The correlation between blood levels of ibuprofen and clinical response

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The correlation between blood levels of ibuprofen and clinical analgesic response

A clinical trial comparing ibuprofen, 400, 600, and 800 mg, with aluminum ibuprofen, 400 mg, and placebo was conducted in patients with moderate or severe pain subsequent to third molar extraction. Pain intensity ratings and ibuprofen serum levels were obtained at baseline, 30 minutes, 1 hour, and hourly thereafter for 3 hours. Pain intensity ratings were also obtained at hours 4, 5, and 6. Serum levels at 1, 2, and 3 hours correlated significantly with the log dose of ibuprofen (r = 0.35, 0.49, and 0.48, respectively) and with global analgesic response as measured by the percentage of the sum of the pain intensity scores (r = 0.28, 0.34, and 0.26, respectively). However, possibly because of differences in drug formulation, the percentage of the sum of the pain intensity scores did not correlate significantly with log dose. The highest correlations were found between contemporaneous serum levels and pain intensity difference values, particularly at hour 1 (r = 0.54). Our results support the proposition that increased ibuprofen serum levels lead to increased analgesia. (CLIN PHARMACOL THER 1986;40:1-7.)

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Our study was designed to investigate the relationship between clinical analgesic efficacy and serum ibuprofen concentrations resulting from the use of graded doses of ibuprofen, 400, 600, and 800 mg, and aluminum ibuprofen, 400 mg, in the treatment of severe postop-

erative pain in patients undergoing dental surgery. Although ibuprofen has been extensively studied since its introduction, the connection between serum levels and clinical analgesia has not been established.

METHODS

Subjects. The study was carried out at the University of Puerto Rico School of Denistry in San Juan. The study population consisted of healthy patients, 18 years of age or older (16 years with parental consent), who had pain after undergoing the surgical removal of one or more third molar impactions under local anesthesia (xylocaine 2% with epinephrine 1/100,000). Excluded
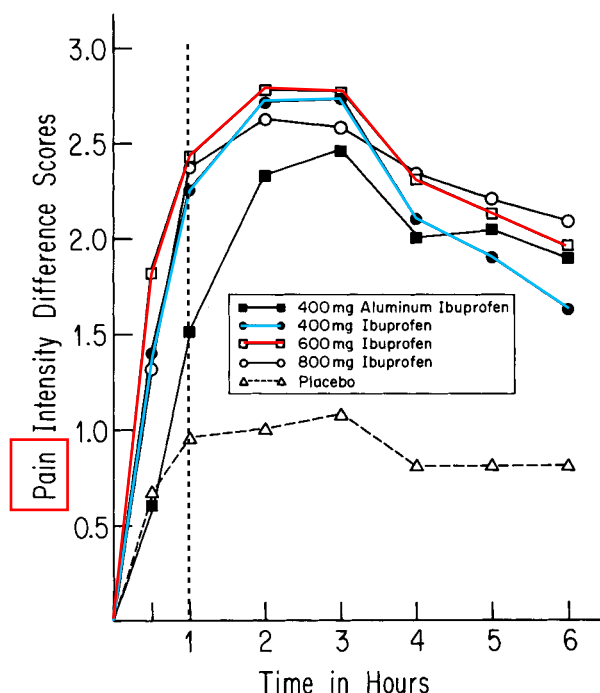
Fig. 1. PID(t) curve.

from the study were patients who were pregnant or lactating or had allergic reactions to any of the test drugs or other nonsteroidal anti-inflammatory drugs, a history of significant gastrointestinal bleeding disorders, or a history of drug dependence.

Study design and drugs. The double-blind study used a parallel-group, single-dose design. Patients were randomly assigned to receive either ibuprofen, 400 mg (I400), 600 mg (I600) or 800 mg (I800); aluminum ibuprofen, 400 mg (AI400); or placebo. The I400, I600, and AI400 tablets varied in appearance and the I800 mg dose consisted of two 400 mg tablets. To maintain double-blind conditions, matching placebos were used to supplement active tablets to permit the administration of identically appearing sets of four tablets. Patients were not permittted to receive drugs that might confound the interpretation of results during the 4 hours before and 6 hours after taking the test drugs.

