Extended Abstracts: Combination Products

Primary Literature

1) Pini LA, Del Bene E, Zanchin G. et al. Tolerability and efficacy of a combination of paracetamol and caffeine in the treatment of tension-type headache: a randomized, double-blind, double-dummy, cross-over study versus placebo and naproxen sodium. J Headache Pain 2008; 9:367 – 373

Study Objectives

The primary objective was to compare and confirm the favourable safety and tolerability profile of combination paracetamol (acetaminophen) 1000 mg and caffeine (130 mg) observed in previous studies to naproxen sodium and placebo in an Italian population affected by tension-type headache (TTH). The secondary objective was to assess the efficacy of the combination paracetamol 1000 mg – caffeine 130 mg in the acute treatment of TTH, versus naproxen sodium 550 mg and placebo

Design: Randomized, double-blind, placebo-controlled, double-dummy, cross-over study

Allocation : From the beginning of the study, patients were required to treat the next three consecutive TTH attacks with the investigational study medications (placebo, naproxen, or acetaminophen+caffeine) Each patient was randomly allocated to one of six sequences shown below:

Table 1: Sequences of study treatments

1. PCF – NAP – PLA
2. NAP – PLA – PCF
3. PLA – PCF – NAP
4. PCF – PLA – NAP
5. NAP – PCF – PLA
6. PLA – NAP – PCF

PCF: Paracetamol 1000 mg + caffeine 130 mg
NAP: Naproxen sodium 550 mg
PLA: Placebo

Eligible patients were assigned in sequential order of entry. Subjects in all treatment groups received three identical boxes (numbered progressively from 1 to 3 to indicate the exact order in which they should have been used) containing:

- One soft gel capsule containing one tablet of placebo and one sachet containing paracetamol 1000 mg + caffeine 130 mg,
- One soft gel capsule containing one tablet of naproxen sodium 550 mg and one sachet of placebo
- One soft gel capsule containing one tablet of placebo and one sachet of placebo

The trial medication was to be taken when the headache occurred, and when the patients would normally have taken their usual analgesic. At each TTH attack patients would have to take one soft gel capsule and one sachet at the same time. Other than study medication, patients received rescue medication (ibuprofen 600 mg) to be taken 2 hours after the administration of the trial medication, if the pain persisted.

Blinding: Randomization was carried out using Microsoft Access 2003. Access to the randomization code was strictly controlled and the treatment assignment remained unknown to all parties involved in

the trial until formal database lock. Blinding was ensured using matched trial supplies identical in colour, size, shape and taste.

Follow-up period: Follow-up period was not specifically stated within the study. Patients were followed for 4 hours for the detection of side effects. Trial was conducted between December 2004 and May 2007.

Setting: Multicenter study conducted in eight headache centres throughout Italy

Participants: A number of inclusion and exclusion criteria were applied to participants entering the study. Outpatient volunteers with a clinical history of TTH, n = 99. 40% male, mean age 35.1±10.9 years, age range 19 – 64. Patients had headache duration of 22.2±9.09 years. The mean number of days with tension type-headache per month was <4 in 2% of patients and 4-14 in 98% of participants. Usual pain intensity was mild in 21.2%, moderate in 75.8% and severe in 3% of participants.

Intervention: Paracetamol+caffeine combination vs naproxen

Outcomes

Efficacy: To assess efficacy, the sum of pain intensity differences (SPID) and the total pain relief (TOTPAR) were calculated

- To assess treatments' efficacy, intensity of pain (on a 4-point scale) and pain relief (on a 5-point scale) were evaluated hourly during the 4-hr dose period.
- Pain intensity difference (PID) was calculated as the sum of differences between pre-dose assessment and every post-dose assessment for each patient
- TOTPAR: Calculated as the sum of every post-dose assessment
- Patients expressed their preference for one of the investigational treatments, answering the following question: "Taking into account both tolerability and efficacy, which of the three treatments would you take again at the next headache attack?"

Tolerability & safety: Tolerability was assessed by recording adverse events by the patient in the 4-hour post-dose treatment

Patient follow-up: 111 subjects entered the study, 99 of these subjects took at least one of the treatments. 12 patients were excluded from the study, since they did not fulfill the inclusion criteria (n=2) or did not take any medication (n=10). The other 6 patients took 1 or 2 investigation medications only. Therefore, the study population included 93 subjects. Reasons why patients did not complete the study were:

- Explicit request to withdraw from the study (n=8)
- Lack of compliance to study procedures (n=5)
- Severe nausea (n=1)
- Unmasking of assigned treatment (N=1)
- Expiry of investigational medication (n=1)
- Intention to treat (ITT) population included 93 subjects, 91 and 81 of these subjects were available for the efficacy analyses concerning pain severity and pain relief, respectively.

