Chapter 83

Acute Pharmacotherapy of Tension-Type Headaches

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This chapter discusses the treatment of individual attacks of headache in patients with episodic and chronic tension-type headache. Most headache episodes in these patients are mild to moderate. Patients with mild tension-type headache rarely consult the physician and can self-manage by using simple analgesics. These patients may consult a physician when the frequency, severity, and duration of the headache increase. Often, such worsening of headache is associated with stress, anxiety, and depression and may be accompanied by pericranial muscle tenderness and spasm. These factors operate in a vicious cycle, and the physician's task is to break this cycle.

METHODOLOGIC CONSIDERATIONS IN CLINICAL STUDIES IN THE ACUTE TREATMENT OF TENSION-TYPE HEADACHE

Several parameters, including visual analog scales (VAS), verbal rating scales (VRS), and global ratings, have been studied to assess the pain relief effected by analgesics (11,22,25,51,52). Global rating was reported to be a sensitive parameter, and this finding was confirmed (10,28). Global rating takes into account overall patient acceptability, including taste, ease of use, side effects, and similar factors, in addition to assessing pain relief. Patient's preference after the intake of two or more different drugs has been a less satisfactory method, because the results depend on the patient's memory of the degree of effectiveness of a previous medication as well as personal biases about taste and color (23). A strong correlation was found between visual analog pain scales, a verbal pain scale, and verbal pain relief scale (30). A combination of scales that includes global rating gives more reliable assessment of pain relief.

Guidelines for trials of drug treatments for tension-type headache published by the International Headache Society (IHS) Committee on clinical trials (24) recommend VRS or VAS combined with a simple verbal scale for global evaluation efficacy measures.

Patient compliance may become a problem in studies using simple analgesics for the treatment in tension-type headache for the following reasons: (a) Most tension-type headaches are mild and patients therefore may not consider it worthwhile to spend the necessary time and effort for the study. (b) Most patients would have already taken analgesics such as aspirin and may not have confidence in test medications that are not known to be far superior to aspirin. (c) Patients chosen from headache clinics and specialty treatment centers may be more resistant to simple analgesics. Population-based studies are recommended for tension-type headache.

Many controlled studies of simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have been performed in tension-type headache, using the headache attack as a model for acute pain. Several studies done in recent years fulfill the standards recommended for drug trials in tension-type headache by the IHS (24). From these studies, one may conclude that NSAIDs are the drugs of first choice. The following is a review of some of the previous studies and recent randomized, controlled trials comparing various NSAIDs and simple analgesics. Although differences between drugs may be small or variable, a hierarchical classification of compounds emerges when efficacy data are considered (Fig. 83-1).

SIMPLE ANALGESICS

Aspirin and Acetaminophen

Aspirin and acetaminophen are the analgesics used most commonly in the treatment of acute episodes of tension-type headache. In an early double-blind, placebo-controlled, crossover trial, aspirin at doses of 1,000 mg,

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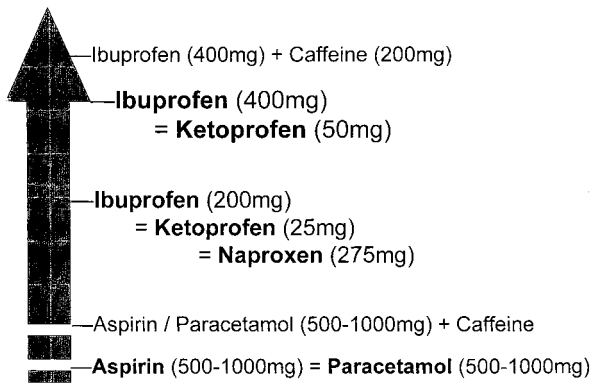

FIGURE 83-1. Tension-type headache: Acute pharmacotherapy.

500 mg, and 250 mg was shown to be more effective than placebo in the treatment of nonmigrainous headache (50). Moreover, a significant dose–response relationship was established for aspirin; 1,000 mg of aspirin was superior to 500 mg and 500 mg was superior to 250 mg.