When postextraction pain was either moderate or severe, study drugs were administered. Observations were made at 0.5 hours, 1 hour, and every hour thereafter until 6 hours after drug dosing. At each observation, patients classified the intensity of their pain as none (0), slight (1), moderate (2), or severe (3) and the amount of pain relief as none (0), a little (1), some (2), a lot (3), or complete (4). In addition, they reported any side effects that might be related to the study drug.

At the final observation, they provided a quantification of their global assessment of the study drug. Patients were required to remain at the clinic for at least the first 3 hours after dosing. If they left the clinic at any time during the final 3 hours, the analgesic rating scales were completed by the patient at home using a patient diary.

Patients were allowed to remedicate with a standard analgesic if they did not obtain sufficient pain relief with the study drug. If this occurred within the first hour of the evaluation period, the patient was excluded from the analysis. If patients required remedication after 1 hour, their pain intensity scores for the remainder of the evaluation period were assigned values equal to the greater of their pain intensity score at the time of remedication or their initial pain level. Their relief scores for the remainder of the period were assumed to be zero.

Serum level assay. While the patients were in the clinic, blood samples were drawn at baseline and at 0.5, 1, 2, and 3 hours after dosing to measure ibuprofen serum levels. The serum was separated, frozen, and analyzed by an independent laboratory by HPLC with a reverse-phase C-18 column for separation and ultraviolet absorbance monitored at 220 nm.[1] This assay provides a sensitivity of 1 µg/ml, with a corresponding coefficient of variation of 9.1%.

Measures of analgesia. Several measures of analgesia were derived from the interview data. These include the pain intensity difference at time t (PID(t)), i.e., the difference between the pain intensity score at an observation point t and the baseline intensity; the sum of the pain intensity differences (SPID), i.e., the sum of the PID(t) scores, weighted by the time interval between observations (an estimate of the area under the time-effect curve of the treatment); and %SPID, i.e., 100 times the SPID divided by the maximum possible SPID computed as if the patients had obtained complete relief for the entire observation period. Also calculated for each patient was the time to reach zero pain intensity, i.e., complete relief. Other measures based on relief scores were derived as well but, for brevity, are not included in this article.

Statistical methods. Analgesic data were analyzed with standard statistical methods.[2] Background variables that might differ among groups were examined by chi-square tests. One-way ANOVA was performed to test the hypothesis of no difference among the five treatment groups for the analgesia and serum level parameters. To test for differences among drugs in the rate of absorption of ibuprofen (measured by the time to peak serum levels), one-way ANOVA and chi-square

tests were performed. All statistical tests were done at the P < 0.05 level of significance. If the ANOVA result was significant, tests were performed to investigate pairwise differences between treatments by Fisher's least significant differences test. To investigate the relationship between dose and analgesic response, log dose-response regression lines were calculated. A similar calculation was performed to study the relationship between dose and serum level. Measures of serum concentration levels at each observation t(C[t]) were correlated with contemporaneous and future observations of PID(t), as well as with %SPID. For observations at the first hour, a logistic regression model[3,4] was fit to relate the probability of zero pain intensity to serum ibuprofen level.

RESULTS

Drugs were dispensed to a total of 200 patients. Five patients were excluded from the efficacy analysis but not from the safety analysis: four requested remedication within 1 hour and one vomited within 5 minutes of ingesting the study drug. Sixty-seven (34%) of the patients were male, and the mean age of the total group was 23 years. There were no significant differences among groups for sex, age, weight, and height. Because only four patients entered the study with moderate initial pain, to keep the population homogeneous, their data were excluded from the analysis. Therefore, statistical analysis of the variables SPID and %SPID would lead to identical results.

