Abstracts and Citations

David S. Millson and Stewart J. Tepper, Editors

As we get our sea legs as co-abstracts editors, we would like to explain how we will manage our section. The journal's editor-in-chief Dr. Rothrock, has asked us to include about 20 abstracts per issue. We will select abstracts that we find interesting, useful, or controversial, and we will comment on some of them. We will sign our initials so that the reader will know which editor wrote which opinion, and we anticipate that we will sometimes write together, and sometimes take issue with each other. We would like to encourage you to send us abstracts that you think merit inclusion, and these should be sent to sjtepper@aol.com or d.millson@mema.keele.ac.uk.

MIGRAINE, ACUTE TREATMENTS

Dib M, Massiou H, Weber M, Henry P, Garcia-Acosta S, Bousser MG. **Efficacy of oral ketoprofen in acute migraine: a double-blind randomized clinical trial.** *Neurology*. 2002 Jun 11;58(11):1660-1665

Background: Certain nonsteroidal anti-inflammatory drugs are effective in the acute treatment of migraine attacks. The authors report a double-blind, placebo-controlled, randomized cross-over trial of a dual-release formulation of oral ketoprofen in the acute treatment of migraine attacks.

Methods: The authors compared the efficacy of two doses of ketoprofen (75 or 150 mg) with that of placebo (primary analysis) and zolmitriptan 2.5 mg (secondary analysis) on one to four consecutive attacks in 235 intent-to-treat patients (out of 257 randomized patients) with migraine with or without aura. The principal efficacy outcome was headache relief (reduction in headache severity from severe or moderate to mild or absent at 2 hours).

Results: Results are based on 838 attacks with a severe or moderate headache that were evaluable at 2 hours. Relief was reported for 62.6% of headaches treated with ketoprofen 75 mg, 61.6% with ketoprofen 150 mg, and 66.8% with zolmitriptan. The difference between the three active treatments and placebo (27.8% relief) was highly significant, both tests of ketoprofen vs placebo being globally controlled at a 5% level for the type I error (primary analysis). Headaches at 2 hours disappeared more frequently for the active treatments than for placebo. The authors also demonstrated efficacy on most other secondary outcomes. The tolerance of ketoprofen was good (similar to that of placebo).

Conclusions: Oral ketoprofen (75 mg or 150 mg) in a dual-release formulation is an effective and well-tolerated drug in the acute treatment of migraine attacks.

Comment: Almost none of the studies comparing triptans to nonsteroidal anti-inflammatory drugs (NSAIDs) or non-triptans show a superiority for triptans for the primary endpoint of headache response at 2 hours. Most of the studies show a superiority for triptans over NSAIDs for the secondary endpoint of pain-free at 2 hours. Pain-free response appears linked to sustained pain-free response, that is to the migraine not recurring. Dr. Julio Pascual's prospective study (Pascual J, Fite B, Lopez-Gil A. Comparison of triptan tablet consumption per attack: a prospective study of migraineurs in Spain. Headache. 2002;42:93-98) on tablet consumption per attack in Spain found that non-triptan tablet use per attack was always higher than triptan use. Dr. Jean Schoenen has raised the issue that this may be due to inadequate doses for the NSAIDs. However, in the aspirin-metoclopramide vs sumatriptan studies (eg, Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen E, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. Lancet. 1995;346:923-926) the 1000-mg dose of aspirin seems adequate, and yet pain-free numbers favored sumatriptan.

It is possible that the key difference in NSAIDs versus triptans is not in the ability to give relief, but in the ability to yield a sustained pain-free result. The probable superiority of triptans in this regard might reduce the likely need for redosing in an attack, and decrease the risk for medication overuse headache. Further studies comparing triptans and non-triptans should use pain-free, sustained pain-free, and number of doses per attack as primary endpoints rather than headache response. SJT

Geraud G, Compagnon A, Rossi A. **Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study.** *Eur Neurol*. 2002;47(2):88-98

This multicentre, randomised, double-blind study compared oral zolmitriptan 2.5 mg with a combination of oral acetylsalicylic acid 900 mg and metoclopramide 10 mg as acute anti-migraine therapy for 3 migraine attacks. In total, 666 patients took at least one dose of study medication (326 took zolmitriptan and 340 took acetylsalicylic acid plus metoclopramide). The percentage of patients with a 2-hour headache response after the first dose for all 3 attacks (the primary end point) was 33.4% with zolmitriptan and 32.9% with acetylsalicylic acid plus metoclopramide [odds ratio 1.06, 95% confidence interval (CI) 0.77-1.47; $p = 0.7228$]. For the majority of secondary end points, the two treatments demonstrated comparable efficacy. However, post hoc analysis showed that significantly more patients receiving zolmitriptan were free of pain 2 h after the first dose in all 3 attacks compared with patients receiving acetylsalicylic acid plus metoclopramide (10.7 vs. 5.3%; odds ratio 2.19, 95% CI 1.23-4.03; $p = 0.0095$). In addition, post hoc analysis showed that the overall 2-hour pain-free response rate was consistently higher with zolmitriptan (34.6%) than with acetylsalicylic acid plus metoclopramide (27.9%) (odds ratio 1.40, 95% CI 1.09-1.78; $p = 0.007$). Both treatments reduced migraine-associated nausea, vomiting,

phonophobia and photophobia. There were no important inter-group differences with respect to the onset of meaningful migraine relief, the frequency of headache recurrence, the usage or efficacy of a second dose of medication or the use of escape medication. However, at the last attack, the proportion of patients who expressed overall satisfaction with the treatment was significantly higher in the zolmitriptan group, i.e. 83.7%, versus 75.0% with acetylsalicylic acid plus metoclopramide ($p = 0.0346$). Both agents were well tolerated. Adverse events were reported by 40.8% (133/326) of zolmitriptan-treated patients and 29.1% (99/340) of those treated with acetylsalicylic acid plus metoclopramide. The incidence of withdrawals due to adverse events was very low with both zolmitriptan (0.9%) and the combination regimen (1.5%); the latter percentage included 1 patient who withdrew from the study due to phlebitis, which was classified as a serious adverse event. This study showed that zolmitriptan is effective and well tolerated for the acute treatment of moderate to severe migraine. Zolmitriptan was at least as effective as acetylsalicylic acid plus metoclopramide in achieving a 2-hour headache response, but significantly more effective than the combination therapy for other end points, including the 2-hour pain-free response. Copyright 2002 S. Karger AG, Basel

