CHAPTER 45

GENERAL ISSUES ARISING IN THE USE OF DRUGS FOR HEADACHE DISORDERS

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Abstract

The WHO's list of essential medicines list for migraine only includes paracetamol, aspirin, ibuprofen and propranolol at present. In the past few years *Lifting The Burden* has been striving to include triptans as a group. It is a clinical reality indeed that patients may not respond to analgesics and NSAIDs, but may be triptan-responders. The benefit to tolerability ratio of triptans favors oral triptans in acute migraine treatment, but we illustrate why subcutaneous sumatriptan is the triptan of choice in acute cluster headache treatment. The individual respons to prophylactic treatment is quite variable, based on individual pharmacokinetic and pharmacodynamic differences. Tailoring of drugs to patients is important in clinical practice. Barriers to optimal drug treatment of headache disorders include undertreatment and mismanagement, despite existing guidelines. Medication-overuse headache has been described in a number of headache disorders, but is most commonly encountered in migraine patients.

Established Knowledge

The treatment of headaches begins with making a diagnosis, explaining it to the patient, and developing a treatment plan taking into account the severity and frequency of the headache. Headache is most often a very painful and bothersome disorder in which drug treatment is needed acutely. In addition, when migraine, cluster headache and tension-type headache are occurring frequently, preventive daily intake of a drug may be needed.

Acute drugs for migraine are specific drugs, such as triptans and ergot alkaloids, and non-specific drugs such as paracetamol, aspirin and other NSAIDs. For acute treatment of cluster headache only quickly absorbed triptans are effective. Tension-type headaches are treated acutely with analgesics. Triptans are not effective in episodic tension-type headache (Brennum et al. 1996).

For prophylaxis of migraine several types of drugs can be used, including β-blockers, anti-epileptics and calcium channel blockers (Steiner et al. 2007). Only one drug, methysergide, was designed for migraine prophylaxis and it is rarely used because of risk of severe side effects. The prophylactic drug of first choice in cluster headache is verapamil. In frequent and chronic tension-type headache tricyclic antidepressant drugs are used.

Worldwide the use of drugs is heavily dependent on the WHO's list of essential drugs and this list will be discussed. Cost is still an important factor, especially with the triptans for which the patent has not expired. With all acute drugs for headache there is the risk for overuse with resulting daily headache (see Chapter 47). Headache disorders are often chronic disorders wherefore tolerability and safety are important issues.

WHO's essential medicines list for migraine

Table 1

7 Antimigraine medicines	
7.1 For treatment of acute attack	
Acetylsalicylic acid	Tablet: 300 mg to 500 mg
Ibuprofen **[c]**	Tablet: 200 mg; 400 mg
Paracetamol	Oral liquid: 125 mg/5 ml **[c]** Tablet 300 mg to 500 mg
7.2 For prophylaxis	
Propranolol	Tablet: 20 mg; 40 mg (hydrochloride)

Legend Table 1: WHO's essential medicines list for migraine (16th Edition, revised March 2010); **[c]** signifies that there is a specific indication for restricting its use to children; Source: http://www.who.int/medicines/publications/essentialmedicines/en/index.html

The WHO List of Essential Medicines (revised March 2010) is shown in Table 1 with respect to migarine. *Lifting The Burden,* The Global Campaign to Reduce the Burden of Headache Worldwide, has in the last years argued that triptans as a group should be included in the list for migraine. WHO has, however, argued that as long as triptans have not been demonstrated to be superior to aspirin there is no need for adding the triptans to the list. Thus a meta-analysis of 3 RCTs provided evidence that effervescent aspirin 1,000 mg is as effective as sumatriptan 50 mg for the acute treatment of migraine attacks, and that both are superior to placebo (Lampl et al. 2007). This is illustrated by the meta-analysis results for pain relief at 2 hours, defined as a decrease in