Relationship between analgesic efficacy and ibuprofen dose. The mean PID(t) scores and indications of those treatment differences that were significant are shown in Fig. 1. The three doses of ibuprofen did not differ significantly in mean PID(t) during the entire 6 hours. Note, however, that from the 0.5-hour to the third hour observation, the mean response was higher for I600 than for I800. Aluminum ibuprofen had lower mean PIDs than the three ibuprofen doses during the first 4 hours, and the differences were significant (p < .05) at 0.5 and 1 hours.

In terms of the summary parameter %SPID, the means were 29.6, 65.6, 71.9, 78.2, and 76.1 for placebo, AI400, I400, I600, and I800, respectively. The active drugs were significantly more efficacious than placebo, the three ibuprofen doses did not differ significantly from each other, and I600 and I800 were significantly superior to AI400.

The least-squares fit of the log dose-response line for ibuprofen for the first hour was: PID(1) = 1.16 + 0.43 log dose. The slope of this line, 0.43, as well as the slope of the log dose-response lines for all PIDs and
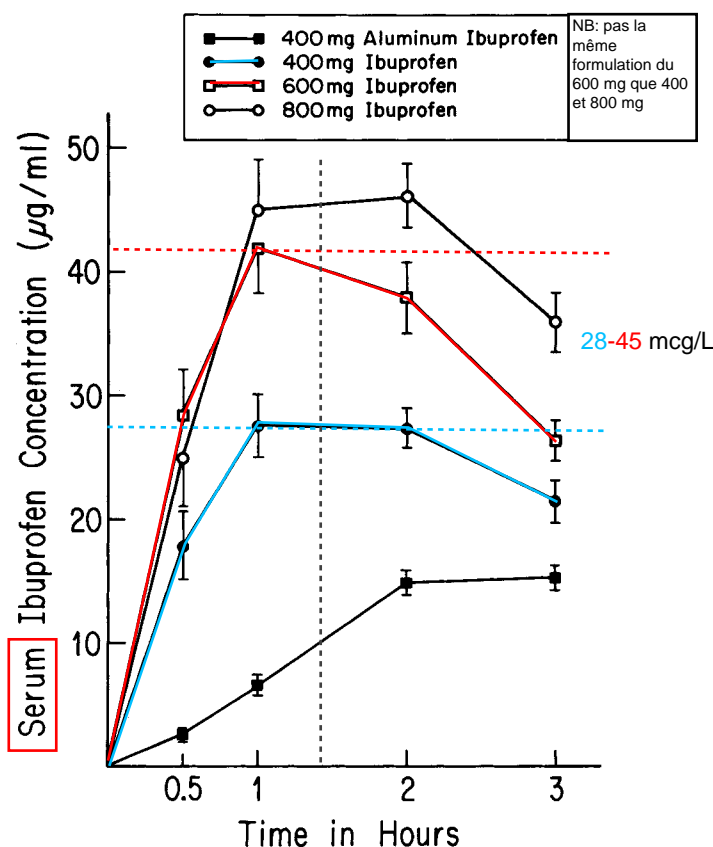

Fig. 2. Serum ibuprofen concentration-time data.

%SPIDs, were not statistically different from zero, indicating that these measures of analgesia were not significantly correlated with log dose.

