Clinical Investigation

Ibuprofen Overdose—A Prospective Study

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Of 61 cases of ibuprofen overdosage reported consecutively to the Rocky Mountain Poison and Drug Center from September 1985 through April 1986, 16 were excluded because of incomplete follow-up or concurrent medication ingestion. A toxic reaction developed in 7 (16%) of the remaining 45 patients. Nausea, vomiting, abdominal cramps, mild central nervous system depression, coma, tachycardia, apnea, metabolic acidosis with or without respiratory alkalosis, hematemesis, and oliguric renal failure were noted. Two of six adults had a toxic reaction, and one died. Among pediatric patients, 5/39 (13%) had a toxic reaction. Of patients whose ibuprofen ingestion was less than 104 mg per kg, none became ill. All patients in whom the time of ingestion was known (six of seven) and who had a toxic reaction did so within four hours of ingestion. An ibuprofen overdose, although usually benign, can occasionally produce serious toxicity.

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Although ibuprofen is often a benign drug in overdosage,[1] the development of serious toxic effects has been reported.[2-5] In a previous combined retrospective and prospective study from the Rocky Mountain Poison and Drug Center (RMPDC), a 19% incidence of ibuprofen toxicity occurred in a series of 126 patients.[5] The present prospective study was carried out to further characterize the toxicity of ibuprofen overdose.

Patients and Methods

We collected prospectively 61 cases of ibuprofen ingestion reported consecutively to the RMPDC over a period of eight months (from September 1985 through April 1986). Data recorded on standard American Association of Poison Control Centers contact forms included demographic information and specified whether the ingested preparation was prescription or nonprescription; the amount of ibuprofen ingested per body weight (milligrams per kilogram); the presence and type of toxicity reported; the time from ingestion to the onset of a toxic reaction; levels of ibuprofen in plasma; and outcome.

The description of signs and symptoms was elicited by experienced poison information specialists using a checklist. Information about the amount ingested was confirmed both with the caller and the health care providers when patients were evaluated in a health care facility. In cases of evaluation by telephone only, the history of the amount ingested was repeatedly checked by methods commonly used by poison centers—that is, having the caller read the container label to the poison information specialist, counting the number of pills remaining in the container, subtracting the number of pills known to have been used from the number dispensed, and having the caller conduct a careful search for any spilled medications. If the amount of medication missing was later determined to be different from that reported during the initial call, the latter amount was used in calculations. All callers were specifically instructed to call back to the poison center immediately if a patient who had been asymptomatic at the time the case was closed by the poison information specialist later had symptoms. No such calls were received.

In all, 12 asymptomatic patients with a total recorded follow-up of one hour or less after ingestion were excluded from analysis because the outcome could not be adequately assessed. Four patients with a history of ingesting other medications in addition to ibuprofen were also excluded.

The 45 cases remaining in the study were divided into adult (16 years and older) and pediatric (0.8 to 3 years) subsets for comparison. There were no patients in this series between 3 and 16 years of age.

Results

Toxic reactions occurred in 7/45 patients (16%) with a history of pure ibuprofen overdosage. Among the 45 patients, 3 had vomiting; 3 had mild central nervous system (CNS) depression; and there was 1 case each of nausea, abdominal cramps, tachycardia, coma, apnea, metabolic acidosis, mixed metabolic acidosis and respiratory alkalosis, hematemesis, and oliguric renal failure, with more than one clinical effect noted in three cases.

Of the 39 pediatric patients, 5 (13%) had toxic reactions. Three of these children had only gastrointestinal symptoms—abdominal cramps, vomiting, or nausea—after ingesting 104, 130, and 131 mg per kg, respectively. The fourth child had gastrointestinal symptoms and mild CNS depression after ingesting 708 mg per kg and had an ibuprofen plasma concentration of 533 μg per ml one hour after ingestion (therapeutic range from the laboratory doing the assay: 10 to 50 μg per ml). The fifth had vomiting, lethargy, transient periods of apnea, and metabolic acidosis (pH 7.27; partial carbon dioxide pressure [P_{CO_2}] 36 torr) after in-

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
P_{CO_2} = partial carbon dioxide pressure
RMPDC = Rocky Mountain Poison and Drug Center
SEM = standard error of the mean

gesting 666 mg per kg. The ibuprofen plasma concentration was 680 μg per ml 3½ hours after ingestion. (This case has been previously reported by the treating physicians.[6])

There were no deaths or permanent sequelae in children. Symptomatic children had a mean (± standard error of the mean [SEM]) drug ingestion of 348 ± 139 mg per kg, whereas in asymptomatic children the mean ibuprofen ingestion was 135 ± 19 mg per kg.

