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TUTORIAL

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Acute pharmacotherapy of migraine, tension-type headache, and cluster headache

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Abstract In most migraine patients acute therapy is needed. Migraine can be treated either with specific drugs, the triptans and ergot alkaloids, or with NSAIDs. Triptans are a major step foreward in migraine therapy. The therapeutic gain for headache relief is 50% for subcutaneous sumatriptan whereas it is 30-40% for most oral triptans. After oral triptans sustained pain free is only 30%. There is thus still ample room for improvement of acute therapy in migraine. For tension-type headache there is no specific therapy and it is treated with NSAIDs. Only 17-32% become pain free after these drugs. For attacks of cluster headache oxygen and subcutaneous sumatriptan can be used. Intranasal triptans can be an alternative.

Keywords Migraine • Tension-type headache • Cluster headache • Acute pharmacotherapy • Triptans

Introduction

The quality of acute pharmacotherapy of migraine has improved recently with the advent of the new specific drugs, the triptans. For tension-type headache there has not been a similar development of specific drugs and tension-type headache is still treated with mild analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Cluster headache is also responding to triptan therapy.

Acute pharmacotherapy of migraine

Migraine can be regarded as an episodic-chronic disorder [1] and in the treatment of migraine one should consider treatment of the migraine attacks and in many cases also preventive treatment. Even with successful prophylactic treatment of migraine the patients will in most cases still suffer from some migraine attacks and need treatment for these. So optimum treatment of acute migraine attacks is the first priority in most cases.

Acute migraine attacks can be treated with either unspecific drugs such as aspirin and NSAIDs or specific medicines like triptans and ergot alkaloids. In addition, prokinetic drugs and neuroleptics may be useful.

Unspecific treatment of migraine attacks

A new highly buffered formulation of 1000 mg effervescent aspirin (53% relief) was similar in efficacy to sumatriptan 50 mg (56% relief) and ibuprofen 400 mg (60% relief) in a large placebo-controlled (31% relief) study [2].

Table 1 Mean TG[a] for different triptans and forms of administration based on published papers and abstracts (for references and number of patients, see [9, 11])

Drug	Dose (mg)	Mean TG[b] (%)	95% CIs (%)
Sumatriptan	Subc. 6	51	48–53
Sumatriptan	Oral 100	32	29–34
Sumatriptan	Oral 50	29	25–34
Sumatriptan	Oral 25	24	18–29
Sumatriptan	Nasal 20	30	25–34
Sumatriptan	Rectal 25	31	25–37
Zolmitriptan	Oral 2.5	32	26–38
Naratriptan	Oral 2.5	22	18–26
Rizatriptan	Oral 10	37	34–40
Rizatriptan	Oral 5	28	23–34
Rizatriptan	Wafer[c] 10	37	29–45
Eletriptan	Oral 80	42	37–47
Eletriptan	Oral 40	37	32–42
Almotriptan	Oral 12.5	26	20–32
Frovatriptan	Oral 2.5	16	8–25

[a]Percentages headache relief after active drug minus percentage headache relief after placebo; [b]based on headache relief (a decrease from severe or moderate headache to none or mild after 2 h (for subcutaneous sumatriptan after 1 h)); [c]a rapidly dissolving wafer

Other NSAIDs with proven efficacy in acute migraine treatment are naproxen, ketoprofen, tolfenamic acid and diclofenac potassium [3]. The NSAID indomethacin plus prochlorperazine plus caffeine suppositories (49% pain free) was more effective than sumatriptan suppositories (34% pain free) in one randomised clinical trial (RCT) [4]. Frequent intake of analgesics, 15 days or more per month, leads to chronic headache and medication overuse headaches, and this can also happen with over-the-counter drugs [5].

Specific treatment of migraine attacks

Triptans

The 5-$HT_{1B/1D}$ receptor agonists, the triptans, have been compared in several meta-analyses of placebo-controlled RCTs [6–10] and in head-to-head comparative RCTs [10]. An example of such a meta-analysis is shown in Table 1.

