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TOXICOLOGY OBSERVATION

Polyuria, Acidosis, and Coma Following Massive Ibuprofen Ingestion

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Abstract Ibuprofen was the first over-the-counter nonsteroidal anti-inflammatory drug available in the United States. Despite being a common agent of ingestion, significant toxicity in overdose is rare. We report a case of a massive ibuprofen ingestion who developed polyuria, acidosis, and coma but survived, despite having a serum ibuprofen concentration greater than previous fatal cases. A 19-year-old man ingested 90 g (1,200 mg/kg) ibuprofen. He was initially awake and alert, but his level of consciousness deteriorated over several hours. Seven hours following the ingestion, he was intubated and mechanically ventilated secondary to loss of airway reflexes. He developed a lactic acidosis and polyuria, which lasted for nearly 24 h. His serum creatinine peaked at 1.12 mg/dL. An ibuprofen level drawn 7 h postingestion was 739.2 mg/L (therapeutic 5–49 mg/L). We describe a case of a massive ibuprofen overdose characterized by metabolic acidosis, coma, and a state of high urine output who survived with aggressive supportive care. This case is unique in several ways. First, ibuprofen levels this high have only rarely been described. Second, polyuria is very poorly described following ibuprofen ingestions.

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Introduction

Ibuprofen is a nonnarcotic analgesic and anti-inflammatory agent which has been available in the United States without a prescription since 1984. In 2007, there were more than 79,000 cases of ibuprofen ingestion reported to poison centers in the United States [1]. While the vast majority of ingestions result in little morbidity, ingestions exceeding 400 mg/kg can produce coma, acidosis, and rarely death.

Case Report

A 19-year-old male with no significant past medical history presented to an emergency department following an ibuprofen ingestion. The patient reportedly got into an argument with his girlfriend, prompting him to drink one 1,180 mL beer, and 3 h later, to ingest 450 tablets of 200 mg ibuprofen (90,000 mg total; 1,200 mg/kg). The ibuprofen ingestion occurred approximately 90 min prior to arrival in the emergency department. He called EMS himself after feeling "remorseful." Upon arrival, the patient's blood pressure was 126/74 mmHg, with a heart rate of 85 bpm. His initial exam was only notable for some diffuse muscle "twitching." The patient was intravenously given 2 L of crystalloid over the first 3 h in the Emergency Department and was placed on a lactated ringers infusion at 250 cm^3/h. His laboratory studies, including a complete blood count, electrolytes, renal and liver function tests, and lactic acid, as well as quantitative levels of ethanol, salicylate, lithium, and acetaminophen, were only notable

for a potassium of 3.2 mmol/L, a lactic acid of 3.6 mmol/L, and an ethanol level of 38 mg/dL. His hemoglobin was 14.1 g/dL, creatinine was 0.89 mg/dL, and glucose was 100 mg/dL. Three hours after the ingestion the patient developed a mild tachycardia and became more agitated. His 12-lead electrocardiogram demonstrated sinus tachycardia at 106 bpm with a normal axis. The PR, QRS, and QTc intervals were 164, 96, and 473 ms, respectively. A CT scan of his head was negative. He was ultimately transferred to our institution.

