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Chapter 49

Nonsteroidal Anti-Inflammatory Drugs in the Acute Treatment of Migraines

Peer Tfelt-Hansen and Paul Rolan

Given the widespread availability of analgesic/nonsteroidal anti-inflammatory drugs (NSAIDs) without prescription, it is likely that by the time most migraine patients consult a physician they have tried at least one of these drugs. This makes them probably the most widely used class of drugs for the acute treatment of headache and migraine, and also the class with the largest number of individual drugs. Whereas aspirin has been used for the treatment of migraine and other headaches for many years, the newer NSAIDs were introduced in migraine therapy based mainly on indirect evidence of the involvement of prostaglandins in the pathophysiology of the migraine process. However, subsequent controlled trials have demonstrated the efficacy of the NSAIDs in migraine therapy.

PHARMACOLOGIC BACKGROUND

NSAIDs possess anti-inflammatory, analgesic, and antipyretic properties. The principal types of drugs are listed in Table 49-1. Acetaminophen is included in this list despite its relative lack of anti-inflammatory activity because its action is thought otherwise to share a common central mechanism with other drugs of this class (38). They exert their effect by blocking cyclooxygenase (COX), thereby inhibiting the synthesis of prostaglandins from arachidonic acid (Fig. 49-1), but they have little or no effect on lipoxygenase and therefore no effect on the formation of leukotrienes. Both prostaglandins and leukotrienes are involved in the inflammatory process (38). Recently, it has been found that there are two forms of COX, COX-1 and COX-2. The conventional NSAIDs are generally nonselective inhibitors of both enzymes. COX-1 is widely distributed and is involved in homeostatic mechanisms. In contrast, the expression of COX-2 is markedly increased in areas of inflammation. There has been a recent flurry of development of selective COX-2 inhibitors on the hypothesis that these drugs will be as effective as the nonselective inhibitors but may be safer, and is discussed in this chapter.

Prostaglandins are associated with the development of pain that accompanies injury or inflammation. The NSAIDs, which inhibit the synthesis of these prostaglandins, are usually classed as mild peripheral analgesics, and a consideration of the type of pain that they suppress is important. They are particularly effective in settings in which inflammation has caused sensitization of pain receptors to normally pain-free mechanical or chemical stimuli. This sensitization appears to result from a lowering of the threshold of the polymodal nociceptor situated on C fibers (38). Although generally described as peripherally acting analgesics, an additional inhibitory effect on the central nociceptive system also may be responsible for their analgesic effect (6,7,47). The mode of action of the central effect of NSAIDs is unknown, but possible relevant effects include the following (6,10):

1. inhibition by NSAIDs of prostaglandin synthesis in brain neurons;
2. prolongation of catecholamine and serotonin turnover in brain neurons; and
3. blockade of the release of serotonin in response to noxious stimuli.

NSAIDs also inhibit platelet COX with consequent inhibition of the formation of thromboxane A_2, a potent aggregating agent. The NSAID can either bind reversibly to this enzyme or, as in the case of aspirin, for the life of the platelet from acetylation (8 to 11 days) (38). This effect on platelets can sometimes result in a prolonged bleeding time.

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TABLE 49-1 NSAIDs Evaluated as Acute Migraine Treatments

Analgesic with little anti-inflammatory activity
Acetaminophen
Nonselective COX inhibitors
Aspirin[a,c]
Diclofenac[a]
Ibuprofen[a]
Ketoprofen[c,d]
Pirprofen[a]
Flurbiprofen[d]
Naproxen[a,e]
Tolfenamic acid[a,e]
Mefenamic acid[c]
Ketorolac[b]
Selective COX-2 inhibitor
Rofecoxib[d]

[a]With demonstrated efficacy in the treatment of migraine attacks (at least two trials demonstrating efficacy).
[b]Only compared with other injections without placebo control.
[c]With possible efficacy in migraine prophylaxis (only one "positive" trial); (see Chapter 58).
[d]With possible effect in migraine attacks (only one "positive" trial).
[e]With demonstrated efficacy in the prophylaxis of migraine (at least two trials demonstrating efficacy).