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Main results:

Efficacy

In terms of SPID & TOTPAR, both PCF and NAP demonstrated improvement over placebo ($p<0.05$), but were not significantly different from each other. The percentage of subjects who used rescue medication were similar for PCF and NAP (4.8% and 3.3% respectively) and both were less than the 10% of subjects who used rescue medication after PLA. In terms of preference for one of the tested treatments, 32.6% of patients preferred PCF, 44.6% of patients preferred NAP, and 22.8% of patients preferred PLA. The results showed a significant superiority of PCF over placebo, and no difference between PCF and NAP, in terms of both the reduction of pain intensity and the pain relief.

Tolerability & safety

Comparing PCF and NAP and PCF and PLA for tolerability, the difference was non-significant but the result regarding non-inferiority was inconclusive. During the 4 hour post-dose period, 224 AEs were recorded: 33.9% after PCF ingestion, 29.5% after NAP and 36.6% after PLA; most AEs were codified as mild or moderate. The most frequently observed AEs were nausea, drowsiness, fatigue, and nervousness. The AEs theoretically attributable to the stimulating effect of caffeine (nervousness, palpitation and insomnia) were roughly the same with the three investigational medications. One patient withdrew from the study due to severe nausea during a headache attack treated with PCF.

Conclusions:

PCF was well-tolerated and effective in the treatment of acute TTH. The combination of paracetamol 1000 mg and caffeine 130 mg seems to be effective and well-tolerated, in particular not showing the specific stimulatory effects of caffeine. It is therefore a viable candidate for the first line treatment of acute episodic TTH.

Comments/critical appraisal

Internal validity

Although a follow-up of four hours may be adequate to detect a difference in the efficacy and short-term safety outcomes of the medications studied, the long-term side effects would not be detected within this timeframe. The follow-up time of patients during the study was insufficient to detect a statistically or clinically significant difference in side effects. NSAIDs can cause gastric irritation and occasionally ulceration over time, which may complicate treatment with aspirin or other NSAIDs, even when they are used intermittently. Therefore, this study was not designed to detect some of the adverse effects associated with prolonged intermittent use of NSAIDs and combination products. The four-hour post-administration window may have been too short of a time frame to measure tolerability and safety of this medication. Adequate and relevant inclusion and exclusion criteria were applied to the study population, and details such as blinding and method of randomization were established. The outcome points as measured by the SPID and TOTPAR were relevant endpoints to measure for the clinical context and objective of this study. Tension type headaches can be a frequent recurrence for many individuals. Within this study, 98% of participants had experienced an average of 4 – 14 tension-type headaches per month, which likely reflects the frequency of these headaches amongst other individuals experiencing TTH. Therefore, the use of treatment for TTH may be frequent among these individuals. As such, trials that evaluate treatment options for TTH should take into account the incidence of medication over use headache (MOH). Medication overuse headache is an undesirable effect that is often seen with combination analgesic products for headache. This study did not consider MOH, especially as it was only designed to compare naproxen to combination therapy, and treatments were only used on three separate occasions, not over the long-term. However, this would have been a relevant and informative outcome to measure to add further merit to this study.

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External validity

This study was conducted in an Italian population; this may have implications for generalizability as the North American population arguably may have different habits and lifestyles with respect to Italian patients, including higher consumption of caffeine, and therefore perhaps a different sensitivity to its peripheral and central stimulatory effects. In terms of product availability, this trial has good generalizability, since the formulations and strengths of the products studied in this trial are similar to products available in Canada. For those who have contraindications to NSAID therapy, or where NSAID use is a concern (e.g. renal failure, heart failure, concomitant ACEI/ARB therapy), the results of this study have shown that combination therapy with acetaminophen and caffeine is non-inferior to NSAIDs, and is a viable option for those with tension-type headache.