Several comparative, randomized, placebo-controlled trials have shown that aspirin (13,28,31,38,40) and acetaminophen (12,35,40,42,48) are effective in the acute therapy of tension-type headache. One of the first placebo-controlled trials demonstrated that 648 mg of solid aspirin and 648 mg of effervescent aspirin were more effective than placebo; there was no difference between solid and effervescent aspirin (28). In another randomized, parallel, double-blind study, a subgroup consisting of 107 patients with tension headaches was treated with 1,000 mg of acetaminophen, 650 mg of aspirin, and placebo (40). Both drugs were more effective than placebo, but no difference was found between the drugs. Steiner et al. (48) reported that two different doses of aspirin (500 and 1,000 mg) and 1,000 mg of acetaminophen were more effective in treating 638 patients with episodic tension-type headache than placebo. In randomized, controlled study of 703 patients, the effects of 1,000 mg of acetaminophen were not significantly different from placebo in a 4-hour sum pain relief intensity differences scores (35). The authors suggested that the spontaneous resolution of headaches could last less than the duration of the evaluation period.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Ibuprofen

In one double-blind, randomized, placebo-controlled trial that included 70 patients with muscle contraction headache (published before the IHS Classification), the administration of 400 mg of ibuprofen was shown to be more effective than placebo 30 minutes after administration (44). There are several comparative randomized, placebo-controlled trials regarding the efficacy of NSAIDs in episodic tension-type headache (12–14,21,35,37–39,41–43,49).

In a comparative randomized, controlled trial, it was demonstrated that 153 patients who were administered 400 mg of ibuprofen had better pain relief than 151 patients who received 1,000 mg of acetaminophen or 151 patients administered placebo (43). Moreover, patients who were administered ibuprofen achieved relief faster than those who were administered acetaminophen. Nebe et al. (38) studied the effects of 200 mg of ibuprofen and 500 mg of aspirin in 65 patients with episode tension-type headache in a double-blind, threefold, crossover, placebo-controlled study. The study showed that ibuprofen was significantly superior to aspirin and placebo in decreasing headache intensity on a VAS by a minimum of 50% 1 hour after treatment.

Soluble Ibuprofen

In a double-blind, parallel group, randomized trial that included 154 patients, a new solubilized formulation of 400 mg of ibuprofen was reported to be more effective than 1,000 mg of acetaminophen and placebo in the treatment of episodic tension-type headache (39). Pain relief was reported 39 minutes after administration of the solubilized formulation of ibuprofen, which was significantly faster than with acetaminophen (47 minutes) and placebo (113 minutes) (39).

Ketoprofen

Steiner and Lange (47) evaluated the efficacy of ketoprofen in a multicenter, randomized, parallel group, placebo-controlled study; 25 mg of ketoprofen and 100 mg of acetaminophen were equally effective in pain relief and superior to placebo. In a double-blind, randomized, parallel group study with 159 patients, ketoprofen (25 and 50 mg) was reported to be more effective than 200 mg of ibuprofen and placebo in the treatment of episodic tension-type headache (49). Mehlisch et al. (35) conducted a double-blind, parallel-group, randomized study of 703 patients with episodic tension-type headache and demonstrated that low doses of ketoprofen (12.5 and 25 mg) also were more effective than placebo.

Naproxen Sodium

Naproxen sodium is the sodium salt of naproxen, a phenylalkanoic acid with potent analgesic, anti-inflammatory, and antipyretic properties. Naproxen sodium is more rapidly absorbed and has a more rapid onset of pain relief than naproxen. Rapid absorption and peak plasma levels within 1 hour are desirable qualities for fast relief of headache.

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In a multicenter, randomized, double-blind, three-way parallel study that included 124 patients, naproxen sodium (550 mg) was more effective than acetaminophen (650 mg), and placebo (37).

In another multicenter, double-blind, randomized, placebo-controlled trial, 375 mg of naproxen (321 patients) was reported to be more effective than placebo (321 patients), but no better than 1,000 mg of acetaminophen (41).

Diclofenac

In a multicenter, double-blind, randomized trial, diclofenac potassium, known to be effective in the treatment of migraine headache at dosages of 50 or 100 mg (34), was shown to be more effective in the treatment of episodic tension-type headache than placebo at low dosages (12.5 and 25 mg) (26). In addition, diclofenac potassium was found to be comparable with 400 mg of ibuprofen.