Possible Mode of Action in Migraine

A role for prostaglandins in migraine genesis was examined by infusion of the two vasodilating prostaglandins prostaglandin E_1 (4,9) and prostacyclin (25,64) to either healthy volunteers or migraine sufferers. Although the infusions induced flushing and a vascular headache, the headache resembled migrainous symptoms in only a few patients (64). Furthermore, intravenous infusion of prostacyclin to eight migraine patients induced only one migraine-like headache, and in two subjects given the infusion after a migraine attack had started, only a short-lived worsening occurred, suggesting that vasodilating prostaglandins were not the sole mediators of vascular headache in these patients (64). Another possible mechanism for the efficacy of NSAIDs in migraine prophylaxis is based on their effect in opposing the suggested hyperaggregability of platelets in migraine. However, neither mechanism is currently thought to be central in migraine genesis, and their efficacy may be a result of inhibition on the sterile inflammatory process caused by neurogenic vascular inflammation (8; see Chapter 33). However, the relatively poor efficacy of indomethacin in migraine (68) might be taken as evidence against this possibility. Another possible explanation for the beneficial effects of aspirin and NSAIDs in the treatment of migraine attacks is their analgesic effect or more specific effects on the trigeminal (44) and antinociceptive (28) systems in the brainstem and thalamus (40).

Pharmacokinetics, Route of Administration, and Role of Formulation

In the treatment of migraine attacks the important pharmacokinetic consideration is the speed of absorption. NSAIDs are generally well-absorbed after oral administration with a time-to-peak plasma concentration (t_{max}) of less than 2 hours (38). However, gastric stasis in migraine has been shown to slow the rate of drug absorption (81). Some NSAIDs have been reformulated as more soluble salts to speed absorption (e.g., lysine aspirin salt, diclofenac-K, naproxen sodium) or as encapsulated liquid preparations (e.g., ibuprofen liquigels, diclofenac softgel). An alternative strategy is to use a prokinetic/antiemetic drug such as metoclopramide (see Chapter 52). Unfortunately, there are few data available that directly compare the pharmacokinetics of these new formulations with conventional formulations during a migraine attack, probably because of the difficulty in undertaking such studies. Thus, the majority of such information comes from healthy volunteers. Nevertheless, it seems appropriate to choose the most rapidly absorbed formulation of each active ingredient. Aspirin is absorbed very quickly, with a t_{max} of less

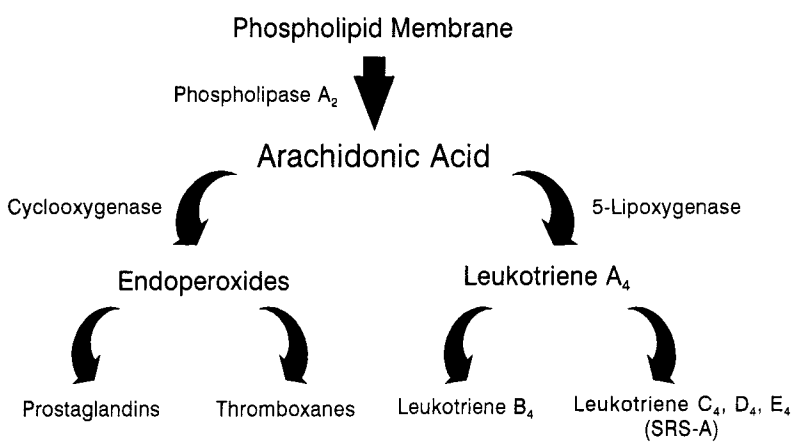

FIGURE 49-1. Principal metabolic pathways of arachidonic acid. NSAIDs block COX, thereby inhibiting the synthesis of prostaglandins from arachidonic acid, but have little or no effect on lipoxygenase and therefore no effect on the formation of leukotrienes (31).