Relationship between serum concentration and ibuprofen dose. Means (±SD) of the hourly serum concentrations are shown in Fig. 2. There are evident differences in the extent of ibuprofen absorption. Mean serum AUCs, calculated by the trapezoidal rule, were 30, 69, 94, and 112 μg·hr/ml for AI400, I400, I600, and I800, respectively. The mean serum levels of all three ibuprofen doses were significantly higher than those of aluminum ibuprofen at each observation point and for the AUC. At 0.5 hours, the group receiving I600 had higher serum levels than the group receiving I800. Thereafter, the rank orderings of mean serum concentration coincided with dosage. There were significant differences in the mean serum levels produced by the three ibuprofen doses beginning at 1 hour, at which time mean levels for the group receiving the 800 and 600 mg ibuprofen doses were greater than those of the group receiving the 400 mg dose. The mean serum concentrations at hours 2 and 3 and the mean AUC of
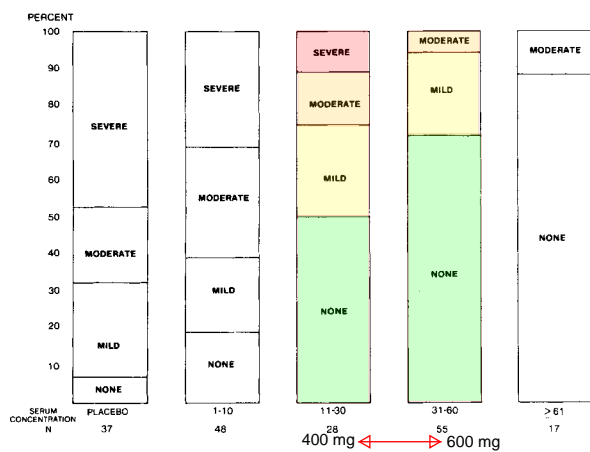
Fig. 3. Distribution of pain intensity at 1 hour by serum concentration.

Douleur à 1h, soit avant le pic plasmatique qui survient entre 1-2h --> relevant?

the three dose groups also differed significantly from each other. The correlations of serum concentration, C(t), with the log dose of ibuprofen were 0.17, 0.35, 0.49, and 0.48 at 0.5, 1, 2, and 3 hours, respectively. All but the 0.5-hour value differed significantly from zero. Evidence of differences in the rate of ibuprofen absorption was found. Table I lists the distribution and mean time to maximum serum concentration by drug. AI400 has a significantly slower rate than all three of the ibuprofen doses. Surprisingly, however, although the mean rates of the three ibuprofen doses are not significantly different in the ANOVA, a chi-square analysis does yield significant differences among treatments. The rate of absorption of the 600 mg tablet is faster than that of the 400 mg tablet, a finding that is consonant with the higher serum levels found for I600 compared with I800 at 0.5 hours.

Although there is a considerable degree of variability and overlap in serum levels for the different doses, there remains a clear dose-serum level relationship. The least-squares regression at hour 1 was found to be: C(1) = −139.8 + 64.67 log dose. The slope, 64.67, was significantly different from zero.

Relationship between serum concentration and analgesia. The degree of linear relationship between serum levels at each test point, C(t), and %SPID and between C(t) and contemporaneous and future PIDs was examined by calculation of correlation coefficients (Table II). The correlations of C(t) with %SPID are quite high, in contrast to the low correlations between log dose and %SPID. The values suggest that hour 2 and, to a lesser extent, hour 1 serum concentrations have the highest correlation with %SPID. Also, note that higher doses

Table I. Number of patients with peak serum concentrations at hour t by active drug

	I400	*I600*	*I800*	*AI400*
0.5 hr	4	9	4	3
1 hr	17	14	19	3
2 hr	13	11	11	20
3 hr	14	2	5	13
Time to peak (hr)	1.5	1.29	1.49	2.14

All drugs: χ^2 = 31.47 (P < 0.001).
Ibuprofen: χ^2 = 13.05 (P < 0.05).
I400 and I800: χ^2 = 3.65 (NS).

yield higher correlations and that for I400 and AI400 there were no values of C(t) for which the correlations were significantly different from zero.

Correlations between contemporaneous serum level and PID values at each hour are also high, but are clearly highest at hour 1. At that point, the correlation is significantly different from zero for all drugs. The correlations between the 0.5-hour serum level and future PID values and between the 1-hour serum level and future PID values sharply decrease over time and become negative by hour 3. Serum levels are more highly correlated with contemporaneous clinical analgesic effect than with future PID values.