headache from moderate or severe to none or mild after 2 hours, amounting to 52 % (95% CI: 47 – 57%) for effervescent aspirin 1,000 mg which is quite comparable to sumatriptan 50 mg (47%, 95% CI: 40-52%), and both are significantly superior to placebo (34%, 95% CI: 29-39%). These results seemingly demonstrate that the two groups of drugs, triptans and NSAIDs, are equivalent in migraine treatment (Lampl et al. 2007). Comparisons of oral triptans with other classes of acute treatments are few, and in general differences between active treatments on the primary endpoints were not dramatic (Lipton et al. 2004). Nevertheless these data have been questioned as there is a discrepancy with experience in clinical practice (Lipton et al. 2004). We are as clinicians confronted every day with migraine patients that do not respond to analgesics or NSAIDs. There is thus the need for more migraine-specific drugs such as triptans or ergot alkaloids. Regardless of this a drug like effervescent aspirin should be the drug of first choice in migraine, but triptans or ergot alkaloids should be available for those patients unresponsive to aspirin. For most migraine sufferers requiring a specific anti-migraine treatment, a triptan is generally a better option from both an efficacy and side-effect perspective (Tfelt-Hansen et al. 2000). The recommended doses of 20 mg and 40 mg for propranolol are not in agreement with the literature on migraine prophylaxis with propranolol in randomised clinical trials (RCTs) (Tfelt-Hansen and Rolan 2006). The most commonly used dose of propranolol in these RCTs is 160 mg per day and the WHO list should be changed to propranolol 40 mg and 80 mg.

Headache in general, and migraine in specific, are probably the stepchild in pain management. The use of drugs in headache and migraine should be evidence-based. “Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”.”The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett et al. 1996). Evidence-based medicine is more than just meta-analyses of drugs and

procedures. WHO seemingly does not understand the second part of evidence-based medicine: the integration of individual clinical expertise into the decision. What do you do when you have a migraine patient who has unsuccessfully tried aspirin for three migraine attacks. As shown in the meta-analysis even with the optimal aspirin, effervescent aspirin 1,000 mg, 50% of the patients don't respond with headache relief and 70% are not pain free after 2 hours (Lampl et al. 2007). Most patients with headache worldwide self-medicate for migraine, using aspirin and paracetamol and thus following the WHO recommendations. In some countries a few triptans are over the counter drugs (Tfelt-Hansen and Steiner 2007). Triptans are currently, however, only used by 10-15% of migraine patients in Denmark and UK (Tfelt-Hansen and Steiner 2007).

Benefit/tolerability ratio for specific migraine drugs

The best available evidence comes from systematic reviews (or meta-analyses) of RCTs. In migraine there are several meta-analyses, mostly on triptans (Tfelt-Hansen et al. 2000; Ferrari et al. 2001; McCrory and Gray 2003; Pascual 2004; Saxena and Tfelt-Hansen 2006). The efficacy is most often well described in RCTs whereas adverse events are currently reported in different ways. This makes comparison of tolerability in systematic reviews problematic. A practical example on the choice between the two administration forms of sumatriptan, oral and subcutaneous, plus the choice in cluster headache, is given in Table 2. As is shown subcutaneous sumatriptan 6 mg is both more effective and causes more adverse events than the oral form of sumatriptan 100 mg. Subcutaneous sumatriptan is also more quickly effective (relevant effect after 20 min) than oral sumatriptan (relevant effect after 60 min) (Saxena and Tfelt-Hansen 2006). Apparently, the simple benefit/tolerability is better for oral sumatriptan (32%/16% = 2) than subcutaneous sumatriptan (51%/33% = 1.5) but clinical treatment is not that simple. Most patients prefer the oral route of

administration. The price of subcutaneous sumatriptan 6 mg is very high, 37 € versus 1 € for sumatriptan 50 mg (current prices in Denmark). In cluster headache the situation is different. The attack is very severe but short-lasting. So the treatment should work quickly with a high response rate. Even if intranasal sumatriptan 20 mg and zolmitriptan 5 mg are statistically superior to placebo, it is only subcutaneous sumatriptan 6 mg which has an early clinically relevant effect (Table 2).