Two of the six adult patients had toxic reactions. One of these had ingested an undetermined amount of ibuprofen and had transient mild CNS depression. The other, a 64-year-old man who had ingested forty 600-mg ibuprofen tablets (24 grams; 407 mg per kg) during the course of a day, was seen in the emergency department the same evening with confusion, tachycardia (120 beats per minute) without hypotension, and Hematest-positive emesis. According to the history, no other drugs or agents had been ingested. His initial serum electrolyte values were as follows: sodium 130, potassium 4.6, chloride 98, and total carbon dioxide 13 mEq per liter (anion gap, 19 mEq per liter). Arterial blood gas determinations in the emergency department showed a pH of 7.47, a P_{CO_2} of 18 torr, and a bicarbonate of 13 mEq per liter. Gastric lavage was followed by the administration of activated charcoal and magnesium sulfate as a cathartic, and the patient was admitted to the intensive care unit. His level of consciousness deteriorated over the following few hours, and the patient became comatose. Oliguria was noted over the next three hours, at which time serum electrolyte levels still showed an anion gap of 17 mEq per liter. The blood urea nitrogen (BUN) value was 103 mg per dl and serum creatinine was 2.8 mg per dl. The patient's condition continued to deteriorate despite supportive measures: Oliguria continued, sepsis developed, and he died on the second hospital day. The patient's family had requested that neither hemodialysis nor resuscitative measures be carried out. The results of a toxicology screen and a salicylate assay on admission were subsequently reported to be normal. An ibuprofen plasma concentration of a specimen obtained at an unknown time more than 12 hours after ingestion was 15.8 μg per ml.

Seven ibuprofen plasma concentrations were measured in four patients included in the analysis. The specimens for six of these plasma levels from three patients were obtained at known times between one and ten hours after ingestion, and the data are shown in Figure 1.

Of the seven patients who had toxic reactions, the six for whom the time of ingestion was known became ill within four hours of ingestion. None of the patients who had ingested less than 104 mg per kg of ibuprofen became ill.

Seven pediatric and three adult patients ingested prescription preparations; one of seven children and two of three adults had toxic reactions. Three adults and 32 children ingested nonprescription preparations; four of the children but none of the adults became ill.

Discussion

Ibuprofen, 2-(4-isobutylphenyl)-propionic acid, is an anti-inflammatory, analgesic, and antipyretic medication available in the United States in both prescription and nonprescription preparations. Serious toxic effects caused by overdosage, including oliguric renal failure, apnea, bradycardia, hypotension, metabolic acidosis, seizures, and coma, have been previously reported.[2-5]

Known pharmacokinetic properties of ibuprofen in therapeutic doses include an elimination half-life (τ½) of about two hours (1.92 to 2.43), volume of distribution 0.11 to 0.19 liters per kg, rapid absorption (80% in ½ to 2 hours), and 90% to 99% protein binding.[8-12] Plasma concentrations in adults given a single 400-mg dose orally peak at about 29 μg per ml after 1½ hours, decrease to about 3 μg per ml after 8 hours, and become undetectable 12 hours after ingestion.[1] A single oral dose is completely excreted (90% as metabolites) in the urine over a 24-hour period.[10]

In an earlier combined retrospective and prospective RMPDC study of 126 patients with a history of pure ibuprofen ingestion, there was no correlation in adults between the amounts of ibuprofen reported by the patients to have been ingested and the development of toxic effects.[5] In the present series, the small adult sample size precluded a meaningful comparison of symptomatic and asymptomatic adult patients. The earlier study found a significant difference between the mean (± SEM) amounts (mg per kg) of ibuprofen reportedly ingested by symptomatic (440 mg per kg ± 146)

