstraZeneca).

Data collection and analysis

Selection of studies—Two review authors will independently carry out the searches and select studies for inclusion. Titles and abstracts of all studies identified by electronic searches will be viewed on screen, and any that clearly do not satisfy inclusion criteria will be excluded. Full copies of the remaining studies will be read to identify those suitable for inclusion. Disagreements will be settled by discussion with a third review author.

Data extraction and management—Two review authors will independently extract data from included studies using a standard data extraction form. Disagreements will be settled by discussion with a third review author. Data will be entered into RevMan 5.0 by one author.

Assessment of risk of bias in included studies—Methodological quality will be assessed using the Oxford Quality Score (Jadad 1996b).

The scale is used as follows:

- Is the study randomised? If yes, give one point.
- Is the randomisation procedure reported and is it appropriate? If yes, add one point; if no, deduct one point.
- Is the study double-blind? If yes, add one point.
- Is the double-blind method reported and is it appropriate? If yes, add one point; if no, deduct one point.
- Are the reasons for patient withdrawals and dropouts described? If yes, add one point.

The scores for each study will be reported in the 'Characteristics of included studies' table.

A risk of bias table will also be completed, using assessments of randomisation, allocation concealment and blinding.

Measures of treatment effect—Relative risk (or ‘risk ratio’, RR) will be used to establish statistical difference. Numbers needed to treat (NNT) and pooled percentages will be used as absolute measures of benefit or harm.

The following terms will be used to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occur with zolmitriptan than with control (placebo or active) we will use the term the number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occur with zolmitriptan compared with control (placebo or active) we will use the term the number needed to harm or cause one event (NNH).

Unit of analysis issues—We will accept randomisation to individual patient only.

Dealing with missing data—The most likely source of missing data is in cross-over studies. Where this is an issue only first-period data will be used where available. In all cases (cross-over or parallel-group) where there are substantial missing data we will comment on this and perform sensitivity analysis if possible.

Assessment of heterogeneity—Heterogeneity of studies will be assessed visually (L’Abbe 1987).

Assessment of reporting biases—Publication bias will be assessed by examining the number of participants in trials with zero effect (relative risk of 1.0) needed for the point estimate of the NNT to increase beyond a clinically useful level (Moore 2008). In this case, we specified a clinically useful level as an NNT of 8.

Data synthesis—Studies using a single dose of zolmitriptan in established pain of at least moderate intensity will be analysed separately from studies in which medication is taken before pain is well established or in which a second dose of medication is permitted.

Effect sizes will be calculated and data combined for analysis only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998). Relative risk of benefit or harm will be calculated with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CIs will be calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control will be assumed when the 95% CI of the relative risk of benefit or harm does not include the number one.

Significant differences between NNT, NNTp and NNH for different doses of active treatment, or between groups in the sensitivity analyses, will be determined using the z test (Tramer 1997). Data from comparisons and outcomes with only one study or fewer than 200

participants will be described in the summary tables where appropriate for information and comparison, but will not be analysed quantitatively.

Subgroup analysis and investigation of heterogeneity—Issues for subgroup analysis are dose, formulation, and route of administration.

Sensitivity analysis—Sensitivity analysis is planned for study quality (Oxford Quality Score of 2 versus 3 or more), and for migraine type (with aura versus without aura). A minimum of two studies and 200 participants must be available for any sensitivity analysis.

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Internal sources

- Oxford Pain Research funds, UK.

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.
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Appendix 1. Search strategy for MEDLINE (via OVID)

1. Serotonin Agonists/ OR Tryptamines/
2. (zolmitriptan OR Zomig OR Zomigon OR Zomigoro OR AscoTop).mp.
3. 1 OR 2
4. Headache/ OR exp Headache Disorders/ OR exp Migraine Disorders/
5. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
6. 4 OR 5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. drug therapy.fs.
12. randomly.ab.
13. trial.ab.
14. groups.ab.
15. OR/7-14
16. 3 AND 6 AND 15

HISTORY

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Indicates the major publication for the study