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BIOAVAILABILITY OF NAPROXEN SODIUM AND ITS RELATIONSHIP TO CLINICAL ANALGESIC EFFECTS

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1 In the first of a series of trials with naproxen sodium it was shown that patients achieved significantly earlier and higher plasma levels of naproxen when naproxen sodium was administered.

2 In a second study comparing naproxen with naproxen sodium in patients with post-partum pain, pain intensity was consistently lower for the group receiving naproxen sodium. However, statistically significant differences were not seen until 4 or 5 h after medication.

3 A final study documented that a more frequent dosage schedule of every 6 h led to clearly higher plasma levels than those achieved with an every 8 h regimen; plasma levels did not plateau. Doses up to 1,375 mg/day were well tolerated.

4 In conclusion, naproxen sodium appears to be an improved form of naproxen for use as an analgesic agent.

Introduction

Naproxen is a nonsteroidal agent with demonstrated anti-inflammatory, analgesic and antipyretic properties (Roszkowski, Rooks, Tomolonis, Miller & Pelczarska, 1973). Studies with single 200 to 600 mg doses of naproxen have shown it to be at least as effective as single standard doses of aspirin or other standard reference analgesics in patients with moderate or severe postoperative pain resulting from orthopaedic (Ruedy & McCullough, 1973), dental (Ruedy, 1973), and other surgical procedures (Mahler, Forrest, Brown, Shroff, Gordon, Brown & James, 1976; Stetson, Robinson, Wardell & Lasagna, 1973). The need for an analgesic agent with an even faster onset of action than naproxen, however, has led to an investigation of methods to increase the speed of absorption of naproxen.

If it is true that a certain minimum effective plasma concentration is necessary for analgesic activity, then it follows that a more rapidly absorbed dosage form should provide a more rapid onset of activity (Swarbrick, 1973). Alkali metal salts of weak organic acids are known to dissolve more rapidly in aqueous solutions than the corresponding weak acid itself (Wagner, 1975). The rate at which a drug dissolves in the gastrointestinal tract often partially or completely controls the rate at which the drug appears in the blood (Levy, 1961). Accordingly, since naproxen is a weak acid (pKa = 4.15), the sodium salt of naproxen was developed since it logically represented one of the best means of providing more rapid absorption of naproxen and, thereby, an earlier effect. A series of studies was then designed to evaluate the bioavailability and efficacy of naproxen sodium.

First the pharmacokinetics of naproxen and naproxen sodium were compared to determine whether the sodium salt was more rapidly absorbed. Then an analgesic study was conducted to determine whether any such differences in absorption rates were clinically significant (Bloomfield, Barden & Mitchell, 1978). While the rate of absorption may affect the onset of analgesic activity, continued plasma levels of the drug are likely to be important in maintaining analgesia. Therefore, the steady state plasma levels of naproxen sodium associated with two different dosage regimens were measured in a third study.

Methods

Bioavailability (*naproxen* v *naproxen sodium*)

Twelve healthy male volunteers participated in this study. All study subjects were within 10% of the average weight for their age, sex and height as determined by the Metropolitan Life Insurance Company weight tables. At the beginning and end of the study, each volunteer underwent a complete physical examination including routine blood

chemistry determinations. During the study, any adverse effects reported by the subjects were recorded. Hypnotics, sedatives, antihistamines or other enzyme inducing drugs were not permitted for 1 month prior to the study, and no other drugs or alcohol were permitted 72 h prior to the start of the study and throughout the study period. Excessive smoking was discouraged during the trial.

At 08.30 h of the test day, following an overnight fast, subjects ingested either a tablet of 500 mg of naproxen or the equimolar 550 mg of naproxen sodium with 100 ml of water (drug was assigned randomly). Blood (10 ml) was obtained from each subject at basline and 10, 20, 40, 60 min, 2, 4, 6, 8 and 24 h after ingestion of the drug. Plasma was separated and frozen for later naproxen plasma level determinations by gas chromatography (Runkel Chaplin, Sevelius, Ortega & Segre, 1976). The subjects remained fasting until after the fourth hour blood sample. After a 1 week interval, they repeated the same procedure with the second drug in a crossover design.

Time course of analgesia (*naproxen* v *naproxen sodium*)

Sixty postpartum women with moderate or severe uterine cramping during the 48 h after an uncomplicated delivery participated in this study. This single-dose, double-blind parallel study evaluated the comparative analgesia of naproxen and its sodium salt. No other analgesic, sedative or psychotropic medications were permitted during the 6 h preceding the study. None of the patients was breast feeding her infant.