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than half an hour, and is metabolized quickly to salicylic acid (38,70). Naproxen sodium has a t_{max} of 1 hour, and naproxen has a t_{max} of 2 hours (38,59).

For patients with early vomiting during the attack or prominent nausea, a nonoral route many be preferable. A suppository formulation is available for diclofenac. Ketorolac is given intravenously or as an intramuscular injection with a t_{max} of 45 to 60 minutes (27).

RESULTS OF RANDOMIZED CONTROLLED CLINICAL TRIALS

Placebo-Controlled Trials

A summary of 38 placebo-controlled double-blind randomized trials on the efficacy of NSAIDs or their combinations with either metoclopramide or caffeine in the treatment of migraine attacks are given in Table 49-2. The size of the trials varied from a small crossover trial with only 20 patients to several trials with parallel group design with more than 100 evaluable patients in each treatment group with the bulk of the later trials being larger and apparently adequately powered. Except for five trials (37,41,51,55,77), in which only migraine patients without aura were included, the trials included a mixture of patients suffering from migraine both with and without aura. The crossover design, which causes few problems in trials concerning treatment of the acute attacks, was used in 24 of 38 trials. As indicated in Table 49-1, NSAIDs have been found to have some efficacy in the acute therapy of migraine.

Aspirin, 500 to 1000 mg, was superior to placebo in 13 trials, 1 of which evaluated the intravenous route (20). Aspirin plus metoclopramide was not superior to aspirin in one trial (77) despite improved absorption of aspirin with metoclopramide in migraine having been demonstrated (81). Highly soluble aspirin salts (equivalent to 900 mg) combined with 10 mg metoclopramide were superior to placebo in five trials (11,37,49,54,76) and in one trial were comparable with 100 mg sumatriptan (76). Intravenous aspirin was less effective but better tolerated than subcutaneous sumatriptan (20). For a combination of 600 mg aspirin plus 400 mg acetaminophen and 200 mg caffeine, a therapeutic gain of 26% (95% confidence interval [CI] 21 to 31%) was found in three trials (53), but it should be noted that patients with the most severe migraine attacks were excluded from these trials.

Acetaminophen combined with metoclopramide was superior to placebo in one trial (17), whereas 650 mg acetaminophen alone was no better than placebo (18). A combination of 400 mg acetaminophen and 25 mg codeine was found to be superior to placebo (5).

Tolfenamic acid 200 mg was shown in three trials to be more effective than placebo (34,60,79), and in one of these (60), a rapid-release form was comparable with 100 mg sumatriptan. In a larger trial sumatriptan 100 mg was superior to rapid-release tolfenamic acid (Tfelt-Hansen, personal communication). In one of the other trials (34), tolfenamic acid was comparable with 500 mg aspirin and 1 mg ergotamine, with fewer side effects than ergotamine. In a small crossover trial ($n = 10$) (32), the addition of caffeine to tolfenamic acid was found to be superior to the addition of pyridoxine to tolfenamic acid, but in a larger double-blind crossover trial ($n = 49$), the effect of the addition of caffeine to tolfenamic acid was not superior to that of tolfenamic acid alone (79). In contrast, the addition of metoclopramide to tolfenamic acid was significantly, if marginally, better than tolfenamic acid alone (79).

Naproxen was shown to be superior to placebo in one trial (61), whereas in another similar trial the effect of naproxen was only superior to placebo after 2 hours, but not for the whole attack (2). Naproxen sodium, which, because of quicker absorption of the naproxen molecule, should be more suitable than naproxen per se (see Pharmacokinetics section), was superior to placebo in one trial (39).

Ibuprofen 800 to 1,200 mg or 400 mg as an arginine salt was more effective than placebo in three trials (36,47,71). Lower doses as a liquigel formulation (200 to 600 mg) were also found to be effective (45), as were 200 and 400 mg of a conventional formulation (13). In both low-dose trials, there was a trend for 200 mg to be less effective by a small margin. In one trial in children, ibuprofen and acetaminophen were comparable, and both were superior to placebo (35). In another, 7.5 mg/kg was found to effective, but only in boys (52).

