Migraine: which triptan?

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A wide variety of drugs are now available for the acute treatment of migraine attacks. Although the new triptans are expensive, clinical trials have shown them to be highly effective, and they are the treatment of choice for disabling attacks unresponsive to cheaper medication. This article discusses the different clinical circumstances in which each preparation may prove the most effective.

Most patients with episodic unilateral headache and nausea, and who are clinically well and have no physical abnormalities between attacks have migraine, but the assessment of every patient must consider and exclude alternatives (e.g. cluster headache, temporal arteritis, cervical spondylosis and causes of raised intracranial pressure) before symptomatic treatment alone is offered.

Although most patients seeking medical advice about their headaches will have tried simple analgesics such as aspirin, paracetamol and ibuprofen, these may often be sufficient, particularly if relatively large doses (such as 800 mg of ibuprofen) are suggested. Combinations of these agents with gastrokinetic anti-emetics, such as metoclopramide or domperidone, may also be of value, and the new preparation Domperamol (Servier Laboratories, Slough), combining paracetamol and domperidone, may be worth offering to some patients, particularly as it is relatively cheap.

Non-steroidal anti-inflammatory drugs remain the main stay of first-line medical treatment for migraine — the best trials have been done with naproxen and diclofenac which remain relatively inexpensive; tolfenamic acid has recently been marketed for the management of migraine, but is substantially more expensive although cheaper than any triptan (Drug and Therapeutics Bulletin, 1998). Patients with relatively frequent attacks, usually taken to be between two and four attacks each month, should be considered for regular prophylactic treatment with propranolol, pizotifen, valproate or perhaps methysergide (Drug and Therapeutics Bulletin, 1998).

Ergotamine was the principal treatment for otherwise intractable migraine attacks for many years. It has extremely complex pharmacology, but Humphrey and his colleagues at Glaxo have established beyond reasonable doubt that its agonist properties at 5-HT_{1B} and 5-HT_{1D} receptors are responsible for suppressing the pain of headache (Parsons et al, 1989). Humphrey and his group then developed a selective agonist at this receptor, sumatriptan, which was marketed for the treatment of migraine attacks in 1991. Zolmitriptan (Rapoport et al, 1997) and naratriptan (Mathew et al, 1997) were marketed in 1997, and rizatriptan (Teall et al, 1998) in 1998. Eletriptan, almotriptan and frovatriptan are expected shortly (*Table 1*). There are a number of headings under which these drugs can be compared and a decision made as to which to offer to which patient.

EFFICACY

In the original trials of sumatriptan, Glaxo analysed the proportion of people whose headaches had improved from 'severe' (incapacitating) or 'moderate' (disabling) to 'mild'

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TABLE 1.
Comparison of different triptans

Triptan	Company	Trade name	Formulation	Percent bioavailability	Cost £ per dose
Sumatriptan	Glaxo	Imigran	6 mg sc	96	19.57
			20 mg nasal	16	8.00
			50 mg tabs	14	4.95
			100 mg	14	8.00
Zolmitriptan	Zeneca	Zomig	2.5 mg tabs	40	4.00
Naratriptan	Glaxo	Naramig	2.5 mg tabs	63–74	4.00
Rizatriptan	MSD	Maxalt	5 mg	45	4.46
			10 mg	36	4.46
Eletriptan	Pfizer		80 mg	>90	
Almotriptan	Almirall		25 mg	80	
Frovatriptan	Vanguard		2.5 mg	22–29	

sc = subcutaneously

(aware) or no headache, 2 hours after the administration of the medication.

This so-called 'Glaxo end-point' has received considerable criticism since then (Goadsby, 1998). It can well be argued that responses at 1 hour or even shorter are of greater clinical relevance, and many authorities feel that 4 hours, which is when naratriptan has its maximal benefit, is a long time to keep the patients waiting — in one trial of rizatriptan (Kramer et al, 1998) the placebo achieved a 46% response rate at 4 hours. It was originally felt that it would be difficult to time the complete cessation of headache while it would be relatively easy for a patient to decide when they were no longer incapacitated, but other authors have argued that the headache-free criterion is actually more robust, and more relevant to the patients (Goadsby, 1998).

The results of the major clinical trials of the four triptans currently on the market are given in *Table 2*, with additional information on the three triptans under development. Several authorities (most notably Goadsby, 1998) have performed meta-analyses of the trials of sumatriptan, zolmitriptan and naratriptan from which the 95% confidence limits given in *Table 2* have been derived. Figures without confidence limits have been taken from the best individual trial available. In each case the proportion of patients reaching the Glaxo end-point at 2 hours has been subtracted from the proportion responding similarly to placebo, which is usually around 20–25% in each trial.

In most of these trials patients treat three attacks with the same medication and obtain reasonably consistent responses; this may, of course, be a reflection of the fact that patients not responding to the first or second treatment may not complete the third. The trials reported all relate to oral medication, but even about 9% of patients fail to respond to parenteral preparations such as subcutaneous sumatriptan, as is discussed below. Extensive clinical analyses of the characteristics of these headaches have not identified any way in which triptan responsiveness or not can be predicted on clinical grounds (Visser et al, 1996a).