In prophylaxis of migraine adverse events are in our experience the most frequent reasons for stopping the treatment. One should be aware of the fact that drugs results in very variable plasma levels, often 5 to 10 fold differences among subjects. In addition, there is a pharmacodynamic variability (Tfelt-Hansen and Edvinsson 2007). This variability is especially important in migraine prophylaxis. The dictum should be “start low, go slow”. Usually we start out with ¼ to ½ of the dose used in RCTs and then slowly over weeks to months increase the dose depending on efficacy and tolerability. Such a tailoring of the drug to the individual patients can usually not be done in RCTs.

These examples hopefully illustrate that the benefit/tolerability ratio is content dependent and it is the responsibility of the physician to try optimize the treatment of the individual patient.

Table 2.

Data from randomised clinical trials (RCTs)	Data not evident from RCTs and personal clinical experiences
Sumatriptan 100 mg is superior to placebo in RCTs with a therapeutic gain (TG) of 32% (Tfelt-Hansen et al. 2000). There are 16% (95% CI: 13-19%) more adverse events after sumatriptan than after placebo. Sumatriptan 100 mg begins to have a clinically relevant effect after 60 min with a maximum after 120 min. Sumatriptan 6 mg subcutaneous (SC) has a TG of 51%. There are 33% (95% CI: 29-37%) more adverse events after sumatriptan 6 mg SC than after placebo. Sumatriptan 6 mg SC begins to have a clinically relevant effect after 20 min with a maximum effect after 60 min.	The plasma level of sumatriptan varies considerably (4-10 fold) after oral administration. Most patients prefer the oral route of administration. Sumatriptan 6 mg SC is very costly (37 €) versus sumatriptan tablets 50 mg (1 €).
Migraine	
Efficacy/tolerability ratio: Both oral (TG: 32%) and SC sumatriptan (TG: 51%) are effective. Sumatriptan 6 mg SC causes more adverse events than oral sumatriptan (33% versus 16% more than placebo).	Because of the more frequent adverse events after sumatriptan 6 mg SC the oral form has clinically the best efficacy/tolerability ratio in migraine. The oral form is also much cheaper (1 € versus 30 €). If very quick effect is needed sumatriptan 6 mg SC is better than the oral form.
Cluster headache	
Sumatriptan 6 mg SC is effective in cluster headache: within 15 min 74% of sumatriptan treated attacks responded (no or mild headache) versus 26% of placebo treated attacks. After nasal sumatriptan 20 mg 57% responded after 30 min versus 26% after placebo. Nasal zolmitriptan 5 mg resulted in 48% response after 30 min versus 19% response after placebo.	Given the short duration and severity of attacks, rapidity of action is a crucial factor. Sumatriptan 6 mg SC has quicker onset of action and is more effective than the nasal triptans. SC sumatriptan is generally the drug of first choice.

Legend Table 2: A practical example of the choice between two administration forms of triptans based on the benefit/risk ratio

Barriers to optimal drug choice in the treatment of headache disorders

Underdiagnosis and diagnostic delay have been well documented in a number of headache disorders, including common syndromes such as migraine and cluster headache (Lipton et al. 2001; Bahra and Goadsby 2004). Even when a correct diagnosis has been made, undertreatment and mismanagement have been observed despite the existence of guidelines for clinical practice (May et al. 2006; Steiner et al. 2007; Evers et al. 2009). Patients may receive acute treatment, but no prevention (when indicated) and vice versa. Ineffective acute drugs or prophylactic drugs may have been proposed to patients. The proportion of IHS-defined migraineurs using only over-the-counter medications to treat their headaches was 57% in the American Migraine Study II (Lipton et al. 2001). There was a clear underuse of migraine prevention in the American Migraine Prevalence and Prevention study (Diamond et al. 2007). A significant fraction of cluster headache patients never have had access to SC sumatriptan or high-flow oxygen, both first line acute treatments according to current recommendations (May et al. 2006; Van Alboom et al. 2009). Cluster headache patients may receive ineffective prophylactic drugs such as propranolol, carbamazepine or amitriptyline (Van Alboom et al. 2009). Medication-overuse headache is a major public health concern and affects 0.7% to 1.7% of the population (Evers and Marziniak 2010). Medication-overuse headache has been described in a variety of headache disorders including tension-type headache, migraine and cluster headache (Diener and Limmroth 2004; Paemeleire et al. 2006). In principle, all acute drugs for the treatment of headache could cause MOH (Evers and Marziniak 2010). Appropriate treatment may have been advised, but patients may lapse from care (Edmeads 2006). It is however important that resources are available to guarantee adequate follow-up of patients to ensure that optimum treatment has been established (Steiner et al. 2007). Stepped care guidelines

are available in acute migraine treatment (Steiner et al. 2007), and we have made the case for triptans in non-responders to NSAIDs in acute migraine.