Diclofenac as an enteric-coated tablet of 50 mg was found to be of marginal efficacy (55). The more rapidly absorbed potassium salt was evaluated in several trials (12,14,24,57,) as well as a sodium salt softgel formulation (66). Both tested doses of 50 and 100 mg were superior to placebo. In one placebo-controlled trial, diclofenac-K was superior to caffeine and ergotamine tartrate (Cafergot) (12) and placebo; whereas in another trial diclofenac and Cafergot were equally effective (57). There appeared to be no increase in efficacy with 50 mg compared to 100 mg (14,24), but caffeine 100 mg enhanced the efficacy of the diclofenac sodium softgel 100 mg (66). Sumatriptan 100 mg orally was of similar efficacy to diclofenac sodium softgel 100 mg but was associated with more adverse effects (66). Intramuscular diclofenac (16) was superior to placebo, and although not directly compared with an oral formulation, appeared to give better efficacy (16).

Pirprofen was comparable with an ergotamine combination in one trial, and both were superior to placebo (46). In a trial including episodic tension-type headache, the results for migraine treated with rectal pirprofen were superior to those for placebo (30). Flurbiprofen was superior to placebo in one trial (3). Ketoprofen 75 and 150 mg were compared with 2.5 mg of oral zolmitriptan and

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TABLE 49-2 Double-Blind Randomized, Placebo-Controlled, Trial With NSAIDs or Combinations Containing NSAIDs in the Treatment of Migraine Attacks

Trial (Ref)	*Drug, Dosage Initial (Maximum) (mg)*	*Study Design*	*No of Attacks Treated*	*No of Patients Evaluated*[a]	*Result of Trial*
Tfelt-Hansen and Olesen (77)	ASA 650 + Metocl 10 ASA 650 Pl	CO	1	85	Escape medication: Metocl + ASA (63/92) = ASA (51/86) > Pl (75/95 Effect on pain: Metocl +ASA = ASA > Pl
Hakkarainen et al. (34)	Tfa 200 Erg 1 ASA 500 Pl	CO	2	20	Mean duration of attacks (h): Tfa (3.2) = Erg (3.8) = ASA (4.2) > Pl (7.1). Preference: all drugs > Pl
Boureau et al. (5)	ASA 1000 Parac 400 +Cod 25 Pl	Co	1	198	Success rate[b]: ASA (52%) = Parac +CA (50%) > Pl (30%)
Chabriat et al. (11)	ASA 900 Metocl 10 Pl	Pa	2 2	111 114	Success rates[b]: ASA +Metoc (59%) > Pl (29%)
Tfelt-Hansen et al. (76)	ASA 900 +Metocl SUM 100 Pl	Pa	2 2 2	133 119 124	Success rates[b]: ASA +Metocl (56%) = Sum (53%) > Pl
Henry et al. (37)	ASA900 Metocl 10 Pl	Pa	1	127 131	Success rates[b]: ASA +Metoc (54%) > Pl (26%)
Lipton et al. (53)	ASA 600 +Parac 400 +Ca 200 Pl	Pa	1	602 618	Success rates[b]: ASA +Parac +Ca (59%) > Pl (33%)
Lange et al. (49)	ASA 1000 Pl	Pa	1	343	2h response[b] ASA (55%) > Pl (37%) 2h pain free ASA (29%) > Pl (17%)
MacGregor et al. (54)	ASA 900 Pl	CO	2	101	2h response[b] ASA (48%) > Pl (19%) 2h pain free ASA (14%) vs Pl (5%) NS 3h painfree ASA (18%) > Pl (5%)
Diener et al. (21)	ASA 1,000 Sum 50 Pl	Pa	1	433	2h response ASA[b] (49%) = Sum (49%) > Pl (33%) 2 h pain free ASA (25%) = Sum (24%) > Pl 15%
Diener et al. (78)	ASA 1,000 Sum 50 Ibupr 400 Pl	CO	1	312	2h response[b] ASA (53%) = Sum (56%) = Ibupr (60%) > Pl 31%) 2 h pain free ASA (27%) < Sum (37%)
Diener et al. (20)	ASA 1000 IV Sum 6 SC Pl	Pa	1	275	2h response[b] Sum (91%) > ASA (74%) > Pl (24%) 2h pain free Sum (76%) > ASA (44%) > Pl (14%) AEs Sum (13%) > ASA (3%) = Pl (2%)
Dexter et al. (17)	Parac 1000 (3000) +Metocl 10 (30) Pl	Pa	>4	42	Duration of attacks and amount of rescue medication: Parac +Metoc > Pl. Severity: Parac + Metoc vs Pl NS
Diamond (18)	Parac[c] 650 (1,625) Pl	CO	2	56	Relief ranking: Parac = Pl
Tokola et al. (79)[d]	Tfa 200 (400) Pl	CO	2	43–48	Duration of attacks (h): Tfa (5.6) > Pl (7.5)
Mathew (56)	TfaR 200 (400) Sum 100 Pl	Pa	2	43 42 41	Success rates[b]: TfaR (77%) = Sum (79%) > Pl (29%) for the first attack treated
Nestvold et al. (61)	Napx 750 (1250) Pl	CO	6	32	Headache severity[e]: Napx (2.1) > Pl (2.3) Napx > Pl for overall rating. Escape medication: Napx (24%) > Pl (46%)

