COMMENTARY


Comments by Sanford N. Cohen, MD

ABSTRACT OF ORIGINAL ARTICLE. Objective. Children with iron poisoning, and mongrel dogs studied under laboratory conditions, were evaluated to explore the safety and effectiveness of the use of desferrioxamine in acute iron intoxication as reported in the 1965 paper. Methodology. Twelve children admitted to a pediatric unit after iron ingestion were subjected to gastric lavage (10) and treatment either with intravenous desferrioxamine (9) or with a combination of intravenous and enteral (gavage) desferrioxamine (3). Serum iron levels before and after therapy, urinary excretion of iron, and symptoms before and after therapy were all measured. Mongrel dogs (23) were fasted overnight and then given toxic doses of ferrous sulfate intraduodenally under general anesthesia. Controls (14) were observed for serum iron, arterial pH, and hematocrit, and mean arterial blood pressures. The 9 dogs treated were given desferrioxamine both intravenously and intraduodenally, whereas the controls were observed without treatment. Four additional dogs were treated with a lethal dose of iron that was first complexed with desferrioxamine and then administered intraduodenally. Another 2 dogs received a slow intravenous infusion of either ferrous or ferric iron, and 2 others were given the same amount of iron, but as a complex with desferrioxamine. Other studies were performed on dogs to evaluate the effect of desferrioxamine on arterial blood pressure and the toxicity of the iron-desferrioxamine complex. Results. Rapid intravenous infusion produced hypotension in two children, one of whom had a seizure. Significant amounts of iron were discovered in the urine of all patients. None had progression of symptoms while in the hospital. One child who was in coma when admitted was noted to be developmentally retarded 5 months later. All 14 control dogs died by 10 hours after duodenal instillation of iron. Three of the dogs treated survived, but these were the three with the lowest pretreatment iron levels. The enteral administration of lethal doses of iron previously complexed with desferrioxamine resulted in the excretion of large amounts of iron in the urine in 4 dogs and in one of three children treated with moderate amounts of iron complexed with desferrioxamine. The children were not affected adversely by this treatment, but the dogs experienced a marked drop in blood pressure and died within a few hours. Conclusions. The use of desferrioxamine results in the rapid excretion of more iron in the urine than would occur without such treatment. The drug produces hypotension when administered rapidly by parenteral infusion. The enteral administration of the drug to poisoned dogs or children does not prevent the absorption of iron; indeed the complex is freely absorbable. The desferrioxamine–iron complex is toxic to the kidneys.
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There are several important reasons why this article and its companion report of additional animal studies are included in this supplement of Pediatrics. The articles are excellent examples of clinician-scientists following clues derived from clinical situations to plan studies in the laboratory that might enhance their ability to understand and treat clinical illness. In this case, the authors developed questions about a clinical condition from their observation of patients in the emergency department and at the bedside that could be studied later in the laboratory. The answers they derived from their experiments in laboratory animals ultimately led to better treatment for children.

Clinical pharmacology was essentially born as a medical discipline soon after Congress passed the 1962 amendments to the Pure Food, Drug and Cosmetic Act. The Congress enacted these amendments after in-depth investigations and prolonged hearings during the preceding year. The hearings had been conducted after it appeared certain that thalidomide, a drug that had not been approved for use in the United States, administered early in the first trimester of pregnancy was the causative agent in the epidemic of severe limb anomalies that had been seen primarily in Europe during the late 1950s. The new amendments charged the US Food and Drug Administration with ensuring that drugs had been studied and shown to be both safe and effective for a specific indication before they were marketed for that indication. In general, drugs on the market at that time, and most of those marketed since, were not tested in infants and children and therefore were marketed without pediatric indications. There were no guidelines to assist the early investigators in this area in either the ethical or the scientific aspects of the conduct of clinical studies in children. Thus, among other things, these articles represent the use of careful clinical observations of pediatric patients after treatment with a new therapeutic agent to help to design experimental laboratory approaches to the questions raised by the clinical observations.

The 1965 article,1 which (among other things) focused on clinical observations and a trial of the new agent in children who had been poisoned accidentally, played a major role in advancing the use of desferrioxamine as a therapeutic agent in iron-poisoned children. These patients had always frustrated clinicians, because there was no effective treatment for this potentially fatal accidental poisoning, and patients could only be treated with supportive measures. Whitten and his colleagues demonstrate in this paper how scientifically trained clinicians tend to approach clinical problems. They wrote it in a way that virtually invites a reader to witness the problem-solving process that they used as they thought through the questions they were researching.

The second paper in this series on acute iron poisoning, published in Pediatrics in 1966,2 contained the report of more extensive studies on dogs, conducted by these investigators in their laboratory, based on their clinical observations and earlier laboratory work. They showed definitively that, as they suspected, the iron–desferrioxamine complex is freely absorbable from the gastrointestinal tract. They also more firmly established that this complex demonstrates significant cardiovascular toxicity when present in the blood in high concentrations. These observations suggested strongly that the use of oral (or enteral) desferrioxamine therapy was not only of questionable value, but also was potentially dangerous to those who were treated in this way. Although it took several years for the enteral use of the chelating agent to fade from clinical use in favor of parenteral use only, the papers reviewed here had a direct and lasting impact on the clinical approach to iron poisoning.

A review of the 1965 paper would be incomplete without noting that there was one experiment reported in that paper that would almost certainly not be proposed by pediatric investigators today, or in any event, would not be approved by an institutional review board, if it were proposed. These authors carried out their studies before new, generally accepted, more explicit ethical principles for protecting vulnerable human subjects of research had been established. The experiment in which a “moderate” dose of the desferrioxamine–iron complex was administered to mentally retarded children is an example of what was generally regarded as acceptable research to many before the late 1960s, the very period when investigators were beginning to develop the field of clinical pharmacology and when the study of drugs for their safety and efficacy first became a high priority in the United States. Thus, what was in almost universal disfavor by the early 1970’s, and was regulated out of practice in the United States by the late 1970s, was still acceptable to many who supervised the conduct of clinical experiments in children in 1964 to 1965. The report of the National Commission on the Protection of Human Subjects of Biomedical and Behavioral Research, concerning the use of members of “vulnerable” groups in research, is credited with stimulating the regulations that fundamentally put an end to the use of developmentally disabled children as subjects of research that is of no benefit to them.

REFERENCES

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