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Drug Induced Liver Injury

Drug – induced liver injury is uncommon and generally unpredictable. It accounts for <5% of cases of jaundice or acute hepatitis and fewer cases of chronic liver disease. Drug reactions produce an array of hepatic lesion that mimic all known hepato-biliary disease, from minor non-specific changes in liver enzymes or ultra-structure to fatal hepatic necrosis, cirrhosis and liver cancer. Prevention of hepato-toxicity is an ethical and legal responsibility of individual doctors as well as society as a whole.

In this brief review all issues related to drug induced hepatitis could not be addressed, therefore the emphasis would be on the important ones.

Diagnosis: As there are no specific diagnostic tests, diagnosis of drug induced hepatitis requires clinical suspicion, a careful drug history, and consideration of the temporal relationships between drug ingestion and liver disease, and exclusion of the disorders. There is always an obligation for doctors and pharmacists to carefully inform their patients about the possibility of adverse reactions to any drugs that they are taking. Isoniazid, a drug known to be hepato-toxic for more than 25 years, is still usually associated with deaths from liver failure (1,2).

It is clearly essential to exclude other liver disease before ascribing hepatic injury to a drug. Drug-induced cholestasis should be considered when dilatation of the common bile duct has been excluded by hepato-biliary imaging. Extrahepatic features such as skin rash, eosinophilia and other organ involvement implicate adverse drug reactions, but as these features are present only in few cases, their absence is not helpful. Specific diagnostic tests for individual drugs-induced liver disease are not yet available, but in the case of dose dependent hepato-toxins like acetaminophen and aspirin, blood levels may be helpful.

The criteria for temporal eligibility include relationship to onset, course of the reaction after discontinuing the drug (dechallenge), and response to readministration of the drug (rechallenge). Deliberate rechallenge is rarely indicated for logistic and ethical reasons (it can be hazardous) but inadvertent rechallenge may have occurred.

In some cases, a liver biopsy may provide further clues to a drug etiology, such as disproportionate or zonal necrosis, microvesicular steatosis, bile duct injury, vascular lesions and a mixed inflammatory infiltrate that contains polymorphs and eosinophils as well as mononuclear cells (3). Currently, however, rechallenge remains the gold standard test for drug induced liver disease.

Factor	Examples	Influence on risk
Age	Isoniazid, Nitrofurantoin, Halothane Valproic acid.	Increases with age, >60 years. More common in young children.
Gender	Methyldopa, Halothane, Nitrofurantoin. Azathioprine.	Acute and chronic hepatitis more in females. More common in males.
Dose	Acetaminophen, AspirinMethotrexate, Vitamin A.	Risk of hepatotoxicity related to blood levels. Total dose, dose frequency and duration of drug.
Genetic factors	Halothane, Phenytoin	Multiple cases in families.
Alcohol abuse	Acetaminophen Isoniazid, Methotrexate.	Lowers dose threshold Increases risk of liver injury.
Obesity	Halothane hepatitis, Methotrexate	Increased risk of liver injury, hepatic fibrosis.
Fasting	Acetaminophen	Increased risk of hepatotoxicity.
Diabetes mellitus	Methotrexate	Increased risk of hepatic fibrosis.
Renal failure	Tetracycline, Methotrexate	Increased risk of liver injury, hepatic fibrosis.

Prevention: **W**ith the exception of acetaminophen hepatotoxicity, there is little effective treatment for drug induced liver disease. Hence, prevention and early detection of liver injury, together with prompt withdrawal of the offending agents are crucial. The majority of drugs associated with drug-induced liver disease are **idiosyncratic** hepato-toxins. **Polypharmacy** should be avoided where possible, as drug reactions are more frequent when more than one agent is being taken. (4)

Early detection of liver injury is critical. While prescribing hepatotoxic drug, patients should be warned to report non-specific features that may represent prodrome, such as unexplained nausea, malaise, right hypochondriac pain, lethargy or fever. These symptoms are an indication to perform liver tests and if the results suggest liver injury, to stop treatment immediately. Protocol screening with liver tests is often recommended, but its efficacy and cost-effectiveness is questionable.
The classic example is **Isoniazid**, which causes some liver test abnormality in 30% of exposed subjects. Generally, it is recommended that the drug should be stopped if patient develops symptoms of liver injury or alanine aminotransferase (ALT) values exceed 250 IU/L or more than 5 times the upper limit of normal. Rise in bilirubin and prothrombin time provides a clearer indication to stop or modify the therapy. Conversely, a rise in gamma-glutamyl transpeptidase (GGT) or minor elevation of serum alkaline phosphatase does not usually indicate liver injury. Thus, protocol screening is not routinely recommended, but it can be useful for agents such as isoniazid, pyrazinamide, valproate, halothane and retinoids (5).

