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Black Box Warnings: Implications for Pediatric Health Care Providers

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The Food and Drug Administration (FDA) is charged with ensuring that accurate information on both the efficacy and safety of prescription medications is available to health care providers. During initial consideration for approval of a new agent or after approval, the FDA may request that the manufacturer highlight information of particular importance. This information is typically offset from the remainder of the adverse effects by use of different lettering or by surrounding it with a box, from which the term "black box warning" has developed.[1]

The Purpose of Black Box Warnings

All drug product labeling contains a listing of adverse effects, provided in descending order of importance under the classifications of Contraindications, Warnings, Precautions, and Adverse Reactions. Black box warnings are not standard for all drugs, but are added only when warranted. They are meant to call attention to situations where considerable risk to the patient may occur or in situations where additional information or monitoring might prevent an adverse event. The information included in a black box warning is not intended to restrict prescribers from using a particular agent, but rather to ensure that adequate consideration of benefit and risk is undertaken and that appropriate administration and monitoring of the drug are completed.[1,2]

The FDA is given the authority to mandate changes to drug labeling through the Federal Food, Drug, and Cosmetic Act (FDCA). Under the FDCA, a drug can be considered misbranded if it lacks adequate directions for use. Drug labeling changes may be requested by the FDA at any time. Black box warnings often are added after the drug has been on the market and routine clinical use has revealed a significant risk. These warnings are typically based on data accumulated from clinical research in humans, postmarketing adverse event reporting, or, occasionally, epidemiologic studies.

In their review of 375 black box warnings from a sample of 206 drugs from the 1995 *Physicians' Desk Reference*, Beach and colleagues developed a classification scheme for the most common types of information provided. They found that most warnings fell into one of the following categories:

- an adverse effect that might be prevented by early monitoring and intervention,
- specific patient populations that may be at greater risk,
- situations where the risks might outweigh the benefits of therapy,
- specific drug interactions or critical dosing information,
- recommendations that a drug should only be given by specially trained personnel or in a special setting,
- provision of specific information about drug administration.[1]

Using this classification system, the authors found that the largest single group of black box warnings, 25% of the total, dealt with identifying specific patient populations at increased risk for adverse effects. The second largest number of warnings, 20% of the total, were related to specific drug interaction/dosing information.[1]

Access to New Warnings

New safety information, including black box warnings, is made available to health care providers through a number of different mechanisms. Traditionally, this information was mailed to prescribers in a format that came to be known as a "Dear Doctor" letter or "Dear Health Care Professional" letter. Unfortunately, the effectiveness of these mass mailings has been less than ideal. In 1995, a black box warning was added to the product labeling for cisapride, highlighting the risk for QT interval prolongation and adding a contraindication for patients taking medications that inhibited cisapride metabolism through cytochrome P450 3A4. Cisapride had been on the market in the United Sates for two

years, during which the FDA had received 34 reports of torsades de pointes and 23 cases of prolonged QT interval associated with the drug. At the time the black box warning was added, a "Dear Health Care Professional" letter was issued. Despite the warning, reports of these toxicities continued, and a second round of labeling changes occurred in June 1998.

In 2000, Smalley and colleagues conducted an analysis of the efficacy of this regulatory action by evaluating cisapride prescribing in three established pharmacoepidemiology research sites, including a managed care organization, a consortium of health maintenance organizations, and a state Medicaid program.[3] Records were reviewed to identify the percentage of patients with a prescription for cisapride for whom the drug should have been contraindicated. In the year prior to the cisapride warnings, cisapride use was contraindicated in 26, 30, and 60% of patients at the three study sites. In the year following the regulatory changes (July 1998 to June 1999), use was contraindicated in 24, 28, and 58% of patients. The authors concluded that, despite increasing the number of contraindications for cisapride and efforts by the manufacturer and the FDA to make health care providers aware of the information, prescribing patterns did not change.

Since that report, there has been renewed interest in attempting to increase prescriber access to new warning information. The wide-spread use of computer-based drug information programs and the availability of the Internet have greatly improved the ability of the FDA and pharmaceutical manufacturers to make new information available to prescribers. While "Dear Health Care Professional" letters are still being sent through standard mail, this information can now also be found on-line using pharmaceutical manufacturers' websites or the FDA's MedWatch Safety Information and Adverse Event Reporting Program webpage.[4] This site allows users to search for warnings by date, drug type, or drug name.

