Chapter 52

Antiemetic, Prokinetic, Neuroleptic, and Miscellaneous Drugs in the Acute Treatment of Migraines

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Nausea and vomiting are common symptoms of migraine (48) and are often as distressing as the headache. Thus, in addition to analgesics or more specific antimigraine drugs, antinauseant agents are often used. For possible future use of antiemetics in migraine, the reader is referred to Dahlöf and Hargreaves (17).

During a migraine attack the absorption of orally administered drugs may be delayed (56,57,59,74,75,77, 79,80). This is most likely caused by gastric stasis, which contributes to the failure of some patients to respond to treatment (79). These pharmacokinetic observations led to the use of metoclopramide in migraine by virtue of its antiemetic property and its ability to promote gastric emptying, the so-called gastric prokinetic effect (10,53).

Neuroleptics have been used in the acute treatment of migraine, as analgesics and as antiemetics. Neuroleptics are also frequently used in the treatment of status migrainous (16). Probably their most important role today is as an alternative to opioids in emergency departments.

Several miscellaneous, alternative drugs for the treatment of migraine attacks deserve mention. These include drugs in common use despite limited evidence of efficacy in controlled double-blind trials (isometheptene combinations, dextropropoxyphene combinations, analgesic combination with antihistamines, morphinomimetics, lidocaine, and magnesium sulphate).

ANTIEMETIC AND PROKINETIC DRUGS

Metoclopramide

Pharmacologic Background

Metoclopramide is a benzamide derivative and, although related to the neuroleptics, has no significant antipsychotic or sedative properties. Metoclopramide is a dopamine and 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist (29,53) and also possesses some 5-HT_4 agonist activity (11,53). The actions of metoclopramide include antagonism of emesis induced by apomorphine or ergotamine (10); it also induces hyperprolactinemia, a characteristic of dopaminergic blockade (10,36,55). It can cause serious extrapyramidal dysfunction, especially after high intravenous dosage (10,36,55).

In the gastrointestinal tract, metoclopramide enhances the motility of smooth muscle from the esophagus through to the proximal small bowel. It thereby accelerates gastric emptying and the transit of intestinal contents from the duodenum to the ileocecal valve (10,53). The mechanism of this prokinetic effect has not been fully elucidated, but an agonistic effect on 5-HT_4 receptors on the enteric nerve plexus has been postulated (11,53).

Pharmacokinetics

Metoclopramide is rapidly and completely absorbed after oral administration, but because of hepatic first-pass metabolism its bioavailability is reduced to about 75%. Metoclopramide is distributed rapidly to most tissues and readily crosses the blood–brain barrier and placenta. The half-life of the drug in plasma is 4 to 6 hours (10).

Pharmacokinetic Investigations of Oral Absorption During Migraine Attacks

In the first classical study by Volans on aspirin absorption during migraine attacks (79), it was shown that during established migraine attacks salicylate concentrations determined 30 and 60 minutes after administration of 900 mg effervescent aspirin were significantly lower than those in the control subjects, but between migraine attacks the

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same patients demonstrated normal aspirin absorption. The impairment of aspirin absorption was ascribed to delayed gastric emptying because radiologic investigations had shown gastric stasis during migraine (43,45). In the next studies, two antinauseant agents, metoclopramide and thiethylperazine (the latter lacking the prokinetic activity), were tested for their possible effect on aspirin absorption during a migraine attack (80,82). Both drugs were given in a dose of 10 mg intramuscularly followed 10 minutes later by 900 mg effervescent aspirin. As was previously found, aspirin absorption was impaired during migraine, but metoclopramide normalized it. In those who had received thiethylperazine, aspirin absorption remained impaired. In a later study in which both aspirin and salicylate concentrations were measured following effervescent aspirin administration to patients during migraine attacks (60), the delay observed for aspirin reaching its absorption sites was not seen after 10 mg metoclopramide, given orally or intramuscularly. The oral absorption of the nonsteroidal anti-inflammatory drug (NSAID) tolfenamic acid was found to be impaired during migraine attacks, but the decreased absorption was reversed after 20 mg metoclopramide rectally (77). The absorption of paracetamol (75), naproxen (56), sumatriptan (57), and zolmitriptan (74) also was found to be slightly delayed during migraine attacks.