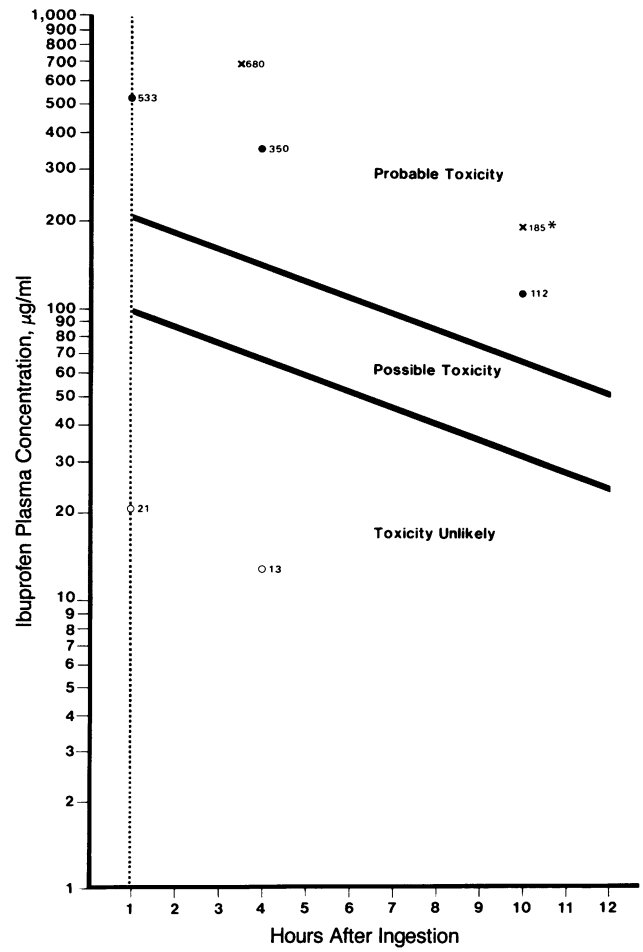

Figure 1.—Ibuprofen plasma concentrations in the present series are plotted on the ibuprofen nomogram developed from data in a previous study (from Hall et al[5]). *Ibuprofen plasma level taken from Lee and Finkler.[7] ○ = asymptomatic, • = mild symptoms, × = severe symptoms

and asymptomatic (114 mg per kg ± 19) children.[5] The mean amounts of the drug reported to have been ingested by children in the present series were 348 ± 139 mg per kg in symptomatic and 135 ± 19 mg per kg in asymptomatic patients, which are reasonably similar to those of the previous study.

There was one ibuprofen-related death among the children in the previous study.[5] There was no death among the children in the present series.

An ibuprofen nomogram (Figure 1) was developed from the earlier study data to aid in predicting which of the patients who are initially asymptomatic or mildly ill are at risk for the later development of more serious toxic reactions.[5] Plasma concentrations of ibuprofen in patients in the present series were compared with those in the nomogram to assess its predictive ability. The most seriously ill child had a plasma level of ibuprofen of 680 μg per ml 3½ hours after ingestion, which is in the "probable toxicity" area of the nomogram. A second child with gastrointestinal symptoms and mild CNS depression had plasma concentrations of the drug of 533 μg per ml after one hour, 350 μg per ml after four hours, and 112 μg per ml ten hours after ingestion, which are all in the "probable toxicity" range. An asymptomatic child had plasma concentrations of ibuprofen of 21 μg per ml after one hour and 13 μg per ml four hours after ingestion, which are both in the "toxicity unlikely" area. The nomogram thus accurately predicted the potential for the development of toxic reactions in the three patients from the present series in whom timed plasma concentrations of ibuprofen were determined.

One adult patient died after ingesting 24 grams of ibuprofen. There was no indication in the patient's history of concurrently ingesting other substances, and toxicology screening and salicylate assay results were normal. All previously reported cases of adults whose deaths were related to ibuprofen ingestion were complicated by concurrent ingestion of other substances, carbon monoxide poisoning, or exsanguination from self-inflicted wounds.[1] The specimen for determining the plasma ibuprofen concentration of 15.8 μg per ml was taken at an unknown time later than 12 hours after ingestion, and the level could only be used to verify the presence of the drug. It could not be compared with the levels on the nomogram.

