ORIGINAL CONTRIBUTION
drug overdose, ibuprofen; ibuprofen, overdose; overdose, ibuprofen

Ibuprofen Overdose: 126 Cases

In this study of ibuprofen overdose, symptoms developed in 19% of patients (24 of 126) — in 7% of children (6 of 88) and in 47% of adults (18 of 38). Central nervous system depression, seizures, gastrointestinal disturbances, bradycardia, hypotension, apnea, abnormal renal functions, hematuria, nystagmus, and blurred vision were observed. No patients became symptomatic more than four hours after ingestion. There was no significant difference (P > .05) between symptomatic and asymptomatic adult groups in either total milligrams or milligram-per-kilogram amounts ingested by history. Pediatric patients who became symptomatic had a mean ingestion by history of 440 mg/kg; those who remained asymptomatic had a mean ingestion by history of 114 mg/kg (P < .001). No patients ingesting less than 99 mg/kg by history developed any symptoms. Two children had seizures or apnea and one died. Ibuprofen occasionally may cause serious toxicity in overdose. [Hall AH, Smolinske SC, Conrad FL, Wruk KM, Kulig KW, Dwelle TL, Rumack BH: Ibuprofen overdose: 126 cases. Ann Emerg Med November 1986;15:1308-1313.]

Alan H Hall, MD*
Susan C Smolinske, RPh*
Frances L Conrad, RN*
Kathleen M Wruk, RN*
Kenneth W Kulig, MD*
Terry L Dwelle, MD†
Barry H Rumack, MD*
Denver, Colorado
Bismark, North Dakota

From the Rocky Mountain Poison and Drug Center, University of Colorado Health Sciences Center, Denver General Hospital, Denver, Colorado;* and the Department of Pediatrics, North Dakota School of Medicine, Bismark, North Dakota.†

Received for publication January 31, 1986.
Accepted for publication April 3, 1986.

Presented in part at the AACT/AAPCC/ABMT/CAPCC Annual Scientific Meeting in Kansas City, Missouri, August 1985.

Address for reprints: Barry H Rumack, MD, Rocky Mountain Poison and Drug Center, 645 Bannock Street, Denver, Colorado 80204-4507.

INTRODUCTION

Ibuprofen overdose generally has been considered to be benign.[1] The recent introduction of ibuprofen preparations as over-the-counter analgesics has increased the availability and thus the potential for both accidental pediatric ingestions and deliberate overdosage.

The appearance of reports of serious toxicity from ibuprofen overdose[1-4] prompted a clinical study of patients with ibuprofen overdosage reported to the Rocky Mountain Poison and Drug Center to determine the incidence and expression of symptoms, the relationship between the amount ingested by history and the development of symptoms, the relationship between ibuprofen plasma levels and the development of symptoms, and whether any changes occur in elimination half-life in overdosage.

METHODS

Records of 218 consecutive calls to the Rocky Mountain Poison and Drug Center involving ibuprofen between January 1984 and August 1985 were examined. All information was collected on standard American Association of Poison Control Centers contact forms. Of the total, 104 contact forms from cases between January and August 1984 were identified by a computer search and examined using a prepared data collection checklist. An additional 114 contact forms from cases between September 1984 and August 1985 were collected prospectively and examined using the same checklist.

Contact forms were examined for demographic data, amount of ibuprofen in milligrams and milligrams-per-kilogram ingested by history, symptoms, the time from ingestion to onset of symptoms, results of ibuprofen plasma levels, outcome, and whether the patient was seen in a health care facility.

Of the 218 cases, 40 asymptomatic patients with total recorded follow-up equal to or less than one hour from the time of ingestion were excluded from analysis as it was thought that the clinical outcome could not be assessed adequately from the limited recorded information. To concentrate on the effects of pure ibuprofen overdose, we excluded 42 patients with coingestants. Nine patients were excluded because they either had no ingestion of ibuprofen by history (information calls, missing medication that was later