Clinical Trials With Metoclopramide

For controlled clinical trials concerning the combination of NSAIDs plus metoclopramide, the reader is referred to Chapter 49.

Metoclopramide alone was not better than placebo in treating nausea (76), whereas the combinations of metoclopramide and tolfenamic acid (76), metoclopramide and paracetamol and diazepam (73), and metoclopramide and aspirin (72) were better than placebo. The possible enhancing effect of metoclopramide on the efficacy of analgesics in migraine has been difficult to demonstrate formally. Thus, metoclopramide just failed to enhance analgesia in one study (73) ($P = .06$), and increased the efficacy of tolfenamic acid only for some parameters, such as intensity of attack as a whole (76), whereas it failed to enhance the analgesic effect of effervescent aspirin (72). The efficacy of combinations of highly soluble aspirin salt and metoclopramide (see Chapter 50) indicate, however, that metoclopramide enhances the analgesic effect of analgesics. In controlled trials there was no convincing evidence for the usefulness of the combination of metoclopramide and ergotamine (33,66).

Metoclopramide (10 mg intravenously) was found to be better than placebo in patients with severe migraine presenting at an emergency department (71), indicating that metoclopramide per se might have an effect on the migraine attack, apparently confirming an earlier anecdotal observation (39). In contrast, intramuscular metoclopramide was without any effect on migraine pain (73). In one study, intravenous metoclopramide was as successful as intravenous chlorpromazine (12), but the lack of a placebo control precludes firm conclusions. In another trial in emergency departments, 10 mg metoclopramide intravenously was inferior to 10 mg prochlorperazine intravenously and not different from placebo (14). In controlled trials there is thus no convincing evidence for the effect of metoclopramide per se on migraine attacks.

Therapeutic Use

Metoclopramide is combined with orally administered drugs in the treatment of migraine attacks based on a two-fold rationale: it is an antiemetic and it can normalize the delayed absorption of orally administered drugs thereby optimizing their use. For the use of metoclopramide in combination with NSAIDs, the reader is referred to Chapter 49. Based on our clinical experience and one study (63) metoclopramide can probably also be used to increase the efficacy of triptans during migraine attacks.

The dose of metoclopramide is 10 to 20 mg orally, 20 mg by suppository, or 10 mg intramuscularly (see Table 52-1).

The side effect of metoclopramide 10 mg intravenously, akathisia, normally precludes its use in the treatment of migraine attacks. Metoclopramide (5 mg intravenously) is sometimes used as an antiemetic when intravenous dihydroergotamine is given (see Chapter 63).

Side effects include sedation and dystonic reactions such as torticollis, trismus, facial spasm, and oculogyric crisis (the extrapyramidal side effects are usually seen after single parenteral doses of metoclopramide).

Contraindications include pheochromocytoma, breastfeeding, and treatment with neuroleptics. Use in children under 12 years of age is also contraindicated.

Domperidone

Domperidone is a derivative of benzimidazole that possesses both antiemetic and prokinetic properties. It is a dopaminergic antagonist and produces marked hyperprolactinemia (9,10). The effects of domperidone on gastrointestinal motility closely resemble those of metoclopramide. Domperidone, however, crosses the blood–brain barrier poorly and, therefore, rarely causes extrapyramidal side effects.

Domperidone is rapidly absorbed after oral administration (time to peak plasma concentration [t_{max}] = 30 minutes]), whereas rectal absorption is slower (t_{max} = 60 minutes). Its oral and rectal bioavailability is only about 15%. The half-time for its elimination from plasma is about 7.5 hours (9).