Clinical Practice Guidelines

2) Haag G, Diener H, May A. et al. Self-medication of migraine & tension-type headache: summary of the evidence-based recommendations of the Deutsche Migane und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft fur Neurologie (DGN), the Oterreichische Kopfschmerzgesellschaft (OKSG) and the Schweizerische Kopfwehgesellschaft (SKG). J Headache Pain 2011; 12: 201 – 217

Study objectives

The objective of this "evidence-based guideline on the self-medication of migraine and tension-type headache" was to update the guidelines from the previous 2004 version based on the new treatment alternatives available and scientific findings and consequently improve the treatment of headaches for patients. The guideline was compiled together by the German Society of Neurology, the Austrian Headache Society, and the Swiss Headache Society.

Scope

Literature Selection (search criteria)

To be included in the therapy recommendations, the publications had to fulfill a number of criteria regarding study quality and scientific evidence, including a full publication of double-blind controlled, clinical studies on the treatment of headache disorders with medications that can be obtained over-the-counter in Germany, Austria, or Switzerland. Also, publications which were controlled studies without a placebo group were only included in the evaluation if there was an active control of a drug or fixed-dose combination thereof, whose efficacy is proven in terms of these recommendations.

Exclusion criteria were applied to the publications and publications were excluded if they met the following criteria:

- Abstracts, congress posters, congress information
- Observational studies, review articles, and case series
- Clinical studies in which the clinical symptoms of headache disorders only constitute an accompanying criterion
- Short publications
- Unpublished study reports
- Pharmacokinetic or bioavailability studies
- Clinical studies with children

Including the additions from the manual searches, a total of 35 studies published in 34 publications were newly considered in these recommendations compared to those from 2004.

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Methods: Systematic research evaluation and synthesis of the best available scientific evidence

1. *Literature search*: MEDLINE and the Cochrane Database were used to conduct a systematic literature search and identify all clinical headache studies including the active ingredients or active ingredient combinations of interest. The search structure included studies and articles relating to the active ingredients for the period of January 2002 to December 2007, and for the newly added active ingredients for the period of 1966 to December 2007. The search was limited to publications in English & German.
2. *Literature Selection (search criteria)*: See 'Literature selection' section, above
3. *Evaluation criteria for the individual clinical studies*: The studies that were identified as "clinically relevant" for the evaluation of drugs and fixed-dose combinations were then rated in terms of study quality (rated on a 4-point scale) and scientific evidence" (rated by a 5-point scale [+++; ++; +; (+); =]

Evaluation criteria for the active ingredients of fixed-dose combinations: The authors refrained from using a pool of data from the therapy studies identified as clinically relevant, since the small number of studies for each active ingredient or fixed-dose combination differed too greatly in methodological terms in many cases.

Recommendations for medicinal therapy: Evaluations of the newly added studies that were not included in the 2004 guidelines were based on three recommendation categories:

- "Remedy of first choice"
    - Quality of scientific evidence was rated with "A"
    - The scientific evidence of efficacy was rated with at least "++"
    - The clinical impression of effectiveness was rated with at least "++" and
    - The tolerability was rated with "++"
- "Remedy of second choice"
    - The quality of scientific evidence was rated with "B"
    - The scientific evidence of efficacy was rated with at least "(+)"
    - The clinical impression of effectiveness was rated with at least "+" and
    - The tolerability was rated with "+"
- "Only in individual cases"
    - The quality of scientific evidence was rated with "C or D"
    - The scientific evidence of efficacy was poorer than "(+)"
    - The clinical impression of efficacy was rated with at least "+", and
    - The tolerability was rated with at east "+"

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<u>Main results</u> (with respect to combination products)

Recommendations for self-medication of tension-type headache

Drug or fixed-dose combination	Quality of the scientific evidence	Scientific evidence of efficacy	Clinical impression of effectiveness	Clinical impression of tolerability	Commentary	Recommendation for self-medication
Two tablets of the fixed combination: ASA (250 – 265 mg) + paracetamol (200 – 265 mg) + caffeine (50 – 65 mg)	A	+++	++	+++	Highlighted recommendation on the basis of the analysed comparative studies.	Drug of first choice

Remarks on active ingredients and active ingredient combinations: Acetylsalicylic acid + paracetamol + caffeine:

In a large, randomized, double-blind study with a parallel group design, patients were only included if they had successfully treated their headaches themselves with prescription-free pain medications. The approximately 1750 patients therefore represented typical OTC headache patients. In the primary target criterion, "time until reaching a 50% pain reduction", the superior efficacy of two tablets of the fixed-dose combination of ASA + paracetamol + caffeine was shown compared to 1000 mg ASA, 1000 paracetamol, the combination of ASA and paracetamol, and compared to 100 mg of caffeine and placebo. All treatments differed significantly from placebo (with the exception of caffeine). The statistical analyses of the secondary endpoints also confirmed the superiority of the triple combination compared to the combination without caffeine, as well as all single substances and placebo. Their clinical relevance was confirmed through analyses of the patient's global efficacy rating.