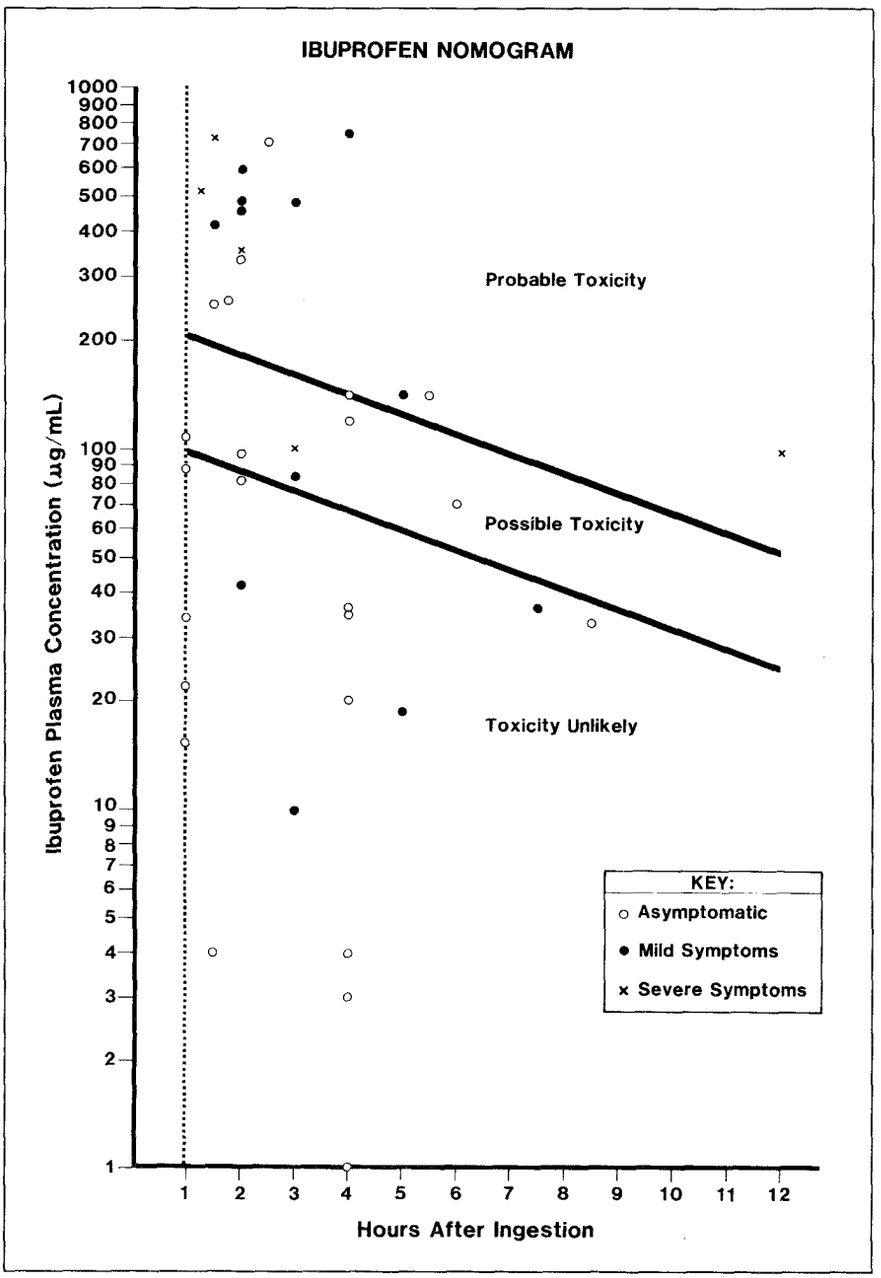

FIGURE. *Twenty-five patients from RMPDC study, seven from Court and Volans,[3] eight reported to the manufacturer (personal communication, William S Barry, MD, Upjohn Company, Kalamazoo, Michigan). Plot is plasma level (µg/mL) versus time (hr). No asymptomatic patients developed symptoms after ibuprofen levels were obtained. No patients with mild symptoms developed severe symptoms after ibuprofen levels were obtained.*

found) or had negative ibuprofen plasma levels between one and four hours after the time of alleged ingestion. One nonhuman ingestion case also was excluded. All symptomatic patients were included in the analysis regardless of the length of follow-up; thus, 126 cases were analyzed.

Cases were divided into subsets for comparison: pediatric (ages 10 months to 5 years) and adult (ages 14 years and older). No patients in the analysis group (126) were between 5 and 14 years old.

The number of follow-up calls made in each case was recorded and the mean number of follow-up calls was calculated for the group of 126 patients.

In the 59 of 126 patients (47%) who were either in a health care facility when the Poison Center was called or who were referred by the Poison Center to a health care facility for evaluation, the history and amount of ingestion were confirmed both from the caller and the health care provider. In cases managed at home, the history was checked repeatedly by usual measures, such as having the caller read the container label to the poison information specialist, counting the number of pills left in the container, subtracting the amount known to be used from the number dispensed, and having the caller search carefully for any spilled medications. If the amount missing was determined later to be different from that given during the initial call, the latter amount was used in calculations.

