

20.201 Review of Q2 2013

C. In testing for DILI in vivo it is common to monitor blood for an aminotransferase (e.g. ALT, AST, etc.), but this fails when the drug causes cholestasis, and testing for alkaline phosphatase is the preferred assay. Please explain. (10 points).

DILI

- Drugs that can cause hepatocellular injury **extensive** enough to reduce the liver's functional ability to clear **bilirubin** from the plasma
- The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals, generally have not shown dose-related toxicity, and generally have caused low rates of severe injury in humans (1 in 5-10K or less)

Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated.

Hy's Law

- **The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo**
- **Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)**
- **No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury**

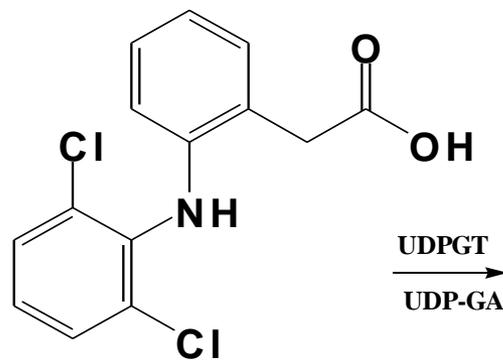
Cholestasis

- Wikipedia
- In **medicine**, **cholestasis** is a condition where **bile** cannot flow from the **liver** to the **duodenum**. The two basic distinctions are an obstructive type of cholestasis where there is a mechanical blockage in the duct system such as can occur from a **gallstone** or **malignancy**, and metabolic types of cholestasis which are disturbances in bile formation that can occur because of **genetic defects** or acquired as a side effect of many medications.

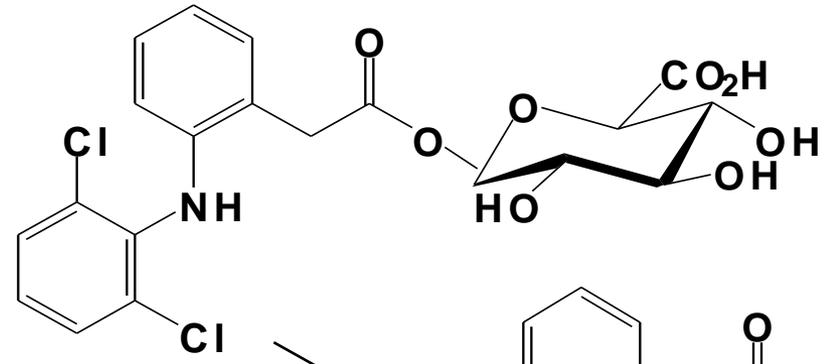
Cholestasis

- Wikipedia
- Cholestasis can be suspected when there is an elevation of both **5'-nucleotidase** and **ALP** enzymes. With a few exceptions, the optimal test for cholestasis would be elevations of serum **bile acid** levels. However, this is not normally available in most clinical settings. The **gamma-glutamyl transferase** (GGT) enzyme was previously thought to be helpful in confirming a hepatic source of ALP; however, GGT elevations are markedly sensitive and lack the necessary specificity to be a useful confirmatory test for ALP. Normally GGT and ALP are anchored to membranes of **hepatocytes** and are released in small amounts in hepatocellular damage. In cholestasis, synthesis of these enzymes is induced and they are made soluble. GGT is elevated because it leaks out from the bile duct cells due to pressure from inside bile ducts.
- In a later stage of cholestasis **AST**, **ALT** and **bilirubin** may be elevated due to liver damage as a secondary effect of cholestasis.

B. In preclinical toxicity testing of Diclofenac in Chinese Hamster Ovary Cells containing the entire complement of human cytochrome p450 metabolic activity the drug was only mildly toxic. When all of the p450 enzymes were killed by exposing the cells briefly to carbon monoxide (CO), the drug was even more toxic. What was going on? (10 points).