On demand, patients randomly received either 500 mg naproxen or 550 mg naproxen sodium tablets with a glass of water. The two treatment groups were comparable in terms of demographic characteristics and degree of cramping. Each patient evaluated pain intensity at baseline (immediately before drug administration) and 15, 30, 60 min, 2, 3, 4, 5 and 6 h after ingestion of the drug. Pain intensity was rated on a scale of 0 to 3 (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) and then Pain Intensity Differences (PID) were calculated by finding the arithmetic difference between the patient's baseline score and each periodic post-treatment score. These periodic PID scores were used to compute the degree of pain relief (SPID—sum of pain intensity differences), and, together with pain intensity scores, were used to measure onset, peak, and duration of pain relief. SPID scores have been shown to be an appropriate and valid technique to evaluate analgesics (Bellville, Forrest & Brown, 1968; Houde, Wallenstein & Rogers, 1960).

Any adverse effects reported during the study period were recorded.

Steady state plasma levels (*two dosage regimens of naproxen sodium*)

Sixteen healthy volunteers (8 males and 8 females) participated in this study. None received any enzyme inducing drugs during the month prior to the study. Subjects did not alter their daily activities or dietary habits. All volunteers were within 10% of average weight for their age, sex and height.

Each subject received a loading dose of naproxen sodium (550 mg) at 09.00 h on the test day. Thereafter, subjects ingested 275 mg naproxen sodium either every 6 h or every 8 h, for a total of 3 consecutive days (drug regimen was assigned randomly). Ten millilitres of blood was obtained at baseline and 4, 8, 24, 32, 48, 52, 56 and 72 h after ingestion of the drug. Plasma was separated and frozen for later naproxen plasma level determinations by gas chromatography. After a 10-day interval, subjects repeated the same procedure with the second dosage regimen.

Routine blood chemistry determinations were performed on all subjects before and after the study, and any adverse effects reported during the study period were recorded.

Results

Bioavailability

Two variables were of primary interest in this study: the rate of absorption of the drug, measured by the upslope of the drug concentration over time curve, and the total absorption, as characterized by the area under that curve. For a drug such as naproxen sodium which is primarily intended as an analgesic, the rate of absorption is particularly important.

Naproxen sodium resulted in significantly earlier and higher plasma levels for the first 2 h. At 20 and 40 min after administration, the plasma concentrations of naproxen sodium were approximately twice as high as those of naproxen (Figure 1). These differences were statistically significant ($P < 0.005$ and $P < 0.01$, respectively). One hour after adminstration the plasma level of naproxen sodium was still approximately 39% higher than the plasma level of naproxen ($P < 0.01$). As can be seen in Figure 1, the mean time to peak plasma level was 1 h for naproxen sodium and 2 h for naproxen, with the sodium salt achieving a significantly higher peak ($P < 0.01$). After 2 h, the plasma levels for the two drugs were approximately equal.

The area under the plasma curve was significantly larger for naproxen sodium during early time periods, i.e., 33% larger during the 0 to 2 h time period ($P < 0.01$). The total absorption of naproxen and

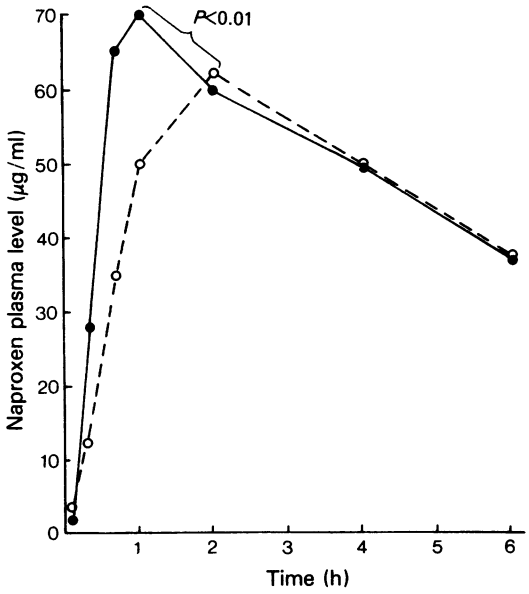

Figure 1 Naproxen plasma levels after administration of 500 mg naproxen (○) or the equimolar 550 mg naproxen sodium (●) to 12 healthy men in a crossover study. Significantly earlier and higher naproxen levels were achieved after naproxen sodium.

