Reported Adverse Drug Events in Infants and Children Under 2 Years of Age

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ABSTRACT. *Objective.* **To characterize risks to infants and young children from drugs and biological products that were identified in spontaneous adverse event reports submitted to the US Food and Drug Administration.**

Methods. **Of >500 000 MedWatch adverse event reports received by the Food and Drug Administration from November 1997 through December 2000, we identified 7111 reports about infants and children younger than age 2. The reports were analyzed for health outcome (eg, death, hospitalization, congenital anomaly), principal suspect drug, and whether the route of drug exposure was direct administration or through the mother in the perinatal period.**

Results. **Drug therapy was associated with an average of 243 reported deaths annually over the 38-month study period, with 100 (41%) occurring during the first month of life and 204 (84%) during the first year. In 1432 (24%) reported adverse event cases of all levels of severity, exposure to the drug was from the mother during pregnancy, delivery, or lactation. Although 1902 different drugs, biological products, and other chemicals were identified in the reports, only 17 drugs or biological products were a suspect in 54% of all serious and fatal adverse events in drugs administered directly.**

Conclusion. **Adverse reactions to drug therapy are a significant cause of death and injury in infants and children under 2 years of age. Drugs administered to the mother in the perinatal period constituted a major route of exposure to adverse drug advents. These results underscore the need for additional drug testing in the youngest pediatric patients and for carefully weighing the risks versus benefits of medication.** *Pediatrics* **2002; 110(5). URL: http://www.pediatrics.org/cgi/content/full/110/5/e53;** ***infant, child, adverse drug reaction reporting systems, drug therapy.***

ABBREVIATIONS. FDA, US Food and Drug Administration; AERS, Adverse Event Reporting System; HIV, human immunodeficiency virus.

Drug therapy in infants and children under 2 years of age is complicated by lack of clinical testing and prescribing information for this patient population. Clinical trials for US Food and Drug Administration (FDA) approval usually exclude children. Therefore, labels for new medications typically provide physicians with little to no guidance on a product's effectiveness, dosing, and safety in pediatric patients. The FDA recently reported, "For most drug classes, there is almost no information on use in patients under 2 years of age."[1] The limited information that is available about adverse drug events in the pediatric population has focused on medical errors such as overdosing and accidental exposure.[2] In addition, the potential for adverse drug reactions in young children is greater than in adults, because young children have immature detoxification mechanisms and because doses must be individually adjusted for a much wider range of body size and weight.

Given the limited clinical testing in the infant population, spontaneous adverse event reports become a primary source of information to the risks of drug therapy in the youngest children. The information in these reports comes from health professionals who observe in clinical practice an adverse event that may be associated with a drug or biological product, and consumers. In the United States, such reports are generally written and submitted by the manufacturer, although reports may be submitted directly to the FDA under the MedWatch Safety Information and Adverse Event Reporting Program.[3] This is the first broad review of adverse event reports about infants and children younger than 2 years of age.

METHODS

The FDA's Adverse Event Reporting System (AERS) is one of the agency's major tools for monitoring the safety of prescription drugs and biological products after approval. In 2000, the FDA received 245 750 adverse event reports, including 15 254 (16%) directly from individuals and health professionals, and 230 496 (84%) from manufacturers.[4] The FDA publishes Quarterly Extracts from AERS after deleting personal identifiers and text of the event narrative.[5] The published data include linked data files for patient demographic information, a list of the medical terms that best describe the event, the names of all products involved (whether ancillary or suspected of causing the reported event), the source of the report (eg, consumer, health professional, company representative), and the event outcome (eg, death, hospitalization, congenital anomaly). From the 595 980 reports in the AERS system as of December 2000, all MedWatch reports for subjects <2 years of age were extracted, covering the period from the inception of the AERS system in November 1997 through December 2000.

Drug names, where possible, were standardized to the ingredient names in the FDA National Drug Code System, including 2 and 3 ingredient combinations. If no exact match was found, irregular entries were edited for stylistic and spelling uniformity, to eliminate parenthesis, extraneous comment, and simultaneous listings of both generic and trade names.