Subcutaneous sumatriptan has the highest therapeutic gain (TG) (percentage response after active drug minus percentage response after placebo) of 51% (95 confidence intervals (CI); 48–53%). Eletriptan 80 mg (mean TG=42%, 95%CI: 37–47%) was also superior to sumatriptan 100 mg (mean TG=32%, 95%CI: 29–34%). Frovatriptan 2.5 mg (mean TG=16%, 95% CI: 8–25%) and naratriptan 2.5 mg (mean TG=22%, 95% CI: 18–26%) were both inferior to the standard triptan, sumatriptan 100 mg. All the other triptans and other administration forms of sumatriptan were roughly comparable to sumatriptan 100 mg (see Table 1).

In head-to-head comparative RCTs zolmitriptan 5 mg [11], rizatriptan 10 mg [12] and almotriptan 12.5 mg [11] were comparable to sumatriptan 100 mg for headache relief (a decrease from moderate or severe to none or mild). In a review of 3 comparative RCTs eletriptan 40 mg (67%) was superior to sumatriptan 100 mg (57%) [13]. Rizatriptan 10 mg (40%) was superior to sumatriptan 100 mg (33%) for pain-free after 2 h [12]. Similarly, eletriptan 40 mg (35%) was superior to sumatriptan 100 mg (25%) for pain-free after 2 h in 3 RCTs [13].

Based on the quicker absorption of rizatriptan than sumatriptan, the two triptans have to be compared for time to headache relief in 3 RCTs [11]. In two of these RCTs rizatriptan 10 mg had a quicker onset of action than sumatriptan 50 mg and 100 mg [12, 14], whereas this was not the case in the third RCT [15]. It should be noted that this time-to-event analysis cannot distinguish onset of action from one drug being marginally superior to the other. Thus this analysis apparently showed that rizatriptan 10 mg had a quicker onset of action than rizatriptan 5 mg [16].

Head-to-head comparisons of triptans with other drugs are shown in Table 2. The 3 oral triptans, sumatriptan, rizatriptan and eletriptan, were superior to oral ergotamine. In contrast, rectal ergotamine 2 mg (73% relief) was superior to rectal sumatriptan 25 mg [11]. Sumatriptan 100 mg (75%) was superior to tolfenamic acid (58%) for headache relief [17]. Highly buffered aspirin, aspirin plus metoclopramide, and lysine acetylsalicylic acid plus metoclopramide were comparable to sumatriptan 50 mg and 100 mg [11]. Diclofenac potassium was comparable

Table 2 RCTs comparing triptans with non-triptan drugs (for further details see [9–11]). Significant differences are shown in bold italics

Drug	Dose (mg)	Headache relief[a] (%)	Difference (%)	95% CI[b]
Sumatriptan	Oral 100	66	***+18***	***+9 to +27%***
Ergotamine+caffeine	Oral 2+200	48		
Sumatriptan	Oral 50	57		
Aspirin[a]	1000	53		
Sumatriptan	Oral 100	56	+11	-1 to +23%
Aspirin+metoclopramide	Oral 900+10	45		
Sumatriptan	Oral 100	53	-4	-17 to +8%
L-ASA[c]+metoclopramide	Oral 1620+10	57		
Sumatriptan	Oral 100	79	+2	-17 to +20%
Tolfenamic acid[d]	Oral 200+200	77		
Sumatriptan	Oral 100	75	***+17***	***+5 to +28%***
Tolfenamic acid[d]	Oral 200+200	58		
Placebo		47		
Sumatriptan	Subc. 6	80	**+30**	***+19 to +41%***
Dihydroergota-mine	Nasal 1+1	50		
Sumatriptan	Subc. 6	85 (83%[e])	***+12***	***+3 to +21%***
Dihydroergota-mine	Subc. 1+1	73 (86%[e])	(-3[e])	(-11 to +5%[e])
Sumatriptan	Nasal 20	63	***+12***	***+4 to +20%***
Dihydroergota-mine	1+1	51		
Sumatriptan	Subc. 6	91	***+17***	***+8 to +27%***
L-ASA[c]	I.v. 1800	74		
Sumatriptan	Rectal 25	63	***-10***	***-18 to –2%***
Ergotamine+caffeine	Rectal 2+200	73		
Eletriptan	80	68	***+35***	***+26 to +44%***
Ergotamine+caffeine	2+200	33		
Eletriptan	40	54	***+21***	***+11 to +30%***
Ergotamine+caffeine	2+200	33		
Rizatriptan	10	76	***+29***	***+19 to 38%***
Ergotamine+caffeine	2+200	47		