(*continued*)

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TABLE 49-2 Double-Blind Randomized, Placebo-Controlled, Trial With NSAIDs or Combinations Containing NSAIDs in the Treatment of Migraine Attacks (Continued)

Trial (Ref)	*Drug, Dosage Initial (Maximum) (mg)*	*Study Design*	*No of Attacks Treated*	*No of Patients Evaluated*[a]	*Result of Trial*
Andersson et al. (2)	Napx 750 (1250) Pl	CO	6	32	Headache severity after 2h[e]: Napx (2.0) > Pl (2.2). Headache severity[e] for whole attack: Napx (2.2) vs. Pl (2.2) NS
Johnson et al. (39)	NapxS 825 (1375) Pl	Pa	10	61	Change in headache severity[f]: NapxS (3.8) > Pl (5.0) Escape medication: NapxS (44%) < Pl (67%)
Dib et al. (19)	Ketopr 75 Ketopr 150 Zol 2.5 Pl	CO	4	235	2h response Zol (67%) = Ketopr 150 (62%) = Ketopr 75 (63%) > Pl
Kangasneimi and Kaaja (41)	Ketopr 100 rectally Erg 2 rectally Pl	CO	6	50	Median change in pain on VAS scale: Ketopr (15%) > Pl (7%), Ketop (15%) = Erg (12%) Working ability: Ketop > Erg = Pl
Havanka-Kanniainen (36)	Ibupr 800 (1200) Pl	CO	5	27	Duration of attacks: Ibupr (5 h) < Pl (11 h). Mild attacks: Ibupr (33%) > Pl (7%)
Kloster et al. (47)	Ibupr 1200 (1600) Pl	CO	3	25	Headache severity[e] Ibupr (1.78) < Pl (2.33) Migraine index[g]: Ibupr (25) < Pl (46)
Sandrini et al. (71)	IbuprA 400 Pl	CO	1	29	IbuprA > Pl for pain reduction
Kellstein et al. (45)	Ibupr 200 liquigel Ibupr 400 liquigel Ibupr 600 liquigel Pl	Pa	1	735	2h response All doses (64–72%) > Pl (50%) 2h pain free All doses (25–29%) > Pl (13%)
Lewis et al. (52)	Ibupr 7.5 / kg (children) Pl	Pa	1	84	2h response Ibupr (76%) > Pl (53%) All response was seen in boys; girls no treatment effect
Hamalainen et al. (35)	Ibupr 10/kg (children) Parac 15/kg Pl	CO	1	88	Reduction in headache severity: Ibupr = Acet > Pl
Codispoti et al. (13)	Ibupr 200 Ibupr 400 Pl	Pa	1	460	2h pain free Ibupr 400 (41%) = Ibupr 200 (42%) . Pl (28%)
Del Bene et al. (16)	Diclo 75 IM Pl	CO	3	32	Response to treatment[h]: Diclo (3.4) > Pl (1.7) Preference: Diclo (21) > Pl (1).
Massiou et al. (55)	Diclo 50 (100) Pl	CO	2	91	Attack aborted within 2 h: Diclo (27%) > Pl (19%) Escape medication: Diclo (54%) < Pl (66%)
Edson (24)	DicloK 50 DicloK 100 Sum 100 Pl	CO	4	115	2h VAS All actives > Pl AEs Sum > DicloK = Pl
Peroutka et al. (66)	DicloNa softgel 100 DicloNa softgel 100 + Caf 100 Pl	CO	3	51	1h response Diclo + Caf (41%) > Diclo (27%) vs Pl (14%) NS
Dahlof et al. (14)	DicloK 50 DicloK 100	CO	3	73	2h VAS Diclo 100 = Diclo 50 > Pl
Cortelli et al. (12)	DicloK Erg + Caf Pl	CO	3	63	VAS Diclo > Erg + Caf = Pl

