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Accelerated Article

Ferrous Sulfate Toxicity

A Review of Autopsy Findings

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ABSTRACT

Ferrous sulfate is the leading cause of accidental pediatric poisonings. Despite the requirement for child-resistant packaging for any oral iron product with 250 mg or more per container, the incidence has continued to increase. Although the clinical presentation of iron toxicity has been well described, pathologic findings in human tissue and correlation with clinical data are scant. We reviewed autopsies from the Armed Forces Institute of Pathology of 11 children who died from ferrous sulfate toxicity. Clinical data, morphologic changes, and iron levels in tissue were evaluated. The children's ages ranged from 11 to 36 mo. Prominent iron deposition in gastric and small intestinal mucosa was associated with necrosis, with some cases demonstrating prominent vascular iron deposition. The clinical courses were rapid and progressed from Stage I to Stage III. These observations were correlated with increased levels of iron in various tissues, as determined by analytical atomic absorption spectrophotometry. The morphologic and chemical analysis data provide information on the pathogenesis of ferrous sulfate poisoning; the vascular iron deposition may be related to subsequent hemorrhage. In the liver the periportal necrosis is probably a direct cytopathic effect of the highest levels of iron carried to these cells by the portal blood flow.

Index Entries: Ferrous sulfate; overdose; poisoning; gastrointestinal hemorrhage.

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INTRODUCTION

Iron-containing products are the leading cause of accidental pediatric poisonings, accounting for approximately 17% of children's deaths reported to poison control centers in the United States from 1988 to 1992 *(1–3)*. Deaths have occurred from ingesting as little as 200 mg to as much as 5.85 g of iron *(4)*. The clinical presentation of iron toxicity has been well described *(4–10)*, although pathologic findings with clinical correlations are scant *(11–14)*.

A large number of products available in pharmacies, food stores, and discount stores contain iron, and the problem is compounded by attractive packaging, high availability, and ambiguous labeling *(3)*. The severity of this problem led the Food and Drug Administration (FDA) to propose reform in 1995 (and, recently, in July 1997) for packaging and labeling of any iron product containing 30 mg or more of iron *(1,2)*. The FDA proposal includes a prominently and conspicuously placed statement on iron-containing products warning adults to secure child-resistant closures properly, to store the products out of reach of children, to keep unit-dose packaged products in their original containers, as well as to seek immediate medical attention if a child accidentally swallows one of the products, as iron overdose could cause harm or death to a child.

Ferrous sulfate is the cheapest, most toxic, and most frequently used iron supplement and has an elemental iron content of approximately 20%. Once ingested, iron may be absorbed in the ferrous from and subsequently oxidized to the ferric state, where it is bound to transferrin. When ferrous sulfate is ingested by children in high doses over a short period of time, the high levels of elemental iron have a direct corrosive action on the mucosa, which can lead to nausea, diarrhea, and gastrointestinal hemorrhage in minutes; shock, coma, and death may follow. If the child survives, gastrointestinal obstruction and extensive liver damage may develop in 3–6 wk. The clinical presentation of severe iron poisoning, which is not immediately fatal, has been well described and is traditionally divided into three stages *(15)*: Stage I lasts approximately 4 h and is associated with signs and symptoms related to gastrointestinal injury; Stage II is one of apparent recovery during which, however, toxic iron compounds are being formed; Stage III begins about 24 h after ingestion of the toxic dose. Multiorgan failure ensues with cerebral dysfunction and coma, myocardial depression, ischemic bowel, and renal and hepatic failure. Invariably, edema and necrosis of the gastric mucosa are found in fatal cases. Survival with late complications related to gastrointestinal scarring may also occur *(16)*.

We reviewed 11 autopsy cases from the files of the Armed Forces Institute of Pathology of children who died from ferrous sulfate toxicity.

Clinical data, morphologic changes, and iron levels in various tissues were studied and correlated.

MATERIALS AND METHODS

Tissue sections of all major organ systems were examined by light microscopy with H&E as well as Mallory's stains.

