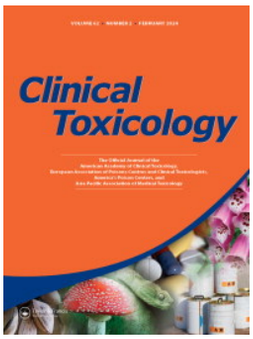

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IBUPROFEN OVERDOSE IN ADULTS

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ABSTRACT

A prospective study of 63 ibuprofen overdose cases in adults (14 years or older) reported to the Rocky Mountain Poison and Drug Center between March 1987 and February 1988 was done to determine the incidence of renal injury and utility of timed plasma levels. No serious toxicity was noted. No CNS or other significant toxicity was seen with ingestion of less than 3 g. Two patients with normal serum creatinines had minor elevations of the blood urea nitrogen after ingesting 4 and 4.8 g. Timed plasma levels (125 total) from patients without coingestants from this study (48) and previously published reports (77) were compared with a previously described nomogram. The resulting nomogram revision may be useful in determining which initially asymptomatic patients are likely to remain so. Renal function tests are not routinely required for patients ingesting less than 6 g. Four h of observation is sufficient for asymptomatic patients not requiring psychiatric

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admission. Plasma ibuprofen levels are not required for proper patient management. *(Key Words: ibuprofen; poisoning, human.)*

INTRODUCTION

Ibuprofen overdosage is most often benign, although serious toxicity and death have been reported (1-5). From 1985 through 1988, 55 800 cases of ibuprofen exposure were reported to the American Association of Poison Control Centers National Data Collection System: 10 312 of these patients (18%) were symptomatic, and 135 had symptoms classified as "major" (potentially life-threatening, lasting longer than 24 h, or resulting in permanent sequelae) (6-9). Health care facility evaluation was sought by 22,726 of these patients (41%). Details were available for only three of the twelve fatalities; in two cases the fatal outcome was more likely due to coingestants.

Ibuprofen overdose has been characterized in five large case series (1,2,4,10,11), as well as in small series and isolated case reports (3,5,12-17). Most ibuprofen-overdosed patients either remain asymptomatic or develop mild gastrointestinal disturbances or minor CNS depression (1,2,4,10,11).

Although all adult ibuprofen-overdosed patients in two case series had symptom onset within 4 h after ingestion (1,2), cases have been reported of symptomatic adults, particularly with oliguric or non-oliguric renal failure, who have first come to medical attention as late as 48 h following ingestion (4,10,17,18). Most adult patients with serious toxicity ingested 20 g or more of ibuprofen (2,15-17). One patient, however, developed reversible non-oliguric renal failure with an elevated blood urea nitrogen (BUN) and serum creatinine, hematuria, and proteinuria after ingesting 6 g in association with salbutamol (18).

A consideration in the emergency department management of ibuprofen overdose is the required duration of observation of asymptomatic patients not requiring admission for psychiatric reasons. A protocol for emergency department observation has been devised from two case series for pediatric patients based on the amount of ibuprofen ingested per kilogram body weight (1,2), but a similar dose-response prediction is not available for adults (1).

Two groups of investigators have attempted to define a relationship between timed ibuprofen plasma levels and the risk of toxicity (1,2,19). The actual need for measuring such levels, however, has been questioned (11,20).

The present study was undertaken to further characterize the toxicity of ibuprofen in adults, to evaluate the potential for development of oliguric or non-oliguric renal failure following acute overdosage, to assess the time of symptom onset in adults, and to gather more data on the possible relationship between timed ibuprofen plasma levels and the potential for subsequent toxicity.

METHODS

All cases of ibuprofen overdose in patients aged 14 years and older reported to the Rocky Mountain Poison and Drug Center (RMPDC) between March 1, 1987 and February 28, 1988 were collected prospectively.

At the time of initial poison center consultation, a protocol for renal function data was suggested to the treating physician; this consisted of a baseline BUN, serum creatinine, and urinalysis. For patients released from the treatment facility, repeat BUN, serum creatinine, and urinalysis were suggested at 24 h after discharge, with daily follow up if abnormal. For patients admitted to the hospital, it was suggested that BUN, serum creatinine, and urinalysis be obtained every two to four h for 24 h or until normalization. Ibuprofen plasma levels at 1, 4, and 12 h postingestion were also suggested.

Patients were managed in a wide variety of settings from tertiary referral centers to rural outpatient facilities in a three-state cachement area, and compliance with the suggested protocol was necessarily variable.