[a]A decrease from severe or moderate headache to none or mild after 2 h; [b]CIs; [c]lysine acetylsalicylate; [d]rapid release formulation; [e]after 4 h

to sumatriptan in one RCT [11]. Subcutaneous sumatriptan 6 mg was comparable to subcutaneous dihydroergotamine 1 mg (DHE) [11, 18]. Intranasal sumatriptan 20 mg (63% relief) was superior to intranasal 1 mg+1 mg DHE (51% relief) [19].

Recently, patients have treated their migraine attacks in the mild phase of migraine in RCTs. Pain-free after 2 h has been the primary efficacy measure in these RCTs. Rizatriptan 10 mg resulted in 70% being pain-free [20] and sumatriptan 100 mg resulted in 58% being pain-free [21] in double-blind, placebo-controlled RCTs. These results are considerable higher than the 30% pain-free found for most triptans when moderate or severe attacks are treated [7, 8]. If patients can distinguish the mild phase of migraine from a tension-type headache, treatment with a triptan in the mild phase can be recommended.

The clinical use of the triptans is shown in Table 3. The oral route is used in most cases but if the patient has severe nausea or is actually vomiting, other routes of

administration such as the rectal and intranasal route can be tried. Subcutaneous sumatriptan 6 mg is the most effective triptan but also the triptan with the most frequent adverse events [9, 11]. The clinical use of subcutaneous sumatriptan is hampered by its very high cost of €30 per injection for 6 mg.

Frequent use of triptans can result in medication-overuse headache and the limit seems to be a maximum of 9 days per month [5, 22]. It is important to note that preventive treatment is not effective during medication-overuse headache.

Ergot alkaloids

Ergotamine [23, 24] is not the drug of first choice for the treatment of migraine attacks. It has an effect on the 5-HT1B/1D receptor but also an effect on 5-HT_{2A} (results in general vasoconstriction) and dopamine D_2 receptor (can result in nausea/vomiting) [25]. It can be used in patients with infrequent long-standing attacks with multiple relapses with triptans. In 5 RCTs ergotamine resulted in less relapses than triptans (Tfelt-Hansen, personal observation). Oral ergotamine has an extremely low (<1%) and erratic bioavailability and if ergotamine is used it should be administered by the rectal route in doses of 1–2 mg [25]. The most frequent adverse event of ergotamine is nausea, which often limits its use. Frequent (10 days or more per month) intake of ergotamine can result in headache-overuse headache [5] and rarely in overt ergotism, which can be treated with a nitroglycerin infusion [26].

DHE acts on the same receptors as ergotamine but the intrinsic activity is apparently less for the 5-HT_{2A} receptor, resulting in less general vasoconstriction [27–29]. Similarly, DHE is less emetic than ergotamine (dopamine D_2) [23]. DHE can be used parenterally [30] or by the nasal route [23, 24] in the treatment of migraine attacks. For adverse potential events of DHE, see ref. [31].

Use of prokinetic drugs and neuroleptics

During migraine attacks the stomach is relatively atonic and the absorption of orally administered drugs is delayed [32], but the absorption can be normalised by the prokinetic and anti-emetic drug metoclopramide [33]. The combination of lysine acetylsalicylic acid and metoclopamide (56%) was as effective as sumatriptan 100 mg (53% relief) and both were superior to placebo (24%) in one RCT [34]. Trimebutine is also a prokinetic drug and in one RCT the combination of trimebutine plus rizatriptan (73% pain-free) was superior to rizatriptan alone (42% pain-free) [35, 36]. The 42% pain-free is similar to what was found in a meta-analysis for rizatriptan 10 mg [7, 8] and the combination with trimebutine thus resulted in a considerable increase of efficacy. One cannot exclude, however, that trimebutine *per se* has an antimigraine effect and further placebo-controlled studies are needed. The use of prokinetic medicines can probably increase the effect of other acute migraine drugs.