Iron levels were measured in paraffin-embedded tissue employing flame atomic absorption spectrophotometry (FAAS) with a deuterium arc lamp as the background correction. The spectrometer was a Varian SpectrAA-400P (Varian Australia Pty Ltd, Mulgrave, Australia) equipped with a computer module for instrument control, data acquisition, and handling. An iron hollow-cathode lamp was operated at 5 mA and the absorption was measured at 248.3 nm with a 0.2-nm slit width. Prior to the FAAS analysis, tissue samples were digested employing a microwave digestor system (CEM Corporation, Indian Trial, NC, USA) at a controlled temperature and pressure. The digestion system is composed of a microwave unit especially designed for the acid-induced decomposition of chemical, biological, and environmental specimens. The unit is equipped with a set of plastic (Teflon-based) vessels. We used approx 50–150 mg of paraffin embedded tissue in 1 mL of 70% HNO_3 (Ultrex, JT Baker, Phillipsburg, NJ, USA), 1 mL of hydrogen peroxide, and 1 mL of distilled deionized water. Microwave powers ranging from 45% to 85% were applied to produce the acid decomposition of tissue and dissolution into its organic and inorganic components. Prior to the microwave digestion, the paraffin was removed by using *n*-hexane and the tissue was dried employing a vacuum oven at 35°C. The control sample included nonexposed cardiac and gastrointestinal tissue from children as well as lyophilized liver powder reference standard material from the National Institute of Standards and Technology (Gaithersburg, MD, USA).

All chemicals were of analytical reagent grade or higher purity, and deionized water from a Milli-Q system (Millipore) was used throughout the analyzes.

RESULTS

The 11 children ranged from 11 to 36 mo of age; five were male and six were female (Table 1). The clinical courses progressed rapidly, the initial symptoms being gastrointestinal, such as hematemesis and diarrhea (Stage I); laboratory findings included prominent leukocytosis (up to 70,000 cells/mL^3). Clinical symptoms progressed to neurologic and cardiorespiratory depression (Stage III), with continued leukocytosis and metabolic acidosis. The time elapsed from ingestion to death ranged from 6 to 42 h.

Table 1
Pathologic Data of Ferrous Sulfate Overdoses

Patient #	*Age (months)*	*Sex*	*Stomach Involvement*	*Small Intestine Involvement*	*Large Intestine Involvement*	*Liver Involvement*	*Iron Intake*
1	20	F	Yes	Ileum		Yes	12 g
2	14	F		Duodenum			20 (0.3grain)
3	13	M	Yes				
4	14	M	Yes			Yes	80 "tablets"
5	17	M		Ileum		Yes	
6	12	F	Yes	Ileum	Yes	Yes	
7	11	F	Yes	Yes		Yes	
8	14	M		Yes			
9	36	F	Yes				
10	19	F		Ileum			
11	24	M	Yes	Yes	Yes		

Histopathologically, there was prominent iron deposition in the stomach and small-intestine mucosa associated with necrosis and ulceration (Fig. 1). Intestinal vascular iron deposition was intense in some cases (Fig. 2). Hepatic toxicity was manifested by periportal (zone 1) necrosis, either periportal or paraportal (Fig. 3). The affected liver cells showed coagulative degeneration with shrinkage, intense cytoplasmic eosinophilia, and nuclear lysis or karyorrhexis (Fig. 4). There was variable "dropout" of cells. Iron stains demonstrated mild to moderate staining of the necrotic hepatocytes, as well as some staining of sinusoids in the affected areas. Significant tissue necrosis was not seen in other organ systems and minimal iron deposition was noted with special stains (kidney, spleen). The histopathologic findings were correlated with increased levels of iron in paraffin-embedded tissue, as determined by analytical atomic absorption spectrophotometry. In the liver, the values ranged from 1600 to 4182 μg of dry tissue (reference value 21–450 μg), whereas in brain tissues, iron levels greater than 259 μg were also measured (reference value 26–164 μg). All tissues demonstrated markedly high values of iron (Table 2).