Although the MedWatch site is useful when looking for information by drug, it groups all types of labeling changes together, as well as drug and device recalls. Until recently, it has been difficult to obtain information specifically on black box warnings. To address this need, Generali published a series of comprehensive tables listing current black box warnings in *Hospital Pharmacy*.[5-8] A wall chart including all the tables may be obtained through the publisher's website, listed in the references, or by calling Facts and Comparisons at 800-223-0554.

Warnings Affecting Pediatric Patients

While all the information contained in the product labeling should be reviewed by prescribers, there are some warnings that may be of particular interest to pediatric health care providers. The following table provides examples of warnings for drugs frequently used in pediatrics, as well as warnings specifically addressing risks in infants and children.

Table. Examples of Warnings Affecting Pediatric Patients [4-8]

Aminoglycosides
- risk of nephrotoxicity
- caution about use in neonates

Amprenavir
- risk of propylene glycol toxicity in children < 4 years of age taking the oral liquid preparation

Angiotensin Converting Enzyme Inhibitors
- use during the second and third trimesters associated with injury or death to the fetus

Baclofen (intrathecal)
- rare cases of life-threatening toxicity following abrupt withdrawal

Carbamazepine
- risk of hematologic adverse effects

Cisapride
- risk of QT prolongation and torsades de pointes

Dextroamphetamine
- abuse potential

Dantrolene
- risk of hepatotoxicity

Droperidol
- risk of QT prolongation and torsades de pointes

Fentanyl (transdermal)
- use contraindicated in children < 12 years of age or < 18 years of age and < 50 kg unless in an investigational research setting

Infliximab
- risk of invasive infections

Iron-containing vitamins
- risk of overdose (iron overdose is the leading cause of fatal poisoning in children < 6 years of age)

Lamotrigine
- risk of serious rashes in 1% of pediatric patients and 0.3% of adults

Methylphenidate
- abuse potential

Midazolam
- risk of severe hypotension and seizures in neonates after rapid intravenous injection, particularly with concurrent fentanyl

Pemoline
- risk of life-threatening hepatotoxicity; requires written informed consent prior to initiation

Phytonadione
- risk of severe hypersensitivity reactions after intravenous injection

Ribavirin
- risk of sudden deterioration of respiratory function during treatment

Succinylcholine
- risk of hyperkalemic rhabdomyolysis in infants and children with undiagnosed skeletal muscle myopathy or Duchenne's muscular dystrophy

Topiramate
- risk of acute myopia and glaucoma

Valproic Acid
- increased risk of hepatotoxicity in children < 2 years receiving multiple anticonvulsants or with congenital metabolic disorders, severe seizure disorders, mental retardation, or organic brain syndromes

Zonisamide
- increased risk of oligohidrosis and hyperthermia in pediatric patients (zonisamide is not currently approved for pediatric use)

The Timing of New Warnings

As a result of changes in the drug approval process, new drugs often come onto the market having undergone less clinical testing than in the past. There has been growing concern that important information on adverse effects may not be available to prescribers at the time of release of a new drug onto the market.

In the May 1, 2002 issue of JAMA, Lasser and colleagues published a thought-provoking assessment of the timing of new black box warnings and withdrawal of drugs from the market.[9] In their review of 548 drugs approved by the FDA between the years of 1975 and 1999, the authors found that by the year 2000, 45 (8.2%) of the drugs had been given one or more new black box warnings. In Kaplan-Meier analyses, half of the warnings were added within the first seven years after the drug was introduced. Sixteen drugs (2.9% of the total) had been withdrawn from the market at the time of analysis, with five of those drugs having acquired a black box warning prior to withdrawal. Half of the withdrawals occurred in the first 2 years after marketing. Based on the timing of these changes, the authors predicted that one in every five new drugs would be given a new black box warning or be withdrawn within 25 years of initial marketing. Since the highest incidence of new adverse effect information was added during the first few years of use, the authors also suggested that prescribers consider selecting older, more well-known agents when possible.

This study generated considerable debate. In an accompanying editorial, two physicians within the FDA urged caution when interpreting the results of this analysis.[10] They reminded readers that many revisions in black box labeling are clarifications of known adverse effects or drug interactions. Other clinicians commented on the article in letters to the journal, addressing issues with how the warnings were categorized and calling attention to the problems inherent with limited patient enrollment in controlled clinical trials and the known under-reporting of adverse effects through voluntary surveillance systems like MedWatch, both of which delay accumulation of adverse effect data.[11-14] Taken together with the original analysis, these comments serve as a useful reminder of the limitations currently present in providing adverse effect information to prescribers.