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TABLE 52-1 Recommendation for the Use of Neuroleptics in the Treatment of Migraine[a]

Drug	*Quality of Evidence[b]*	*Scientific Effect[c]*	*Clinical Impression of Effect[d]*	*Adverse Effects*	*Comments (See Full Prescribing Information for Complete List of Adverse Events and Contraindications)*	*Role (by Consensus)*
Antiemetics						
Chlorpromazine IM (0.1 mg/kg for 1–3 doses to 1 mg/kg)	C	++	++	Mild to moderate	Extrapyramidal adverse events (e.g., dystonia), and sedation are associated with metoclopramide but rarely reported in the clinical trials reviewed. In some patients with migraine, sedation may be useful. Has role in pregnancy. Postural hypotension is an adverse event with chlorpromazine.	Adjunct therapy
IV (12.5 to 37.5 mg)	B	++	++			
Metoclopramide						
IM (10 mg)	B	+	+	Infrequent to occasional		Adjunct therapy
PR (20 mg)	B	++	?			
IV (0.1 mg/kg for 1–3 doses to 10 mg)	B	++	++			
Prochlorperazine					Consider IM or IV as adjunct first-line therapy in ED or office; consider PR as adjunct.	
PR (25 mg)	B	+++	+	Occasional		
IM (10 mg)	B	+++	++	Occasional		
IV (10 mg)	B	+++	+++	Frequent		
Other Antiemetics						
Domperidone[e] (30 to 120 mg)	B	?	?	?	?	Possible use for pre-emptive treatment of migraine (i.e., given during prodrome).

[a] United States Headache Consortium Evidence Summary.
? = Not known.
[b] Quality of the evidence: A, Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings. B, Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, either few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group of the recommendation. C, The US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials.
[c] Scientific effect: 0, The drug is ineffective or harmful; +, The effect is either not statistically or not clinically significant (i.e., less than the minimal clinically significant benefit); ++, The effect is statistically significant and exceeds the minimally clinically significant benefit; +++, The effect is statistically significant and far exceeds the minimally clinically significant benefit.
[d] Clinical impression of effect: 0, Most patients do not get relief; +, Few people get complete relief; some get some relief; ++, Some people get complete relief; most get some relief; +++, Most people get complete or nearly complete relief.
[e] Currently not available in the U.S.

In one double-blind, crossover controlled trial, domperidone 20 mg and 30 mg orally plus 1 g paracetamol in repeated doses was found to decrease the duration of migraine attacks compared with placebo plus paracetamol, although there was no statistically significant effect on headache and nausea (50).

In addition, in two placebo-controlled trials, domperidone 30 mg given orally at the start of premonitory symptoms of migraine was better than placebo for the prevention of impending attacks of migraine (3,81).

Therapeutically, domperidone is an alternative for patients who have previously experienced side effects with metoclopramide. It also can be recommended for children under the age of 12, a group especially at risk of developing extrapyramidal side effects after metoclopramide use. The dose in children is 0.2 mg/kg. For adults the oral dose is 10 to 20 mg and 30 to 60 mg by suppository. Our personal experience with the use of domperidone during premonitory symptoms have been rather disappointing.

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Side effects include sedation, acute dystonia (rarely), hyperprolactinemia, and galactorrhea. Contraindications include pheochromocytoma and concomitant treatment with neuroleptics.

Other Antiemetics

Neuroleptics such as chlorpromazine and prochlorperazine have, for many years, been given either by injection or suppository to combat the nausea of migraine, but there is little evidence from controlled clinical trials to substantiate their usefulness. In one small study (42), prochlorperazine 10 mg intravenously was superior to placebo in treating nausea and vomiting. In another trial, chlorpromazine 1 mg/kg intramuscularly was superior to placebo for relief of nausea (52).