The MedWatch form allows the reporter to check 1 or more of

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the following event outcomes: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, requiring intervention to prevent permanent impairment/damage, and other. To analyze the adverse event outcome, we created 4 mutually exclusive subgroups. In order of decreasing severity the groups were: 1) death, 2) congenital anomaly or disability, 3) serious nonfatal (hospitalization, required intervention, or life-threatening), and 4) either other or no outcome given. If the report noted >1 outcome (such as both hospitalization and death), the more severe outcome was selected. When there were both initial and follow-up reports for the same case, the most severe outcome was selected.

Although the report narrative is not included in the data abstracts, the medical terms describing the event are listed by FDA reviewers after being standardized using MedDRA, a special medical dictionary used internationally for drug regulation.[6]

We also separated cases where the suspect drug was transmitted from the mother during pregnancy, delivery, or lactation, rather than administered to the infant directly. Drugs were flagged as resulting from maternal exposure for the following reasons: 1) any report with an outcome of congenital anomaly, 2) a preferred term in the narrative indicating "maternal exposure to therapeutic drug," 3) a "transplacental" or "transmammary" route of administration, and 4) an indication of maternal exposure in association with the drug name section of the reporting form.

Reports with missing or inconsistent information were not excluded from the analysis, except that missing values were automatically omitted from totals and percentages for that particular variable. Although most infant ages were provided in days, weeks, or months, those reports with an age of 0 years were coded as <1 month, and 1 year as 12 months.

Statistical Analysis

The adverse event reports in this study constitute a population and permit direct comparisons without confidence intervals or assessing the probability that the differences might have occurred by chance. The FDA AERS reports were maintained in a relational database, and SAS Version 8.2 (SAS Institute, Cary, NC) was used for descriptive statistics.

RESULTS

Overview of Reports

From November 1997 through December 2000, the FDA received 7111 adverse event reports for children up to 2 years of age. These consisted of 5976 (84%) unique cases and 1135 (16%) follow-up reports about an event already in this data set (Table 1). The 7111 reports of all kinds amount to 1.1% of adverse event reports for all ages during this period, while the age cohort comprises ~3% of the US population. Of the report total, 6718 (94%) were prepared by manufacturers, with only 393 (6%) reports submitted by health professionals or consumers directly to the FDA.

TABLE 1. Number and Type of Reports

	Reports	Percentage
MedWatch reports	7111	100
Unique cases*	5976	84
Initial	5631	79
Follow-up	1475	21
Unknown	5	0
Type of report		
Direct to FDA	393	6
Mfr-Expedited	4280	60
Mfr-Periodic	2438	34
Year received		
1997†	329	5
1998	1817	26
1999	2632	37
2000	2333	33

Mfr indicates manufacturer.
* Unique case in AERS system even if first report on file was a follow-up.
† November and December only.

The reported adverse events were concentrated in the first months of life, with 1873 (31%) events identified in the first month, and another 3002 (50%) from the 2 days to the 12th month (Table 2). The number of events declined with age except for an increase at 12 months, thought to be an artifact of a tendency to round age to 1 year. More adverse events were reported among males (57%) than females (43%; Table 2).

The adverse drug events that were reported were mostly severe with 61% resulting in death, disability, congenital anomaly, hospitalization, or other serious outcome (Table 3). This is an expected result from a surveillance program that solicits reports primarily of new serious adverse events and medication errors.

Reported Deaths

In the 38-month study period, 769 deaths associated with a drug or biological product were reported to the FDA among infants and children under 2 years of age. This was an average of 243 deaths a year, but increased from 184 in 1998 to 326 in 2000. Overall, 41% of all deaths occurred in the first month of life, and 84% within the first year. This is similar to overall infant mortality in which half of all infant deaths occur in the perinatal period.[7]

Although 183 different drugs were identified as principal suspect drug on at least 1 report with an outcome of death, only 4 drugs accounted for 38% of the reported deaths. Those drugs were palivizumab, 113 cases (15%); nitric oxide, 87 cases (11%); indomethacin, 78 cases (10%); and cisapride, 24 cases (3%). Palivizumab is a monoclonal antibody indicated for prevention of severe respiratory syncytial virus disease in high-risk pediatric patients.[8] Nitric oxide is indicated as an adjunct to mechanical ventilation in neonates with hypoxic respiratory failure.[9] Indomethacin is a nonsteroidal antiinflammatory drug used in IV formulation for reduction of intraventricular hemorrhage in infants with patent ductus arteriosus.[10] Although it was not FDA-approved for use in infants, cisapride was widely used to treat infants with gastroesophageal reflux. It was withdrawn from the market in 2000 because of adverse event reports (similar to those analyzed here) linking

TABLE 2. Characterics of Adverse Events

	Cases	Percentage
Total unique cases	5976	100
Gender		
Male	3051	57
Female	2324	43
Unknown	601	NA
Route of exposure		
Direct therapy	4544	76
Maternal exposure	1432	24
Age (mo)		
First month	1873	31
1–12	3002	50
13–23	1101	18

NA indicates not applicable.