Injectable Ketorolac

Intramuscular injection of 60 mg of ketorolac, which is an injectable NSAID approved for the management of acute pain, was found to be superior to placebo in relieving pain at 0.5 and 1 hour after administration in patients with tension-type headache compared with placebo (21).

COMPARATIVE CLINICAL TRIALS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Table 83-1 shows recently conducted randomized, controlled trials. Five comparative trials of ketoprofen have been published in recent years (12,27,35,47,49). These studies indicate that ketoprofen 50 mg is more effective than ibuprofen 200 mg or paracetamol 1,000 mg, whereas ketoprofen 25 mg is not clearly superior to the latter. The efficacy of ketoprofen 12.5 mg did not significantly exceed that of placebo in one study, nor did Extra-Strength Tylenol. Naproxen 550 mg provided superior analgesia compared with paracetamol or placebo, whereas the 220-mg dose was equally effective as ibuprofen 200 mg (3). Other NSAIDs such as ketorolac, (21) diclofenac, or indomethacin are also effective, but less well studied.

The therapeutic efficacy of NSAIDs in tension-type headache, although undisputable, has to be put in perspective. For instance, the low proportion of patients becoming pain free 2 hours after dosing in most trials underscores the relative insufficiency of these drugs: 32% for ketoprofen 50 mg, 25% for the 25 mg dose; 17 to 22% for paracetamol 1,000 mg; and 17% for placebo. There is thus clearly room for better acute treatments of tension-type headache and a need for prophylactic therapy for frequent tension-type headache attacks.

THERAPEUTIC USE

Aspirin, acetaminophen, ibuprofen, naproxen, and ketoprofen are usually bought without a physician's prescription. Many patients do not take an adequate dosage and hence do not get the expected benefit. The recommended doses for the commonly used analgesics for the acute treatment of tension-type headache are given in Table 83-2.

At present time, ibuprofen (800 mg) can probably be considered the first choice for acute tension-type headache, followed by naproxen sodium (825 mg) because of the all-over better gastrointestinal tolerability (Fig. 83-1). Several surveys indeed have shown that ibuprofen is associated with the lowest risk of gastrointestinal bleeding or perforation (odds ration [OR] 2.9), whereas ketoprofen carries a much higher risk (OR) 23.7, with naproxen occupying an intermediate position (OR 9.1) (17,29).

COMBINATION ANALGESICS AND SEDATIVE/ANALGESIC COMBINATIONS

Combination analgesics and sedatives and tranquilizers/analgesic combinations may have a place in the acute treatment of tension-type headache. Many such drug combinations are on the market (Table 83-3). Just as adding caffeine to an analgesic can enhance its effect, the same can occur when two analgesics with different mechanisms of action are combined. The use of a combination also may reduce the risk of side effects, because lower doses of each medication can be used. The patient's anxiety may be alleviated by the addition of a barbiturate or a benzodiazepine to the regimen, and nausea decreased by the addition of an antiemetic. Compliance with therapy may be encouraged when the patient no longer needs to take several different drugs (4).

CONTROLLED TRIALS OF COMBINATION ANALGESICS

Caffeine has long been used as an analgesic adjuvant. In a double-blind, placebo-controlled trials, Schachtel et al. (45) showed that a combination of 1,000 mg of aspirin with 64 mg of caffeine was more effective than 1,000 mg of acetaminophen in the treatment of muscle contraction headache. Headache relief was significantly greater with a combination of aspirin and caffeine compared with placebo at 40 minutes; significant headache relief with acetaminophen was noted at 60 minutes. In a randomized, double-blind, parallel, multicenter, single-dose, placebo- and active-controlled study with 301 patients, Diamond et al. (14) reported significantly better headache relief with a combination of 400 mg of ibuprofen and 200 mg of