Data analysis was limited to patients ingesting ibuprofen without coingestants. As in previous studies (1,2), nausea or vomiting following administration of ipecac syrup or activated charcoal/cathartic were not considered symptoms due to ibuprofen.

The amounts of ibuprofen said to have been ingested by symptomatic and asymptomatic patients were compared using Student's *t*-test (two-tailed). The possible association between different gastric decontamination procedures

and the absence of symptoms was evaluated using the Chi square test (Yates Correction).

To evaluate the predictive value of a previously developed nomogram relating timed ibuprofen plasma levels to symptoms (1), data from the present study (48 samples, 34 patients) were combined with previously reported data (77 samples, 64 patients), if the following criteria pertained: no coingestants; levels obtained between 1 and 12 h after ingestion; adequate clinical data available to classify toxicity as asymptomatic, mild/moderate, or severe. Some of these published plasma levels have appeared in more than one report, but duplications were avoided whenever possible. All ibuprofen plasma levels obtained from each patient were utilized.

The relative numbers of symptomatic and asymptomatic patients with ibuprofen plasma levels obtained between 1 and 12 h after ingestion and falling either above or below the lower line on the previously developed nomogram (1) were compared using the Chi square test (Yates Correction). Because other investigators evaluating the relationship between timed plasma levels and symptoms utilized only the first (19) or highest (11) levels, mean ibuprofen levels obtained between 1 and 5 h after ingestion (when initial or predicted peak levels would have been obtained) from symptomatic vs. asymptomatic patients which were either above or below the lower nomogram line were also compared using Student's *t*-test (two tailed). Values of $p < 0.05$ were considered significant.

RESULTS

During the 12-month study period, 154 cases of adult ibuprofen overdose were reported to the RMPDC. The history was erroneous in one case and 90 involved coingestants, leaving 63 patients, all of whom were evaluated in a health care facility, as the study group.

Of these 63 cases, 37 patients (59%) remained asymptomatic following reported ingestion of 1.2 to 48 g (mean: 9.5 g). There were 26 symptomatic patients (41%) who reportedly ingested 1.2 to 60 g (mean: 11.5 g). There was no difference in the amounts of ibuprofen said to have been ingested between these two groups (Student's *t*-test [2 tailed]; $p = 0.493$).

The symptomatic and asymptomatic groups had a similar number of poison center follow up calls (mean: 5 vs. 4) and prevalence of hospital admissions (62% vs. 59%).

No severe or potentially life-threatening toxicity was reported in the 26 symptomatic patients. Mild central nervous system (CNS) depression and gastrointestinal upsets were the most common findings (Table 1). The lowest reported dose causing any CNS depression was 3 g. In 23 of 26 symptomatic patients (88%), the onset of symptoms was within 4 h of ingestion. Dizziness was noted beginning 8 h after ingestion in one patient; mild CNS depression began at 11 h after ingestion in one patient; and headache, nausea, and abdominal pain developed at 11 h after ingestion in one patient. Ibuprofen doses said to have been ingested by these three patients were 3, 11, and 14 g respectively.

In the symptomatic group, prescription ibuprofen preparations were ingested by 17 patients (65%) and nonprescription preparations by 8 patients (31%) (preparation class not recorded in one case). In the asymptomatic group, prescription preparations were ingested by 18 patients (49%) and nonprescription preparations by 19 patients (51%).

Initial treatments are listed in Table 2. No technique or combination of techniques was shown to be superior in this study. Nearly twice the percentage of asymptomatic patients had gastric lavage (35% vs. 19%), and a larger percentage of the asymptomatic group also had both a gastric emptying procedure and activated charcoal/cathartic (59% vs. 42%); these were not significantly different (gastric lavage vs. other treatment, $p = 0.27$; gastric emptying plus administration of activated charcoal/cathartic vs. gastric emptying alone, $p = 0.28$; Chi square test [Yates Correction]).

