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Ibuprofen and Chronic Pyloric Stricture

Thomas Flass* and Edward J. Hoffenberg†

*Department of Pediatrics, University of Colorado, Denver

†Section of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Colorado, Denver

Ibuprofen and acetaminophen are the most widely used over-the-counter (OTC) pain relievers and antipyretics in the United States. Ibuprofen 2-(isobutylphenyl) propionic acid has been available without a prescription for those older than 12 years of age since 1984. Prescription for pediatric-strength liquid ibuprofen in children older than 6 months of age was approved by the Food and Drug Administration in 1989, and OTC administration for children older than 2 years of age since 1995. Its OTC use is now recommended by the American Academy of Pediatrics for children as young as 6 months of age.

Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin increases the risk for gastrointestinal (GI) toxicity. The majority of peptic ulcers result from *Helicobacter pylori* infection and/or chronic NSAID use. An estimated 3% to 4.5% of adults taking regular NSAIDs for arthritis develop significant GI complications, with endoscopy revealing ulcers in 15% to 30%. (1) A single dose of aspirin may cause subepithelial hemorrhage, and a 1-week course of aspirin or NSAIDs is associated with ulcers in 8% of adults (1).

In children, the frequency of GI bleed with ibuprofen, 17 in 100,000, is similar to that for acetaminophen (2). Although the gastric mucosa is most often affected, the intestinal mucosa may also be injured (3–5).

Despite the increased use of NSAIDs in adults and children, current reports describe adverse events with high-dose short-term use, or with chronic exposure, primarily in adults. Reports of single exposures causing adverse events are few and represent the sequelae of massive 1-time ingestions (6).

We report a previously healthy 2-year-old male who developed chronic gastric outlet obstruction and pyloric stricture after a single ingestion of liquid ibuprofen at a dose not thought to cause adverse events.

Case Report

Initial Presentation

A 2-year-old previously healthy white male was discovered by parents at home with a nearly empty bottle of liquid ibuprofen that had been approximately 30% to 50% full minutes before. The Rocky Mountain Poison Control hotline advised his mother that no intervention

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Address correspondence and reprint requests to Edward J. Hoffenberg, MD, B290, The Children's Hospital, 13123 E 16th Ave, Aurora, CO 80045 (Hoffenberg.edward@tchden.org).

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was necessary because the dose was unlikely to be toxic. For the remainder of the day, he behaved normally, with normal oral intake, no abdominal pain, vomiting, or diarrhea.

The day following ingestion, 2 episodes of coffee ground emesis and 2 episodes of hematochezia were noted, but resolved within hours. At this time, the patient was behaving normally and tolerating solids and liquids, so medical care was not sought.

One week after ingestion, the patient's entire family developed nausea, emesis, diarrhea, and mild fever for several days, thought to be an acute gastroenteritis. Although the family recovered within several days, the patient continued to have nonbloody, nonbilious emesis 3 to 5 times per day, with decreased oral intake, tolerating only small sips of clear liquids. The patient was brought to his primary care physician approximately 2 weeks following initial ingestion for concern of emesis and feeding intolerance. The physician identified a 0.5-kg weight loss, but otherwise found him appearing well and not dehydrated. He was started on lansoprazole 7.5mg daily, which was increased to 15mg 3 days before his hospital admission.

The emesis and feeding intolerance persisted, and 1 day before hospital admission, a comprehensive metabolic panel was normal. An upper gastrointestinal (UGI) series at an outside hospital showed pyloric channel stricturing. He was transferred to our hospital.

On arrival, he was in no apparent distress. Weight was 10.5 kg, 0.6% weight-for-age, and decreased from his prior weight of 12kg, 18% weight-for-age. The abdomen was noted to be soft, nondistended, nontender, with no organomegaly or peritoneal signs. Tests for fecal occult blood were negative. An abdominal radiograph showed a distended stomach containing residual barium from the UGI the previous day. An esophagogastroscope revealed stomach wall edema, pyloric thickening, erythema, and stiffness with inability to advance the Olympus GIF 160 (8.6mm diameter) endoscope into the duodenum. Biopsies of the gastric mucosa were normal. A computed tomography scan with intravenous (IV) contrast revealed nonspecific thickening of the posterior gastric wall and pyloric region without lymphadenopathy, and normal duodenum and small bowel (Fig. 1). Because of continued intolerance of oral intake, treatment included IV fluid resuscitation, parenteral nutrition, acid suppression, and oral sucralfate. The patient was discharged to his home after 8 days to continue parenteral nutrition while tolerating only sips of clear liquids.