Parenteral neuroleptic medicines can be used in the emergency department. Prochlorperazine given intravenously or intramuscularly has been shown to be effective in several placebo-controlled RCTs [37].

Potential new drugs for acute migraine

The triptans are 5-$HT_{1B/1D}$ receptors and it is important for future drug development to investigate what sub-type of the receptor the antimigraine effect depends on. No 5-HT_{1B} receptor agonist is available but the 5-HT_{1D} receptor agonist PNU 142633 (29% relief) was similar to placebo (40% relief) and thus ineffective in the treatment of migraine [38]. This result shows that the effect on the 5-HT_{1B} receptor is needed for the antimigraine effect.

The somatostatin receptor agonist octreotide given in a dose of 100 µg subcutaneously (14% response) was no more effective than placebo (20% response) in the treatment of migraine attacks [39]; but octreotide (52%) was effective in cluster headache in a placebo-controlled (36%) RCT [40].

Calcitonin gene-related peptide (CGRP) was increased in the jugular vein during migraine attacks in one study [41] but not in a recent study [42]. A CGRP infusion can induce migraine attacks [43]. This is the background for using a CGRP antagonist in the treatment of migraine. The CGRP receptor antagonist BIBN4096BS (66%) given intravenously was superior to placebo (27%) in one recent RCT [44].

Conclusion from a clinician's point of view

Patients want to be pain-free, without relapses and have consistency of response [45]. Current drugs such as the triptans have been a major step forward in migraine treatment. However, the standard triptan sumatriptan 100 mg results in only 30% of patients being sustained pain-free (pain-free after 2 h, no relapse within 24 h, and no use of escape medication) and other triptans like rizatriptan 10 mg and eletriptan 40 mg are only marginally better [7, 8,

Table 3 Therapeutic use of marketed triptans in currently recommended doses (for details, see [23])

Contraindications to triptans	Ischaemic heart disease, variant angina, cerebral and peripheral vascular disease, and uncontrolled hypertension. Pregnancy. Use of ergot alkaloids within 24 h. Current use or use of MAO-inhibitors within the last 2 weeks. Hypersensitivity to the triptan. Hemiplegic and basilar migraine.	
Cautious use	Patients on SSRIs can be treated with triptans but should be warned about the symptoms of the serotonin syndrome.	
Recommended doses of triptans	Dose	Maximum daily dosage
	6 mg subcutaneous sumatriptan	12
	50–100 mg oral sumatriptan	300
	50 mg sumatriptan rapidly dissolving tablets (25 mg tablets available in the US)	300
	20 mg intranasal sumatriptan	40
	25 mg sumatriptan as suppositories	50
	2.5–5 mg oral zolmitriptan	0
	2.5 mg orally melting tablets of zolmitriptan	10
	2.5 mg oral naratriptan	5
	10 mg oral rizatriptan[a]	20
	10 mg oral rizatriptan wafer[a]	20
	40 mg oral eletriptan	80
	12.5 mg oral almotriptan	25
	2.5 mg frovatriptan	5?
Clinical efficacy in the treatment of migraine attacks	Subcutaneous sumatriptan (6 mg)>eletriptan (40 mg)≥oral sumatriptan (50–100 mg)=intranasal sumatriptan (20 mg)=rectal sumatriptan (25 mg)= oral zolmitriptan (2.5–5 mg)=oral rizatriptan (10 mg)>oral sumatriptan (25 mg), oral naratriptan (2.5 mg)=oral frovatriptan (2.5 mg).	
Speed of onset of effect compared with placebo	Subcutaneous sumatriptan (10 min)> intranasal sumatriptan (15 min) > oral sumatriptan = oral eletriptan = oral rizatriptan (30 min)> rectal sumatriptan (30–60 min)> oral zolmitriptan and oral naratriptan (60 min). It should be noted, however, that these "early responses", apart from subcuta neous sumatriptan, are often of relative small magnitude.	
Speed of onset of effect compared directly among two triptans or two administration forms of a triptan	Oral rizatriptan > oral sumatriptan. Oral rizatriptan = oral zolmitriptan. Oral rizatriptan > oral naratriptan. Intranasal sumatriptan > oral sumatriptan.	
Adverse events with triptans	So-called "triptan" symptoms: tingling, numbness, warm/hot sensation, pressure or tightness in different part of the body, including chest and neck. Rarely regular chest pain. Dizziness and sedation. Naratriptan and almotriptan cause no more adverse events than placebo.	
Choice of form of administration	Tablets generally most convenient. If severe nausea/vomiting is present the patient could alternatively use an injection, nasal spray or a suppository.	
Additional dose if the first dose of a triptan is not effective	There is no evidence that a second dose of a triptan increases the efficacy. Instead patients should if the chosen dose of a triptan is ineffective try another dose or different forms of administration or another triptan.	
Relapse or secondary treatment failure	Most triptans have the same relapse rate of 20-40%. Naratriptan have in some trials a lower relapse rate than sumatriptan and could be tried in relapse-prone patients.	