Therapeutically, neuroleptics and neuroleptic-type antiemetics can be used in the treatment of severe nausea and vomiting accompanying migraine attacks. The doses of chlorpromazine are 25 mg orally, 50 to 100 mg by suppository, and 25 mg intramuscularly. For prochlorperazine the doses are 10 mg orally, 25 mg by suppository, and 10 mg intramuscular. Thiethylperazine can be given as 10 mg orally, by suppository, and intramuscularly (10). Some of these drugs may have an effect per se on the migraine attack as discussed later in this chapter.

Several histamine H_1-receptor antagonists (e.g., diphenhydramine, cyclizine, and promethazine) are muscarinic receptor antagonists, a property that may add to their antiemetic effect (4,53). The major disadvantage in the use of these drugs is drowsiness. In some countries these drugs (e.g., buclizine) are used as antiemetics in fixed combinations with analgesics.

Therapeutically, for the treatment of nausea and vomiting the dose of diphenhydramine is 25 to 50 mg by all routes of administration. For cyclizine the dose is 50 mg orally or intramuscularly. The dose of promethazine is 12.5 to 25 mg by all routes (10).

Side effects include drowsiness, dizziness, and dry mouth. Contraindications include hypersensitivity, glaucoma, and prostatic hypertrophy.

Neuroleptics

Pharmacologic Background

The phenothiazines are dopamine antagonists with a broad spectrum of pharmacologic activity. They also have varying degrees of activity on the serotonergic, histaminic, adrenergic, and cholinergic neurotransmitter systems, giving them differing efficacy and toxicity profiles (5,28,49). Regarding other actions of phenothiazines, the neuroleptics are believed to exert their powerful antiemetic effects by blocking dopamine receptors in the chemoreceptor trigger zone on the floor of the fourth ventricle. The phenothiazine methotrimeprazine has an analgesic effect (48). The phenothiazines are often strong α-adrenergic antagonists and can induce postural hypotension. This is less prominent with the piperazine phenothiazine prochlorperazine, which is mainly used as an antiemetic. Chlorpromazine as well as methotrimeprazine have sedative effects, whereas this is less prominent with prochlorperazine. The risk for acute extrapyramidal reactions is greatest with prochlorperazine (5).

Results of Clinical Trials With Neuroleptics

A summary of six placebo-controlled randomized clinical trials (14,28,41,42,52,65) with parenteral neuroleptics in the treatment of migraine attacks in emergency departments is given in Table 52-2. In one trial (42) prochlorperazine (10 mg intravenously) was superior to placebo, but both patients with severe migraine and tension-type headaches were included. The efficacy of prochlorperazine (10 mg intravenously) was, however, confirmed in a trial (14) demonstrating its superiority compared with both metoclopramide (10 mg intravenously) and placebo. Intramuscular prochlorperazine (10 mg) was found superior to metoclopramide (10 mg intramuscularly) and placebo (41) regarding decrease in perceived pain. In one study, intravenous prochlorperazine was superior to intravenous magnesium sulphate in the treatment of headaches in an emergency department (31), and in another study in migraine it was superior to intravenous ketorolac (62). Chlorpromazine (1 mg/kg intramuscularly) was not superior to placebo for headache relief, but was better for relief of nausea (52). In one trial intravenous haloperidol (5 mg) was superior to placebo (38). In a randomized, double-blind, placebo-controlled, dose-ranging, multicenter study the efficacy and tolerability of intramuscular droperidol 0.1 mg, 2.75, 5.5, and 8.25 mg was assessed in 305 migraine patients (65). Headache response at 2 hours was better in the treatment groups receiving droperidol at doses of 2.75 mg (87%), 5.5 mg (81%), and 8.25 mg (85%) compared with placebo (57%). In another study intramuscular droperidol was found comparable to intramuscular meperidine (59).