TABLE 83-1 Comparative Trials of NSAIDs in Episodic Tension-Type Headache

Study of Objective	*Design*	*Results*	*Authors*
Ibuprofen vs paracetamol	RCT, parallel Ibuprofen 400 mg Paracetamol 1,000 mg Placebo	Ibu > Para > placebo	Schachtel et al., 1996 (43)
Ketoprofen vs ibuprofen vs naproxen	RCT, parallel Ketoprofen 25 mg Ketoprofen 12.5 mg Ibuprofen 200 mg Naproxen 275 mg	Equal efficacy	Lange and Lentz, 1995 (27)
Ketoprofen vs ibuprofen	RCT, parallel, home monitored (electronic diary) Ketoprofen 50 mg Ketoprofen 25 mg Ibuprofen 200 mg Placebo	Keto50 + Keto25 > Ibu200 > placebo	Vangerven et al., 1996 (49)
Ketoprofen vs paracetamol	RCT, crossover Ketoprofen 50 mg Ketoprofen 25 mg Paracetamol 500 mg Paracetamol 1,000 mg Placebo	Keto50 > placebo Keto50 > Para Plac > Keto25 = Para < Keto50	Dahlöf and Jacobs, 1996 (12)
Ketoprofen vs ES Tylenol	RCT, parallel Ketoprofen 25 mg Ketoprofen 12.5 mg ES Tylenol 1,000 mg Placebo	Keto25 > Keto12.5 ES Tylenol = placebo	Mehlisch et al., 1997 (35)
Naproxen sodium vs ibuprofen	RCT, parallel Naproxen 220 mg Ibuprofen 200 mg	Napro = Ibu	Autret et al., 1997 (3)
Naproxen sodium vs acetaminophen	RCT, 3-way Parallel Naproxen sodium 500 mg Acetaminophen 1,000 mg Placebo	Napro > Placebo = Aceta	Miller and Talbot 1987 (37)
Naproxen sodium vs aspirin	RCT, parallel Naproxen sodium 550 mg Aspirin 500 mg Placebo	Napro > Aspirin > Placebo	Sevelius et al., 1980 (46)
Caffeine as adjuvant	RCT, crossover (6 studies) Para 1,000 + Caf 30 Para + Asp 500 + Caf 30 Paracetamol 1,000 mg Placebo	1 = 2 > 3 > 4	Migliardi et al., 1994 (36)
Caffeine as adjuvant	RCT, parallel Ibu 400 + Caf 200 Ibu 400 Caf 200 Placebo	1 > 2 > 3 = 4	Diamond et al., 1997 (14)

Abbreviations: TTH, tension-type headache; Asp, aspirin; Caf, caffeine; Ibu, ibuprofen; Para, paracetamol; RCT, randomized controlled trial; Aceta, acetaminophen.

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TABLE 83-2 Recommended Dose of Analgesics and NSAIDs in the Acute Treatment of Tension-Type Headache

Medication	*Initial dose (mg)*	*Repeat dose in 1–2 h (mg)*
Aspirin (325 mg)	975	975
Acetaminophen	1,000	1,000
Ibuprofen	800	400
Naproxen sodium	825	275
Ketoprofen	75	50
Ketorolac oral	20	10
Ketorolac intramuscular	60	
Indomethacin suppository	50	

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

caffeine than with 400 mg of ibuprofen, 200 mg of caffeine, or placebo. Another comparative study reported that a combination of 500 mg of acetaminophen, 500 mg of aspirin, and 130 mg of caffeine and a combination of 1,000 mg of acetaminophen and 130 mg of caffeine was more effective than 1,000 mg of acetaminophen alone and placebo (43).

Codeine, an opioid analgesic, is another compound that is combined in formulations containing aspirin or acetaminophen. One study reported that a combination of acetaminophen and codeine (doses not reported) was better than placebo in relieving pain in patients with tension headache who experienced an average of six attacks per month (15).

A single-dose, placebo-controlled study to assess the effectiveness of adding a muscle relaxant to a compound analgesic in the treatment of tension-type headache concluded that such a combination is complementary, with an analgesic for pain relief and an anti-anxiety agent to relieve the psychic tension (2). A comparison of a combination of meprobamate and aspirin with a butalbital-aspirin-phenacetin combination in 214 patients with tension-type headache found the combinations to be equally effective, but the latter had significantly more side effects, particularly of the central nervous system (19).