Symptoms were elicited by experienced poison information specialists using a symptom checklist. All callers were specifically requested to call back to the Poison Center if a patient who had been asymptomatic at the time the case was closed by the poison information specialist later developed symptoms. There were no instances of call-backs reporting the development of symptoms after a case was closed in an asymptomatic patient.

Ibuprofen plasma levels were requested on as many patients as possible who were either symptomatic or had ingested more than 100 mg/kg of ibuprofen by history. All plasma levels were done by a gas chromatographic method.

Symptoms defined as severe were potentially life threatening (seizures, apnea, symptomatic bradycardia or hypotension, anuric renal failure, coma). Mild to moderate symptoms were defined as non-life-threatening (mild central nervous system depression, gastrointestinal upsets, rash, headache, nystagmus or blurred vision, muscle fasciculations).

Amounts of ibuprofen ingested by history (mg/kg in children, total mg and mg/kg in adults) between symptomatic and asymptomatic groups were compared using Student's t test (two-tailed); $P < .05$ was considered significant.

TABLE 1. *Symptoms/signs and frequency (N=126)**

Symptom/Sign	Pediatric (n)	Adult (n)
Mild CNS depression	1	10
Gastrointestinal upset	4	4
Fasciculations	—	1
Nystagmus/blurred vision	—	1
Headache	—	1
Maculopapular rash	—	1
Seizures	2	—
Apnea	1	—
Elevated renal function	—	2
Hematuria	—	1
Hypotension/bradycardia	1	1
Hepatomegaly	1	—
Death	1	—

*Six patients with more than one symptom.

RESULTS

The mean number of follow-up calls made in the group of 126 cases was 2.7 calls per case (range, none to eight).

Symptoms developed in 19% of patients (24 of 126) with pure ibuprofen overdose (Table 1). In the 88 pediatric patients (ages 8 months to 5 years), six (7%) became symptomatic. Of this group, two children developed severe symptoms.

One 16-month-old child ingested 469 mg/kg ibuprofen by history and developed apneic episodes four hours after ingestion. An aspiration pneumonitis developed following the apneic episodes and led to sepsis. The child also had generalized seizures. This patient died on the seventh day following hospital admission despite vigorous supportive care, and was the only death in the series. A 5-year-old child had one generalized seizure within four hours of ingesting an unknown amount of ibuprofen. This patient recovered fully.

Of the 38 adult patients, 18 (47%) became symptomatic, but no life-threatening symptoms occurred. One patient developed mild bradycardia and hypotension without compromise of sensorium or organ perfusion. A second patient with a history of stable, chronic nephritis had an increased elevation over baseline of creatinine from 3.4 mg/dL to 4.1 mg/dL after ingesting 4,000 mg ibuprofen. Subsequent follow up showed a return to the baseline level over one month. A third patient developed hematuria and elevated BUN and creatinine after ingesting 14,000 mg ibuprofen. All patients who developed symptoms did so within four hours of the ingestion.

A total of 37 ibuprofen plasma levels were obtained from 23 patients in the study between 0.5 and 8.5 hours after ingestion (Table 2). Of these, six levels from five patients showed no ibuprofen to be present. These five patients were excluded from analysis. Two patients had plasma levels reported as "< 10 μg/mL," and were not used in construction of the nomogram (Figure). Plasma levels obtained from patients with coingestants were used in nomogram construction if the patients remained asymptomatic. Plasma ibuprofen levels drawn between 1.0 and 8.5 hours after ingestion from this study, together with seven plasma levels from Court and Volans[3] and eight reported to the Upjohn Company, are shown (Figure 1). Plasma levels from the Upjohn Company and Court and Volans[3] are either from patients ingesting only ibuprofen or from asymptomatic patients with coingestants.

Ten patients had at least two ibuprofen plasma levels, allowing calculation of an approximation of the elimination half-life. The mean elimination half-life was 1.53 hours (range, 0.86 to 3.06 hours). The longest elimination half-life of 3.06 hours was in a patient with mild chronic renal failure. Two patients had three ibuprofen plasma levels, permitting a better elimination half-life calculation. These were 1.46 and 1.40 hours.