<u>Conclusions</u>

Concerning the self-medication in tension-type headache, the fixed-dose combination of acetaminophen, acetylsalicylic acid and caffeine can be recommended as first-line therapy.

<u>Comments/Critical Appraisal</u>

Internal validity

Instead of being based on expert opinion, the inclusion/exclusion criteria employed in these guidelines appear to be mostly evidence-based. The inclusion criteria did take into account if therapies were relevant and included only high-quality of evidence randomized, double-blind, placebo controlled trials. The exclusion criteria applied were stringent (e.g. no observational studies or case series or review articles). The evidence that the authors provided to support the recommendation for the combination of ASA+acetaminophen+caffeine is based on only one large, randomized, double-blind study with approximately 1750 patients. Although this trial was of good quality, this was the only study that was included as the rationale for its place in first line therapy.

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External validity

Although these guidelines were based on evidence, their recommendation of combination products as first line therapy may not be the most practical or safest. There is a risk of medication-overuse headache, which can result from the overuse of analgesics; although they ideally should be used less than 15 days per month, combination products are available over-the-counter, and can be used by patients inappropriately without the proper education and monitoring. The first-line combination listed in these guidelines are combinations containing ASA, acetaminophen (paracetamol) and caffeine; however, such preparations are not available in Canada – analgesic products, especially for headache, contain either ASA or acetaminophen, but not both in one product. Combination therapies that contain codeine may be considered as therapeutic options for tension-type headaches; however, such combinations were not included in the guidelines, which may possibly be due to the restricted availability of codeine-containing preparations.

Tertiary literature/Other literature types

3) DiPiro JT, Talbert RL, Yee GC. et al. Pharmacotherapy: A Pathophysiologic Approach. 7th Edition. McGraw-Hill Companies Inc 2008.

Source Description:

- DiPiro JT et al. Pharmacotherapy: A Pathophysiologic Approach. 7th Edition. 2008. Minor DS, Wofford MR. Section 6: Neurologic Disorders, Chapter 63: Headache Disorders. McGraw-Hill Medical. Pp. 1016
- Textbook reference
- Referencing: Referencing embedded within the text; each chapter provides a list of references in chronological order at the end of the chapter.
- Date of last update: 2011

Summary:

Simple analgesics (alone or in combination with caffeine) and NSAIDs are effective for the treatment of mild to moderate tension-type headache. High-dose NSAIDs and the combination of aspirin or acetaminophen with butalbital or, rarely, codeine are effective options. Use of butalbital and codeine combinations should be avoided when possible owing to the high potential for overuse and dependency. Acute medication should be taken for episodic tension-type headache no more than 2 days per week to prevent the development of chronic tension-type headache.

Comments/Critical Appraisal:

Internal validity

These statements are very general, and no specific information is given regarding efficacy, safety, and the place in therapy for each of these agents. The section dedicated to the pharmacologic therapy of tension-type headaches in particular was not very extensive. Although the authors acknowledge the possible utility of analgesics in combination with caffeine, there were only two references to support these statements. Additionally, the statements themselves were not supported by high-quality evidence, as the two references used were from tertiary sources (textbooks). Evidence in the form of randomized controlled trials, systematic reviews, and meta-analyses were lacking.

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External validity

Although the statements in this textbook were not based upon high-quality evidence, the recommendations from such a well-known and utilized textbook such as Pharmacotherapy will likely have the best external validity, as the information within this textbook is intended to serve as a general references for everyone.

Primary Literature

4) Diamond S and Freitag, FG. The Use of Ibuprofen Plus Caffeine to Treat Tension-type Headache. Current Pain and Headache Reports. 2001 [cited March 7, 2012]; 5: 472-478. Available from: PubMed

Study objectives

The primary objective of this study was to evaluate the efficacy and safety of ibuprofen plus caffeine for tension-type headache compared to placebo. The secondary objective was to develop an adequately sensitive trial methodology for determining sufficient analgesia in the treatment of tension-type headaches. The final objective was to establish if caffeine is an independent analgesic or if it acted only in conjunction with other analgesics.