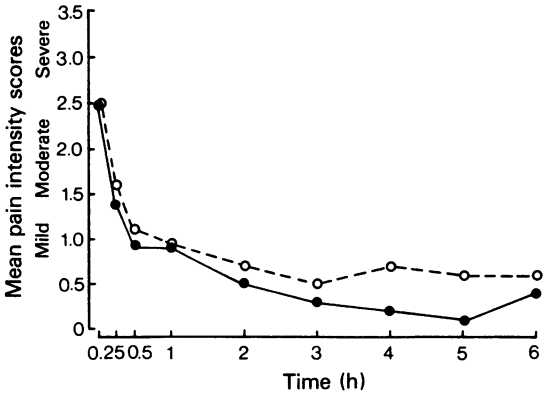

Figure 2 Mean pain intensity scores before and after administration of 500 mg naproxen (○) or the equimolar 550 mg naproxen sodium (●) to 30 postpartum women with moderate or severe uterine cramps. Scores were consistently lower for those patients receiving naproxen sodium.

naproxen sodium, as indicated by the total areas under the curve, was equal.

No clinically significant adverse effects were noted during the study.

Time course of analgesia

There were no differences between the 30 patients who received naproxen and the 30 who received naproxen sodium with respect to age distribution, type of labor and delivery, premedication, initial severity of pain or any other baseline parameter measured.

Mean pain intensity scores during the study are illustrated in Figure 2. On the average, patients in both groups obtained greater than a 50% reduction in initial pain (24 of 30 in the naproxen sodium group and 25 of 30 in the naproxen group). However, naproxen sodium resulted in consistently lower mean pain intensity scores than did naproxen.

Figure 3 illustrates the mean pain intensity differences (PID) for the two groups. At all time points, except 1 h, the PID scores were higher for the naproxen sodium group (i.e., greater pain relief) than for the naproxen group. However, these differences between the naproxen and naproxen sodium groups became statistically significant only 4 and 5 h after administration of medication. The naproxen sodium group achieved a peak PID score of 2.37 in the fifth hour, while the naproxen group achieved a lower peak PID score (2.00) in the third hour. The sum of pain intensity differences (SPID) was also greater for the naproxen sodium group than for the naproxen group. These data suggest that naproxen sodium resulted in better analgesia than naproxen in this clinical setting.

No clinically significant side effects were noted during the study.

Steady state plasma levels

More frequent dosing (i.e., larger total dose of drug ingested) was reflected in higher mean plasma levels of naproxen. Those patients on the every 6 h regimen achieved mean naproxen plasma levels approximately 20 μg/ml higher than those on every 8 h regimen (Figure 4). Differences between the two regimens at 24, 48 and 72 h were highly statistically significant ($P < 0.001$).

No clinically significant adverse effects were noted during the study.

Discussion

The results of the first study document the theoretical advantages of utilizing the sodium salt of naproxen to achieve more rapid absorption of the drug. Patients achieved significantly earlier and higher plasma levels of naproxen with naproxen sodium.

This improved bioavailability was not immediately evident, however, in a clinical setting. Both these

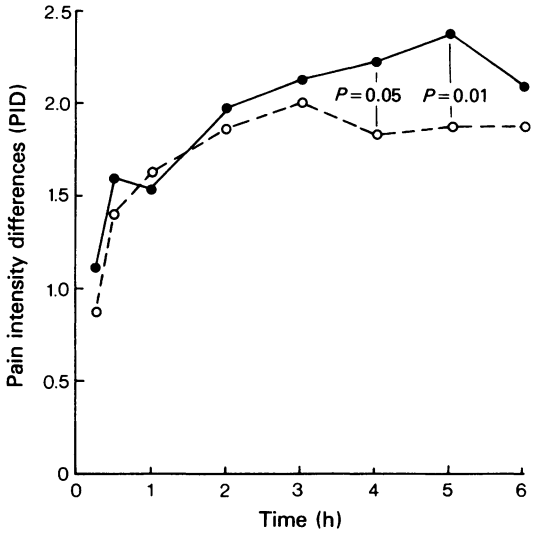

Figure 3 Mean pain intensity differences (PID; arithmetic differences between baseline and each post-treatment score) after administration of 500 mg naproxen (○) or 550 mg naproxen sodium (●) to 30 postpartum women with moderate to severe uterine cramps.

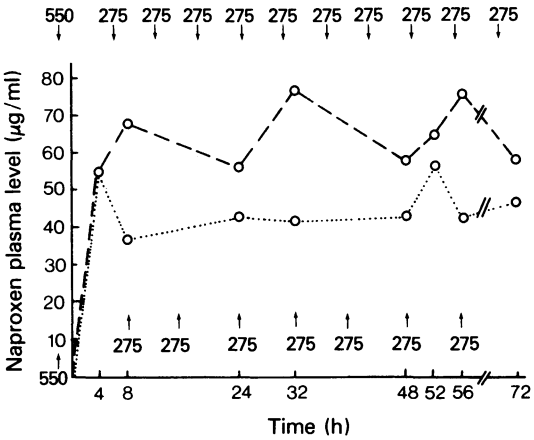

Figure 4 Comparison of the mean naproxen plasma levels between naproxen sodium administered every 6 h (○----○) or every 8 h (○····○) to 16 healthy men and women in a crossover study. The every 6 h regimen produced average naproxen plasma levels approximately 20 μg/ml higher than the every 8 h regimen.