There was a statistically significant difference ($P < .001$) in the milligram-per-kilogram amounts ingested by history between the pediatric symptomatic and asymptomatic groups. There was no significant difference ($P > .05$) in either total milligrams or milligram-per-kilogram amounts ingested by history between the adult symptomatic and asymptomatic groups (Table 3). No patient who ingested less than 99 mg/kg by history became symptomatic.

DISCUSSION

Ibuprofen, 2-(4-isobutylphenyl) propionic acid, has been available in the United States for approximately ten years as a prescription antiinflammatory and analgesic medication. Nonprescription forms recently have been introduced. Serious toxic effects, including coma, bradycardia, hypotension, apnea, metabolic acidosis, and renal failure, may occur when the drug is taken in overdosage.[2-5]

Serious side effects may occur with therapeutic use, and include hemolysis,[6] renal failure,[7] gastrointestinal hemorrhage, various blood dyscrasias, and minor central nervous system and visual disturbances.[8] A recent review comparing the safety of ibuprofen to that of aspirin and other nonsteroidal antiinflammatory medications showed ibuprofen to be a safe agent.[9]

A previous report of overdose detailed coma and hypotension in a 70-year-old man who ingested 12 g ibuprofen. Diazepam and chlorpheniramine also were ingested. It was unclear how much of the toxicity could be ascribed to the ibuprofen.[2,10] Two reports from the National Poison Information Service in London have described the British experience with ibuprofen overdose.[3,5] Of 73 cases reported during 1980 and 1981, details were available for 42 patients. Among children, 17 developed no symptoms after ingesting 0.2 to 2.4 g; two developed drowsiness and diaphoresis after ingesting up to 3.6 g. Of 23 adults, 13 with 1.4- to 2.4-g ingestions developed mild symptoms (abdominal pain, nausea, vomiting, drowsiness, nystagmus, diplopia, tinnitus). One patient ingested between 9.6 and 16 g and devel-

TABLE 2. *Patients with ibuprofen plasma levels*

Patient No.	Age (yr)	Amount Ibuprofen Ingested by History mg	mg/kg	Symptoms	Ibuprofen Plasma Level (μg/mL)	Time Plasma Level Drawn Post Ingestion (hr)
1	2.5	7,400	544	None	34†	1
					3†	4
2	2.8	2,000	181	None	0	2.75
3	2.8	2,000	—	None	0	2.75
4	1.8	4,000	275	None	88†	1
					35†	4
5*	18	2,000	34	None	36†	4
6	15	12,000	—	None	327†	2
					125†	4
7	2	2,200	193	None	0	4
8*	20	—	—	None	150†	4
					150†	5.5
					33†	8.5
9*	14	3,200	59	Drowsiness/ lethargy	5	4
10	18	—	—	None	0	2
					0	5
11*	16	18,000	—	Drowsiness/ lethargy	93	5
12	1.8	800	59	None	22†	1
					4†	4
13	2	2,000	147	None	108†	1
					20†	4
14	16	17,400	294	Nausea	48	0.5
					10†	3
15	2.3	200	14	None	0	4
16	28	10,000	159	Abdominal cramps	148†	5
17	2	4,200	385	None	4†	1.5
					1†	4
18	33	3,600	—	Drowsiness/ lethargy	742†	4
19	2	6,800	427	None	< 10	1.5
					< 10	4.5
20	17	18,000	305	Nystagmus/ blurred vision	490†	2
					485†	3
					36†	7.5
21‡	15	4,000	—	Elevated renal functions	42†	2
					19†	5
22*	"Adult"	—	—	Drowsiness/ lethargy	32	2.5
23	1.3	8,800	807	Drowsiness/ lethargy	460†	2

*Coingestants.
†Plasma levels used for nomogram.
‡Patient with chronic nephritis.

All patients who developed symptoms did so within four hours of ingestion.

TABLE 3. *Amount of ibuprofen ingested by history vs development of symptoms in adults and children*

	Pediatric Mean (± SEM) Amount Ingested by History	Adult Mean (± SEM) Amount Ingested by History	
	mg/kg	Total mg	mg/kg
Symptomatic	440 (±146)*	9,900 (±1,637)†	58 (±27)†
Asymptomatic	114 (±19)*	8,558 (±1,361)†	17 (±10)†

*$P < .001$ (Student's t test, two-tailed).
†$P > .5$ (Student's t test, two-tailed).