Course

One week after discharge and approximately 3 weeks after ingestion, he had regained his previous weight (12.4 kg) and was tolerating liquids. By 7 to 8 weeks postingestion, he began to tolerate increasing amounts of liquids and soft solids, except for corn or popcorn, which caused vomiting. The parenteral nutrition was discontinued. He continued to have 1 to 2 episodes of emesis daily, but maintained his weight.

At 11 weeks postingestion, the frequency of emesis decreased to twice weekly with continued weight gain tracking along his previous growth curve.

At 5 months postingestion, because of continued low level vomiting and concern for a circumferential ulcer, a repeat endoscopy was performed, revealing a pinpoint, stiff, noncompliant antral opening through which neither the Olympus XP160 (5.9mm diameter) nor the Olympus GIF 160 endoscope (8.6 mm diameter) would pass even after pyloric dilation for 1 minute with a through-the scope (TTS) 9-mm balloon.

At 6, 9, 17, and 24 months postingestion, endoscopies showed persistence of the pyloric narrowing, the noncompliant antral opening increased minimally in size, and inability to

advance the 5.9-mm diameter endoscope into the duodenum despite repeated attempts at dilation with TTS balloons. Dilations were attempted using 6-, 7-, and 8-F TTS dilators over a guidewire. At 24 months, with the 10-mm size dilator, a tiny waist was noted. After each of these attempts at dilation, the patient would have up to 5 to 7 days of vomiting and dehydration refractory to antiemetics and steroids, during which he would keep down only small amounts of liquids. These episodes were managed with intravenous fluids.

He continues with normal growth and tolerates solids except for corn/popcorn. His most recent UGI, 24 months after initial ingestion, revealed significant gastric antral/pyloric spasm and thickening requiring multiple gastric contractions to empty into the duodenum. Thickening appears more prominent than on the previous examination.

Discussion

On the basis of the lack of previous significant medical history, the estimated ingestion of 600 to 1200 mg or 57 to 114 mg/kg of ibuprofen in this patient led to chronic pyloric channel injury. Endoscopy and computed tomography scan would suggest that this patient has developed fibrotic changes of the pylorus leading to stricturing. The patient was not taking any other medications concurrently, nor did he have any known risk factors for increased GI toxicity. His family history is significant for maternal grandmother with celiac and autoimmune thyroid disease and father with factor V Leiden. Because the reported level of ibuprofen ingestion has not previously been associated with adverse outcomes, this case raises several important questions:

1. What is the mechanism of the initial insult? Why did this patient experience such a severe outcome from a historically harmless overdose?
2. How did this lead to the chronic pyloric stricture?
3. Is the mechanism of injury and repair different for single doses than for repeated doses?

The most popular of the NSAIDs, ibuprofen is a relatively water-insoluble compound with a pKa of 4.43. Ibuprofen is well absorbed from the gut, with peak levels within 1 hour after ingestion and a plasma half-life of approximately 2 hours. It is transported largely protein bound in plasma and rapidly metabolized and excreted in the urine. It is well known in adults to have a significant GI adverse effect profile, with upper GI ulcers, gross bleeding, or perforation in 1% of patients treated for 3 to 6 months and 2% to 4% of patients treated for 1 year (7). Risk factors for GI adverse effects include smoking, corticosteroids, alcohol, advanced age, and poor overall health (8,9). The most frequently reported acute overdose symptoms include abdominal pain, nausea, vomiting, lethargy, and drowsiness (7). Metabolic acidosis, apnea, coma, and acute renal failure are rare adverse effects in young children.

Despite its known adverse effect profile, ibuprofen is considered relatively safe compared with other NSAIDs. In a metaanalysis of 3 retrospective case-control studies in England, Scotland, and Sweden, ibuprofen showed the lowest odds ratio (1.7) for upper GI bleeding compared with diclofenac (4.9), indomethacin (6.0), naproxen (9.1), piroxicam (13.1), and ketoprofen (34.9) (10). Ibuprofen doses less than 1200 mg daily were not associated with increase risk for GI bleed (odds ratio 1.1). There were significant dose-response relations and risk was highest in all groups during the first week of use. However, this study included only adults, with mean ages between 58 and 74 years (10).