During transport, the patient's level of consciousness continued to decline. Upon arrival at our institution, approximately 7 h postingestion, his blood pressure was 133/49 mmHg with a heart rate of 130 bpm. He was hypothermic with a core temperature of 35.8°C, and his oxygen saturation on 2 L O_2 via nasal cannula was 98%. His skin was warm and well perfused with moist mucosal membranes. Abdomen was soft and nondistended with bowel sounds present. Rectal exam revealed guaiac positive stools, but no melena. He had occasional muscular twitches and fasciculations in all major muscle groups and would withdraw to painful stimuli. His face was symmetric without droop, and his pupils were symmetric at 4 mm. No posturing was noted. Because he had no gag reflex, he was intubated upon arrival at our institution. An orogastric tube was placed which revealed bloody aspirate. A venous blood gas, performed immediately before intubation, revealed a metabolic acidosis with a pH of 7.21. His anion gap was 15. Other laboratory studies obtained at that time included a lactic acid of 5.9 mmol/L, sodium 145 mmol/L, potassium 4.4 mmol/L, chloride 111 mmol/L, bicarbonate 19 mmol/L, BUN 8 mg/dL, creatinine 0.98 mg/dL, and a glucose of 98 mg/dL. An abdominal radiograph revealed no radiopaque foreign bodies, and a chest radiograph revealed the presence of an orogastric tube and an endotracheal tube, with no acute cardiopulmonary process. A serum ibuprofen concentration obtained 7.5 h postingestion was 739.2 mg/L (therapeutic 5–49 mg/L). Gas chromatography/mass spectrometry testing of urine detected only ibuprofen, caffeine, nicotine, and cotinine.

He was empirically placed on propofol and fentanyl drips, as he did have some spontaneous movements, although no purposeful movements. In the hour after intubating him and starting propofol and fentanyl, the mean arterial pressure decreased approximately 20 mmHg, and the heart rate decreased approximately 25 bpm. He remained hypothermic for nearly 24 h postingestion. An arterial blood gas obtained 12 h postingestion revealed a pH of 7.27 with a PCO_2 of 43.8 and base deficit of 6.8. Thirteen hours after the ingestion, the anion gap had closed, but the lactic acid was still elevated at 3.3 mmol/L. The lactic acid normalized (1.1 mmol/L) approximately 24 h postingestion. The patient's creatinine rose slightly, peaking at 1.2 mg/dL 30 h postingestion, despite aggressive fluid resuscitation. His urine sodium was 157 mmol/L, and the urine creatinine was 26 mg/dL, with a fractional excretion of sodium more than 1%, consistent with acute tubular necrosis (ATN).

Despite receiving only 2.5 L of fluid in the first 7 h after the ingestion, the patient voided nearly 1,800 cm^3/h for the first 2 h after arrival at our center. He was given an additional 2 L of lactated ringers over 2 h and continued on a maintenance IVF rate of 200 mL/h. He continued to void more than 400 cm^3/h for the subsequent 12 h. Further boluses were administered as needed to keep up with his urine output. Approximately 21 h postingestion, the patient became oliguric for 3 h, at which time he received an additional liter of lactated ringers, resulting in a substantial increase in his urine output. In total, during the first 2 days, the patient received 11.23 L of IVF with an output of 15.18 L of urine. The large volume of IVF was in response to his excessive output. Postextubation, the patient was drinking 240–320 cm^3/h of fluid.

The urinalysis revealed 31–60 red blood cells per high power field, and 1–5 white blood cells per high power field. No protein, ketones, or bacteria were observed in the urine. He never had any significant serum sodium abnormalities (sodium fluctuated from 139 to 146 mmol/L).

The patient's mental status also began improving approximately 18 h postingestion, and he was able to be extubated 25 h postingestion. The patient did confirm the history of ingesting approximately 450 tablets of ibuprofen. He was seen by the psychiatry service, and was ultimately transferred to in-patient psychiatric care.

Discussion

In 1984, ibuprofen (2-4-isobutylphhenyl propionic acid) became the first nonsteroidal anti-inflammatory agent to be approved for use without a prescription. Because of its availability and low cost, overdose with this agent remains common. Following ingestion, most patients remain asymptomatic or develop only mild gastrointestinal upset, including nausea, vomiting, and epigastric pain. Neurologic symptoms, such as lethargy, headache, and nystagmus can occur as well [2, 3]. Acute renal injury has uncommonly been described [4]. While mefenamic acid has classically been associated with seizures, both muscle twitches and seizures have been reported with acute ibuprofen overdose as well [3, 5]. As a general rule, ibuprofen ingestions exceeding 400 mg/kg are potentially toxic. Nonetheless, life-threatening reactions, such as coma, acidosis, or renal failure remain rare.