Comment: As the global project physician for zolmitriptan (1976-1978), I was personally involved in designing this study, which surprisingly did not show greater efficacy for zolmitriptan when compared to high-dose aspirin-metoclopramide. However, as pointed out by Stew Tepper above, this pattern has been described with the other triptans and only when compared against pain-free and sustained pain-free responses do the triptans deliver the goods. This study also raises symmetry issues in the comparison groups regarding previous baseline treatments. In this study, the majority of patients had previously successfully used the aspirin-metoclopramide product, whereas triptan users were in the minority, due to the lack of availability of triptans for the treatment of migraine in France at this time. DSM

Keam SJ, Goa KL, Figgitt DP. **Almotriptan: a review of its use in migraine.** *Drugs*. 2002;62(2):387-414

Almotriptan is a selective serotonin 5-HT(1B/1D) receptor agonist ('triptan'). Its efficacy and tolerability have been assessed in a number of randomised, controlled trials in over 4800 adults with moderate or severe attacks of migraine. Oral almotriptan has a rapid onset of action (significant headache relief is observed 0.5 hours after administration of a 12.5mg dose) and efficacy is sustained in most patients who respond by 2 hours. The drug is significantly more effective than placebo as measured by a number of parameters including 2-hour headache response and pain-free response rates. Other symptoms of migraine, including nausea, photophobia and phonophobia, are also alleviated by almotriptan. The efficacy of oral almotriptan appears to be maintained over repeated doses for multiple attacks of migraine treated over a long period (up to 1 year). High headache response rates were reported over all attacks without tachyphylaxis. For the relief of single attacks of migraine, oral almotriptan 12.5mg had similar efficacy to oral sumatriptan 50mg. Patients given almotriptan report less concern with adverse effects than patients given sumatriptan. The lower incidence of chest pain following treatment with almotriptan than with sumatriptan may lead to a reduction in direct costs, with fewer patients requiring management of chest pain. Almotriptan is well tolerated. Most adverse events were of mild or moderate intensity, transient, and generally resolved without intervention or the need for treatment withdrawal. The most common adverse events associated with oral almotriptan 12.5mg treatment were dizziness, paraesthesia, nausea, fatigue, headache, somnolence, skeletal pain, vomiting and chest symptoms. The incidence of adverse events did not differ from placebo and decreased in the longer term. Almotriptan can be coadministered with drugs that share a common hepatic metabolic path; in addition, dosage reduction is required only in the presence of severe renal or hepatic impairment. CONCLUSIONS: Almotriptan is an effective drug for the acute treatment of moderate or severe attacks of migraine in adults. An oral dose of almotriptan 12.5mg has shown greater efficacy than placebo; current data indicate that efficacy is similar to that of oral sumatriptan 50mg, and is maintained in the long term (<or=1 year). Almotriptan has a good adverse event profile and a generally similar overall tolerability profile to sumatriptan; of note, almotriptan is associated with a significantly lower incidence of chest pain than sumatriptan. However, further clinical experience is required to clearly define the place of almotriptan among the other currently available triptans. Nevertheless, because triptans have an important place in various management regimens, and because the nature of individual patient response to triptans is idiosyncratic, almotriptan is likely to become a useful treatment option in the management of adults with moderate or severe migraine headaches.

Comment: Why does almotriptan buck the trend compared with other triptans and show placebolike tolerability, and yet efficacy and time to onset of effect comparable to sumatriptan? Does this represent truly different pharmacology or are there subtle differences in the trial populations/methodologies used to collect adverse events (AEs) in the almotriptan trial program? One possible reason for diminished AEs in the almotriptan users in this study might be the higher smoking prevalence in southern Europe and hence hepatic enzyme induction resulting in more rapid metabolism of almotriptan. It would be interesting to query the databases on other triptan studies in North America and Europe to check for differences in AE reporting for other triptans vis a vis smoking.

Naratriptan also has very low AEs reported, and this has always been attributed to a low dose, since efficacy was correspondingly lower as well. Was hepatic induction an issue in the naratriptan population as well, or are these two triptans demonstrably better tolerated clinically? DSM and SJT

Mahmood T, Silverstone T, Connor R, Herbison P. **Sumatriptan challenge in bipolar patients with and without migraine: a neuroendocrine study of 5-HT1D receptor function.** *Int Clin Psychopharmacol*. 2002 Jan;17(1):33-36

An association between bipolar disorder and migraine has been lately recognized and an abnormality of central serotonergic function is suggested as the underlying neurophysiological disturbance. To examine the role of serotonin

in bipolar disorder and migraine, we used the neuroendocrine challenge paradigm, and we chose sumatriptan, a 5HT1D agonist, as the pharmacological probe. We studied nine bipolar patients with migraine, nine bipolar patients without it, seven migraine patients, and nine matched normal controls. A post-hoc analysis showed subsensitivity of serotonergic function, reflected in a blunted growth hormone response to sumatriptan challenge in bipolar patients who also suffered from migraine.

Comment: Given regulatory and labelling concerns about the potential for triptans to provoke serotonin syndrome, the apparent down-regulation of serotonergic function in patients with bipolar disorder may suggest cause for cautious optimism and encourage future study of triptans in these patients to establish true causality or otherwise.

A prospective trial of sumatriptan injectable identified 1700 patients who repetitively used the triptan and were concomitantly on selective serotonin reuptake inhibitor (SSRI) medication. No serotonin syndrome was reported in any patient (Putnam GP, O'Quinn S, Bolden-Watson CP, Davis RL, Gutterman DL, Fox AW. Migraine polypharmacy and the tolerability of sumatriptan: a large-scale, prospective study. Cephalalgia. 1999;19:668-675). Since SSRIs can rarely induce serotonin syndrome alone, there is a significant difficulty in establishing a risk of coadministration. DSM and SJT

Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ. **Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison.** *Eur Neurol*. 2002; 47(2):99-107

