Unit-Dose Packaging of Iron Supplements and Reduction of Iron Poisoning in Young Children

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Background: Iron poisoning is a major cause of unintentional poisoning death in young children. The US Food and Drug Administration proclaimed a regulation for unit-dose packaging of iron supplements in 1997.

Objective: To determine whether the requirement for unit-dose packaging of iron supplements decreases the incidence of iron ingestion and the incidence of deaths due to iron poisoning in children younger than 6 years.

Methods: This is a preintervention-postintervention study of the US federally mandated requirement for unit-dose packaging of iron supplements. The 10 years prior to the intervention were compared with the 5 years after its promulgation. The incidences of iron ingestion and of iron poisoning deaths for children younger than 6 years were obtained from the annual reports of the American Association of Poison Control Centers (Washington, DC).

Results: The average number of iron ingestion calls per 1000 of all calls to poison control centers regarding children younger than 6 years decreased from 2.99 per 1000 to 1.91 per 1000 (odds ratio, 1.29 [95% confidence interval, 1.27-1.32]; P < .001). The number of deaths decreased from 29 to 1 (odds ratio, 13.56 [95% confidence interval, 1.85-99.52]; P = .03).

Conclusions: These are the first data that show a decrease in the incidence of nonintentional ingestion of a specific drug by young children and a decrease in mortality from poisoning by this drug after the introduction of unit-dose packaging. This validates unit-dose packaging as an effective strategy for the prevention of iron poisoning and iron poisoning deaths in young children. This highly effective intervention should be considered for other medications with a high hazard for morbidity and mortality when taken as an overdose.

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IRON HAS LONG BEEN KNOWN AS A chief cause of unintentional poisoning death in young children. It was first documented in the 1940s as the most common cause of poisoning death in children aged 1 to 4 years. In the 8-year period from 1983 to 1990, it was the single most frequent cause of unintentional pharmaceutical ingestion fatality in children younger than 6 years, accounting for 30.2% of these events in the United States. To address this problem, the US Food and Drug Administration proclaimed a regulation for unit-dose packaging of iron supplements in 1997. The specific requirement for this packaging applied to iron-containing dietary supplements and drug products that contain 30 mg or more of iron per dosage unit. Unit-dose packaging, such as strip or blister packs, is purported to decrease the risk for morbidity and mortality of unintentional poisoning in children younger than 6 years. However, there is little, if any, evidence to support this belief. The purpose of this study is to examine the effect of this regulation on the incidence of iron ingestion and on the incidence of death due to iron poisoning in children younger than 6 years.

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METHODS

This is a preintervention-postintervention study using data from the annual reports of the American Association of Poison Control Centers (Washington, DC) Toxic Exposure Surveillance System (TESS). Poison centers report their cases to TESS using standardized definitions and compatible computer systems. The 15-year period between 1988 and 2002 was studied. The 5 years between 1998 and 2002 were considered the postintervention period. The year 1997 was included in the preintervention period because it was assumed that most
iron exposures during that year involved iron products distributed prior to the passage of the unit-dose packaging regulation. Cases are calls to poison control centers regarding exposures to presumed toxic substances. Calls are received from heterogeneous sources ranging from laypersons calling from home regarding well-appearing individuals to physicians calling from hospitals regarding obviously poisoned patients. Poison center personnel follow up all patients by telephone until outcome is known.

Products containing iron are listed in TESS annual reports as iron; multiple vitamin tablets with iron; adult formulations; multiple vitamin tablets with iron; pediatric formulations; multiple vitamin liquids with iron, adult formulations; and multiple vitamin liquids with iron, pediatric formulations. Only those products listed in the iron category were analyzed since this was the group affected by the unit-dose packaging regulation.

The following data were extracted from the 15 annual TESS reports regarding children younger than 6 years: the number of all cases, the number of iron cases, and the number of iron deaths. Because the total number of cases reported to TESS has increased over the years because of the increased population served by certified regional poison control centers, the number of iron cases per 1000 total cases was calculated for each year to determine whether there was an effect on the incidence of iron ingestion in this age group. The odds ratios, 95% confidence intervals, and P values were calculated for these 2 outcomes.

