Adverse Drug Reactions

Type A (Intrinsic) or Type B (Idiosyncratic)

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KEYWORDS

• Hepatotoxicity • Drug-induced liver injury • Adverse drug reaction
• Type A adverse drug reaction • Type B adverse drug reaction • Intrinsic
• Idiosyncratic • LiverTox

KEY POINTS

- Type A, or intrinsic, adverse drug reactions are dose-related, predictable toxic effects of medications, such as acute liver failure resulting from acetaminophen overdose.
- Type B or idiosyncratic adverse drug reactions are less related to dose and are associated with drug, patient, and environmental risk factors, which can be difficult to predict.
- Resources such as LiverTox assist with earlier detection of idiosyncratic adverse reactions in postmarketing use and can help guide diagnosis and management.

INTRODUCTION

In the United States today, drug-induced liver injury is the leading cause of acute liver failure (ALF), ahead of viral hepatitis and other causes.[1,2] More than1000 agents have been identified as causes of hepatic injury and, as reporting increases and new agents come to market, this number will continue to rise.[3] The adverse drug reactions experienced from these substances have typically been divided into Type A intrinsic reactions or Type B idiosyncratic reactions. Type A adverse drug reactions are dose-dependent, predictable toxicities. Type B adverse reactions are not easily explained by dose or expected pharmacologic response, rather they involve less predictable responses in susceptible individuals. Both types of adverse drug reactions are responsible for significant morbidity and mortality in many Western countries.

Most cases of drug-induced liver injury are the result of Type A adverse events; however, many more medications have been reported as causing Type B events. From 1990 to 2002, drug-induced liver injury from acetaminophen, isoniazid,

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valproate, phenytoin, and propylthiouracil was responsible for 15% of all liver transplantations in the United States.[4] More than half of these cases involved therapeutic use of the medications rather than intentional overdose. Although acetaminophen, which causes a Type A adverse event, accounts for most drug-induced ALF, Type B adverse drug events are implicated in more than 10% of ALF cases.[5]

Although understanding of Type A adverse events is relatively well established, new information about Type B responses and their risk factors continue to shape how clinicians diagnose and manage these responses. Drug-induced liver injury identified in postmarketing experience is the leading cause of withdrawal or new warnings for medications that have already been approved.[5,6] Most medications that require postmarketing action cause Type B responses. These reactions are difficult to detect in clinical trials because they often do not occur in animal models and occur rarely in the general population. This means that idiosyncratic reactions may not be observed in premarketing studies in which the number of participants is limited and duration of exposure is short, and are only seen in postmarketing surveillance, as depicted in **Fig. 1**. Fortunately, resources such as LiverTox, an online database maintained by the National Institutes of Health, exist to assist clinicians with identifying, managing, and reporting drug-induced liver injury.

TYPE A (INTRINSIC) ADVERSE DRUG REACTIONS

Adverse drug reactions classified as Type A, or intrinsic, are defined as predictable adverse effects associated with an agent and are related to dose.[7] As the dose of the administered agent increases, the risk of adverse event increases with it, in accordance with the pharmacologic profile of the agent.[7,8] Type A adverse effects are predictable side effects and may also be characterized as drug toxicities. Because of their predictable nature, Type A adverse effects generally have relatively low mortality because responses can be monitored and managed.[7] Because intrinsic adverse effects are usually identified in animal models or clinical trials in humans, medications that demonstrate these effects at therapeutic doses often never come to market.

Common examples of medications causing Type A adverse effects leading to liver injury are listed in **Table 1**. The classic example of a dose-dependent hepatotoxic response is acetaminophen. Acetaminophen is associated with fulminant hepatic failure when administered at toxic doses; however, hepatic dysfunction is rarely seen at doses below 4 g per day in healthy patients. As long as the drug is administered at the therapeutically appropriate dose, hepatic adverse effects are very rare.

Chronic exposure to certain medications can increase the risk of developing Type A adverse reactions. In a mouse model, chronic exposure to acetaminophen in combination with subacute high-dose exposures resulted in severe hepatotoxicity, ALF, and death.[9] Additionally, chronic exposure alone, without the acute overdose, led to ALF in some older mice. Finally, N-acetylcysteine (NAC), which is normally an effective antidote for acetaminophen hepatotoxicity, did not significantly improve ALF prevention or recovery compared with placebo. These findings suggest that exposure to hepatotoxic medications over time may be important in the development of intrinsic hepatotoxic reactions.

TYPE B (IDIOSYNCRATIC) ADVERSE DRUG REACTIONS

Type B adverse drug reactions, or idiosyncratic drug reactions, are unanticipated adverse effects associated with an agent.[7] They result from a combination of factors unique to the individual.[5,8,10–12] Differences between Type A and Type B adverse drug