The 5-HT(1B/1D/1F) agonist eletriptan, at an oral dose of 80 mg, has been shown to be more efficacious than sumatriptan 100 mg and placebo in the treatment of migraine attacks with or without aura. Another commonly prescribed oral treatment for migraine attacks is Cafergot (1 mg ergotamine tartrate with 100 mg caffeine per tablet). The efficacy, tolerability and safety of 40- and 80-mg doses of eletriptan and 2 tablets of Cafergot were compared in a double-blind, randomised, placebo-controlled, parallel-group trial involving 733 migraine patients. Patients recorded symptoms at baseline (before treatment) and 1, 2, 4 and 24 h after dosing. Headache intensity was assessed on a 4-point scale (3 = severe pain, 2 = moderate pain, 1 = mild pain, 0 = no pain). Significantly more eletriptan-treated patients (80 mg, 68%; 40 mg, 54%) than Cafergot-treated patients (33%; $p < 0.001$) reported headache response (improvement from moderate-to-severe to mild or no pain) at 2 h. Substantially more eletriptan recipients reported no pain (80 mg, 38%; 40 mg, 28%; Cafergot, 10%; placebo, 5%; $p < 0.001$). Eletriptan headache response rates at 1 h were significantly higher (80 mg, 39%; 40 mg, 29%; Cafergot, 13%; placebo, 13%; $p < 0.002$ for each comparison). Both doses of eletriptan were significantly more effective than Cafergot in reducing nausea ($p < 0.0001$), photophobia (80 mg, $p < 0.0001$; 40 mg, $p < 0.002$), phonophobia (80 mg, $p < 0.0001$; 40 mg, $p < 0.003$) and functional impairment ($p <$ or $= 0.001$) at 2 h. Adverse events were generally mild or moderate and transient. This randomised trial shows that oral eletriptan is more efficacious in the acute treatment of migraine than oral Cafergot and is well tolerated. Copyright 2002 S. Karger AG, Basel

Comment: As with all comparative trials with eletriptan, this comparative trial raises the important issue of blinding. Was the Cafergot encapsulated (hence potentially hindering the early phase of absorbtion)? This approach has been a major issue with previous eletriptan studies and may potentially make the results from this trial difficult to interpret. DSM

One key issue in ensuring methodologically rigorous comparative trials is symmetry of comparative groups. I have come to believe that the controversy over encapsulation for blinding is neither about the pharmacokinetics of encapsulation, nor about the effectiveness of eletriptan, but rather about the methodology of comparison, which requires as much symmetry as possible. As Gawel and Wiebe wrote in a superb article explaining how to critically evaluate a comparison trial, "When faced with a potential confounder . . . readers need to estimate in which direction the results would be biased" in any comparative trial (Gawel M, Wiebe S. Evidence-based analysis of a migraine treatment drug comparison trial. Cephalalgia. 2000;20[suppl 2]:33-38). SJT

Sayfan J. **Ergotamine-induced anorectal strictures: report of five cases.** *Dis Colon Rectum*. 2002 Feb;45(2):271-2

Purpose: Ergotamine tartrate suppositories are used for treatment of migraine headache attacks. Chronic abuse may lead to severe anorectal complications such as ulceration, stricture, and rectovaginal fistula. These complications are rare, and only sporadic reports may be found. Nevertheless, awareness of this entity on the part of prescribing physicians and treating colorectal surgeons is essential for a successful outcome, because withdrawal of this medication is an inherent part of treatment.

Patients: Five female patients were referred for treatment of symptomatic strictures of the anal canal and lower rectum. All of these patients admitted prolonged, nearly daily use of three to seven ergotamine tartrate suppositories.

Results: Three patients with severe stenosis of the anal verge and anal canal were treated by Y-V anoplasty, and two patients with circular stricture of the lower third of the rectum had balloon dilatations. In all patients the use of ergotamine suppositories was stopped, and alternative medication was instituted. Long-term follow-up (3-12 years) showed complete resolution of symptoms.

Conclusion: In view of the availability of new effective drugs for treatment of migraine headache (serotonin agonists) and considering the potentially severe complications of chronic use of ergotamine, the use of this medication should be abandoned.

Comment: Ergotamine users beware of the sting in the tail! DSM.

Wang JT, Barr CE, Torigoe Y, Wang E, Rowland CR, Goldfarb SD. **Cost savings in migraine associated with less chest pain on new triptan therapy.** *Am J Manag Care*. 2002 Feb;8(3 Suppl):S102-S107

Objectives: This article constructs an economic model to estimate cost of chest-pain-related care in migraine patients

receiving almotriptan 12.5 mg compared with those receiving sumatriptan 50 mg.

Study Design: This population-based, retrospective cohort study used data from the MEDSTAT Marketscan database (Ann Arbor, Michigan) to quantify incidence and costs of chest-pain-related diagnoses and procedures. After a 6-month exclusion period, the study used a pre-post design, with baseline and treatment periods defined, respectively, as 5 months before and after receiving sumatriptan therapy. An economic model was constructed to estimate annual cost savings per 1,000 patients receiving almotriptan instead of sumatriptan as a function of differing rates of chest pain. Annual direct medical cost avoided was calculated for a hypothetical health plan covering 1 million lives.

Results: Among a cohort of 1,390 patients, the incidence of chest-pain-related diagnoses increased significantly (43.6%) with sumatriptan, from 110 during the baseline period to 158 during the treatment period ($P = .003$). Aggregate costs for chest-pain-related diagnoses and procedures increased 33.1%, from $22,713 to $30,234. Payments for inpatient hospital services rose 10-fold; costs for primary care visits and outpatient hospital visits rose 53.1% and 14.4%, respectively. Payments for angiography increased from $0 to $462, and costs for chest radiographs and electrocardiograms increased 58.7% and 31.2%, respectively. Sumatriptan treatment was associated with a 3-fold increase in payments for services for painful respiration and other chest pain. The model predicted $11,215 in direct medical cost savings annually per 1000 patients treated with almotriptan instead of sumatriptan. Annual direct medical costs avoided for the health plan totaled $195,913.

Conclusion: Using almotriptan instead of sumatriptan will likely reduce the cost of chest-pain-related care for patients with migraine headaches.