In two trials comparing the efficacy of repeated intravenous chlorpromazine (0.1 mg/kg [46] and 12.5 mg [7] with meperidine [0.4 mg/kg] [46], and dihydroergotamine [1 mg] and lidocaine [50 mg] [7]), chlorpromazine was superior to the comparative drugs. The use of the single-blind design (7) weakens the conclusions to some extent, but the two trials taken together indicate some efficacy of intravenous chlorpromazine for the treatment of migraine attacks.

In one trial comparing methotrimeprazine intramuscularly (37.5 mg) with meperidine (75 mg) in combination with dimenhydrinate (50 mg), the results were quite similar in the two treatment groups (70).

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TABLE 52-2 Placebo-Controlled, Double-Blind Randomized Trials of Neuroleptics for the Treatment of Migraine Attacks

Trial (Ref.)	*Drug*	*Drug Dosage (mg)*	*Study Design*	*Patients Evaluated (N)*	*Results of Trials*
(52)	CPZ PL	1/kg (IM)	Pa	36	Treatment success[a] CPZ (9/19) versus Pl (4/17), NS. Relief of nausea: CPZ (15/17) > Pl (4/14)
(42)[b]	PCPZ	10 (IV)	Pa	82	Complete headache relief: PCPZ (31/42) > Pl (5/40)
(14)	PCPZ Metoc PL	10 (IV) 10 (IV)	Pa	70	Clinical success[c]: PCPZ (82%) > Metoc (46%) = Pl (29%)
(41)	PCPZ Meto PL	10 (IM) 10 (IM)	Pa	86	Changes in median pain score (10 cm VAS scale): (67%) > Metoc (34%) = Pl (16%)
(38)	Halop Pl	5 (IV)	Pa	39	Changes in men pain score (10cmVAS scale): Halop (92%) > Pl (21%)
(65)	Drop Pl	2.75 (IM) 5.5 (IM) 8.5 (IM	Pa	305	87% (2.75 mg) = 81% (5.6 mg) = 85% (8.5 mg) > 57% (PL)

[a]Enough improvement to perform everyday activities and complete relief.
[b]Plus 5 mg dimenhydrinate IV; the trial included both migraine attacks ($n = 41$), tension-type headaches ($n = 18$), and combined migraine–tension headaches ($n = 23$); only 10 of 23 migraine patients had nausea and vomiting.
[c]Patients satisfied and a decrease of more than 50% in pain score on a VAS scale after 30 minutes.
Abbreviations: CPZ, chlorpromazine; Drop, droperidol; Halop, haloperidol; Metoc, metoclopramide; PCPZ, prochlorperazine; Pa, parallel group; Pl, placebo; VAS, visual analogue scale; NS, no significant difference; >, significantly better; IM, intramuscularly; IV, intravenously.

In one double-blind trial in an emergency department, prochlorperazine (25 mg rectally) was superior to placebo in the treatment of migraine attacks (40).

The side effects of neuroleptics are a major concern when given parenterally. Intramuscular chlorpromazine caused more drowsiness (79%) and asymptomatic blood pressure decrease than did placebo (18%) (52); intravenous chlorpromazine in patients pretreated with normal intravenous saline induced either the same incidence of side effects as meperidine (7) or less than dihydroergotamine (46). Methotrimeprazine intramuscularly caused more prolonged drowsiness (52%) than did meperidine (17%) (70). In contrast, intravenous prochlorperazine caused no more side effects than placebo (42), and intramuscular prochlorperazine caused no more side effects than metoclopramide (41). Two thirds of patients treated with haloperidol had side effects, mainly sedation and drowsiness (38). The most frequent adverse events after droperidol were akathisia and asthenia, which occurred in 16 to 32% of patients, depending on dose received and they were rated a severe in 30% of patients who experienced those symptoms (65). No patient had QT prolongation.

In conclusion, there is evidence for prochlorperazine being effective in the treatment of migraine attacks. Based on its being more effective than meperidine, intravenous chlorpromazine probably have some efficacy in migraine attacks. Droperidol is of proven efficacy in migraine.