In a recent case report, Lee and Finkler described a similar clinical course in a 48-year-old man who had ingested more than 20 grams of ibuprofen.[7] Coma, metabolic acidosis, mild hypotension, elevated BUN and creatinine levels, proteinuria and occult hematuria, mildly abnormal liver function, thrombocytopenia, and prolongation of both prothrombin and partial thromboplastin times were noted. No other agents were found on urine and blood toxicology screening. While the clinical course was complicated by acute renal failure, the adult respiratory distress syndrome, fever, and upper gastrointestinal tract bleeding, the patient survived with intensive supportive care.[7] The specimen for determining ibuprofen plasma level was obtained ten hours after ingestion, and the level was 185 μg per ml, which on the nomogram in Figure 1 falls in the "probable toxicity" area.

Adult patients ingesting between 6 and 54 grams of ibuprofen have been reported to have such symptoms and signs as nausea, vomiting, abdominal cramps, coma, elevated prothrombin and partial thromboplastin times, upper gastrointestinal tract bleeding, metabolic acidosis, and oliguric or nonoliguric renal insufficiency that required hemodialysis treatment in some cases.[2-4,7,13-15] It is currently unclear whether all adult patients who have taken an overdose of ibuprofen will become symptomatic within the first four hours after ingestion. Such patients have first come to medical attention between 1 and 48 hours after the ingestion, and the exact time of symptom onset was not reported in all cases.[2-5,7,13-15] The time of symptom onset following ingestion could not be determined in the patient in the present series who died.

Treatment of patients who have ingested an ibuprofen overdose is primarily supportive. Airway control and artificial ventilation, pulse and blood pressure support with fluids, the administration of atropine sulfate or vasopressors, correction of acidosis, and anticonvulsant therapy may be required. Gastric emptying may be beneficial soon after ingestion. Seizures have been reported in children in whom ibuprofen ingestion exceeded 400 mg per kg, and induced emesis may be dangerous in such cases.[5] Activated charcoal and a cathartic should be administered in an attempt to decrease drug absorption. Multiple-dose oral activated charcoal therapy has not yet been evaluated in ibuprofen overdosage.

Conclusion

Although many patients who ingest an overdose of ibuprofen remain asymptomatic, serious drug toxicity, including death from the complications of overdosage, occasionally occurs. Based on data from the medical literature, the previously published RMPDC study, and the present series, the following protocol is suggested as a rational way to proceed with assessment and referral of patients with an ibuprofen overdose.

Knowing the amount of drug ingested by adult patients is not predictive of the need for medical referral and observation. All symptomatic adults and those attempting suicide should be referred to a health care facility. Those who either remain actively suicidal or have any symptoms should be admitted to hospital until these conditions have cleared. Adult patients with no initial symptoms should be observed for a minimum of four hours in a controlled setting. If no symptoms develop during this period of observation, the decision to discharge patients not requiring admission for psychiatric reasons must be made on an individual basis. As the frequency of occurrence and time of onset of ibuprofen-induced renal insufficiency are presently poorly understood, obtaining baseline urinalysis, BUN, and serum creatinine values at the initial visit is suggested, with a follow-up evaluation scheduled for patients not admitted to hospital.

In children, the amount of ibuprofen ingested per body weight, as determined from the history, appears to be predictive of the potential for a toxic reaction developing and the need for medical referral. At levels of ingestion of less than 100 mg per kg, drug toxicity is unlikely to develop, and the children may be safely observed at home. Those ingesting 100 to 200 mg per kg may be managed with induced emesis and home observation for at least four hours, with referral to a health care facility reserved for those children in whom a toxic reaction develops. Children ingesting 200 to 400 mg per kg of ibuprofen should have immediate gastric emptying, activated charcoal and a cathartic administered, and they should be observed for at least four hours in a health care facility. Ingesting more than 400 mg per kg of the drug places

children at greater risk for a serious toxic reaction, and they should have immediate medical referral and careful observation, with supportive therapy as indicated by the clinical presentation and course. If gastric emptying is judged necessary, a gastric lavage is indicated instead of ipecac-induced emesis in children whose ibuprofen ingestion exceeds 400 mg per kg, because of the danger of convulsions and possible aspiration of gastric contents.

In both children and adults, the ibuprofen nomogram may be useful in predicting the potential for the development of drug toxicity and estimating its potential degree of severity when plasma levels can be measured.

The treatment of patients with ibuprofen overdosage is primarily supportive. Although uncommon, serious toxic reactions or death can result from an ibuprofen overdosage.

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