TABLE 3. Health Outcome of Adverse Events

	Maternal Exposure	Percentage	Direct Therapy	Percentage	Total	Percentage
Outcome groups*	1432	100	4544	100	5976	100
Death	154	11	615	14	769	13
Congenital anomaly/disability	583	41	81	2	664	11
Serious nonfatal	433	30	1882	41	2315	39
Other or unknown	262	18	1966	43	2228	37

* Mutually exclusive groups for most severe outcome.
Unique cases in AERS system.

cisapride with cardiac arrhythmia and sudden death.[11,12]

Maternal Exposure

In 1432 cases (24%), the drug or biological product causing the adverse event was administered to the mother rather than the infant. In this category, congenital anomaly or disability was the most common outcome, occurring in 41% of the reported events. As might be expected, 90% of the adverse events involving maternal exposure occurred within the first 4 months of life.

Drugs typically administered to prevent the transmission of human immunodeficiency virus (HIV) accounted for 25% of all the reported adverse events through maternal exposure. HIV drugs with >10 case reports each were zidovudine (177), lamivudine (57), nelfinavir (56), and nevirapine (44). Without data about how frequently these drugs were prescribed to prevent HIV transmission, it is not possible to tell whether zidovudine was more toxic in this therapeutic setting than similar drugs or was prescribed more often because it was the first drug proven to reduce maternal transmission.[13] A wide spectrum of adverse events were associated with the HIV-related drugs, including 110 cases (35%) with an outcome of congenital defect or permanent disability, 103 (34%) cases involving initial or prolonged hospitalization or a life-threatening event, and 23 (7%) with death as the reported outcome.

Specific Drugs

The adverse event reports identify 1902 different therapeutic drugs, nontherapeutic chemicals, biological products, vaccines, over-the-counter medications, vitamins, minerals, dietary supplements, blood products, and illegal substances. Many were among those listed as concomitant therapy rather than being suspected of causing an adverse event. However, the list is relatively short when focusing only on cases that met these criteria: 1) product identified as the principal suspect in 20 or more reports, 2) the product was administered directly to the infant, and 3) an outcome of death or serious adverse event. Only 17 drugs and biological products accounted for 54% of all serious and fatal adverse events under these criteria. A single biological product, palivizumab, accounted for 28% of all such cases. The number of reported deaths and serious events in infants treated with palivizumab was 8 times more than any other drug or biological product administered to this patient population. The adverse event profile of palivizumab has been summarized separately.[14]

The 17 most frequently reported drugs and biological products with serious or fatal adverse event include 2 treatments for prophylaxis of respiratory syncytial virus, 6 antibiotics, and 2 analgesics. The drugs and therapeutic classes are listed in Table 4.

Some widely used drugs appeared frequently as concomitant therapy but were seldom suspected of being responsible for the adverse event being re-

TABLE 4. Most Common Drugs Listed as Principal Suspect (Serious or Fatal Outcome [Maternal Exposure Excluded])

Drug or Product	Cases	Percentage	Major Drug Class*
Palivizumab	705	27.9	Immunologics
Cisapride	102	4.0	Disorders, acid/peptic
Indomethacin	97	3.8	NSAID
Nitric oxide	86	3.4	Medicinal gases
Azithromycin	52	2.1	Lincosamides/macrolides
Acetaminophen	41	1.6	Analgesics, general
Fluconazole	37	1.5	Antifungals
Ibuprofen	33	1.3	NSAID
Respigam	32	1.3	Immune serums
Ceftriaxone	28	1.1	Cephalosporins
Cefaclor	26	1.0	Cephalosporins
Cefoperazone	25	1.0	Cephalosporins
Zidovudine	25	1.0	Antivirals
Erythromycin	22	0.9	Lincosamides/macrolides
Vincristine	21	0.8	Antineoplastics
Sevoflurane	20	0.8	Anesthetics, general
Vancomycin	20	0.8	Antibacterials, miscellaneous

