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Sumatriptan plus naproxen 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 sumatriptan plus naproxen, administered together as separate agents or taken as a fixed-dose combination tablet, 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).

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CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

RAM has consulted for various pharmaceutical companies. RAM has received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. RAM and SD have received research support from charities, government and industry sources at various times. Support for this review was from Pain Research Funds, the NHS Cochrane Collaboration Programme Grant Scheme, and the NIHR Biomedical Research Centre Programme. None had any input into the review at any stage.

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 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 (McCrory 2003). Sumatriptan is available as 50 mg and 100 mg oral tablets (maximum 300 mg in 24 hours) and also as a subcutaneous injection (6 mg dose, maximum 12 mg in 24 hours) and intranasal spray (20 mg, maximum 40 mg in 24 hours). In most parts of the world it is available only by prescription, but in some countries it is available to the public without prescription. Naproxen is an OTC NSAID that has also been shown to be an effective treatment for migraine (Nestvold 1985). It is available as 250 mg or 275 mg tablets. A fixed-dose combination tablet (trade name Trexima or Treximet; GlaxoSmithKline) containing 500 mg naproxen with 85 mg sumatriptan is now available.

In order to establish whether sumatriptan plus naproxen is an effective analgesic combination 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

The challenge in optimising therapy for acute migraine headaches is in providing broad coverage of the multiple pathogenic processes involved, which are thought to include several neural pathways becoming sequentially activated and sensitized as an attack develops (Goadsby 2002).

Early in an attack, trigeminal nerve endings release vasoactive and inflammatory substances such as calcitonin gene-related peptide and kinins. Calcitonin gene-related peptide causes meningeal vasodilation, and kinins induce inflammatory prostaglandins. The resulting vascular and meningeal inflammation stimulates trigeminal nociceptors and activates central pathways via ascending pain pathways. Prolonged nociceptive input causes central foci to fire in a sustained continuous manner causing a full blown migraine attack. This is characteristic of the central sensitization hypothesis. (Burstein 2001).

Sumatriptan is a 5-HT₁ agonist, selectively targeting the 5-HT (serotonin) 1B and 1D receptors. It is suggested that it inhibits synaptic transmission from the periphery before central sensitization occurs. Three putative mechanisms of therapeutic action are involved (Ferrari 2002):

- 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.

NSAIDs block the effect of cyclo-oxygenase on arachidonic acid, which is responsible for the synthesis of prostaglandins. Prostaglandins mediate a variety of physiological functions including maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone, and they also play an important role in inflammatory and nociceptive processes. Naproxen is a reversible inhibitor of cyclo-oxygenase. Unlike the triptans, which exert their effect peripherally, naproxen is thought to inhibit central sensitization by attenuating meningeal inflammation and preventing central sensitization arising from glial cells in the brain stem. In a recent study, naproxen suppressed central trigeminal neurons in an animal model of intracranial pain (Jakubowski 2007). Because multiple mechanisms are involved in migraine, multi-mechanism targeted therapy with sumatriptan plus naproxen may confer advantages over conventional monotherapy.

Why it is important to do this review

Earlier studies of sumatriptan and naproxen support their efficacy as individual agents in the treatment of acute migraine headaches. It is important to assess and analyse the data now available for combination therapy involving these two agents, particularly in the light of more recent studies investigating different combination treatment regimens.

OBJECTIVES

The objective of the review will be to determine the efficacy and tolerability of sumatriptan plus naproxen, administered together as separate agents or taken as a fixed-dose combination tablet, 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 sumatriptan plus naproxen 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 (≥ 48 hours) washout 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 sumatriptan plus naproxen (as separate agents administered together, or as a fixed-dose combination tablet) 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 sumatriptan plus naproxen 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 have rated complete pain relief, no headache recurrence, rapid onset of pain relief, and no side effects as the four most important outcome (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;
- Use of rescue medication;
- 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);
- <http://www.gsk-clinicalstudyregister.com>

See Appendix 1 for the search strategy for MEDLINE (via OVID); this will be modified for searching EMBASE (Appendix 2) and Cochrane CENTRAL (Appendix 3). 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 manufacturer of the fixed-dose combination agent (GlaxoSmithKline) will be contacted to ask for details of published, unpublished or ongoing studies.

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 1996a; 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 or NNH) and pooled percentages of participants achieving each outcome 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 sumatriptan plus naproxen 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 sumatriptan plus naproxen 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. 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).

Data synthesis—Studies using a single dose of sumatriptan plus naproxen 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 are 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 1996). 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 text and/or 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, timing of doses, route of administration and multiple dosing strategies.

Sensitivity analysis—Sensitivity analysis is anticipated 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.
- NIHR Biomedical Research Centre Programme, UK.

Appendix 1. Search Strategy for MEDLINE via OVID

1. Sumatriptan/AND Naproxen/
2. (sumatriptan AND naproxen) OR Treximet OR Trexima.mp
3. 1 OR 2
4. Headache/OR exp Headache Disorders/
5. exp Migraine Disorders/
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. drug therapy.fs.
13. randomly.ab.
14. trial.ab.
15. groups.ab.
16. OR/8-15
17. 3 AND 7 AND 16

Appendix 2. Search Strategy for EMBASE via Ovid

1. Naproxen plus Sumatriptan/
2. (sumatriptan AND naproxen) OR Treximet OR Trexima.mp
3. 1 OR 2
4. Headache/OR exp Headache and facial pain/
5. exp Migraine/
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. clinical trials.sh.

9. controlled clinical trials.sh.
10. randomized controlled trial.sh.
11. double-blind procedure.sh.
12. (clin* adj25 trial*).ab.
13. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.
14. placebo*.ab.
15. random*.ab.
16. OR/8-15
17. 3 AND 7 AND 16

Appendix 3. Search strategy for Cochrane CENTRAL

1. MeSH descriptor Sumatriptan AND MeSH descriptor Naproxen
2. (sumatriptan AND naproxen) OR Treximet OR Trexima:ti,ab,kw.
3. 1 OR 2
4. MeSH descriptor Headache/OR MeSH descriptor Headache Disorders explode all trees
5. MeSH descriptor Migraine Disorders explode all trees
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw.
7. 4 OR 5 OR 6
8. Randomized controlled trial:pt.
9. MESH descriptor Double-blind Method
10. random*:ti,ab,kw.
11. OR/8-10
12. 3 AND 7 AND 11
13. Limit 12 to Clinical Trials (CENTRAL)

HISTORY

Protocol first published: Issue 6, 2010

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* *Indicates the major publication for the study*