Comment: In my view, this study takes conjecture a step too far. The lower reported chest adverse events (AEs) reported in clinical trials where all AEs are scrutinized will not necessarily lead to lower reporting in the clinic. This hypothesis remains to be proven in a well-designed post-marketing surveillance program, untarnished by commercial sponsorship. Until such an independent prospective study is carried out, the extrapolations described here and in similar papers are pure conjecture and should be classed as the lowest grade of evidence on a par with uncorroborated clinical opinion. DSM

MIGRAINE, PROPHYLAXIS

Guyuron B, Tucker T, Davis J. **Surgical treatment of migraine headaches.** *Plast Reconstr Surg.* 2002 Jun;109(7): 2183-2189

This prospective study was conducted to investigate the role of removal of corrugator supercilii muscles, transection of the zygomaticotemporal branch of the trigeminal nerve, and temple soft-tissue repositioning in the treatment of migraine headaches. Using the criteria set forth by the International Headache Society, the research team's neurologist evaluated patients with moderate to severe migraine headaches, to confirm the diagnosis. Subsequently, the patients completed a comprehensive migraine headaches questionnaire and the team's plastic surgeon injected 25 units of botulinum toxin type A (Botox) into each corrugator supercilii muscle. The patients were asked to maintain an accurate diary of their migraine headaches and to complete a monthly questionnaire documenting pertinent information related to their headaches. Patients in whom the injection of Botox resulted in complete elimination of the migraine headaches then underwent resection of the corrugator supercilii muscles. Those who experienced only significant improvement underwent transection of the zygomaticotemporal branch of the trigeminal nerve with repositioning of the temple soft tissues, in addition to removal of the corrugator supercilii muscles. Once again, patients kept a detailed postoperative record of their headaches. Of the 29 patients included in the study, 24 were women and five were men, with an average age of 44.9 years (range, 24 to 63 years). Twenty-four of 29 patients (82.8 percent, $p < 0.001$) reported a positive response to the injection of Botox, 16 (55.2 percent, $p < 0.001$) observed complete elimination, eight (27.6 percent, $p < 0.04$) experienced significant improvement (at least 50 percent reduction in intensity or severity), and five (17.2 percent, not significant) did not notice a change in their migraine headaches. Twenty-two of the 24 patients who had a favorable response to the injection of Botox underwent surgery, and 21 (95.5 percent, $p < 0.001$) observed a postoperative improvement. Ten patients (45.5 percent, $p < 0.01$) reported elimination of migraine headaches and 11 patients (50.0 percent, $p < 0.004$) noted a considerable improvement. For the entire surgical group, the average intensity of the migraine headaches reduced from 8.9 to 4.1 on an analogue scale of 1 to 10, and the frequency of migraine headaches changed from an average of 5.2 per month to an average of 0.8 per month. For the group who only experienced an improvement, the intensity fell from 9.0 to 7.5 and the frequency was reduced from 5.6 to 1.0 per month. Only one patient (4.5 percent, not significant) did not notice any change. The follow-up ranged from 222 to 494 days, the average being 347 days. In conclusion, this study confirms the value of surgical treatment of migraine headaches, inasmuch as 21 of 22 patients benefited significantly from the surgery. It is also evident that injection of Botox is an extremely reliable predictor of surgical outcome.

Comment: Many small placebo-controlled studies and much anecdotal literature suggests that botulinum toxin may be effective in prevention of migraine, perhaps to the same extent as conventional prophylactic treatment. Larger, randomized clinical trials are underway to resolve this issue. In the meantime, those who believe in the effectiveness of botulinum toxin prophylaxis argue about how it works, that is whether its antinociceptive properties are due to peripheral effects, central or presynaptic effects, or both. Dr. Guyuron's group favors the idea that botulinum toxin interrupts a reflex arc between the central nervous system (CNS) and peripheral musculature, and that after establishing efficacy by low dose botulinum injection in the corrugator supercilii muscles, surgical resection of these muscles results in prolonged and effective prophylaxis. The idea is radical but intriguing and should not be dismissed out of hand. However, a trial is necessary in which both the botulinum toxin injections are blinded with vehicle, and the study of the surgery involves a sham surgery control group with extended long-term follow-up, before these forms of prophylaxis can be recommended to patients. SJT

MIGRAINE, PATHOPHYSIOLOGY

Terwindt G, Kors E, Haan J, Vermeulen F, Van den Maagdenberg A, Frants R, Ferrari M. **Mutation analysis of the CACNA1A calcium channel subunit gene in 27 patients with sporadic hemiplegic migraine.** *Arch Neurol.* 2002 Jun; 59(6):1016-1018

Background: Familial hemiplegic migraine is a rare autosomal dominant subtype of migraine with aura that in half of the families is caused by mutations in the CACNA1A gene on chromosome 19p13. In sporadic hemiplegic migraine (SHM), that is, hemiplegic migraine without affected family members, the contribution of the CACNA1A gene is unknown.

Objective: To investigate the involvement of the CACNA1A calcium channel subunit gene in SHM.

Methods: We screened 27 patients with SHM for mutations in the CACNA1A gene by a combination of single-strand conformational polymorphism analysis and sequence analysis.

Results: One patient with SHM also had ataxia, nystagmus, and cerebellar atrophy on computed tomography and carried a T666M mutation. Another patient with SHM who had no cerebellar signs carried an R583Q mutation. No mutations or interictal neurological abnormalities were found in the remaining 25 patients with SHM.

Conclusions: Most patients with SHM do not have a CACNA1A mutation. The results of this study, combined with the findings reported in the literature, show that the presence of cerebellar symptoms in addition to the hemiplegic attacks increases the chance of finding a CACNA1A mutation. In addition, to our knowledge, we have found a first patient with SHM without cerebellar signs with a mutation.

Comment: The story on calcium channelopathies and neurologic disorders becomes ever more complex, as multiple neurologic disorders appear linked to varying forms of calcium-channel mutations. Professor Ferrari has described links to cerebellar disorders, to a peculiar and severe response to head trauma, and to epilepsy, as well as to familial hemiplegic migraine. Now his group finds that the most frequently found calcium channelopathy mutations are not found in most patients with spontaneous hemiplegic migraine. Does this just mean that other mutations, not yet described, cause a common phenotypic expression? Or are there multiple causes for the hemiplegic migraine syndrome, and not all of them due to calcium channelopathies? SJT

de Tommaso M, Murasecco D, Libro G, Guido M, Sciruicchio V, Specchio LM, Gallai V, Puca F. **Modulation of trigeminal reflex excitability in migraine: effects of attention and habituation on the blink reflex.** *Int J Psychophysiol.* 2002 Jun;44(3):239-249

The modulation of trigeminal reflex excitability in migraine patients was evaluated during the asymptomatic phase by studying the effects of attention, habituation and preconditioning stimulus on the R2 and R3 components of the blink reflex (BR). Fifty patients suffering from migraine without aura, 20 affected by migraine with aura and 35 sex- and age-matched controls were selected. In subgroups of migraine with-aura and without-aura patients, and normal controls, the blink reflex was elicited during different cognitive situations: (a) spontaneous mental activity; (b) stimulus anticipation; (c) recognition of target numbers. In the remaining subjects, R2 and R3 habituation was evaluated by repetitive stimulation at 1, 5, 10, 15, 20, 25 and 30 s intervals. The R2 and R3 recovery curves were also computed. A reduced R3 threshold with a normal pain threshold was found in migraine with-aura and without-aura patients; the R3 component was not significantly correlated with the pain thresholds in patients and controls. The R2 and R3 components were less influenced by the warning of the stimulus in migraine without-aura and migraine with-aura patients, in comparison with the control group. A slight increase of both R2 and R3 recovery after preconditioning stimulus was also observed in migraine patients, probably caused by a phenomenon of trigeminal hyperexcitability persisting after the last attack. The abnormal BR modulation by alerting expresses in migraine a dysfunction of adaptation capacity to environmental conditions, probably predisposing to migraine.