Table III lists the distribution of time to reach complete pain relief (zero pain intensity) for all active drugs. The modal time to reach complete relief (no pain) is 1 hour, by which time 54% of patients have reported they have no pain. At 0.5 and 1 hour, the difference between the mean, as well as the median, serum levels of those patients who obtain complete relief for the first time and those who still have pain (Table III) is significant, but at hours 2 and 3 it is not.

Fig. 3 shows the distribution of pain intensity for several ranges of serum concentration at 1 hour. Note how the proportion of patients with no pain increases dramatically with serum level. Also, no patient with a serum level >30 μg/ml reported severe pain.

The least-squares linear regression at the first hour is: PID(1) = 1.39 + 0.024 serum level(1). The estimated slope is significantly different from zero.

The results of the logistic regression relating the probability of no pain at hour 1 as a function of serum level at hour 1 was found to be: P(no pain at hour 1) = (1 + exp[−1.35 + 0.051 C(1)])$^{-1}$. According to this model, a concentration of approximately 26 μg/ml would yield an even chance of reporting no pain and a concentration of 48 μg/ml would yield a 3-to-1 chance of reporting no pain.

Table II. Correlation between serum concentrations and analgesic efficacy measures

Drug	Serum level (hr)	PID(0.5)	PID(1)	PID(2)	PID(3)	%SPID
All	C(0.5)	0.44*	0.43*	0.16*	-0.02	0.15
	C(1)		0.54*	0.24*	0.08	0.28*
	C(2)			0.23*	0.19*	0.34
	C(3)				0.19*	0.26*
I400	C(0.5)	0.32*	0.36*	0.15	-0.05	0.08
	C(1)		0.40*	0.15	-0.18	-0.15
	C(2)			0.13	-0.12	-0.05
	C(3)				-0.19	0.01
I600	C(0.5)	0.26	0.36*	0.09	-0.02	-0.09
	C(1)		0.54*	0.27	0.23	0.23
	C(2)			0.16	0.39*	0.33*
	C(3)				0.51*	0.40*
I800	C(0.5)	0.48*	0.39*	0.05	-0.05	0.22
	C(1)		0.56*	0.11	0.11	0.41*
	C(2)			0.24	0.39*	0.43*
	C(3)				0.33*	0.22
AI400	C(0.5)	0.17	0.32*	0.19	-0.36*	-0.01
	C(1)		0.40*	0.28	-0.00	0.25
	C(2)			0.01	0.09	0.27
	C(3)				0.16	0.04

*Significantly different ($P \leq 0.05$) from zero.

Table III. Relationship between serum levels and time to first recorded complete relief (FRCR)

	Time (hr)			
	0.5	1	2	3
Cumulative no. with FRCR ≤ t	30 (19.4%)	83 (53.9%)	118 (76.6%)	130 (84.4%)
Serum levels of patients at time t*				
Mean ± SD				
FRCR = t	30.1 ± 4.0†	39.2 ± 3.2†	27.6 ± 2.7	24.1 ± 4.5
FRCR > t	15.4 ± 1.8	18.0 ± 2.3	24.2 ± 3.2	21.1 ± 2.8
Median				
FRCR = t	34.4‡	41.4‡	26.8	19.1
FRCR > t	5.0‡	8.8‡	19.2	18.9

*Based on n = 150, 119, 64, and 28 patients whose FRCR ≥ t at t = 0.5, 1, 2, and 3 hours, respectively.
†Mean serum levels of those with FRCR at t significantly greater than those who still have pain ($P \leq 0.05$ by t test).
‡Median serum levels of those with FRCR at t significantly greater than those who still have pain ($P \leq 0.05$ by Wilcoxon).

Remedication. Forty-six (22%) of the 195 patients obtained inadequate pain relief at 1 hour or later and required remediation. Twenty-one of these were in the placebo group. There were seven, nine, five, and eight patients who required remediation among the I400, I600, I800, and AI400 groups, respectively.