### RESULTS

There was a decrease in the incidence of iron ingestion and a dramatic decrease in the number of deaths due to iron poisoning in children younger than 6 years after the introduction of the requirement for unit-dose packaging of iron supplements (Table). The mean number of calls to poison control centers for iron ingestion by children younger than 6 years was 2.99 per 1000 of all calls during the preintervention period (1988-1997) compared with 1.91 per 1000 during the following 5 years (odds ratio, 1.29 [95% confidence interval, 1.27-1.32]; P<.001). There was only 1 death during the 5 years after the promulgation of this regulation compared with 29 deaths during the previous 10 years (odds ratio, 13.56 [95% confidence interval, 1.85-99.52]; P=.03). Because the 11 deaths of 1991 make it a somewhat atypical year, the data were also analyzed excluding that year (1988-1990 + 1992-1997 vs 1998-2002). The odds ratio was 9.41 with a 95% confidence interval of 1.26 to 70.48 (P=.01).

### Table. Annual Rates of Iron Ingestion and Iron Poisoning Death in Children Younger Than 6 Years (1988-2002)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Cases</th>
<th>No. of Iron Cases</th>
<th>No. of Iron Cases per 1000 Total Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preintervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>843,646</td>
<td>2,667</td>
<td>3.16</td>
<td>1</td>
</tr>
<tr>
<td>1989</td>
<td>966,652</td>
<td>3,003</td>
<td>3.11</td>
<td>1</td>
</tr>
<tr>
<td>1990</td>
<td>1,041,256</td>
<td>3,120</td>
<td>3.00</td>
<td>5</td>
</tr>
<tr>
<td>1991</td>
<td>1,101,333</td>
<td>3,578</td>
<td>3.25</td>
<td>11</td>
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<tr>
<td>1992</td>
<td>1,092,568</td>
<td>3,693</td>
<td>3.38</td>
<td>3</td>
</tr>
<tr>
<td>1993</td>
<td>980,861</td>
<td>3,114</td>
<td>3.17</td>
<td>2</td>
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<tr>
<td>1994</td>
<td>1,042,424</td>
<td>3,104</td>
<td>2.98</td>
<td>2</td>
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<td>1,137,295</td>
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<td>2.59</td>
<td>2</td>
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<tr>
<td>1997</td>
<td>1,150,931</td>
<td>2,810</td>
<td>2.44</td>
<td>1</td>
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<tr>
<td>Intervention</td>
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<tr>
<td>1998</td>
<td>1,181,006</td>
<td>2,506</td>
<td>2.12</td>
<td>0</td>
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<tr>
<td>1999</td>
<td>1,154,799</td>
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<td>1.96</td>
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<td>1,169,478</td>
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<tr>
<td>2002</td>
<td>1,227,381</td>
<td>2,157</td>
<td>1.76</td>
<td>0</td>
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</table>

To my knowledge, these are the first data that show a decrease in the incidence of nonintentional ingestion of a specific drug by young children and a decrease in mortality from poisoning by this drug after the introduction of unit-dose packaging. The decrease in number of fatalities was dramatic with the odds ratio of preintervention vs postintervention approaching 14. The corresponding odds ratio for ingestion was less impressive (1.29). Therefore, many children were still able to remove some iron tablets from their unit-dose packaging; however, they were not able to remove enough to cause significant harm.

It has been clearly shown that child-resistant closures reduce both the incidence of ingestion of poisons and of death due to poisoning in young children. Indeed, the American Academy of Pediatrics (Elk Grove Village, Ill) has cited this preventive intervention as a key factor in the dramatic decrease of poisoning deaths in this age group during the past 50 years. But the relatively high hazard associated with iron requires a greater degree of protection than child-resistant closures. While unit-dose packaging is perceived as being effective in the prevention of unintentional poisoning in young children, there are sparse published data supporting this belief. Therefore, the data in this report are especially important.

The only study regarding the effectiveness of unit-dose packaging in preventing unintentional poisoning in young children was reported by Wiseman et al in 1987. Their goal was to assess the effectiveness of both child-resistant closures and unit-dose packaging. They used 2 surveys to collect data. One was a survey of 14 hospitals that collected all unintentional poisonings in children younger than 5 years. The other was a survey of households with children younger than 5 years in the catchment area of these hospitals. This survey collected data on the type of medications in the homes, the location of storage, and the type of packaging. These were not the homes of the children with poison ingestion who had been treated at the hospitals. The safety of various drug packaging and of the drugs they contained was assessed by comparing their frequency of ingestion with their availability in the home. Four types of unit-dose packaging were assessed: transparent blisters, opaque blisters, strip packaging, and sachets. All were found to be protective except for clear blister packs. The failure of this packaging was associated with oral contraceptives. The authors found that these drugs were more likely to be less safely stored and stated that this was a contributing factor. They identified the small numbers of unit-dose packages involved in their study as a limitation and called for the need for continued monitoring of the effectiveness...
of this type of packaging. Their observation regarding clear blister packaging of oral contraceptives demonstrates that unit-dose packaging does not necessarily result in child resistance and led them to recommend “the need to develop national and international standards for the child-resistance of unit-dose packs.”1