Renal function tests were obtained in 50 of the 63 study patients. Minor abnormalities were noted in only two cases. One patient, who developed abdominal pain after stated ingestion of 4.8 g, had a BUN of 26 mg/dL (9.282 mmol/L) within 24 h of ingestion, but a concomitantly obtained serum creatinine was normal at 1.0 mg/dL (88.4 umol/L). An otherwise asymptomatic patient had a BUN of 23 mg/dL (8.211 mmol/L) within 24 h of ingesting a stated 4 g. The serum creatinine was normal at 0.8 mg/dL (70.72 umol/L). The BUN had decreased to 9 mg/dL (3.213 mmol/L)

TABLE 1

Observed Clinical Effects in Adult Ibuprofen Overdose Patients (N = 26)

Clinical Effects	No.*
CNS Effects	
Mild CNS Depression	10
Dizziness	5
Headache	1
Tinnitus	1
Gastrointestinal Effects	
Vomiting	6
Nausea	4
Abdominal Pain	4
Other Effects	
Mild Metabolic Acidosis	2
Muscle Fasciculations	2
Mydriasis	1
Chills	1
Diaphoresis	1
Hyperventilation	1
Mildly Elevated Systolic Blood Pressure	1
Asymptomatic Bradycardia and Intermittent Junctional Rhythm	1

*10 patients with more than one clinical effect

with a concomitant serum creatinine of 0.7 mg/dL (61.88 umol/L) when repeated a few hours later.

Plasma ibuprofen levels were assayed 55 times in 41 patients. Seven of the assays from seven patients were excluded from analysis as below the limit of detection (2 cases), obtained less than one h or more than 12 h after ingestion (3 cases), obtained at an unknown time (1 case), or having only a qualitative assay (1 case). The remaining 48 ibuprofen plasma concentrations obtained from 34 patients between one and 12 h after ingestion are displayed in Figure 1. Seventeen ibuprofen plasma levels ranging from 7 to 513 mcg/mL were obtained from 12 symptomatic patients, and 31 levels ranging from 4 to 750 mcg/mL were obtained from 22 asymptomatic patients.

TABLE 2

Initial Treatments

Treatment	Symptomatic (n = 26)*		Asymptomatic (n = 37)†	
	No.	%	No.	%
Ipecac Syrup	10	38	15	41
Gastric Lavage	5	19	13	35
Activated Charcoal/ Cathartic	21	81	32	86
None	4	15	1	3

* 11 patients (42%) received either syrup of ipecac + activated charcoal/cathartic or gastric lavage + activated charcoal/cathartic; 1 patient received all 3 treatments.

† 22 patients (59%) received either syrup of ipecac + activated charcoal/cathartic or gastric lavage + activated charcoal/cathartic; 1 patient received all 3 treatments.

All previously reported ibuprofen plasma levels meeting the criteria described above are also displayed in Figure 1. A total of 77 ibuprofen plasma levels obtained from 64 patents were retrieved in this manner (1-3,10,12,17,19,21- 25). Eight of these cases reported to the Upjohn Company were obtained previously by personal communication with William H. Barry, M.D. (1). A recent study (11) described 36 additional ibuprofen plasma levels from patients without coingestants; these were reported as ranges with the times obtained postingestion not listed, and could not be used in the present analysis.

The 125 ibuprofen plasma levels were plotted on the previously developed nomogram (Figure 1) (1). In the area below the lower line ("Toxicity Unlikely"), there were 48 levels representing no patients with severe (potentially life-threatening) symptoms, 14 levels (29%) from patients with mild/moderate symptoms, and 34 (71%) from patients who were asymptomatic. In the area above the lower line, there were 77 plasma levels representing 49 levels (64%) from patients with any symptoms, 13 (17%) from patients with severe symptoms, 36 (47%) from patients with mild/moderate symptoms, and 28 (36%) from patients who were

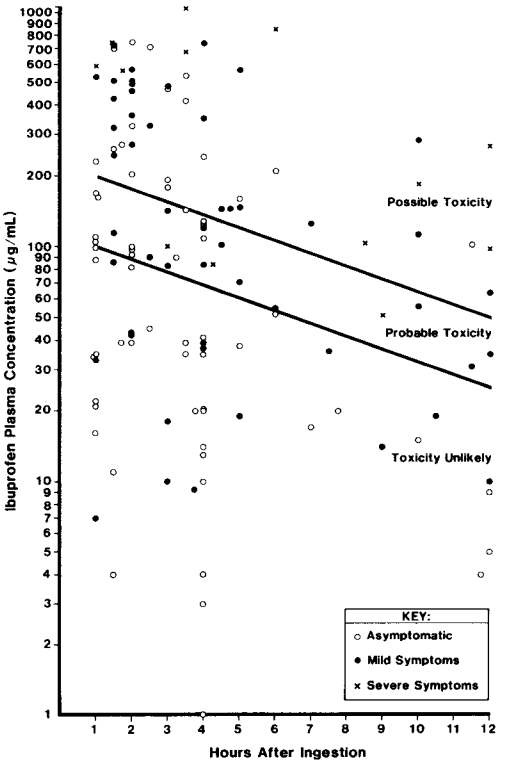

Figure 1. Ibuprofen plasma levels from the present study and the published literature plotted on the previously developed nomogram. (Original nomogram copyright *Annals of Emergency Medicine*, 1986 (1); Used by permission.)

asymptomatic. Symptoms noted in patients with ibuprofen plasma levels below the lower nomogram line are listed in Table 3.