Therapeutic Use

The phenothiazine neuroleptics have been studied primarily in emergency departments as an alternative to opioids, and to triptans because of their costs (for a summary see Table 52-1).

Prochlorperazine 10 mg intravenously can be given without the need for administering saline and repeated after 30 minutes. The patient should rest for 1 hour. Methotriperazine can be given intramuscularly in doses of 12.5 to 25 mg. Again, there should be at least 1 hour of rest and the patient should be accompanied and advised to remain in bed for 6 hours (70). Given the risk of hypotension, an intravenous line should be established and 500 mL of normal saline should be administered before chlorpromazine. We recommend an initial dose of 10 mg chlorpromazine intravenously, to be repeated if necessary after 30 to 60 minutes. At least 1 hour of bed rest is required after chlorpromazine administration. The most common side effects after parenteral neuroleptics are sedation and postural hypotension (both less with prochlorperazine), and

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extrapyramidal symptoms such as a feeling of restlessness (probably akathisia).

Contraindications include hypersensitivity to the drugs, pregnancy, treatment with neuroleptics, patients with a history of seizures, low blood pressure, postural hypotension, treatment with antihypertensive drugs, and cardiac disease.

Droperidol can be used as a rescue medication in patients who have no history of cardiac disease, have a normal electrocardiogram, and are not on other medications that prolong the QT. Doses are 1.25 to 2.5 mg intramuscular droperidol up to twice daily with a limit of 2 days in any week.

MISCELLANEOUS DRUGS

Isometheptene

Isometheptene, a sympathomimetic amine, is used in combination medications together with dichloralphenazone (in the United States) and acetaminophen. The rationale for this combination is the supposed combined action of a vasoconstrictor, isometheptene, a mild sedative, dichloralphenazone, and a mild analgesic, acetaminophen. However, as described below, there is no evidence from controlled trials that the combination is more effective than isometheptene alone (61).

Pharmacologic Background

Isometheptene is an indirectly acting sympathomimetic that causes vasoconstriction and stimulation of the heart (68). In cats isometheptene caused a decrease in carotid blood flow and vigorously reduced the fraction of carotid blood flow shunted through the arteriovenous anastomoses, similar to the effect reported with ergotamine and dihydroergotamine (68). The pharmacokinetics of isometheptene mucate are not well established.

Results of Controlled Double-Blind Trials With Isometheptene

In two trials, the isometheptene combination (65 mg isometheptene mucate 100 mg, dichloralphenazone 100 mg, and mg paracetamol 325) was found to be superior (61) or marginally superior (19) to placebo. Isometheptene 130 mg was found to be superior to placebo (21) and comparable with the isometheptene combination (61). In one trial, the isometheptene combination was not superior to paracetamol alone (19). In two trials, the isometheptene combination was either found marginally inferior (2) or superior (83) to a combination of ergotamine and caffeine. Side effects, mainly nausea and vomiting, occurred less frequently with the isometheptene combination than with ergotamine in both studies (2,83). In conclusion, these controlled trials demonstrate some efficacy of the isometheptene combination in the treatment of migraine attacks, but the combination has not been shown to be better than isometheptene alone.

Therapeutic Use

Two capsules can be given at onset of attack, followed by 1 capsule every hour if necessary (maximum five capsules in 12 hours). Side effects include dizziness and circulatory disturbances. Contraindications include glaucoma, concomitant treatment with monoamine oxidase inhibitors or within 2 weeks of this treatment, porphyria, severe cases of renal disease, hypertension, organic heart disease, and hepatic disease.

Combinations of Analgesics and Antihistamines

The combination of an analgesic and an antihistamine with antiemetic effects in one tablet is motivated by the desire to simultaneously treat two symptoms of a migraine attack: head pain and nausea and vomiting. The analgesics used have been paracetamol and small doses of codeine (8 to 15 mg) with probably only minor analgesic effects. The histamine H_1-receptor antagonists used are buclizine and doxylamine.