Reports of acute ibuprofen toxicity are relatively rare. Of 61 cases reported to the Rocky Mountain Poison Control Center from 1985 to 1986, 5 of 39 children reported adverse

events (11,12). Isolated GI symptoms of cramping, nausea, and emesis were reported in 3 patients with moderately high doses. The doses ingested were higher than that of our patient, ranging between 104 and 131 mg/kg. Two massive ingestions of 708 mg/kg and 666 mg/kg yielded central nervous system symptoms of decreased level of consciousness and apnea as well as GI symptoms. No permanent damage or deaths were reported (12).

On the basis of the relatively low numbers of acute overdose or serious outcomes, recommendations for ibuprofen overdosing have changed in the past 20 years. Original recommendations for ingestion of <100 mg/kg were observation only, 100 to 200 mg/kg were to induce emesis and observe, and 200 to 400 mg/kg were to induce emesis, give activated charcoal, and seek medical care (11,12). On the basis of a limited number of prior cases, risk for serious adverse events increases significantly with doses of 200 to 400 mg/kg. Current recommendations from the Rocky Mountain Poison Control Center (which directly reflect the position of the American Association of Poison Control Centers) are observation at home for ingestions of <200 mg/kg. For ingestions >200 mg/kg, medical care should be sought, with possible charcoal administration and renal function testing. Induction of emesis is not recommended for any ingestion currently.

In a thorough review of the current medical literature, we have identified only 2 other pediatric cases of chronic sequelae secondary to high-dose ibuprofen ingestion. A duodenal perforation was reported in a 17-year-old girl who ingested a large dose (14 g) of ibuprofen at one time (6). Similar to our patient, a nonobstructive pyloric deformity was still present after almost 2 years. A pyloric stricture, similar to our patient, was reported after 1 month of high-dose ibuprofen (1000 mg twice daily) in a 12-year-old white girl with cystic fibrosis (13). Unlike our patient, balloon dilation successfully opened the pyloric channel.

Several possible mechanisms for ibuprofen toxicity have been postulated. The interruption of the formation of cyclooxygenase (COX)-1 (constitutive) by NSAIDs may reduce the protective mechanisms of the gut (9). Nonsteroidal anti-inflammatory drugs are known to decrease the mucus and bicarbonate formation in the gastric/duodenal mucosa, as well as reduce mucosal blood flow. Intestinal mucosal blood flow is reduced within 7 days of NSAID administration (14). In addition, there is an increase in neutrophil adherence to mucosa that may induce free radical formation as well as reduce mucosal blood flow (15). However, other studies suggest that gut damage by NSAIDs is independent of level of COX inhibition (16).

More recently, direct mucosal toxicity independent of COX-1 has been proposed. The role of ion trapping of substances with a lower pKa in the mucosa of the stomach or pylorus has been suggested. Most NSAIDs, including ibuprofen, are weak acids that are nonionized in the acidic environment of the stomach. However, when these weak acids diffuse readily into the gastric or proximal duodenal mucosa, they become ionized in the higher pH environment and trapped intracellularly. When this process involves supratherapeutic doses, they can become directly toxic to cells (9,17).

In several experiments with rat models using indomethacin, high doses induced uncoupling of oxidative phosphorylation and mitochondrial damage in rat enterocytes in vivo as well as in rat intestinal villus cells in vitro. There was also evidence of uncoupling in rat liver mitochondria in vitro by indomethacin, aminosalicylic acid, naproxyn, and piroxicam (18). This appears to be a topical rather than systemic effect because of localized "topical" effects in the gut mucosa before these drugs become bound to albumin in the bloodstream. There was no evidence of uncoupling in rat enterocytes when indomethacin was given parenterally (17).

In conclusion, we report a chronic pyloric stricture in a previously healthy 2-year-old boy after a single ingestion of a dose of liquid ibuprofen that was not thought to be sufficient to cause adverse events. The chronic course seen after a moderate dose ingestion has not previously been reported. It is unlikely that he had some previously undiagnosed pathology that was uncovered by this ingestion. The mechanism of injury is still unknown, but could include any or all of the proposed pathways of COX inhibition, drug trapping, reduced blood flow/ischemia, or direct injury via mitochondrial damage. This leads us to wonder whether he and perhaps other children have some unknown physiological predisposition toward mucosal injury from NSAIDs. Clinicians should be aware of the possibility of ibuprofen toxicity and chronic sequelae even with lower doses and single exposures. The optimal management of these cases remains to be determined. It seems reasonable to begin acid suppression and possibly sucralfate early and monitor for sequelae.

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Figure 1.
Computed tomography scan with intravenous and oral contrast performed 3 weeks after ibuprofen ingestion shows nonspecific thickening of the posterior gastric wall and pylorus. There is shouldering at the gastric antrum.