Adverse effects. Five patients reported adverse reactions. One patient who received I400 reported mild sleepiness, and one patient who received AI400 complained of severe edema of the hands. Of three patients with adverse reactions in the placebo group, two complained of mild weakness and skin rash, while one patient vomited the test drug within 5 minutes of ingestion.

DISCUSSION

The basic pharmacokinetic properties of ibuprofen have been well studied.[5-12] It is reported to be rapidly absorbed, with a mean peak serum level between 1.5 and 2 hours. The drug is almost completely bound to plasma protein. The dose and the serum AUC have been found to be linear between 200 to 800 mg after single

doses. The apparent serum $t_{1/2}$ is approximately 2 hours.

In our study, aluminum ibuprofen produced less analgesia as well as lower serum levels as compared with the same dose of ibuprofen alone. This was particularly apparent in the first 2 hours. It seems likely that the observed differences in analgesia are the result of the observed serum level differences. (We have been informed by the manufacturer that the aluminum formulation we used was experimental, and no attempt had been made to maximize bioavailability.)

For ibuprofen, the mean analgesic scores provide little or no evidence of a dose-response relationship between 400 and 800 mg in terms of clinical efficacy. There are many possible reasons for the lack of correlation between the dose of ibuprofen and clinical response. There is some evidence of "ceiling effects," i.e., almost all patients received a considerable amount of relief. Also, a relatively high degree of variability in the serum levels obtained from a dose of the drug was noted. That is, the distributions of serum levels for different doses overlap considerably. Individual patient variation in pharmacokinetic parameters, such as absorption metabolism, protein binding, volume of distribution, or clearance, may very well explain individual variation in analgesic efficacy for a given dose. It must also be noted that the formulation of the 400 mg tablet used in the I400 and I800 groups was different than the formulation of the 600 mg tablet. Differences in formulation could very well influence rate of absorption and, in turn, clinical response. There was a clear and substanatial linear relationship between ibuprofen serum levels and degree of pain relief, particularly in the first 2 hours. There were several unexpected dose-related reversals in serum levels and drug effects. For example, in the first 0.5 hour the serum level and clinical efficacy were greater for I600 than for I800. While this strengthens the evidence for a linear correlation, one cannot help but wonder why it occurred. As shown in Table I, there is evidence that the rate of absorption for I800 was slower than that for I600. The dissolution characteristics of the tablets may be indicative of the problem. Dissolution rates were determined in a phosphate-buffered medium at pH 7.2, with the tablet rotated in a basket at 150 rpm until 50% of the tablet was dissolved. The mean dissolution rate for the 400 mg tablet was 7 minutes at the start of the study (n = 6) and 12 minutes (n = 2) for the tablets remaining at the end of the study. The mean dissolution rate for the 600 mg tablet was 4 minutes (n = 6) before the study and 6 minutes (n = 2) at the end of the study. Although the difference is small and too few tablets

were analyzed to make a definitive statement, the data do suggest that the 600 mg dose may have been more bioavailable than the tablets used in the 400 and 800 mg groups. This would help to explain the higher serum levels observed at 0.5 hours for I600. At that time, 36.1% of those receiving I600 had no pain, compared with 20.5%, 17.5%, and 4.8% for those receiving I400, I800 and AI400, respectively. The longer dissolution time for the 400 mg tablets, two of which comprised the 800 mg dose of ibuprofen, may also contribute to the shorter time to maximum serum concentration for the 600 mg tablet and, in turn, for the higher SPID scores for the I600 group in comparison with the I400 and I800 groups.

There are few clinical studies that demonstrate a significant correlation between analgesic effect and serum concentration. There are many possible reasons for this failure. Some studies have attempted to relate maximum serum concentration, AUCs, other measures of the serum concentration-time curve to summary measures of pain relief such as SPID or TOTPAR. It may be that for acute single-dose studies, the choice of parameters to correlate and their temporal relation is critical. Our data support the proposition that, particularly in the first few hours after dosing, an increased serum ibuprofen concentration tends to increase analgesia.

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