A significantly greater number of patients with levels above the lower nomogram line were symptomatic (Chi square test [Yates Correction]; $p = 0.0004$). There was also a significant difference in the means of the 100 ibuprofen plasma levels (55 from asymptomatic; 45 from symptomatic patients) obtained from 1-5 h after ingestion (the time of initial or predicted peak levels based on the known kinetics of ibuprofen in therapeutic and overdose amounts) between the asymptomatic group (144 mcg/mL $\pm$ 183 mcg/mL; S.D.) and the symptomatic group (294 mcg/mL $\pm$ 261 mcg/mL; S.D.) (Student's t-test, two tailed; $p = 0.002$).

TABLE 3

Symptoms in Patients with Ibuprofen Plasma Levels Below the Revised Nomogram Line (N = 14)

Symptoms	No. Patients*
Epigastric Pain	3
Nausea	3
Vomiting	3
Dizziness	2
Tinnitus	2
Diaphoresis	1
Elevated Renal Function Tests (transient; patient with pre-existing chronic nephritis)	1
Headache	1
Mild CNS Depression	1
Nystagmus/Blurred vision	1
Tachycardia	1

* Some patients with more than one symptom.
(References: 1,19,21,Current Study)

DISCUSSION

In two previous ibuprofen overdose case series, no patients had symptom onset later than 4 h following ingestion (1,2). In the current study, three patients developed mild symptoms similar to known therapeutic side effects (dizziness, mild gastrointestinal upsets, and mild CNS depression) (26-29) at 8 and 11 h after ingestion. If these patients had been discharged from the emergency department following 4 h of observation, it is quite unlikely that any harm would have resulted.

The dose said to have been ingested in adult ibuprofen overdose was not correlated with the development of symptoms in a previous (1) or the present study. However, the lowest dose causing any CNS depression was 3 g, which was also the lowest dose ingested by one of the three patients who developed symptoms more than 4 h after ingestion. Patients ingesting 3 g or less who remain asymptomatic during 4 h of observation thus have little risk of developing any significant delayed toxicity.

Initial treatment was similar for the symptomatic and asymptomatic groups (Table 2). The numbers of untreated patients were too small for any meaningful statistical comparison. Despite the lack of definite evidence for clinical benefit, measures to decrease absorption are recommended for patients who present shortly after ingestion and have ingested 3 or more g.

Development of oliguric or non-oliguric renal failure has been previously reported in adult ibuprofen overdoses (2,10,15-18). In most such cases (when coingestants were not involved), ingested doses have been in excess of 20 g (2,4,15-17). However, in one case, ingestion of 8 g was associated with acute oliguric renal failure (4). Ingestion of between 9.6 and 16 g has also been associated with elevated levels of BUN and serum creatinine (10). Reversible non-oliguric renal failure was associated with reported ingestion of only 6 g in another case, but salbutamol was also involved (18).

Systematic evaluation for renal compromise following acute ibuprofen overdose has not been reported (1,2,4,10,11,19). The present study of renal function in 50 of 63 patients disclosed slightly elevated BUNs in two patients with normal serum creatinines. In the one case where the test was repeated, BUN returned to normal in a few hours. Renal function tests do not seem to be indicated unless the patient has ingested 6-20 g or more.

Appreciating the possible relationship between ibuprofen plasma levels and the potential for development of symptoms has been limited by the available data (1,2,19). If plasma ibuprofen levels are of predictive value, then a level obtained at any point in time covered by the graph should be predictive of the potential for toxicity. For this reason, all available levels from patients from the present study and the published literature meeting the criteria described above were utilized in one portion of the analysis.

Because two other groups of investigators approached the potential relationship between plasma levels and symptoms utilizing either the first or the highest ibuprofen plasma levels (11,19), an analysis was also done of plasma levels obtained between 1 and 5 h after ingestion, when initial levels were obtained or peak levels were predicted to occur following ingestion of both therapeutic and overdose amounts (1,2,25,30-32). A significant difference was demonstrated in mean levels between the symptomatic and

asymptomatic groups, indicating that plasma levels may indeed be predictive of the potential for developing toxicity.