There have, so far, been very few direct comparisons between different triptan drugs. A small trial comparing 10 mg rizatriptan and sumatriptan (Visser et al, 1996b) showed little difference between the two preparations during the study, although a significantly higher proportion of patients preferred rizatriptan in an open study conducted afterwards. The major published study of eletriptan, in contrast, does show that the relatively large dose of 80 mg causes a statistically significant greater percentage improvement than 100 mg of sumatriptan (Eletriptan Steering Committee, 1998).

SPEED OF ONSET

Although the time with which patients can expect a clinical improvement would seem to be of considerable importance, few of the early trials of oral medication measured this at all, concentrating entirely on responses at 2 and also at 4 hours. About 70–77% of patients, however, can expect relief within 1 hour of subcutaneous sumatriptan (Blakeborough et al, 1994).

The later trials of sumatriptan, and most trials of the more recent preparations, have measured the proportions of patients both headache free and reaching the Glaxo end-point at 1 hour; typical figures for sumatriptan are 22–26% relief, using the Glaxo end-point. It must be emphasized that the only way to determine the exact time at which a patient's headache is relieved is to assemble this information prospectively, e.g. by giving the patient a stopwatch, and there is a danger of inferring clinical responsiveness that may have already taken place before the 1-hour observation point.

TABLE 2.
Characteristics of different triptans

	% relief difference from placebo (to mild or none at 2 hours) ±95% CI		% relapsing at 24 hours	Peak time to relapse (hours)	Reference
	1 hour	2 hours			
Sumatriptan 100 mg	22	33±3	36	10.5	Pfaffenrath (1996)
Sumatriptan 50 mg	26	33±7	36	10.5	
Zolmitriptan 2.5 mg	18	34±7	32	10.5	Rapoport et al (1997)
Naratriptan 2.5 mg	8	21±3	27	12	Mathew et al (1997)
Rizatriptan 10 mg	21*	36	47	12	Teall et al (1998)
Eletriptan 80 mg	28	53†	?	?	Eletriptan Steering Committee (1998)
Almotriptan 25 mg	No information	26	30		Robert et al (1998)
Frovatriptan 2.5 mg	No information	13	17		Goldstein and Keywood (1998)

*Less functional disability at 1 and 2 hours compared to sumatriptan in a direct trial (Visser et al, 1996b). †Statistically superior to sumatriptan in a direct trial. 95% confidence intervals (CIs) all derived from Goadsby (1998).

It would be inappropriate to over-interpret the 1-hour figures in *Table 2* in the absence of any direct comparative trials at all, let alone any actually establishing the time point of clinical response. It would seem that the response rates with sumatriptan, zolmitriptan and rizatriptan are wholly comparable, whereas that of naratriptan is rather slower, reflecting the fact that its maximum clinical benefit is achieved at 4 hours. Some trials of rizatriptan do suggest that it may work a little more rapidly, with a demonstrable effect within 30 minutes, but, overall, the only sensible conclusion that can be drawn from currently published information is that naratriptan should not be used in patients in whom speed of onset is an important consideration.

RECURRENCE RATE

It became clear in the early sumatriptan trials that a substantial proportion of patients find that their headache recurs within 24 hours. In many cases this probably merely reflects the fact that the pathogenetic process itself goes on for longer than the duration of action of the medication, although there is a poor correlation between the relapse rate or its timing and the circulating half life of the medication. The recurrence seems to respond to a second dose of treatment, but prescribers must bear in mind that a small proportion of patients who treat second and third recurrences with further doses may actually be prolonging the whole attack in a manner akin to the well-recognized abuse of ergotamine and codeine.

The likelihood of a recurrence may, however, correlate inversely with the speed of onset. It will be seen that naratriptan and frovatriptan, which are the drugs showing peak effect at 4–6 hours, have the lowest recurrence rate — that of naratriptan is not statistically significant from the recurrence rate for placebo in the trials. Naratriptan, therefore, may be the treatment of choice in a patient in whom headache recurrence is a major problem, whereas speed of onset is not.

AVAILABLE ROUTES OF ADMINISTRATION

All triptans are available as oral tablets — in the case of sumatriptan and rizatriptan there are two different sizes of tablet. Most patients who are going to respond to sumatriptan do so to 50 mg, but occasional patients do require 100 mg although the effect plateaus at doses above this. In contrast, rizatriptan 10 mg is the recommended dose, with the 5 mg dose made available for patients receiving propranolol as the drug interacts with this, although not with other beta-blockers.

MSD have marketed a 'melt' preparation of rizatriptan, at the same price as the tablets — this is a paper film which dissolves rapidly on the tongue. It may be of social convenience, although pharmacokinetic studies have shown that the drug is absorbed no faster than tablets, presumably because it still has to be swallowed.