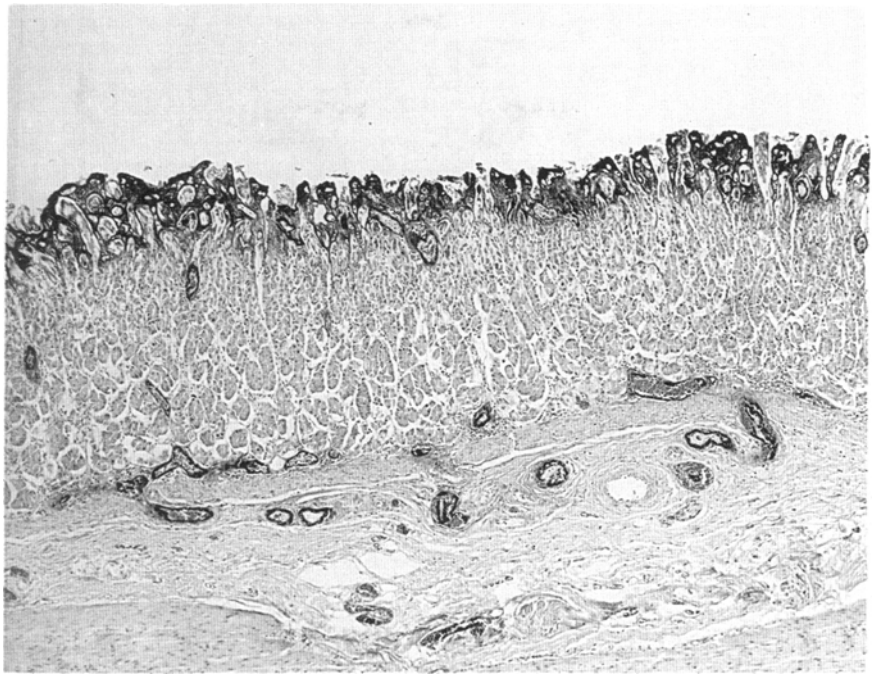

Fig. 1. Section of stomach showing incrustation of the superficial mucosa by iron, as well as heavy staining of vessels in the submucosa (Mallory's stain for iron, 50×).

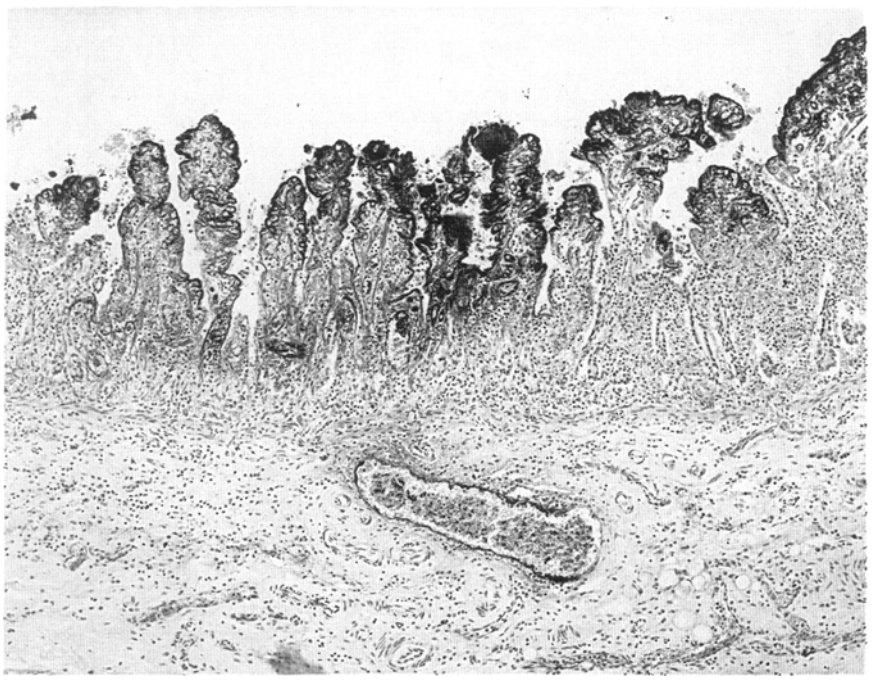

Fig. 2. Section of small intestine showing loss of the epithelium of the villi and heavy incrustation with iron. Note the vessel that is also stained with iron (Mallory's stain for iron, 75×).

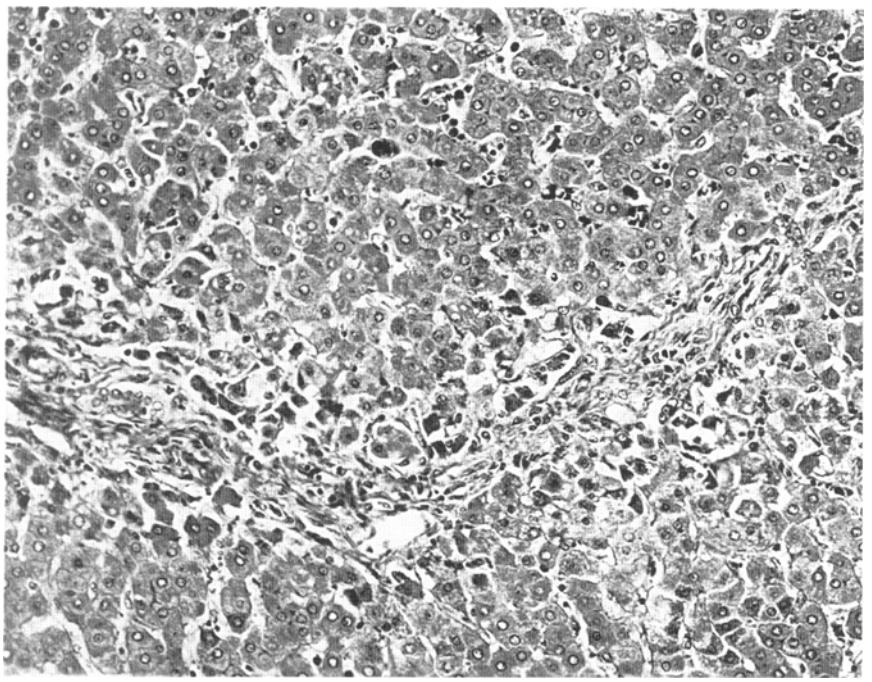

Fig. 3. Section of liver showing zone 3 (periportal) necrosis (H&E, 200×).