Previous investigators have also described massive ingestions, with variable outcomes. In the late 1980s, Linden and colleagues reported two pediatric patients who developed CNS and respiratory depression, along with a metabolic acidosis. A serum ibuprofen level of 680 mg/L

was obtained in one of these children. Both children survived [3]. Lee and Finkler reported an ingestion of >20 g of ibuprofen which resulted in multisystem organ failure, but the patient ultimately survived. The serum level in this case was 185 mg/L [6]. Oker and colleagues described an 18-month-old who ingested 600 mg/kg of ibuprofen. He developed a tonic–clonic seizure, respiratory failure, and metabolic acidosis. In their case, a 4-h ibuprofen level was 640 mg/L. The child survived without long-term sequelae [7]. Lastly, Holubek and colleagues described two fatal ibuprofen ingestions. One patient, a 17-year-old woman who was found unresponsive, had a capillary glucose of 2 mg/dL and a lactic acid of 17 mmol/L. She had diffuse cerebral edema on neuroimaging. Her toxicology studies revealed the presence of cocaine in her urine and a serum ibuprofen concentration of 352 mcg/L. Their second case was a 49-year-old man who presented unresponsive and hypotensive with metabolic acidosis. The patient's ammonia was 639 mcg/dL. Toxicology testing revealed a valproic acid concentration of 560 mg/L and an ibuprofen concentration of 260 mg/L [8]. Wood and colleagues describe a fatal ingestion of ibuprofen in a 26-year-old female who ingested up to 105 g of sustained-release ibuprofen. She developed central nervous system depression, metabolic acidosis, and ultimately, died. Her ante-mortem ibuprofen level from peripheral blood was 760 mg/L [9].

Marciniak and colleagues have described a 75-kg 14-year-old who was found unresponsive next to an empty bottle of 500 tablets of ibuprofen (200 mg each). This patient was hypotensive, tachycardic, and acidotic. His toxicology studies revealed an ibuprofen concentration of 776 mg/L. This patient also had a high output state with 29 L of urine produced during the first 16 h of admission. However, this patient developed renal failure. The patient ultimately was placed on full venoarterial extracorporeal membrane oxygenation before making a full recovery [10].

Our patient's renal abnormalities have not been previously described. In the absence of significant comorbidities or hypovolemia, angiotensin concentrations are typically low. In patients with hypovolemia or intrinsic renal disease, however, there is a high angiotensin state with GFR maintained by prostaglandin-mediated afferent arteriolar vasodilatation and angiotensin II-dependent efferent arteriolar vasoconstriction. The NSAID-induced reduction in prostaglandins can result in vasoconstriction of the afferent arterioles and, hence, reduced GFR [11]. Prolonged reduction in afferent blood flow can lead to ischemic ATN, which is probably what happened to our patient.

Other renal conditions associated with NSAID use include tubulointerstitial nephritis, minimal change disease, membranous nephropathy, papillary necrosis, hyperkalemia, and exacerbation of hypertension [12]. Our patient never had proteinuria, although his creatinine did increase mildly.

The acidosis has been previously described. While its exact mechanism of action is not known, it is likely from accumulation of propionic acid [3]. Despite occasionally finding significantly elevated levels in symptomatic patients, the routine use of ibuprofen levels is not warranted, as it does not change management [13].

This case has several unique aspects. First, our patient developed polyuria, which is generally defined as a urine output of more than 3 L urine per 24 h. Polyuria following ibuprofen ingestions has not previously been described in the absence of more significant acute renal failure. Secondly, the serum ibuprofen concentrations are rarely elevated to this degree. Our case demonstrates that with prompt and aggressive supportive care, even patients with truly massive ibuprofen ingestions can make full recovery.

Conflict of Interest There are no financial, litigable, or other conflicts of interest to disclose.

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