Sumatriptan was originally marketed as a subcutaneous preparation, and nasal and rectal preparations are now available in some countries. The original trials suggest that the response rate following subcutaneous sumatriptan (at the lower dose of 6 mg reflecting the high first pass metabolism rate following oral administration) is somewhat higher than 100 mg tablets (Blakeborough et al, 1994) and this preparation, despite its much greater price, should certainly be considered in patients failing to respond to any of the oral triptans and in patients in whom vomiting is a prominent early symptom.

One interesting trial (Bates et al, 1994) in which subcutaneous sumatriptan was given during the aura phase of migraines, before the development of the headache, gave extremely disappointing results which suggest that these drugs have to be in the circulation at the time the headache phase begins; patients receiving subcutaneous sumatriptan should therefore be warned to only treat the headache and not the aura. There have been no comparable trials of other triptans, but it seems reasonable to assume that oral drugs are absorbed rather more slowly and will therefore still be available as the headache phase begins, even if taken earlier.

SIDE-EFFECT PROFILE

Short-term side-effects of this group of drugs are extremely common, although less so with naratriptan. Indeed they can be so common as to virtually preclude crossover studies with placebo. Dizziness, somnolence, fatigue and worsening nausea are the commonest side-effects mentioned in formal trials, but many patients also complain of paraesthesiae and generalized aching which often settles down as the headache starts to improve. When questioned afterwards, the majority of patients in trials are happy to tolerate these side-effects because of the substantial later clinical improvement.

The tendency for a minority of patients to appear to abuse these drugs by taking them once or twice daily for several consecutive days has already been mentioned. Chest tightness is a rare but potentially alarming side-effect, which in most cases is believed to be of oesophageal origin and fundamentally harmless, although there is a theoretical risk of coronary vasoconstriction which means that these drugs should all be contraindicated in patients with ischaemic heart disease.

There are a number of potentially serious drug interactions. Sumatriptan and rizatriptan are metabolized by monoamine oxidase, and should not be given to patients receiving monoamine oxidase inhibitors. A major metabolite of zolmitriptan, which is pharmacologically active, is also metabolized by monoamine oxidase and the manufacturers recommend that the dose be adjusted to account for this. Naratriptan, in contrast, does not seem to interact at all with monoamine oxidase inhibitors and concurrent administration is considered safe.

There are theoretical interactions between sumatriptan in both lithium and selective serotonin-reuptake inhibitors (SSRIs), but the remaining triptans do not seem to interact, at least with SSRIs. The 5 mg dose of rizatriptan should be given to patients on propranolol, but not on other beta-blockers.

PRICE

Although all the triptans are substantially more expensive than well-established preparations previously discussed, this has not proved as important a factor in practical prescribing as originally feared. Most patients only receive one or two doses each month; patients needing more than this should certainly be considered for prophylactic treatment as well, as this is substantially cheaper. Zolmitriptan and naratriptan have been marketed at a price half that of 100 mg sumatriptan tablets, although it can be argued that the dose of naratriptan is relatively low, and better results were obtained in trials using larger doses. It is yet to be established whether the alleged clinical superiority of rizatriptan justifies its slightly higher price.

KEY POINTS

- There are now a large number of analgesic preparations available for migraine. Once migraine has been diagnosed, it is no longer appropriate to expect patients to use only over the counter medication, and physicians must be prepared to prescribe more potent and expensive remedies if appropriate.
- The possibility that codeine- or ergotamine-containing analgesics are contributing to the headache should be considered.
- Many patients respond to realistic doses of simple analgesics, particularly naproxen, diclofenac and domperidone, and patients with relatively frequent attacks should be offered regular treatment as well as appropriate analgesia.
- There are four triptans on the market, with at least three further preparations in development. They are more expensive, but in many cases much more potent.
- There have been very few direct comparative trials, but from the information currently available there are few differences between the efficacy rates of these preparations. Rizatriptan may be a little faster and naratriptan is certainly much slower. Recurrence rate, in contrast, is rather lower for naratriptan.
- Subcutaneous or nasal sumatriptan is still the treatment of choice for patients whose headaches are unresponsive to all other preparations, and in particular those in whom early vomiting is prominent.
- Zolmitriptan is relatively inexpensive, well absorbed and reasonably rapidly effective and is a realistic preparation to try first.

A number of authorities have now attempted cost–benefit analyses for triptans. Much depends on whether the economic benefit of an earlier return to work can be legitimately offset against the cost of the medication, but even if only the costs to the NHS of additional consultations and emergency call outs are considered, these drugs are probably cost effective at their current prices.

CONCLUSIONS

In clinical practice it often becomes evident that some patients respond to one triptan and others to a different one, often, but by no means always, for reasons related to the pharmacological distinctions discussed in this article. On many occasions patients may respond to relatively large doses or alternative routes of administration or even by the simultaneous administration of an antiemetic, such as domperidone. In the final analysis, however, patients' preferences are all important. HM

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