Initial analysis of all available data indicated that a three-tiered nomogram as previously described (1) is not more predictive of the relationship between timed plasma levels and toxicity than a two-tiered nomogram based on a line connecting 100 mcg/mL at 1 h with 25 mcg/mL at 12 h after ingestion on a semilogarithmic plot (the lower line from the previously developed nomogram) (Figure 2).

No patients with severe (potentially life-threatening) toxicity had levels below the revised nomogram line. Symptoms in the patients with ibuprofen plasma levels below this line were limited to previously described side effects of therapeutic doses (26-29) (Table 3). The area below the line on the revised nomogram should thus be renamed "Significant Toxicity Unlikely" and the area above the line "Possible Toxicity" (Figure 2).

The clinical utility of plasma ibuprofen levels, however, is minimal (11,19,33). The use of supportive measures is dictated solely by the patient's symptoms, most of which develop by 4 h after ingestion. In selected cases, including the stated ingestion of large doses, the revised nomogram could predict whether an initially asymptomatic ibuprofen-overdosed patient not requiring admission for psychiatric observation might be safely discharged from the emergency department.

A recent study by McElwee *et al.* (11) concluded that the nomogram is without prognostic value. However, these authors appear to have classified as symptomatic those patients who developed nothing more than nausea or vomiting following administration of ipecac syrup or activated charcoal/ cathartic, and also included data from symptomatic patients with coingestants. As symptomatic cases were not defined in a manner similar to that used by other investigators who have found a relationship between timed ibuprofen plasma levels and toxicity (1,19), the poor positive predictive value found for the nomogram in this study (11) cannot be assumed to be conclusive.

A potentially valuable conclusion from the McElwee *et al.* study (11), however, is a negative predictive value for the lower nomogram line in patients without a history of coingestants of 95.2%. This finding correlates with the present study, and supports the use of the nomogram to predict whether initially asymptomatic patients are likely to remain so.

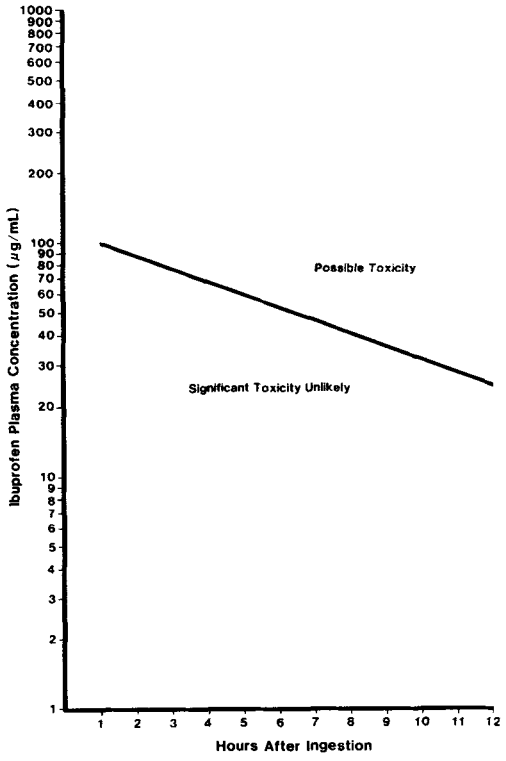

Figure 2. Revised ibuprofen nomogram.

CONCLUSION

Ibuprofen overdose in adults only rarely results in significant toxicity. However, infrequent must not be confused with unimportant. Significant toxicity and death have occurred following ibuprofen-only overdosage, mandating careful emergency department evaluation and observation, especially in the absence of a correlation between the dose said to have been ingested by adults and the potential for symptom development.

The majority of symptomatic patients develop toxicity similar to side effects seen with therapeutic doses. The prevalence of significant renal injury following acute overdose with ibuprofen alone appears low, and has previously been associated with ingestion of 6-20 g or more. Baseline renal function tests are thus generally unnecessary for patients ingesting less than 6 g of ibuprofen.

The clinical utility of the nomogram is minimal, especially as treatment is symptomatic and based on the clinical condition. Obtaining or monitoring ibuprofen plasma levels is unnecessary for the proper evaluation and management of most cases of ibuprofen overdose.

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