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Table 3 cont.

Use of a second dose for the treatment of a relapse when the first dose of a triptan is primarily effective	A second dose of a triptan will probably be effective, but with multiple relapses for days alternative drugs[b] should probably be tried.
Abuse or inappropriate use of triptans	Triptans should not be used on a daily basis (except in the treatment of chronic cluster headache). Set an upper limit of 9 days per months with triptan use. Use triptans with extreme caution in previous drug abusers.
Breast feeding	Sumatriptan can be used if milk is expressed and discarded for 8 hours after the dose. Not recommended with the other triptans.
Possible drug interactions	In patients on propranolol 5 mg rizatriptan should used. Eletriptan should not be used in patients on CYP3A4 inhibitors.

[a]5 mg rizatriptan in patients on propranolol; [b]this is one of the few possible indications for rectal ergotaminee

13]. The majority of patients are thus not treated optimally with currently available therapy and there is still ample room for improvement.

Acute pharmacotherapy of tension-type headache

In RCTs aspirin and paracetamol were superior to placebo [46]. The most commonly used dose is 1000 mg for both drugs. The following NSAIDs were superior to placebo in the treatment of tension-type headache: ibuprofen, ketoprofen, naproxen sodium and diclofenac potassium [46]. The low proportion (17–32%) of patients becoming pain-free 2 h after dosing underscores the insufficiency of these drugs [46] and there is therefore clearly room for better acute therapy of tension-type headache. Aspirin, paracetamol and NSAIDs should not be used on a daily basis [5].

The fixed combination of aspirin, paracetamol and caffeine was superior to the single substances and the combination of aspirin and paracetamol in one RCT for time to 50% reduction in pain [47]. One should, however, be careful with frequent use of such a combination because of the risk of medication-overuse headache.

Acute pharmacotherapy of cluster headache

Oxygen was, in one RCT [48], better than air and is the first choice in the acute treatment of cluster headache. It is, however, often impractical to bring a tank around in case an attack occurs outside home. In clinical practice not all patients respond to oxygen.

The attacks of cluster headache are short-lived (maximum 3 h) and non-oral routes of administration of drugs should be used. Subcutaneous sumatriptan is the most effective treatment, but very costly, see above. In one RCT, sumatriptan (74% relief) was superior to placebo (26% relief) already after 15 min [49]. Intranasal sumatriptan 20 mg (57% relief) was superior to placebo (26% relief) after 30 min [50]. In another RTC zolmitriptan 10 mg (62% relief) was superior to placebo (21% relief) after 30 min [51].

Usually the triptans are limited to 2 doses per day. Some patients have more cluster headache attacks than that per day and triptans are not effective in all patients. Furthermore, some patients cannot afford triptans. Preventive therapy of cluster headache is therefore still the first priority.

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