Results of Controlled Trials

Three double-blind, placebo-controlled randomized trials (1,67,78) with the combination of analgesics and antihistamines have been conducted.

In one trial the combination with doxylamine (Mersyndol; paracetamol 450 mg, codeine phosphate 9.75 mg, caffeine 30 mg, and doxylamine 5 mg) was superior to placebo (67). Drowsiness occurred more frequently with Mersyndol (57%) than with placebo (18%).

Two studies (1,78) compared the buclizine combination (Migraleve; paracetamol 500 mg, buclizine 6.25 mg, and codeine 8 mg [1] or 15 mg [78]) with placebo, and in our opinion even the study (1) claiming superiority for Migraleve is questionable given the choice of endpoint variable. In this study the mean duration of attacks was quite similar after Migraleve (8.6 hours) and placebo (9.9 hours) (1). In the other study, there was no evidence of a benefit compared with placebo (67). There is thus no convincing evidence from these trials demonstrating that Migraleve is superior to placebo.

Therapeutic Use

The combination of buclizine and analgesics can be given as two tablets containing 12.5 mg buclizine at the onset of a migraine attack, followed by two tablets without buclizine

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but the other components every 4 hours if necessary, to a maximum of six extra tablets.

Side effects include drowsiness, fatigue, and dry mouth. Contraindications include hypersensitivity to drugs, glaucoma, and driving a car or operating dangerous instruments.

Dextropropoxyphene Combinations

Dextropropoxyphene has been evaluated in the acute treatment of migraine with drug combinations consisting of dextropropoxyphene chloride (65 mg), acetyl salicylic acid (350 mg), and phenazone (150 mg) (35) or these drugs plus phentiazin carboxyl chloride (5 mg) and caffeine (50 mg) (34). Dextropropoxyphene produces analgesic and other central nervous system effects by binding primarily to μ-opioid receptors (58). Combinations of dextropropoxyphene and aspirin afford a higher level of analgesia than does either agent alone (6).

In two randomized, double-blind crossover trials (34,35) the drugs were taken at the onset of attacks, and the main efficacy parameter was prevention of an attack. The dextropropoxyphene combination was comparable with ergotamine and both were superior to aspirin (34,35).

These two trials demonstrate some efficacy of the dextropropoxyphene combination with aspirin and phenazone in the treatment of migraine attacks (for contraindications and side effects, see, e.g., Reisine and Pasternak [58]).

Morphinomimetics

Despite evidence of poor efficacy and a high addiction potential, meperidine and other opioid analgesics remain in common use as abortive migraine drugs, particularly in the emergency department. Butorphanol nasal spray has been introduced for self-treatment of migraine attacks.

In a double-blind trial, meperidine with dimenhydrinate given intravenously was found inferior to chlorpromazine intravenously (46), and in another double-blind trial where this combination was given intramuscularly, it was comparable with methotrimeperazine (70). The NSAID ketorolac 30 mg intramuscularly was found to be less effective than meperidine 75 mg (47), whereas a dose of 60 mg ketorolac intramuscularly was as effective as 75 mg meperidine (plus 25 mg promethazine) (18), and 100 mg meperidine (plus 50 mg hydroxyzine) (24). In one double-blind trial, 1 mg dihydroergotamine intramuscularly was found to have similar effect as meperidine (1.5 mg/kg intramuscularly), both combined with the antinauseant hydroxyzine (13). All these trials with meperidine lacked placebo controls, precluding a real judgment of the effect of meperidine in migraine attacks.

The available clinical studies fail to support firmly the usefulness of parenteral opioids in the treatment of migraine headache, and with the current alternatives their use is limited.