Management: Active management of drug-induced hepatotoxicity includes removal of the drug and administration of antidotes, anti-inflammatory and cytoprotective agents. In practice, it is usually confined to the discontinuation of hepatotoxic drugs. For ingested hepatotoxins like metal, poisonous mushrooms and acetaminophen, removal of unabsorbed drugs by aspirating stomach contents may be appropriate in initial hours. **N-acetylcysteine** is indicated as antidote for acetaminophen poisoning; whether it has a role in other types of acute hepatotoxicity is unclear.

The management of drug hepatitis and cholestasis is otherwise symptomatic and supportive. In severe cases hepatic transplantation should be considered, while ursodeoxycholic acid has some promise for chronic cholestasis. (6,7). Corticosteroids have little role, although case reports at least show occasional effectiveness in few cases of hepatitis due to diclofenac and ketoconazole (5).

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A Story of A Pharmacist In a Busy Pharmacy

A pharmacist, who was working alone in a busy hospital pharmacy, received a stat order for oral clonidine 1 mg and levodopa 125 mg for a growth hormone stimulation test on an 8year-old child.

Despite significant pressure from the stat order and a backlog of work, the pharmacist, who was unfamiliar with the test, took time to research the information and discovered that the correct test dose of clonidine for a pediatric patient was 0.15 mg/meter square.

After calling the physician, the order was changed to clonidine 0.1 mg. Unfortunately, even successful outcomes like this one may not be widely appreciated if productivity is sacrificed to enhance patient safety. Nevertheless, numerous errors reported through the USP-ISMP Medication Errors Reporting Program have resulted when practitioners felt significant pressure to place productivity above patient safety, especially when faced with inadequate staffing. Institute for Safe Medication Practices (ISMP).

Drug Expiration Date Clarification

Expiration dating of original, unopened manufacturer drug packaging is based on both accelerated degradation studies and real-time stability data. Typically, newly marketed drugs will be limited to a maximum 2-year shelf life beyond packaging, even if extrapolated data from the accelerated degradation studies done with excessive temperature, humidity, and lighting conditions suggest stability beyond this time. The shelf-life can be extended based on further real-time data, with an outside limitation of 5 years. However, once the original packaging is opened, further claims on product stability and shelf life no longer apply (Anon, 1996).

Guidelines for the labeling of expiration dates have been established by the United States Pharmacopeia. Labeling on all official drug product, nutritional, or dietary supplements must display the expiration date in a format which can be read and interpreted "by an ordinary individual under customary conditions of purchase and use". An exception is made for those drug products or nutritional supplements packaged for sale without a prescription where the labeling states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions (USP/NF, 2000). The Convention also notes that when an expiration date is stated only in terms of the month and the year, this is a representation that the intended expiration date is the last day of the expressed month (USP/NF, 2000).

Beyond-use dating establishes a reasonable time period for the patient to retain a drug product dispensed on prescription. The USP recommends such dating be limited to not later than (1) the expiration date on the manufacturer's container or (2) one year from the date the drug is dispensed, whichever is earlier. Other factors which the dispenser must consider prior to

establishing this beyond-use date include: the nature of the drug; the characteristics of the container in which the product is dispensed; any unusual storage conditions expected to be encountered; and the expected length of therapy (USP/NF, 2000).

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The Pharmacy Newsletter is intended to provide information regarding the Pharmacy & Therapeutic Committee's decisions, current concepts in drug therapy, MOH (Pakistan), FDA (USA), CSM (UK) and other regulatory agencies warnings, drug interactions, ADR and matters related to drug usage. Opinions expressed are of the authors and do not necessarily represent Hospital views and recommendations.

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