(*continued*)

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TABLE 49-2 Double-Blind Randomized, Placebo-Controlled, Trial With NSAIDs or Combinations Containing NSAIDs in the Treatment of Migraine Attacks (Continued)

Trial (Ref)	*Drug, Dosage Initial (Maximum) (mg)*	*Study Design*	*No of Attacks Treated*	*No of Patients Evaluated*[a]	*Result of Trial*
Kinnunen et al. (46)	Pirp 200 (500) Erg[f] 2 (5) Pl	CO	1	55	Escape medication: Pirp (18/58) = Erg (18/59) > Pl (32/60) Duration of attacks (h): Erg (6.5) > Pl (10.5) but vs Pirp NS For most parameters Pirp vs. Erg Ns
Guidotti et al. (30)	Pirp 600 rectally Pl	CO	2	20	Escape medication: Pirp (58%) < Pl (98%)
Awidi (3)	Flurbp 100 (300) Pl	CO	2	19	Relief score[j]: Flurbp (3.2) > Pl (0.7)
Silberstein et al. (75)	Rof 25 Rof 50 Pl	Pa	1	557	2h response[b] Rof 50 (57%) = Rof 25 (54%) > Pl (34%) AEs Rof 50 (40%); Rof 25 (27%); Pl (23%)

[a]Maximum number of attacks treated with each drug (in some trials the trial was terminated at a fixed date).
[b]A success defined as a decrease in headache from severe or moderate to none or mild.
[c]Only results for acetaminophen and placebo given, see (18).
[d]A complicated study comparing Tfa, caffeine, metoclopramide, and their combinations with placebo (62). Only the comparison with placebo is shown here.
[e]Severity on a 4-point verbal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).
[f]Score: 2 = complete relief, 3 = substantial relief, 4 = slight relief, 5 = no change, 6 = worse.
[g]Severity times duration in hours.
[h]Response scale: 4 (excellent) to 1 (insufficient).
[i]An ergotamine combination with 1 mg ergotamine tartrate, 100 mg caffeine, 50 mg butalbital, and 0.125 mg bellafoline.
[j]Relief score: 4 (very good relief) to 0 (no relief).
Abbreviations: AEs, adverse effects; ASA, aspirin; Ca, caffeine; Cod, codeine; Diclo, diclofenac; DicloK, diclofenac potassium; Erg, ergotamine; Flurb, flurbiprofen; Ibupr, ibuprofen; IbuprA, ibuprofen-arginine; Ketopr, ketoprofen; Metocl, metoclopramide; Napx, naproxen; NapxS, naproxen sodium; Acet, acetaminophen; Pirp, pirprofen; Rof, rofecoxib; Sum, sumatriptan; Tfa, tolfenamic acid; TfaR, rapid release tolfenamic acid; Pl, placebo; CO, Crossover; Pa, Parallel group; NS or =, no statistical significant difference; SC, subcutaneous; VAS, visual analogue scale; IM, intramuscularly; IV, intravenously; Zol, zolmitriptan.