Methods

Design: The trial was designed as a randomized, double-blind, parallel, single-dose placebo-controlled trial enrolling patients with tension-type headaches.

Allocation: Subjects were stratified by gender and randomized to a study group in a ratio of two subjects in the ibuprofen + caffeine group, two subjects in the ibuprofen group, one subject in the caffeine group and one subject in the placebo group.

Blinding: A double-blind trial. However, the details of how the patients and investigators were blinded for the stated double-blind protocol were not outlined.

Follow-up period: 2 months total. Patients followed up with the physician within 1 week of having a tension-type headache.

Setting: A multicenter trial involving 19 sites across the United States

Participants: There were 385 male and female patients, at least 18 years of age, with a history of acute tension-type headaches (3-15 headaches per month for the previous year that responded to an over-the-counter analgesic 75% of the time).

Intervention: Each subject received a diary, two stopwatches and a bottle with a single two-tablet dose of either ibuprofen (400mg) + caffeine (200mg), ibuprofen (400mg) or caffeine (200mg) alone or placebo. The medication was to be used for the treatment of a single tension-type headache of at least moderate severity.

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Outcomes:

- These were not outlined clearly
- In general, subjects in the various treatment allocations recorded:
    - Pain intensity before taking the medication from 0 (none) to 3 (severe)
    - Time to the first onset of pain relief (measured by stopwatch)
    - Time to the first onset of meaningful pain relief (measured by stopwatch)
    - Pain intensity, measured at specific time points over 6 hours on a scale of 0 (none) to 3 (severe)
    - Pain relief, measured at specific time points over 6 hours on a scale of 0 (none) to 4 (complete relief)
    - An overall rating of the study medication on a scale from 0 (poor) to 4 (excellent)

  Based on these records, subjects in the various allocations were compared in terms of pain intensity difference scores (calculated by subtracting post-dose pain score from the baseline pain score), total pain relief scores, time to peak pain intensity difference, and time to peak relief

Patient follow-up: Patients were to follow up with the physician within 1 week after treating the headache to review the diaries recording their pain levels before and after treatment.

Main results:

Pain relief scores for subjects taking ibuprofen + caffeine were significantly improved compared to ibuprofen or placebo ($p<0.05$) starting 90 minutes after taking the medication. During the last 4 hours of the study, ibuprofen + caffeine provided better pain relief than caffeine alone.

Overall pain reduction was significantly greater through hours 4-6 with ibuprofen + caffeine compared to all other groups ($p=0.045$). Peak pain reduction was also greater with ibuprofen + caffeine ($p=0.020$).

Overall 71% of patients in the ibuprofen + caffeine group had complete relief of their headache, compared to 58% in the ibuprofen and caffeine alone groups and 48% in the placebo group. The median time to meaningful improvement for subjects taking ibuprofen + caffeine was 53 minutes faster than those taking ibuprofen, 24 minutes faster than those taking caffeine and 3 hours faster than those taking placebo (all statistically significant). Finally, the overall evaluation of ibuprofen + caffeine was significantly higher than the other groups.

Conclusions

The combination of ibuprofen + caffeine is superior to ibuprofen, caffeine or placebo alone over a 6 hour period for tension-type headaches in terms of time to the onset of pain relief, time to meaningful pain relief, overall pain reduction from baseline, and subject's overall evaluation of the medication. In addition, caffeine alone in this study also had similar efficacy to ibuprofen therapy.

Comments/Critical Appraisal:

Internal validity was achieved overall. Randomization was confirmed by comparing the groups based on gender, race, height, and caffeine intake. The study protocol was strictly followed with exclusion of subjects who violated the protocol, had caffeine or alcohol in the 4 hours before experiencing a headache or if the patients experienced a migraine rather than a tension-type headache.

However, there were some issues with internal validity. The article did not discuss how subjects and investigators were blinded. Subjects were all given a bottle with medication but there was no discussion if the tablets looked similar. In addition, it was difficult to determine internal validity since the methodology and results seemed unnecessarily complicated and difficult to follow in the paper when what the investigators were really aiming for was a simple comparison of ibuprofen, caffeine and placebo in tension type headaches. A more simple approach may have yielded more meaningful results. Finally, there are other confounding variables such as usual headache severity which could have been controlled between groups to ensure there was no selection bias.