Comment: Further physiologic and functional evidence for the interictal hyperexcitability of neurons in patients with migraine, in this case trigeminal neurons involved in the blink reflex. SJT

Sandrini G, Proietti Cecchini A, Milanov I, Tassorelli C, Buzzi MG, Nappi G. **Electrophysiological evidence for trigeminal neuron sensitization in patients with migraine.** *Neurosci Lett.* 2002 Jan 14;317(3):135-138

The electrically elicited corneal reflex is a useful tool for exploring the trigeminal system in humans and it may provide additional evidence pointing to a dysfunction of this system in migrainous patients. Tactile perception, corneal reflex and pain thresholds were studied in 48 migraine without aura patients during pain-free periods and compared with those observed in 24 controls. Twenty-eight of the patients had strictly unilateral headache, while the other 20 had bilateral or side-shifting pain during attacks. Both migraine subgroups (bilateral and unilateral) showed significantly lower thresholds compared with controls. The lowest values were observed on the symptomatic side of unilateral migraine patients. These findings suggest that sensorimotor mechanisms and/or pain control systems at the trigeminal level are impaired in migraine. The bilateral location of these abnormalities seems to point to a centrally located dysfunction.

Comment: This is an important paper which describes a noninvasive method of studying sensorimotor/pain control mechanism in humans. This approach may help in the development of potential prophylactic agents, to establish likely clinically effective doses and duration of treatments in small-scale phase II trials, before exposing larger numbers of subjects to potentially ineffective doses in phase III trials. DSM

Mulleners WM, Chronicle EP, Vredeveld JW, Koehler PJ. **Visual cortex excitability in migraine before and after valproate prophylaxis: a pilot study using TMS.** *Eur J Neurol.* 2002 Jan;9(1):35-40

We examined the effect of standard migraine prophylaxis with sodium valproate on repeated measures of occipital ex-

citability using transcranial magnetic stimulation (TMS). We predicted that, comparing pre- and post-treatment assessments, a reduction in clinical migraine parameters would be paralleled by a decrease in excitability measurements.A total of 31 migraine patients enrolled in the study, for assessment prior to and 1 month after commencement of sodium valproate prophylaxis. At each assessment, we used a standardized protocol to stimulate the occipital cortex with a 90-mm circular (coil A) and 70 mm figure-of-eight (coil B) coil. We recorded the threshold stimulation intensity at which subjects just perceived phosphenes. Subjects kept detailed records of headache parameters 1 month before and also during the study period.Valproate therapy significantly improved headache indexes, as expected. In MA subjects assessed with coil B, phosphene thresholds were significantly higher post-treatment than pre-treatment, but those for MO did not change. Modest correlations were observed in MA patients between increase in phosphene threshold and decrease in headache index. Although preliminary, the findings with coil B lend some support to the notion that effective migraine prophylaxis may be achieved through lowering cortical excitability by gamma-aminobutyric acid (GABA)-ergic intervention. Further investigation of the effect of sodium valproate or other similarly acting substances on cortical excitability in migraine is warranted.

Comment: This paper provides a useful noninvasive human model in which to study the potential development of prophylactic treatments for migraine with aura. It will be important to standardize experimental conditions and to establish a rigorous experimental protocol for simulation parameters. However, this promises to be an important technique for use in future drug development. DSM

MIGRAINE, REVIEW ARTICLES

Diamond S, Wenzel R. **Practical approaches to migraine management.** *CNS Drugs*. 2002;16(6):385-403

Migraine is a recurrent clinical syndrome characterised by combinations of neurological, gastrointestinal and autonomic manifestations. The exact pathophysiological disturbances that occur with migraine have yet to be elucidated; however, cervico-trigemino-vascular dysfunctions appear to be the primary cause. Despite advances in the understanding of the pathophysiology of migraine and new effective treatment options, migraine remains an under-diagnosed, under-treated and poorly treated health condition. Most patients will unsuccessfully attempt to treat their headaches with over-the-counter medications. Few well designed, placebo-controlled studies are available to guide physicians in medication selection. Recently published evidence-based guidelines advocate migraine-specific drugs, such as serotonin 5-HT(1B/1D) agonists (the `triptans') and dihydroergotamine mesylate, for patients experiencing moderate to severe migraine attacks. Additional headache attack therapy options include other ergotamine derivatives, phenothiazines, nonsteroidal anti-inflammatory agents and opioids. Preventative medication therapy is indicated for patients experiencing frequent and/or refractory attacks.

Comment: A nicely written, practical review article which I recommend for medical students, residents, and primary care physicians. SJT

MIGRAINE, EPIDEMIOLOGY AND DIAGNOSIS

Heinrichs L. **Linking olfaction with nausea and vomiting of pregnancy, recurrent abortion, hyperemesis gravidarum, and migraine headache.** *Am J Obstet Gynecol.* 2002 May; 185(5 Suppl Understanding):S215-S219

Objective: The experience of women was sought about nausea and vomiting, its relation to olfaction, its occurrence among pregnant women with anosmia, and the potential association of hyperemesis gravidarum and migraine headache.

Methods: We performed a community-based study with a physician/patient-directed questionnaire, and a retrospective analysis of hospital records.

Results: Nearly all women (n = 163 parous women) experience nausea (98%) and vomiting (97%). The highest frequency causes of nausea and vomiting were "food poisoning" (65%), "flu" (58%), pregnancy (54%), and offensive odors (52%); vomiting occurred as frequently as nausea for the first 2 causes, and one half as often for the latter causes. Most women reported that the pain experienced during vomiting exceeded that of parturition. Among 9 women with hypogonadotropic anosmia with advanced reproductive technology-induced pregnancies, 2 experienced nausea and vomiting, one from "food poisoning." Among 37 women with migraine headache, 10 (27%) had experienced hyperemesis gravidarum, and among 16 who experienced hyperemesis gravidarum, 5 (37%) had migraine headaches.