NSAID indicates nonsteroidal antiinflammatory agent.
* Selected from FDA National Drug Code Directory.

ported. One example was albuterol, appearing on 365 reports, but identified as a primary suspect in only 8 serious or fatal events; ranitidine appeared in 299 reports, but was primary suspect in only 14 serious or fatal events. Other widely used drugs were listed as being used in concomitant therapy, but were also frequently identified as the suspect drug. Most notable was acetaminophen, which appeared in 413 reports, and was also ranked number 7 (41 cases) on the list of primary suspect drugs among reports of serious events or death.

Comment

The results of this study underscore the need for additional testing in the youngest pediatric patients and for greater vigilance in the use of higher risk drugs and in medications for pregnant or lactating women. However, the results should be interpreted with caution in light of the known limitations of these data.

An adverse event report itself does not establish a causal link between the event and the medication. It usually establishes that an observer believed the suspect drug might be involved in the adverse event and therefore took the initiative to report the event to the manufacturer or the FDA. In addition, the volume of reports for any individual drug can be influenced by the length of time on the market, severity of underlying illness, the manufacturer's marketing and postmarket surveillance activities, and whether the event was already recognized on the product label.[3] Most of these factors are unrelated to the safety of the drug. In addition, FDA public statements, media publicity, and manufacturer warning letters to doctors may increase awareness of particular adverse reactions and increase spontaneous reporting.

It is almost certain that the overall total of death and serious injury associated with drug adverse events is substantially higher than reported here. According to a recent FDA report, "About 90% of serious or fatal adverse drug reactions are never reported. Some studies have found reporting rates around 1%."[15] In addition, several of the specific drugs most frequently named principal suspect were not on the market for the entire study period. Palivizumab was only marketed during 24 of the 38 months, nitric oxide for 12 months, and cisapride for 31 months.[12,16,19] It is unknown whether the adverse event reporting rate in this special population might differ from reporting rates for persons of other ages.

By itself, this study does not provide enough information to judge the risks and benefits of any specific drug, or to form the basis for identifying the need for new or additional warnings. A risk assessment of a particular drug requires analysis of the specific reports, information from clinical trials, and evaluation of the characteristics of the specific event.[3] These results do provide an overview of reported adverse events in this special population and a frame of reference for additional research on specific drugs.

The 24% share of reported adverse events that occur through maternal exposure underlines the potential hazards that prescription drugs pose to infants exposed to medications in utero. On approval, safety information about the risks of new medications during pregnancy is generally limited to animal studies and perhaps, a small number of case reports.[17] One survey of 1152 drugs found only 6 had been tested for safety in pregnant women, and only 206 had produced no adverse effects in animal and in vitro testing for genetic mutation, teratogenicity, or effect on fertility.[18] Approximately a dozen pregnancy registry studies, mostly sponsored by manufacturers, are now ongoing to establish the overall safety of particular drugs and drug classes commonly used during pregnancy.[17] However, these studies take years to conduct and because of power and design limitations, often are limited to identifying elevations in overall rates of major congenital malformations that are readily apparent at birth. For most medications, the adverse event reports provide the first signal of potential risks of drug exposure in utero.

As an incentive to conduct pediatric studies, the federal Pediatric Exclusivity Provision grants the manufacturer a 6-month patent extension for conducting pediatric studies.[1] Of the 27 products studied under this initiative between July 1998 and March 2001, 16 now have pediatric labeling, and 6 required major revisions to the dosing or safety sections of the label.[1] In addition, the Best Pharmaceuticals for Children Act of 2002 renewed the Pediatric Exclusivity Provision, provided additional funds from pharmaceutical company user fees to expedite the review of pediatric studies, and permitted the FDA to contract for needed pediatric studies of generic drugs.[19]

CONCLUSION

The number of reported deaths and serious adverse events associated with drug therapy emphasizes the need to weigh the benefits of drug treatment versus the risks in this vulnerable population. Practitioners can help make the drug safety system more effective by reporting suspected adverse drug events in the infant population, especially those that involve a drug interaction, a product problem, or a serious adverse event that is not already included in the product labeling.

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