A multicenter, double-blind, randomized clinical study comparing the efficacy of Micrainin (meprobamate and acetylsalicylic acid) and tension-type headache was conducted (20). Each patient treated one episode of moderate to severe tension-type headache and scored the effects for head pain, activity impairment, tension (tense/uptight feeling), muscle stiffness, and overall relief using a VRS and a linear VAS. In general, overall agreements occurred between the two rating scales. Micrainin was significantly more effective than aspirin in relieving the symptoms complex of tension-type headache.

In some patients, the combination of analgesics with caffeine, sedatives, or tranquilizers may be more effective than simple analgesics or NSAIDs, but in many cases, this impression comes from too low a dosage of the latter. It has been proven, nonetheless, in controlled trials that the adjunction of caffeine (130 or 200 mg) significantly increases the efficacy of simple analgesics (36) and of ibuprofen (14) (see Table 83-2).

The main disadvantages of combination analgesics are the potential for medication overuse headache (32), risk of episodic headache transforming into chronic headache (33), and development of dependency to caffeine, butalbital, and codeine. Use of these kinds of combination medications should be discouraged in patients with tension-type headache. If they are used, the number of tablets or capsules taken in a month should be limited by prescribing relatively low doses with only one refill. Table 83-3 indicates the limits.

TABLE 83-3 Combination Analgesics for Acute Tension-Type Headache

Combination	*Individual Attack*	*Monthly Limit*
Aspirin 325 mg Caffeine 40 mg Butalbital 50 mg	1 or 2 tablets or capsules immediately; maximum 6 per attack	10 events, or 24 tablets or capsules
Acetaminophen 325 mg Caffeine 40 mg Butalbital 50 mg	1 or 2 tablets or capsules immediately; maximum 6 per attack	10 events, or 24 tablets or capsules
Aspirin 325 mg Caffeine 40 mg Butalbital 50 mg Codeine 30 mg	1 or 2 capsules immediately; maximum 6 per attack	8 events, or 16 capsules
Acetaminophen 325 g Isometheptene 65 mg Dichloralphenazone 100 mg	2 capsules immediately; maximum 6 per attack	12 events, or 40 capsules

Muscle Relaxants

Peripherally acting muscle relaxants are considered to be effective because of lack of evidence and the risk of habituation.

Triptans

The triptans are migraine-specific agents. In one study, Brennum et al. (8) reported that subcutaneous administration of 2 mg and 4 mg of sumatriptan induced a modest but significantly greater headache relief than placebo in patients with chronic tension-type headache. It also has been reported that subcutaneous injections of 6 mg of sumatriptan in patients with tension-type headache and coexisting migraine headache had an effect equal to that

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experienced in migraine headache (9). However, the oral formulation of sumatriptan 100 mg was not effective in the treatment of episodic tension-type headache (7). The possible mechanism responsible for the modest effect of subcutaneous sumatriptan in the chronic form of tension-type headache could be a reduction of the increased excitability of neurons in the central nervous system (18). Experimental studies of patients with chronic tension-type suggested increased excitability of the central nervous system (5). The role of triptans in the treatment of tension-type headache is unclear.

CONCLUSIONS ON CURRENT ACUTE THERAPY OF TENSION-TYPE HEADACHE

Simple analgesics and NSAIDs are the mainstays in the acute therapy of tension-type headache (see Table 83-1 and Fig. 83-1). Muscle relaxants and triptans are not recommended in the treatment of acute episodes of tension-type headache. In addition, physicians should be aware of the risk of developing medication overuse headache as a result of frequent and excessive use of analgesics in acute therapy.

Future Drugs For Acute Pharmacotherapy of Tension-Type Headache

Selective cyclooxygenase-2 (COX-2) inhibitors were developed to maintain the therapeutic efficacy of NSAIDs and to provide improved gastrointestinal safety (6). Controlled, randomized trials showed that COX-2 inhibitors have analgesic efficacy comparable with conventional NSAIDs (16). There are no studies on the efficacy of COX-2 inhibitors in tension-type headache. Experimental studies in animals showed that COX-2 inhibitors may act in the central nervous system by reducing nociceptive transmission (53). Therefore, it would be relevant to study the efficacy of COX-2 inhibitors in the treatment of tension-type headache (1).

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