Conclusions: The frequency of nausea and vomiting, caused most often by nonpregnancy-related triggers, is high among women. In a small sample of women with congenital anosmia, nausea and vomiting of pregnancy occurred in only 1 pregnancy, suggesting that olfaction is a highly selected trigger for nausea and vomiting of pregnancy. The shared nausea and vomiting experience of hyperemesis gravidarum and migraine headache among women suggests a common mechanism, possibly based on allelic variations within the DRD2 (dopaminergic receptor) gene. Because olfactory receptors, odor types, and MHC antigens are closely integrated, and because olfactory stimuli often incite episodes of pregnancy, nausea, and vomiting, hyperemesis gravidarum, and migraine headache, these genes and their products invite further scrutiny. The pregnancy-conserving effect of PNV and the MHC antigen overlap in couples with recurrent abortion are important clues possibly relating olfaction, MHC antigens, and reproductive success or failure.

Comment: Dr Stephen Peroutka described a group of patients with migraine with DRD2 gene abnormalities that he thought might predict for antidopamine medication efficacy in treating their migraines. He felt these patients had prominent dopaminergic manifestations in their migraine presentations: yawning and severe nausea and vomiting. (Peroutka SJ. Dopamine and migraine. Neurology. 1997;49:650-656). The current study suggests that we may be able to look for

other comorbid illnesses, such as hyperemesis gravidarum, to find patients with "dopaminergic migraine," if this entity exists. SJT

Cady RK, Schreiber CP. **Sinus headache or migraine? Considerations in making a differential diagnosis.** *Neurology*. 2002 May 14;58(9 Suppl 6):S10-S14

Sinus headache is commonly diagnosed, and patients with headache often cite sinus pain and pressure as a cause of their headaches. A high frequency of diagnosis of sinus headache, which specialists consider to be relatively rare, among patients meeting International Headache Society (IHS) diagnostic criteria for migraine raises the possibility that migraine and perhaps other headache types are sometimes mistaken for sinus headache. This article considers clinical, epidemiologic, and pathophysiologic relationships between sinus headache and migraine and discusses the implications for clinical management of headache. Both historic and new data show that nasal symptoms frequently accompany migraine, although these symptoms are not part of the IHS diagnostic criteria for migraine. Parasympathetic activation, as well as the hypothesized mechanism of neurogenic or immunogenic switching (i.e., crossover interactions of neurogenic and immunogenic inflammation), may account for both the frequent occurrence of nasal symptoms in migraine and the possibility that sinus inflammation can sometimes act as a migraine trigger. Considered in aggregate, the data show that the occurrence of nasal symptoms associated with a headache should neither trigger a diagnosis of sinus disease nor exclude a diagnosis of migraine. It should, in fact, prompt diagnostic consideration of both conditions.

Comment: This article summarizes a small pilot study performed in the United States, in which patients with self-diagnosed "sinus headache" were evaluated as to International Headache Society (IHS) diagnosis. Ninety-six percent met IHS criteria for migraine or migrainous headache, suggesting that this entity, at least in the United States, is most frequently migraine with accompanying cranial parasympathetic activation. The article is worth tracking down and reading in its entirety, as the section of the article on pathophysiology is quite original and thought provoking. SJT

Sztajzel R, Genoud D, Roth S, Mermillod B, Le Floch-Rohr J. **Patent foramen ovale, a possible cause of symptomatic migraine: a study of 74 patients with acute ischemic stroke.** *Cerebrovasc Dis*. 2002;13(2):102-106

Recent studies reported an increased prevalence of patent foramen ovale (PFO) in patients with migraine with aura (MA +). To investigate the possible relationship between MA + and paradoxical embolism, we studied the prevalence of both conditions. Investigation of PFO was undertaken in 74 consecutive patients presenting with an acute stroke of undetermined origin. The patients were questioned about MA + or migraine without aura (MA −) according to the criteria of the International Headache Society. Follow-up was performed to investigate the evolution of MA + and MA − according to different treatments of stroke. PFO was found in 44 of 74 patients, 16 of whom had MA + (36%), compared to 4 (13%) MA + patients without PFO ($p = 0.03$). Of 25 patients in whom the PFO was considered to play a causal role in the stroke, 13 (52%) had MA +, whereas only 3 (16%) of 19 patients in whom PFO was considered unrelated had MA + ($p = 0.014$). Thirty-nine of the patients with MA + and MA − were studied over a mean follow-up of 13 months. Seven of 15 patients with MA + and PFO, treated either with surgical closure or anticoagulants, noticed complete disappearance of MA + attacks. The prevalence of MA + is high among stroke patients with PFO. In patients with a high presumption of paradoxical embolism, the proportion of MA + is increased, and this suggests a possible role of this association in the occurrence of the cerebrovascular event. Forty-seven percent of patients with PFO and MA + reported complete suppression of their aura attacks after surgical closure or anticoagulant treatment. This finding suggests that at least in some patients, MA + attacks may be due to paradoxical embolism. Copyright 2002 S. Karger AG, Basel.

Comment: Reach for the stethoscope/echocardiogram! This paper emphasizes the importance of physicians adopting a holistic approach to patients with migraine, not forgetting to check for clinical signs of a septal defect and, if in doubt, to refer for cardiological review to exclude a surgically treatable source of paradoxical emboli. DSM

TRIGEMINAL AUTONOMIC CEPHALGIAS (TACS), INCLUDING CLUSTER

Pareja JA, Caminero AB, Sjaastad O. **SUNCT Syndrome: diagnosis and treatment.** 8: *CNS Drugs*. 2002;16(6): 373-383

Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) is a syndrome predominant in males, with a mean age of onset around 50 years. The attacks are strictly unilateral, generally with the pain persistently confined to the ocular/periocular area. Most attacks are moderate to severe in intensity and burning, stabbing or electrical in character. The mean duration of paroxysms is 1 minute, with a usual range of 10 to 120 seconds (total range 5 to 250 seconds). Prominent, ipsilateral conjunctival injection and lacrimation regularly accompany the attacks. Nasal stuffiness/rhinorrhoea are frequently noted. In addition, there is subclinical forehead sweating. During attacks, there is increased intraocular pressure on the symptomatic side and swelling of the eyelids. No changes in pupil diameter have been observed. Attacks can be triggered mostly from trigeminally innervated areas, but also from the extratrigeminal territory. There are also spontaneous attacks. An irregular temporal pattern is the rule, with symptomatic periods alternating with remissions in an unpredictable fashion. During active periods, the frequency of attacks may vary from <1 attack/day to >30 attacks/hour. The attacks predominate during the daytime, nocturnal attacks being seldom reported. A SUNCT-like picture has been described in some patients with either intra-axial or extra-axial posterior fossa lesions, mostly vascular disturbances/ malformations. In the vast majority of patients, however, aetiology and pathogenesis are unknown. In SUNCT syndrome, there is a lack of persistent,

convincingly beneficial effect of drugs or anaesthetic blockades that are generally effective in cluster headache, chronic paroxysmal hemicrania, trigeminal neuralgia, idiopathic stabbing headache (`jabs and jolts syndrome'), and other headaches more faintly resembling SUNCT syndrome. Single reports have claimed that carbamazepine, lamotrigine, gabapentin, corticosteroids or surgical procedures may be of help. However, caution is recommended when assessing any therapy in a disorder such as SUNCT syndrome, in which the rather chaotic and unpredictable temporal pattern makes the assessment of any drug/therapeutic effect per se a particularly difficult matter.

Comment: Another excellent review article. If you want to learn about the rare, short trigeminal autonomic cephalgia (TAC), this is a thorough and thoughtful place to start. SJT

Torelli P, Manzoni GC. **What predicts evolution from episodic to chronic cluster headache?** *Curr Pain Headache Rep* 2002 Feb;6(1):65-70

Over the last few years, attention has increasingly been focused on the evolution of cluster headache over time. Predictive factors have been identified that are correlated with an increased risk of unfavorable evolution from the episodic form to the chronic form of cluster headache. Late onset, the presence of sporadic attacks, a high frequency of cluster periods, and short-lived duration of remission periods when the headache is still in its episodic form all correlate with a possible worsening of the clinical picture over time. The reasons for evolution of episodic cluster headache to chronic are still unknown, but some factors, such as head trauma and other lifestyle factors—eg, cigarette smoking and alcohol intake—have been suggested as having a negative influence on the course of cluster headache over time.

Comment: Further longitudinal epidemiological research is needed to assess the impact of smoking cessation in these patients and to confirm or refute the hypotheses suggested in this paper. DSM

Lee Kudrow documented that smoking, like nitroglycerin, lowers oxygen tension, which in turn can precipitate cluster attacks. Another possibility is that smoking and nitroglycerine are nitric oxide (NO) delivery systems and that the NO both precipitates attacks and worsens long-term cluster prognosis. SJT

Saper JR, Klapper J, Mathew NT, Rapoport A, Phillips SB, Bernstein JE. **Intranasal civamide for the treatment of episodic cluster headaches.** *Arch Neurol.* 2002 Jun;59(6): 990-994

Objective: To evaluate the safety and efficacy of intranasal civamide solution for preventive treatment during an episodic cluster headache period.

Subjects And Methods: This was a multicenter, double-blind, randomized, vehicle-controlled study with a 7-day treatment period and a 20-day posttreatment period performed at 14 headache/neurology centers in the United States. Twenty-eight subjects were randomized to receive civamide or its vehicle in a 2:1 ratio; 18 received civamide and 10 received the vehicle. Subjects received 100 microL of 0.025% civamide (25 microg) or 100 microL of the vehicle to each nostril via dropper once daily for 7 days. The total daily dose of civamide was 50 microg.

Main Outcome Measures: The number of cluster headaches per week during the treatment and posttreatment periods, pain intensity, presence of associated symptoms, and the incidence of adverse events were assessed.

Results: Subjects in the civamide group had a significantly greater percent decrease in the number of headaches from baseline to posttreatment during days 1 through 7 (−55.5% vs −25.9%; P = .03) and a trend toward significance during days 8 through 14 (−66.9% vs −32.3%; P = .07) and days 15 through 20 (−70.6% vs −34.9%; P = .07), as well as a near-significant decrease during the entire posttreatment period (days 1 through 20 [P = .054]) compared with the vehicle group. There were larger decreases in the number of headaches per week during the posttreatment period in the civamide-treated group, with trends toward significance during posttreatment days 8 through 14 (−8.6 vs −3.6; P = .09) and days 15 through 20 (−8.9 vs −3.6; P = .07). There were no significant differences between groups in cluster headache pain intensity, number of severe headaches, or associated symptoms. The most common adverse events included nasal burning (14 of 18 civamide-treated subjects, 1 of 10 vehicle-treated subjects; P = .001) and lacrimation (9 of 18 civamide-treated subjects, 0 of 10 vehicle-treated subjects; P = .01).

Conclusion: Intranasal civamide solution at a dose of 50 microg may be modestly effective in the preventive treatment of episodic cluster headache.

Comment: Civamide is a capsaicin-like medication being studied for the prevention of cluster headache, a follow-up compound to an idea first described in a study published in 1993 suggesting that intranasal capsaicin appeared useful in preventing episodic cluster (Marks DR, Rapoport A, Padla D, Weeks R, Rosum R, Sheftell F, Arrowsmith F. A double-blind placebo-controlled trial of intranasal capsaicin for cluster headache. Cephalalgia. 1993;13:114-116). The current study did not meet several primary endpoints; the question is whether a larger study would. The issue is not insignificant. Dr. Peter Goadsby has pointed out that there is a specific need for nonvascular treatments for cluster, given the epidemiology of patients with cluster as smoking, middle-aged men at high risk for vascular disease. Civamide, if it can be shown effective in prophylaxis, depletes substance P and other nociceptive peptides, without causing vascular changes or cardiac effects, as can be seen with calcium-channel blockers. It has far less systemic toxicity than lithium or antiepileptic drugs. Further study seems warranted, even if overall clinical effect is moderate. SJT

Moore K. **Cluster headache: the challenge of clinical trials.** *Curr Pain Headache.* Rep 2002 Feb;6(1):52-56

The design and execution of clinical trials poses special problems for cluster headache. Although there is less inter-individual and intra-individual variability of attacks than seen with migraine, the brevity of attacks, spontaneous remissions unrelated to treatment, and the relative rarity of cluster headaches challenge investigators. The International Headache Society has developed guidelines that represent a compromise between scientific rigor and practicality. Only injectable sumatriptan for acute attacks and

verapamil for prophylaxis have demonstrated a robust therapeutic effect in controlled clinical trials.