oped renal failure with elevated BUN and creatinine. One patient died after ingesting both ibuprofen and salicylates, and was found to have plasma levels of 240 μg/mL of salicylates and 170 μg/mL of ibuprofen at postmortem examination.[3,5] Some ibuprofen plasma levels were obtained in this series, but the authors did not find a correlation between plasma level and the potential for toxicity.[5]

In 67 patients reported to the Upjohn Company as a part of the voluntary post-marketing reporting system, there were no deaths or permanent sequelae from overdosage in patients 3 years old and younger and in patients 3 to 20 years old.[1] There were three deaths in the 20 years and older/unknown group. The first had coingested salicylates, the second had coingested salicylates and ethyl alcohol, and the third died in hypovolemic shock after ingesting ibuprofen and slashing both wrists. There were no deaths among patients with pure ibuprofen overdose. Plasma levels as high as 539 μg/mL were reported in survivors.[1]

A recent case report describes a patient who developed acute oliguric renal failure requiring hemodialysis after ingesting 54 g ibuprofen. Plasma ibuprofen levels were 53 μg/mL at 48 hours and 16 μg/mL at 59 hours after ingestion.[4]

In this study, no correlation was found in adults between the total milligrams or milligram-per-kilogram amounts ingested by history and the development of symptoms (Table 3). Although no adult patients in this study developed life-threatening symptoms, coma, hypotension, bradycardia, and oliguric renal failure have been reported previously in this age group.[2-4] In pediatric patients, there was a statistically significant correlation between the milligram-per-kilogram amount ingested by history and the development of symptoms. Symptomatic children had a mean ingestion of 440 mg/kg (Table 3). No patient developed any symptoms with an ingestion of less than 99 mg/kg.

Pharmacokinetic properties of ibuprofen in therapeutic doses are rapid absorption (80% in one-half to two hours), elimination half-life of approximately two hours (1.92 to 2.43), no appreciable accumulation with repeated dosing, 90% to 99% protein binding, and a volume of distribution of 0.11 to 0.19 L/kg.[11-15] A single 400-mg dose in adults produces a peak plasma concentration of about 29 μg/mL at 90 minutes after ingestion, which decreases to about 3 μg/mL at eight hours and is not detectable at 12 hours.[1] All of a single administered dose is excreted in the urine within 24 hours, 90% as metabolites.[14] LD_{50}s were found to be 800 mg/kg in mice and 1,600 mg/kg in rats.[16]

In the overdose setting, the elimination half-life does not appear to be prolonged. The mean approximate half-life for the ten patients with at least two plasma levels in this study was 1.53 hours (range, 0.86 to 3.06 hours). These data suggest that the onset of symptoms should be relatively rapid and the duration relatively short in ibuprofen-overdosed patients.

Combining ibuprofen plasma levels from this study (n=25) with those of Court and Volans[3] (n=7), and levels reported to the manufacturer (n=8) (personal communication, William S Barry, MD, Upjohn Company, Kalamazoo, Michigan) allows the construction of a nomogram (Figure).

With levels above the upper ("probable toxicity") line, 11 of 17 patients (65%) were symptomatic. Mild symptoms (gastrointestinal upset, mild central nervous system depression, rash) occurred in seven of these 17 patients. Severe symptoms (coma, seizures, apnea, symptomatic hypotension, or bradycardia) occurred in four of these 17 patients (24%), and six patients remained asymptomatic.

Between the lines ("possible toxicity"), two of six patients (33%) became symptomatic (mild, one; severe, one; asymptomatic, four).

Below the lower line ("toxicity unlikely"), four of 17 patients (24%) developed mild symptoms. No patients with severe symptoms had plasma levels below the lower line.

When ibuprofen plasma levels are available, the nomogram may aid in predicting which initially asymptomatic patients (adult and pediatric) are at risk to develop symptoms later.

Treatment has generally been supportive.[3,5] Airway control as indicated by the patient's condition, support of blood pressure with fluids and vasopressors if necessary, correction of acidosis, and atropine for symptomatic bradycardia may be required. Gastric emptying procedures may be of benefit soon after the ingestion. Induced emesis must be considered carefully because of the possibility for seizures in children ingesting large amounts of ibuprofen. Activated charcoal and a cathartic should be administered in an attempt to decrease absorption. The possible existence of an enterohepatic circulation of ibuprofen[12] suggests that multiple-dose activated charcoal may be of benefit and requires further investigation. Although it has been theorized that forced alkaline diuresis may be useful in overdose,[17] the short half-life in the overdose setting and the fact that 90% of an ingested dose is excreted as metabolites[14] argue against this treatment. No published reports of ibuprofen overdose mention forced alkaline diuresis, and the procedure is unlikely to be necessary or useful.