Current Research

Not applicable to this chapter

References

Bahra A, Goadsby PJ (2006) Diagnostic delays and mis-management in cluster headache. Acta Neurol Scand 109: 175-179

Brennum J, Brinck T, Schriver L, Wanscher B, Soelberg Sørensen P, Tfelt-hansen P, Olesen J (1996) Sumatriptan has no clinically relevant effect in the treatment of episodic tension-type headache. Eur J Neurol 3: 23-28

Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB (2007) Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 47: 355-363

Diener HC, Limmroth V (2004) Medication-overuse headache: a worldwide problem. Lancet Neurol 3: 475-483

Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor P (2009) EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol 16: 968-981

Evers S, Marziniak M (2010) Clinical features, pathophysiology, and treatment of medication-overuse headache. Lancet Neurol 9: 391-401

Ferrari MD, Roon KI, Lipton RB, Goadsby PJ (2001) Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 358: 1668-1675

Lampl C, Voelker M, Diener HC (2007) Efficacy and safety of 1,000 mg effervescent aspirin: individual patient data meta-analysis of three trials in migraine headache and migraine accompanying symptoms. J Neurol 254: 705-712

Lipton RB, Bigal ME, Goadsby PJ (2004) Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. Cephalalgia 24: 321-332

Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF (2001) Migraine diagnosis and treatment: results from the American Migraine Study II. Headache 41: 638-645

May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, Goadsby PJ (2006) EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 13: 1066-1077

McCrory DC, Gray RN (2003) Oral sumatriptan for acute migraine. Cochrane Database Syst Rev: CD002915

Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ (2006) Medication-overuse headache in patients with cluster headache. Neurology 67: 109-113

Pascual J (2004) A review of rizatriptan, a quick and consistent 5-HT1B/1D agonist for the acute treatment of migraine. Expert Opin Pharmacother 5: 669-677

Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996) Evidence based medicine: what it is and what it isn't. BMJ 312: 71-72

Saxena PR, Tfelt-Hansen P (2006). Triptans, 5HT1B/1D agonists in the acute treatment of migraine. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds).The Headaches 3rd Edition, Lippincott Williams & Wilkins**,** Philadelphia, pp 469-503

Steiner TJ, Paemeleire K, Jensen R, Valade D, Savi L, Lainez MJ, Diener HC, Marteletti P, Couturier EG (2007) European principles of management of common headache disorders in primary care. J Headache Pain 8 Suppl 1: S3-47

Tfelt-Hansen P, De Vries P, Saxena PR (2000) Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. Drugs 60: 1259-1287

Tfelt-Hansen P, Edvinsson L (2007) Pharmacokinetic and pharmacodynamic variability as possible causes for different drug responses in migraine. A comment. Cephalalgia 27: 1091-1093

Tfelt-Hansen P, Rolan P (2006). Beta-adrenoceptor blocking drugs in migraine prophylaxis. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds).The Headaches 3rd Edition, Lippincott Williams & Wilkins**,** Philadelphia, pp 519-528

Tfelt-Hansen P, Saxena PR, Dahlof C, Pascual J, Lainez M, Henry P, Diener HC, Schoenen J, Ferrari MD, Goadsby PJ (2000) Ergotamine in the acute treatment of migraine: a review and European consensus. Brain 123 (Pt 1): 9-18

Tfelt-Hansen P, Steiner TJ (2007) Over-the-counter triptans for migraine : what are the implications? CNS Drugs 21: 877-883

Van Alboom E, Louis P, Van Zandijcke M, Crevits L, Vakaet A, Paemeleire K (2009) Diagnostic and therapeutic trajectory of cluster headache patients in Flanders. Acta Neurol Belg 109: 10-17