Since intentional drug overdose as a suicidal gesture is often an impulsive act, it has been hypothesized that strip or blister packaging would decrease both its incidence and its severity.26 Turvill et al27 reported that in a hospital in London, England, there was a 21% decrease of acetaminophen overdoses and a 64% decrease of acetaminophen overdose requiring treatment with an antidote following the introduction of blister packaging of this drug. Coincident with the requirement of blister packaging was the limitation of package sizes to 8 g in supermarkets and 16 g in pharmacies. This would likely moderate the severity of overdose but would not be expected to decrease its incidence. Buckley et al28 in one hospital in Newcastle, Australia, similarly demonstrated that adults who took an overdose of carbamazepine as a suicidal gesture consumed fewer tablets after the introduction of blister packaging of this medication. Although the median serum carbamazepine concentration was 27% lower in the postintervention group, this did not reach statistical significance (P = .15). This may have been due to an overestimation of the tablets consumed by the preintervention group since there is an inherent increased precision in determining this number from blister packs. If indeed the number of tablets consumed from conventional packages was systematically overestimated, it would then be a true nondifference. Or, the lack of statistical significance may be a β error due to the small numbers of patients, 51 and 16 in the preintervention and postintervention groups, respectively. Chan,29 in a study of patients admitted to a hospital in Hong Kong, China, for acetaminophen poisoning, compared patients who had obtained this drug from blister packs with patients who had used conventional drug packaging. He found that the blister pack group had ingested fewer tablets and fewer of them had detectable serum acetaminophen concentrations. However, this outcome could be a consequence of fewer tablets available in the blister packs rather than a protective effect of this type of packaging.

If unit-dose packaging decreases the incidence and severity of intentional overdose in adults, it is reasonable to expect an even greater effect in young children because they are less determined to obtain the drug. Indeed, the results of this study support this speculation.

The US Consumer Product Safety Commission (Washington, DC) has required child-resistant closures on containers with 250 mg or greater of elemental iron since 1978.22 However, TESS data show that this has not provided the desired degree of protection. It has been estimated that the use of child-resistant closures should reduce the rate of unintentional poisoning in young children by as much as 90%.30 However, the observed results were 40% to 55% for aspirin31 and 67% for all regulated products.25 The most effective injury prevention strategy is a passive primary intervention,32 an intervention that does not require an action by the user. Child-resistant closures require the user to reengage the closure in its protective position. Users do not always do so.30,31 In one study, approximately one half of the poisonings associated with child-resistant closures were the consequence of improper use of this type of packaging. This included leaving the container open, incompletely closing it, or transferring the contents to another container.31 In addition to this generic issue, perceptions regarding iron may result in less stringent safety behaviors compared with prescription drugs. Iron is an over-the-counter product, and this group is often perceived as having a less toxic potential than prescription drugs.32 Furthermore, iron is considered as a nutrient or a supplement rather than as a drug, thereby providing an additional false sense of security. This is somewhat ironic since iron is more hazardous than most prescription drugs.2

In October of 2003, the US District Court struck down the requirement for unit-dose packaging of iron on the grounds that the Food and Drug Administration did not have the authority to regulate its packaging.33 The findings of this study clearly support the need for the reinstatement of this regulation.

Unit-dose packaging may be more convenient than conventional medication containers because there is no need to reengage the child-resistant closure. As recommended by Wiseman et al,4 to ensure the child resistance of unit-dose packaging, there is a need for standards to assess effectiveness of each type. Unit-dose packaging is a true primary prevention intervention because each tablet is individually protected rather than all tablets in a container being communally protected by a single child-resistant closure.

These data clearly show that unit-dose packaging is an effective intervention for decreasing fatal iron poisonings in children younger than 6 years, and it should be considered for other medications with a high hazard for morbidity and mortality when taken in overdose. The requirement for unit-dose packaging of iron should be reinstated in the United States.

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REFERENCES