patients who received naproxen and those who received naproxen sodium noted a rapid reduction in pain. The early differences between the two groups were small, and statistically significant differences in analgesic response were not seen until 4 and 5 h after medication. However, pain is a very subjective variable, and statistically significant differences are notoriously difficult to achieve between two active analgesic agents. Nonetheless, pain intensity was consistently lower for the group receiving naproxen sodium, even 15 min after administration. It may be that much larger numbers of patients are necessary to demonstrate statistically significant differences, particularly during the first hours of study. This remains to be resolved by future studies.

In two earlier studies of analgesics in patients with postpartum pain (one comparing naproxen to placebo and codeine and the other comparing naproxen sodium to placebo and aspirin), statistically significant differences between naproxen or naproxen sodium and placebo were seen only 2 to 3 h after medication (Bloomfield, Barden & Mitchell, 1977). The dose of naproxen was 300 or 600 mg and the dose of naproxen sodium was 275 mg (half the recommended therapeutic dose). However, in a separate study using the full therapeutic dose of naproxen sodium (550 mg), patients with pain of varying origin (musculoskeletal, dental, headache, etc.) found naproxen sodium significantly superior to both placebo and aspirin 1 hour after dosing (Sevelius, Segre & Bursick, 1980).

Whether naproxen or naproxen sodium is administered, the circulating moiety is the same, and the two drugs thus share the same long biological half-life (13-14 h). This long half-life is particularly useful when naproxen is used for chronic anti-inflammatory therapy, since the drug can be administered on a twice daily regimen and still reach adequate steady-state plasma levels to maintain therapeutic efficacy. In addition, using a single dose of naproxen sodium, a previous study demonstrated a sustained duration of analgesic effect for up to 7 h (entire length of follow-up period in study) (Bloomfield *et al.*, 1977).

For analgesia, it may be desirable to reach quickly and maintain high plasma levels in order to obtain fast and continuous maximum therapeutic benefits. The more rapid bioavailability of the sodium salt of naproxen was shown in the first study. The final study documented that a more frequent dosage schedule of every 6 h led to clearly higher plasma levels than those achieved with an every 8 h regimen. This study did not evaluate the potential therapeutic benefits of more frequent dosing. It did demonstrate, however, that when more drug was ingested plasma levels increased. While many patients may receive rapid and good pain relief with an every 8 h regimen, others may receive added benefit from the higher plasma levels achieved with an every 6 h regimen. Individual patient variations in response to pain and initial level of pain make it difficult to draw any conclusions for

even the 'average' patient. However, further studies may help clarify this question.

Including the loading dose of 550 mg, the total daily dosage in the final study was 1,375 mg/day and 1,100 mg/day for the every 6 and every 8 h regimens, respectively. The ability to tolerate doses in this range was evaluated in an earlier study with naproxen during which single doses of 1, 2, 3 or 4 g were administered to 16 healthy volunteers (Runkel *et al.*, 1976). Aside from 1 person who reported mild epigastric pain after receiving 3 g of naproxen, no other subjects reported any side effects. In addition, there were no abnormal findings on physical examination nor were there any clinically meaningful changes in blood chemistry values. These high doses of naproxen were quickly cleared by the kidney without saturating any of the body's eliminating mechanisms. In another study, healthy subjects received 1,800 mg/day of naproxen for 30 days without significant side effects or changes in laboratory values (unpublished data, Syntex Corporation). In contrast, studies have shown that doses of 1 g or more of aspirin result in salicylate accumulation and a threat of salicylate intoxication (Levy, 1965; Wagner, 1971).

Thus, the regimens employed in our study (550 mg naproxen sodium as a loading dose, followed by 275 mg every 6 or 8 h appear to fall within a range which is well tolerated in man. It has the advantage of allowing one rapidly to achieve and then maintain therapeutic plasma levels of the drug thereby minimizing fluctuations which might lead to some loss of analgesic effect.

In conclusion, naproxen sodium appears to be an improved form of naproxen for use as an analgesic agent. It is more rapidly available to the body and appears to provide greater pain relief than naproxen. Earlier studies suggested that, at the doses employed in this study, naproxen sodium is well tolerated. The analgesic efficacy of naproxen sodium in single doses as low as 275 mg has been demonstrated previously. This, coupled with the long duration of efficacy for the recommended 550 mg dose and wide safety margin, should provide good flexibility in dosing for patients with pain of various origins. In addition, since many causes of pain are frequently accompanied by inflammation, the use of an analgesic which is also an anti-inflammatory agent may provide added benefit.

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