External validity is strong as the study was a multicenter study across various sites in the United States, enrolling both male and female subjects of various races with can be considered highly applicable to a typical Canadian patient population. The study enrolled patients experiencing 3 to 15 tension-type headaches monthly which is common in a clinical setting. Therefore ibuprofen + caffeine can be considered as a more effective treatment for tension-type headaches than ibuprofen or caffeine alone. However, it is important to note that patients taking caffeine reported a higher frequency of side effects compared to those taking ibuprofen alone or placebo which should be taken into consideration when recommending therapy to patients. Finally, since the study medications were only taken once, medication over-use headaches were not considered with combination therapy.

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5) Diener HC, Pfaffenrath V, Pageler L, Peil H and Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalagia. 2005 [cited March 9, 2012[; 25: 776-787. Available from: PubMed

Study objectives

To investigate the combination of acetylsalicylic acid + paracetamol + caffeine compared to acetylsalicylic acid + paracetamol (no caffeine), monotherapy with each of the three agents and placebo for the treatment of migraine or tension-type headaches.

Methods

Design: A randomized, placebo-controlled, double-blind, multicentre, parallel group trial

Allocation: Patients were randomly allocated to one of six treatment groups using a 4:4:2:2:1:1 scheme (ASA+PAR+CAF: ASA+PAR: ASA: PAR: CAF: PL). See below for a further outline of the treatment groups. The randomization was completed in blocks of 14 using the ClinPro/LBL program, version 6.0

Blinding: Ensured by using matched trial supplies/medications that with identical colours, shape, size and taste. The independent headache expert was blinded as well when completing a classification of headache episodes using a structured questionnaire.

Setting: A multicentre study including 133 centres across Germany

Participants: 1983 male and female patients aged 18-65 were enrolled by practitioners and general and internal medicine specialists. The patients experienced migraine or tension-type headaches for at least 12 months with a minimum of two headaches in the previous 3 months

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Intervention

- 2 tablets of:
    - ASA+PAR+CAF: 250mg Acetylsalicylic acid + 200mg paracetamol + 50mg caffeine
    - ASA+PAR: 250mg Acetylsalicylic acid + 200mg paracetamol
    - ASA: 500mg acetylsalicylic acid
    - PAR: 500mg paracetamol
    - CAF: 50mg caffeine
    - PL: Placebo

Outcomes

- The primary outcome was the calculated time to 50% pain relief
- Other endpoints included:
    - Percentage of patients with 50% pain relief at least after 2 hours
    - Time until reduction of pain intensity to 10mm (using a visual analogue scale)
    - Weight of sum of the pain intensity difference
    - Extent of impairment of daily activities
    - Global assessment of efficacy

Patient follow-up: Patients were required to follow-up with the investigator after each headache episode. The investigator reviewed the patient's diary of their headache episode to ensure it was complete.

Main results

The median time to 50% relief of pain in the ASA+PAR+CAF group was 1hr5min, compared to 1hr13min, 1h19min, 1h21min, 1hr47min and 2hr13min for ASA+PAR, ASA, paracetamol, caffeine and placebo respectively. Overall, all active treatments were statistically superior to placebo with the exception of caffeine. For the secondary outcomes, ASA+PAR+CAF resulted in a statistically significant shortened time to reduce pain intensity to 10mm (1hr56min) compared to all other groups. The pain intensity difference was also more pronounced over all time points with ASA+PAR+CAF. A statistically significant larger percentage of patients taking the triple combination did not experience impairment of usual daily activities and patients rated the triple combination highest on a global assessment of efficacy.

Conclusions

The combination of acetylsalicylic acid + paracetamol + caffeine was superior to all other groups in terms of time to 50% pain relief, time until reduction of pain intensity to 10mm, sum of the pain intensity difference (weighted), extent of daily activity impairment and global efficacy. All of these outcomes were statistically significant.

Comments/Critical Appraisal

This study had strong internal validity. Blinding was completed using a validated systematic method and all patients were given identical looking tablets. Randomization was also completed using a systematic method and it was confirmed that all groups were similar in terms of confounding variables such as age, gender, race, and usual headache type and intensity. This results in a low risk of selection bias. The study design was relatively simple meaning patients were likely to be able to strictly follow the protocol and yield valid results.