placebo in a crossover trial (19). Zolmitriptan had a slightly higher response than either dose of ketoprofen, which were identical in response; all active treatments were superior to placebo. Ketoprofen by suppository was superior to placebo and superior to ergotamine for working capacity in one trial (41).

The COX-2 inhibitor rofecoxib at doses of 25 and 50 mg was compared with placebo in a large parallel-groups trial (75). There was a slight trend for higher efficacy with the higher dose (2 hour response rate 57 versus 54%), with both being clearly superior to placebo (34%). However, there was a clear dose–response relationship with regard to adverse effects, namely, a 40% incidence with the higher dose compared to 27% at the lower dose and 23% with placebo.

Comparative Trials Without Placebo Control

In two trials, aspirin taken at the onset of an attack was inferior to ergotamine and a dextropropoxyphene compound in preventing migraine attacks (31,33) (see Table 49-2 and Chapter 50). In one trial the success rate of the combination of 1,000 mg aspirin and 10 mg metoclopramide (45%) was not significantly different from 100 mg sumatriptan (56%) for the primary efficacy parameter—effect on head pain in the first attack—but inferior to sumatriptan for all other parameters (62). Similarly, aspirin 900 mg plus metoclopramide 10 mg was slightly less effective than 2.5 mg oral zolmitriptan (26).

Tolfenamic acid was superior to acetaminophen in a reasonably large crossover trial with 58 evaluable patients (51), but there was no difference between the efficacy of 200 and 400 mg of tolfenamic acid.

In one trial, naproxen sodium was found to be superior to an ergotamine combination for some parameters (69), but in other studies naproxen sodium was found to be equally effective as ergotamine (80) or ergotamine plus caffeine (72).

Ibuprofen was superior to acetaminophen in one trial (63), and intramuscular diclofenac was superior to intramuscular acetaminophen in one trial (42), whereas mefenamic acid was not superior to acetaminophen when each was combined with metoclopramide (65).

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Ketorolac 30 mg intramuscularly was found to be less effective than 75 mg meperidine (50), whereas a dose of 60 mg ketorolac was as effective as 75 mg meperidine (plus 25 mg promethazine) (15), 100 mg meperidine (plus 50 mg hydroxyzine) (23), and 25 mg chlorpromazine intravenously (74) in rather small ($n = 30$ to 47) randomized trials in emergency departments. In one trial ($n = 64$), 30 mg intravenous ketorolac was inferior to 10 mg intravenous prochlorperazine (73). Ketorolac 30 mg IV ketorolac was superior to 20 mg nasal sumatriptan, in one trial ($n = 29$) (58). There have been no placebo-controlled trials with ketorolac (27). Ketoprofen 100 mg intramuscularly was superior to an injection of 500 mg acetaminophen (43).

In an open randomized study, rofecoxib plus rizatriptan was superior to tolfenamic acid plus rizatriptan and rizatriptan alone (48). A combination drug Fiorinal with codeine (butalbital 50 mg, caffeine 50 mg, aspirin 325 mg, and codeine phosphate 30 mg) was found to be inferior to intranasal butorphanol 1 mg for treating migraine pain during the first 2 hours (29) (see Chapter 52). In one open, randomized study the fixed rectal combination of indomethacin, prochlorperazine, and caffeine was superior to rectal sumatriptan (22).