Comment: Kenneth Moore raises important methodological considerations. It is possible to undertake crossover trials comparing different active treatments? He is correct in his assertion that few agents show robust efficacy. A major issue relates to the proportion of patients with episodic versus chronic cluster headache where efficacy of active treatments can vary. For example, oral zolmitriptan was effective against placebo only in those patients with episodic disease (Bahra A, Gawel MJ, Hardebo JE, Millson DS, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology. 2000;54:1832-1839). And a set of small studies on melatonin and cluster demonstrate the problems Dr. Moore describes. In one study (Leone M, D'Amico D, Moschiano F, Fraschini F, Busonne G. Metalonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia. 1996;16:494-496), the melatonin worked only in episodic, not chronic cluster patients. In the second study (Prinsheim T, Magnoux E, Dobson CF, Hamel E, Aube M. Melatonin as adjuctive therapy in the prophylaxis of cluster headache: a pilot study. Headache. 2002;42:787-792), melatonin did not work better than placebo in either episodic or chronic cluster patients. Furthermore, the paper abstracted above by Torelli and Manzoni suggests that episodic cluster may progress to chronic cluster as a result of extrinsic factors such as smoking. Finally, there are ethical issues in placebo-controlled cluster studies, given the severity of the pain and the availability of effective acute and chronic treatments. As noted above, Dr. Peter Goadsby points out the need to persevere with these studies to find nonvasoactive treatments for patients with cluster headache. DSM and SJT

Tonon C, Guttmann S, Volpini M, Naccarato S, Cortelli P, D'Alessandro R. **Prevalence and incidence of cluster headache in the Republic of San Marino.** *Neurology*. 2002 May 14;58(9):1407-1409

Based on a preceding survey performed in 1985, the authors estimated the prevalence and incidence of cluster headache (CH) in the Republic of San Marino (26628 inhabitants at 31 December 1999). All cases were diagnosed by direct interview according to International Headache Society criteria. The prevalence rate was $^{56}/_{100}000$ (95% CI 31.3 to 92.4), and the incidence rate was 2.5/100000/year (95% CI 1.14 to 4.75). Most cases showed rare clusters. This is the first prospective study on the incidence of CH.

Comment: There continues to be debate on the prevalence of cluster in the general population. Since San Marino is small, the entire cluster population, with a smaller denominator for the general population, could be estimated, making this a very important study. SJT

Ekbom K, Hardebo JE. **Cluster headache: aetiology, diagnosis and management.** *Drugs*. 2002;62(1):61-69

Cluster headache is characterised by repeated attacks of strictly unilateral pain in the orbital region associated with local autonomic symptoms or signs. The attacks are brief but of a very severe, almost excruciating intensity. For unknown reasons males are affected more often than females. Recent studies suggest that an autosomal dominant gene has a role in some families with cluster headache. Hormonal studies indicate a dysfunction in the central nervous system. Neuroimaging has revealed primary defects in the hypothalamic grey matter. Local homolateral dilatation in the intracranial segment of the internal carotid and ophthalmic arteries during attacks is the result of a generic neurovascular activation, probably mediated by trigeminal parasympathetic reflexes. Sumatriptan 6mg subcutaneously is the drug of choice in the treatment of acute attacks. Inhalation of 100% oxygen can also be recommended. In the prophylactic treatment, verapamil is the first option. Other drugs that can be considered are corticosteroids, which may induce a remission of frequent, severe attacks, and lithium. Oral ergotamine tartrate may be sufficient for patients with night attacks and/or short, rather mild to moderately severe cluster headache periods. Third line drugs are serotonin inhibitors (methysergide and pizotifen) and valproic acid. Patients should be encouraged to keep headache diaries and be carefully instructed about the nature and treatment of the headaches. Alcohol can bring on extra attacks and should not be consumed during active periods of cluster headache.

Comment: A useful review of clinical options. Given the effectiveness of injectable sumatriptan and the prophylactic use of ergotamine mentioned, one might speculate that the new intranasal formulations of triptans (eg, zolmitriptan) and triptans with a longer half-life (eg, frovatriptan) may prove to be effective in the treatment of cluster headache. DSM

TENSION-TYPE HEADACHE

Ashina M, Stallknecht B, Bendtsen L, Pedersen JF, Galbo H, Dalgaard P, Olesen J. **In vivo evidence of altered skeletal muscle blood flow in chronic tension-type headache.** *Brain*. 2002 Feb;125(Pt 2):320-326

Painful impulses from tender pericranial muscles may play a major role in the pathophysiology of chronic tension-type headache. Firm evidence for peripheral muscle pathology as a cause of muscle pain and chronic headache is still lacking. Using a microdialysis technique, we aimed to estimate in vivo blood flow and interstitial lactate concentrations in the trapezius muscle at rest and during static exercise in patients with chronic tension-type headache and in healthy subjects. We recruited 16 patients with chronic tension-type headache and 17 healthy control subjects. Two microdialysis catheters were inserted into the trapezius muscle (on the non-dominant side) of subjects, and dialysates were collected at rest, 15 and 30 min after the start of static exercise (10% of maximal force) and 15 and 30 min after the exercise was completed. All samples were coded and analysed blind. The primary endpoints were to detect a difference between patients and controls in changes of

muscle blood flow and the interstitial lactate concentration from baseline to exercise and post-exercise periods. The increase in muscle blood flow from baseline to exercise and post-exercise periods was significantly lower in patients than controls ($P = 0.03$). There was no difference in resting blood flow between patients and controls ($P = 0.43$). Resting interstitial concentration of lactate did not differ between patients ($2.51 \pm$ *T0.18 mM; mean $\pm$ standard error of the mean) and controls (2.35 ± 0.23 mM, $P = 0.57$). There was no difference in change in interstitial lactate from baseline to exercise and post-exercise periods between patients and controls ($P = 0.38$). The present study provides in vivo evidence of decreased blood flow in response to static exercise in a tender muscle in patients with chronic tension-type headache. We suggest that, because of increased excitability of neurones in the CNS, the central interpretation and response to normal sensory input are altered in patients with chronic tension-type headache. This may lead to enhanced sympathetically mediated vasoconstriction and thereby a decreased blood flow in response to static exercise.

Comment: An important study which links decreased blood flow in statically exercised trapezius muscle in patients with chronic tension-type headache (CTTH) with muscle tenderness. A better understanding of the pathophysiology of CTTH may provide a clue to novel therapeutic maneuvers. DSM

Have you read an article that other readers of *Headache* would find useful or interesting? If so, send the article or abstract with the citation to sjtepper@aol.com or d.millson@mema.keele.ac.uk