Transnasal butorphanol, a synthetic opioid agonist (κ-opioid receptor) antagonist (μ-opioid receptor) analgesic, has been introduced as a noninvasive presentation of an analgesic for moderate to severe pain (30). There is no pharmacokinetic interaction between intranasal butorphanol and sumatriptan (69). In a double-blind trial in migraine and a few cluster headache patients in an emergency department, 2 mg and 3 mg butorphanol intramuscularly produced more pain relief than 1 mg butorphanol (26).

Transnasal butorphanol 1 mg in repeated doses has been compared with placebo in two double-blind trials. In the first trial, butorphanol 1 mg followed by 1 mg 1 hour later, was more effective than placebo (20). Butorphanol was also superior to methadone 10 mg intramuscularly at some, but not all, time points (20). In another trial, migraine patients could use up to 12 sprays of either butorphanol or placebo over 24 hours (37). From half an hour up to 40 hours, butorphanol was significantly better than placebo ($P < .01$). The adverse events, drowsiness (29% versus 0%) and dizziness (58% versus 4%) were often intense; and 26% of butorphanol-treated patients chose not to repeat use of the drug for the remainder of the headache because of side effects. In addition, 7% of butorphanol-treated patients experienced euphoria versus none on placebo; and a few patients described strong psychotropic effects such as an out-of-body sensation. Fifty-seven percent of patients rated the drug as poor.

In a comparative double-blind trial, the combination of the oral drug Fiorinal with codeine (butalbital 50 mg, caffeine 50 mg, aspirin 325 mg, and codeine phosphate 30 mg) was found inferior to intranasal butorphanol 1 mg plus an optional 1 mg for treating migraine pain (32). In contrast, more patients rated Fiorinal with codeine (46%) than butorphanol (27%) as good to excellent, most likely because there were more adverse events with butorphanol (78%) than with Fiorinal with codeine (31%). In conclusion, these trials with transnasal butorphanol demonstrated a rapid onset of action, but its use is hampered by many adverse events, probably leading to the low rating of the drug by the patients in the controlled trials (32,37). Furthermore, the addiction potential of the drug is not sufficiently elucidated (27), and may be a problem according to the unpublished experiences of many headache experts. The use of transnasal butorphanol in migraine must therefore be regarded as controversial. Transnasal butorphanol should only be used as a last resort in patients failing to respond to several other acute migraine treatments. Its use should probably be restricted to a maximum of eight doses per month.

Analgesic medications are commonly used by migraineurs who are unable to tolerate triptans or for whom triptans are contraindicated. In a multicenter

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study the combination of 37.5 mg tramadol and 325 mg acetaminophen was found superior to placebo (64). The most common treatment- related side effects in the tramadol/acetaminophen group were nausea (13%) and dizziness (10%).

Other Drugs

Intranasal lidocaine administered as a 4% solution was found superior to placebo in the treatment of migraine attacks in one double-blind controlled trial (51). Within 15 minutes, 29 of 53 lidocaine-treated patients had a more than 50% reduction in headache. Relapse of headache occurred in 42% of patients responding to lidocaine, usually within the first hour after treatment. Intranasal lidocaine can thus be tried when a quick effect is needed, but probably only in a minority of attacks will a sustained effect result. Repeated dosing may be needed.

In one trial 1 g magnesium sulphate was superior to placebo in migraine with aura but not in migraine without aura (8). In another study 2 g magnesium sulphate intravenously was not effective as an adjunctive medication to intravenous metoclopramide (15).

In open clinical studies, corticosteroids have mainly been used in the treatment of status migrainosus, a migraine attack lasting more than 72 hours (see Chapter 66). Based on the anecdotal evidence, corticosteroids, particularly dexamethasone 12 to 20 mg intravenously, can be used in the treatment of status migrainosus. A repeated parenteral dose, or its oral equivalent, may be necessary in 8 to 12 hours, but treatment beyond 24 hours is not generally recommended (25). If corticosteroids have not terminated status migrainosus within 24 hours, they are unlikely to do so later (25).

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