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For external validity, it is important to note that most patients in this study were enrolled because they experienced frequent migraines rather than tension-type headaches. Therefore it is problematic to extrapolate the results to a general population of patients with tension-type headaches. In addition, combination products with acetylsalicylic acid and acetaminophen (paracetamol) are not available in Canada. Additionally, the study was done in Germany, a population which cannot be considered as representative of a Canadian population in terms of lifestyle and habits. Finally, the study medication was taken only once therefore medication over-use headaches were not assessed.

Clinical Guidelines

6) Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G and Schoenen J. EFNS guideline on the treatment of tension-type headache – Report of an EFNS task force. European Journal of Neurology. 2010 [cited March 9, 2012]; 17: 1318-1325. Available from: PubMed.

Study objectives:

The objective of this study was to outline acute and preventative treatment for tension-type headaches using the best evidence from meta-analysis, controlled trials and reviews. Additionally, the study gives a brief introduction to non-pharmacological options for tension-type headaches using evidence-based recommendations.

Scope: A very wide search strategy was performed with the term 'tension-type headache' (last search October 2009). The studies included in the review were trials published in English, with adult patients aged 18 and older. The studies all had to include criteria distinguishing tension-type headaches from migraines (only patients with tension-type headaches were included). Both drug trials and non-drug trials were included. Further information on inclusion and exclusion criteria were not provided.

Methods:

Studies were identified through an independent literature search by each of the authors. For the drug treatments, randomized controlled trials and any trials comparing two or more treatments were included. For non-pharmacological therapies, only controlled trials were considered. The recommendations were graded based on EFNS guidelines. A level A rating (established as effective, ineffective or harmful) was given to a therapy with at least one convincing class I study or two consistent class II studies. A level B rating (probably effective, ineffective or harmful) required at least one convincing class II study or overwhelming class III evidence. Finally a level C rating (possibly effective, ineffective or harmful) required at least two convincing class III studies.

Main results:

Paracetamol 1000mg has been demonstrated to be better than placebo in most, but not all trials. Acetylsalicylic acid in strengths of 1000mg, 500mg, 650mg and 250mg has consistently been reported as more effective than placebo across studies. Ibuprofen in strengths of 800mg, 400mg and 200mg has likewise been consistently demonstrated as effective. Five studies demonstrated NSAIDs were more effective than paracetamol, while 3 studies reported no difference. There is no evidence for the superiority of one NSAID over another. A thorough review of treatment could also not detect any difference in adverse effects between paracetamol and NSAIDs but it is well-known that NSAIDs have more side effects. The effectiveness of paracetamol and NSAIDs has been demonstrated to be increased when they are taken with caffeine 64-200mg but there are no studies with codeine. It is likely that combinations with caffeine and particularly codeine can cause medication-overuse headache therefore

paracetamol or NSAIDs as monotherapy is recommended for first-line treatment. Non-pharmacological therapies should be considered for all patients although there is little evidence to support their use. Non-pharmacological therapies include information, reassurance and identification of triggers and psycho-behavioural treatments like relaxation techniques, cognitive-behavioural therapy and EMG biofeedback. EMG biofeedback has been demonstrated to have some benefit in tension-type headaches while more evidence is required for the other techniques.

Conclusions:

There is level A evidence for ibuprofen, acetylsalicylic acid, naproxen and paracetamol for episodic treatment of tension-type headaches. Caffeine-containing products should only be used second line due to a risk of medication-overuse headaches and codeine-containing products should be avoided. Analgesics are likely ineffective for patients with chronic tension-type headaches. Finally, non-pharmacological treatments do not have strong evidence for their use but should be recommended for all patients.

Comments/Critical Appraisal

In terms of internal validity, all conflicts of interest were declared. The authors outlined how the search strategy was performed and in general the search strategy was very wide and inclusive. References were thoroughly analyzed with recommendations based on guidelines from an expert consensus. All recommendations were thoroughly supported by evidence presented in the paper. There were concerns however. The authors should have provided more details on the patient populations included and how many papers were analyzed. In particular the quality of the trials included in the guidelines should have been analyzed as there is a risk that recommendations were made based on poor quality data.

In terms of external validity, the review was completed by investigators in Europe with a primarily European focus. Europe's population is similar to but not necessarily representative of Canadian patients in terms of lifestyle and habits. The authors did give clearly outlined evidence-based recommendations for the use of paracetamol or NSAIDs first-line with combination therapies only if these are not effective. This clinical bottom line can be considered as applicable to a Canadian population and used in practice.