Overall Efficacy Interpretation

Although some early trials were small, many of the later trials were large and well powered. With the substantial body of evidence, it is clear that NSAIDs are effective as acute migraine treatments although the beneficial effects often seem marginal in some trials. Despite the trials in children being few and small, the drugs tested appear to be effective although the high placebo response in girls makes interpretation difficult. Few active agents among the class have been compared directly, perhaps because of a low expectation of finding a difference; response rates appear similar for all drugs. However, despite the number of trials, there are still many questions. When a dose–response relationship has been sought, there have been no differences between doses, despite a dose-related increase in adverse effects. This suggests that a low dose should initially be chosen, although in clinical practice the highest dose a patient can tolerate may be suggested. There is no evidence whether it is worth trying another NSAID after failure of one; few trials comment on previous experience with NSAIDs as a determinant of outcome.

Adverse Effects

Side effects after NSAIDs in all of the trials were minor and mostly referable to the gastrointestinal tract, such as epigastric pain. One major argument for the original introduction of NSAIDs in migraine treatment has been the high incidence of the side effects of the then standard drug ergotamine (34,69). In several trials with NSAIDs (34,41,46,69,72,80), ergotamine has been the reference drug, and generally the NSAIDs were comparable with oral ergotamine with regard to efficacy. The differences have been mainly those of tolerability: on the whole, ergotamine caused more gastrointestinal side effects such as nausea and vomiting, although this was only statistically significant in two trials (34,69). When triptans and NSAIDs have been compared directly, there is a trend for adverse effects to be higher with the triptans (20,76).

THERAPEUTIC USE

Aspirin and acetaminophen are the most frequently used drugs for the treatment of migraine, and many patients have already tried them before consulting a physician. For those for whom self-medication has proved ineffective, one can endeavor to optimize aspirin or acetaminophen treatment by giving the drugs in effervescent form in combination with metoclopramide 10 mg orally or highly soluble aspirin salts plus metoclopramide, if available. One should also maximize the dose and ensure that medication is taken at the onset of the first symptoms. If the patient does not respond to this, then either other NSAIDs plus metoclopramide, triptans, or ergotamine should be tried (see Chapter 53). However, no controlled trial has shown another NSAID to be superior to aspirin in the treatment of migraine attacks and so an agent with different pharmacology seems logical, but clearly patient profile and preference should be considered. NSAIDs may be the acute treatments of choice in patients who cannot receive ergotamine or triptans because of cardiovascular disease or who are intolerant of them. Although the COX-2 inhibitors cause

TABLE 49-3 Recommended Dose of NSAIDs in the Treatment of Migraine Attacks

Drug	*Initial Dose (mg)*	*Repeated Dose if Necessary After 1–2 hours[a] (mg)*
Aspirin	900 or 1,000	900 or 1,000
Aspirin +metoclopramide	900 +10	900 +10
Acetaminophen	1,000	1,000
Tolfenamic acid	200	200
Naproxen sodium	825	550
Piprofen	200	200
Ibuprofen	400–1,200	400
Ketoprofen by suppository	100	
Diclofenac intramuscularly	75	
Diclofenac K	50–100	50
Flurbiprofen	100	
Mefenamic acid	500	

[a]There are no trials demonstrating that repeated dosing increases the effectiveness of NSAIDs.

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less gastrointestinal toxicity than nonselective drugs, this is only likely to be a factor in patients requiring frequent dosing or who are at higher risk of such complications. NSAIDs can be used during the drug withdrawal period in patients with a history of ergotamine abuse (1,56) and probably also after triptan abuse. In the emergency room intramuscular diclofenac or ketorolac may be useful.

The recommended doses of the NSAIDs are given in Table 49-3. Side effects include epigastric pain and diarrhea. Contraindications include hypersensitivity to aspirin or any NSAID, peptic ulcer, and concomitant treatment with anticoagulants (except the COX-2 inhibitors where use under caution is possible).

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