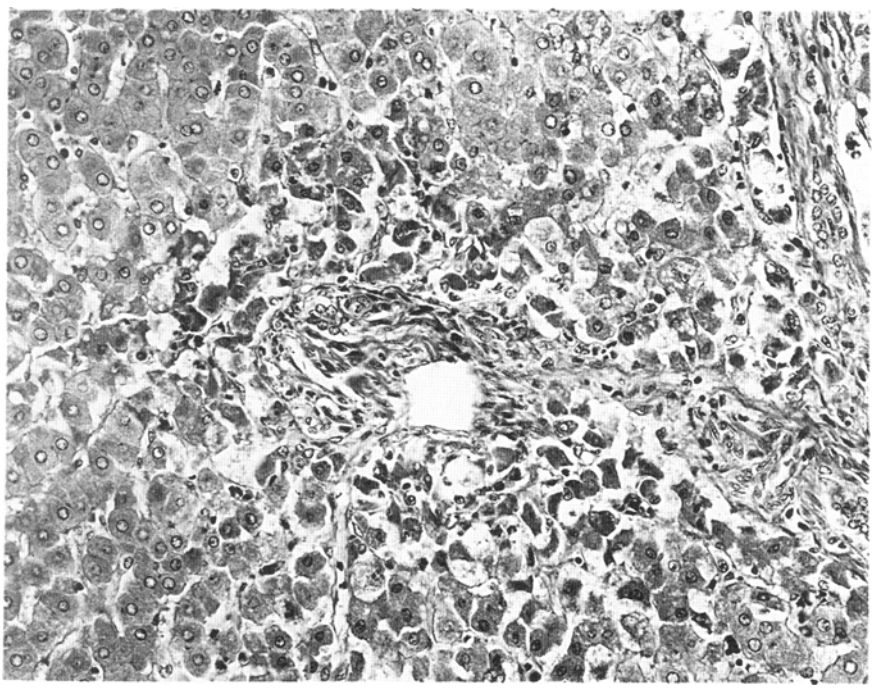

Fig. 4. Section of same liver illustrated in Fig. 3 at higher magnification. The liver cells in zone 3 are coagulated and shrunken, and there is some focal "dropout" of cells (H&E, 240×).

Table 2
Iron Levels in Pediatric Autopsy Cases in Ferrous Sulfate Toxicity*

Patient #	*Tissue Specimen Examination*	*Iron Level (micrograms/g dry tissue)*	*Reference Values (micrograms/g dry tissue)*
1	Stomach	8910.2	
	Liver	2988.0	205 (21 - 450)
2	Brain	291.0	52 (26 - 164)
	Heart	349.0	
	Liver	1618.0	
	Lung	1048.0	293 ± 47
3	Liver	1686.0	
	Small Bowel	5630.0	
4	Small Bowel	6962.0	
5	Liver	4182.0	
6	Brain	259.0	
	Liver	1600.0	
	Kidney	777.0	98 ± 10.2

*Although autopsy and clinical information was available on 11 pediatric cases, tissue material was available from only 6 cases. Reference values were taken from Lievens et al. *(17)* and Caroli et al. *(18)*.

DISCUSSION

Iron-containing products remain a continuing toxicologic hazard to children less than 6 yr of age who accidentally ingest multivitamin preparations and develop minimal toxicity. However, ingestion of concentrated iron can be lethal for children and remains a serious problem in the United States. Iron is the most abundant trace metal in the human body and is believed to be essential for all living cells, but it is lethal to children when taken in large amounts.

Gastrointestinal hemorrhage caused by the corrosive action of the iron was the main mechanism of death in the cases examined, with shock and neurologic symptoms ranging from sensory deficits to coma. The clinical courses were rapid and progressed from an initial stage where the main symptomology was related to injury to the gastrointestinal tract

and, subsequently, to the central nervous system, followed by death. Iron levels were abnormally elevated in all tissues examined by atomic absorption spectrophotometry, including the stomach, small intestine, liver, brain, heart, and lung, although iron stains of these respective tissues revealed only scattered foci of iron deposition.

The morphologic and chemical analytic data obtained provide information into the pathogenesis of ferrous sulfate poisoning; vascular iron deposition may be the cause of the subsequent gastrointestinal hemorrhage. The damage to liver cells is probably related to direct toxicity by the metal absorbed from the gastrointestinal tract and reaching these cells via the portal vein.

ACKNOWLEDGMENTS

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