Summary

Black box warnings have evolved as a mechanism to highlight serious adverse effects and communicate information about drug interactions and dosing within the product labeling. Increasingly, this information is appearing after FDA approval, making it important for health care providers to have access to this information in a timely manner in order to appropriately weigh the risks and benefits of therapy.

References

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Pharmacology Literature Review

Atomoxetine inhibition by paroxetine

Atomoxetine has recently been approved for the treatment of children with attention-deficit/ hyperactivity disorder. Atomoxetine is metabolized through the cytochrome P450 2D6 pathway, making it susceptible to interactions with drugs that inhibit this enzyme, such as paroxetine. In this study, the effects of paroxetine on atomoxetine metabolism were evaluated in 22 healthy adults. Administration of paroxetine resulted in an increase in the mean atomoxetine maximum serum concentration at steady state from 172.7 to 611.6 ng/ml. Mean atomoxetine elimination half-life increased from 3.92 hours when given alone to 10.02 hours when given with paroxetine. No changes in paroxetine pharmacokinetics were observed. Belle DJ, Ernest CS, Sauer J, et al. Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. **J Clin Pharmacol 2002;42:1219-27.**

Celecoxib pharmacokinetics

Celecoxib is one of the selective cyclooxygenase 2 (COX-2) inhibitors. Although widely used in adults for their analgesic and anti-inflammatory effects, this class of agents has not been studied in children. In this study, the pharmacokinetic profile of celecoxib was evaluated in 10 children (6-16 years of age) with cancer. Serum concentrations were evaluated after a single 250 mg/m^2 dose and after a week of twice daily dosing. The mean apparent volume of distribution was 7.9$\pm$7.8 L/kg with a clearance of 1.4 $\pm$1.0 L/hr/kg, and an elimination half-life of 3.7$\pm$1.1 hours. The rate of clearance was increased with continued dosing, compared to the initial values from the single dose. In comparison with adults, the elimination of celecoxib in children was considerably more rapid, with a clearance twice as fast and a half-life approximately half as long. Stempak D, Gammon J, Klein J, et al. Single-dose and steady-state pharmacokinetics of celecoxib in children. **Clin Pharmacol Ther 2002;72:490-7.**

Developmental pharmacokinetics review

This two part series describes our current knowledge of the development of hepatic and renal drug clearance in infants. The first part of the series focuses on the data available on drug elimination in infants, while the second article provides a mathematical framework developed from those data, referred to as the Infant Scaling Factor, to serve as a tool for future research. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. Part I. **Clin Pharmacokinet 2002;41:959-98** and Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. Part II. **Clin Pharmacokinet 2002;41:1077-94.**

Nizatidine pharmacokinetics

The pharmacokinetic profile of nizatidine, an H_2-receptor antagonist, was studied in 12 healthy children between the ages of 4 and 12 years. A single 5 mg/kg oral dose was given as an extemporaneous liquid in apple juice. When corrected for the decrease in bioavailability produced by the dosage formulation, all pharmacokinetic parameters assessed were similar to values observed in adults. The mean terminal elimination rate in the pediatric subjects was 0.58$\pm$0.8 hr^{-1}, similar to the value reported in adults (0.54$\pm$0.13 hr^{-1}). The single 5 mg/kg dose given provided effective gastric acid suppression for approximately 6 hours. Abdel-Rahman SM, Johnson FK, Manowitz N, et al. Single-dose pharmacokinetics of nizatidine (Axid®) in children. **J Clin Pharmacol 2002;42:1089-96.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 11/22/02:

1. Fulvestrant (Faslodex®) was added to the Formulary for the treatment of hormone receptor positive metastatic breast cancer.
2. Pegfilgrastim (Neulasta®) was also added. This long-acting form of granulocyte colony-stimulating factor (G-CSF) is given subcutaneously once per chemotherapy cycle.
3. Darbepoetin (Aranesp®) was rejected for use in patients with chemotherapy-induced anemia. It is still available for use in patients with anemia due to chronic renal failure.
4. Several changes to the Outpatient Formulary were approved. The full list is available at http://hsc.virginia.edu/pharmacy-services/outpatient/outpatienthome.html

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