SUMMARY

The history of the total amount or milligram-per-kilogram amount of ibuprofen ingested by adults is not predictive of the potential for developing symptoms. In children, the milligram-per-kilogram amount of ibuprofen ingested by history does allow assessment of the symptomatic potential. Because the elimination half-life does not appear to be prolonged in the overdose situation, initial manifestations might be expected to have a rela-

tively rapid onset and to be short-lived. No patient in this study developed the onset of symptoms later than four hours after ingestion. The nomogram may aid in predicting which initially asymptomatic patients (adult and pediatric) have the potential to develop symptoms later.

Children with a history of ingesting less than 100 mg/kg may be observed at home. Those with an ingestion of 100 to 200 mg/kg should have induced emesis and be observed at home for four hours with referral to a medical facility if symptoms develop. With ingestion of 200 to 400 mg/kg, immediate gastric emptying and observation in a health care facility for at least four hours with administration of activated charcoal and a cathartic are indicated. Children ingesting more than 400 mg/kg have the greatest risk for developing serious symptoms, and immediate medical referral is appropriate for this group. Induced emesis must be considered in the light of the potential for seizures.

The history of the amount of ingestion is not useful in determining which adult patients need referral to a medical facility. All symptomatic patients and those who have ingested an overdose in a suicide attempt certainly should be evaluated by a health care provider.

Treatment is supportive. There is some evidence for an enterohepatic circulation of ibuprofen,[12] and multiple-dose oral activated charcoal therapy should be evaluated. Children less than 5 years old are particularly susceptible to developing such severe symptoms as apnea, coma, and seizures. Adults ingesting large amounts of ibuprofen also may develop renal failure. Although ibuprofen overdose is often benign, serious symptoms and death may occur.

REFERENCES

1. Barry WS, Meinzinger MM, Howse CR: Ibuprofen overdose and exposure in utero: Results from a postmarketing voluntary reporting system. *Am J Med* 1984;77: 35-39.

2. Hunt DP, Leigh RJ: Overdose with ibuprofen causing unconsciousness and hypotension. *Br Med J* 1980;281:1458-1459.

3. Court H, Volans GN: Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adv Drug React Ac Pois Rev* 1984;3:1-21.

4. Bennett RR, Dunkelburg JC, Marks ES: Acute oliguric renal failure due to ibuprofen overdose. *South Med J* 1985; 78:490-491.

5. Court H, Streete P, Volans GN: Acute poisoning with ibuprofen. *Human Toxicol* 1983;2:381-384.

6. Korsager S: Haemolysis complicating ibuprofen treatment. *Br Med J* 1978;1:79.

7. Poirier TI: Reversible renal failure associated with ibuprofen: Case report and review of the literature. *Drug Intell Clin Pharm* 1984;18:27-32.

8. Cuthbert MF: Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974;2:600-610.

9. Royer GL, Seckman CE, Welshman IR: Safety profile: Fifteen years of clinical experience with ibuprofen. *Am J Med* 1984;77:25-34.

10. Court H, Streete PJ, Volans GN: Overdose with ibuprofen causing unconsciousness and hypotension. *Br Med J* 1981;282:1073.

11. Adams SS, Cliffe EE, Lessel B, et al: Some biological properties of 2-(4-isobutylphenyl)-propionic acid. *J Pharm Sci* 1967;56:1686.

12. Davis LJ: Ibuprofen. *Drug Intell Clin Pharm* 1975;9:501-503.

13. Technical information: *Pharmacokinetic profile for ibuprofen: Motrin® tablets.* Kalamazoo, Michigan, The Upjohn Company, 1981.

14. Adams SS, Buckler JW: Ibuprofen and flurbiprofen. *Clin Rheumatic Dis* 1979; 5:359-379.

15. Greenblatt DJ, Abernethy DR, Matlis R, et al: Absorption and disposition of ibuprofen in the elderly. *Arthritis Rheum* 1984;27:1066-1069.

16. Adams SS, Bough RG, Cliffe EE, et al: Absorption, distribution and toxicity of ibuprofen. *Toxicol Appl Pharmacol* 1969; 15:310-330.

17. Upjohn Company: Production Information, Motrin®, in: *Physicians' Desk Reference, 39th ed.* Oradell, New Jersey, Medical Economics Co, 1985, p 2128-2130.