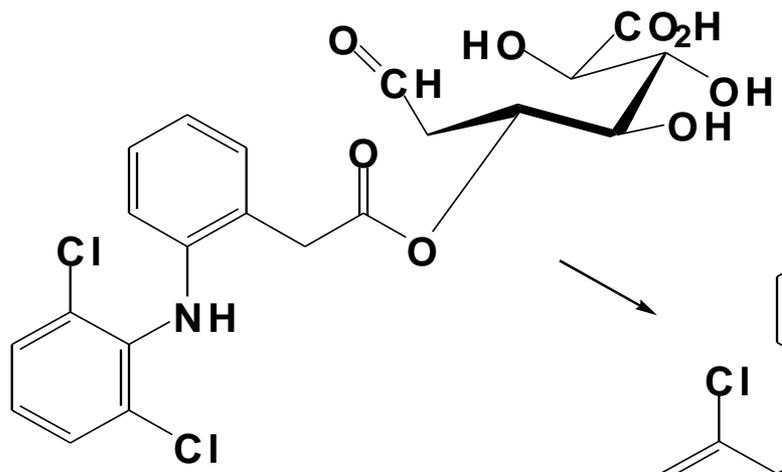


UDPGT
→
UDP-GA

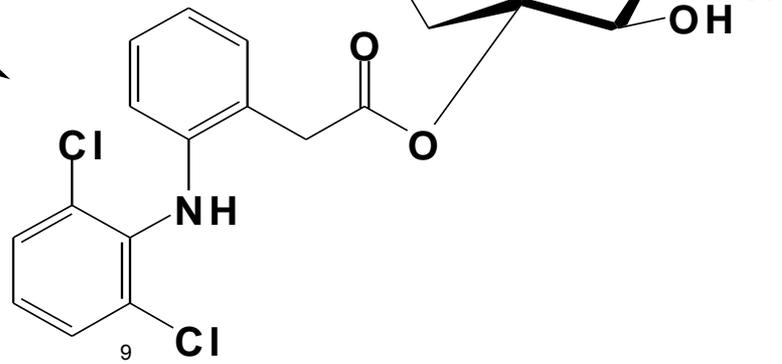


Diclofenac

X-protein



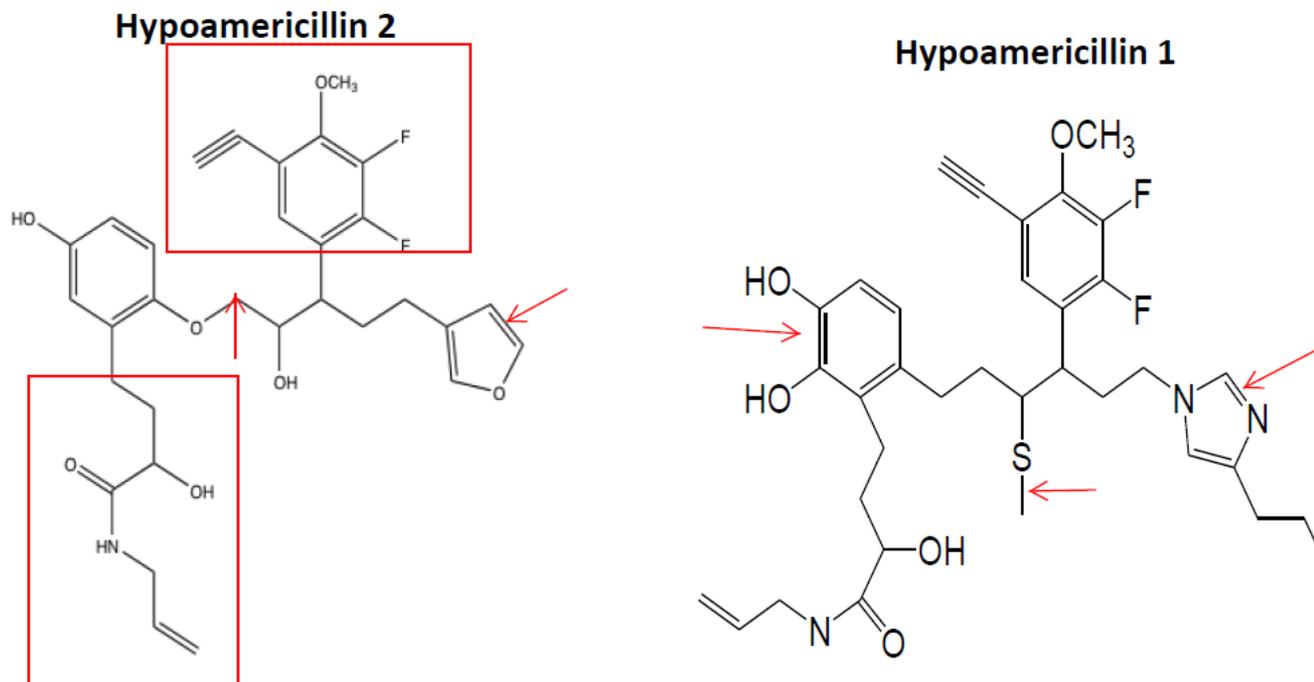
Protein



Literature info Diclofenac

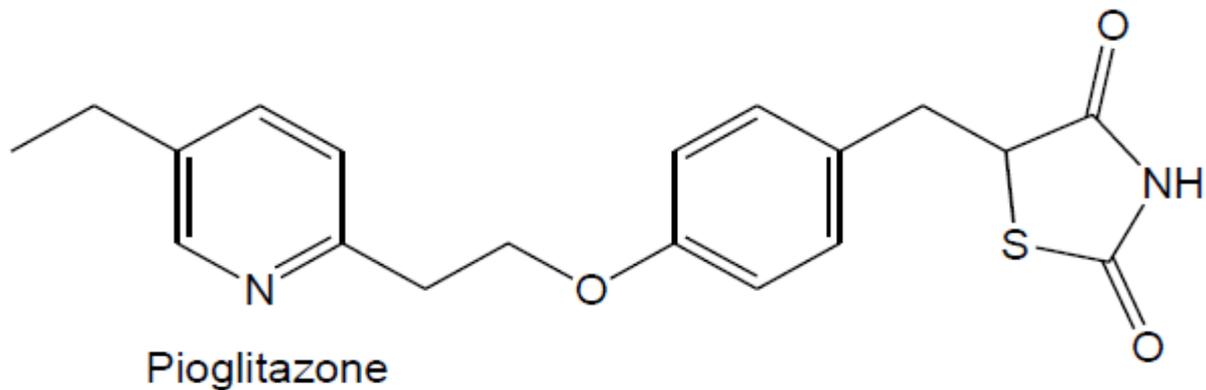
- [Evaluation and Mechanistic Analysis of The Cytotoxicity of The Acyl Glucuronide of Nonsteroidal Anti-inflammatory Drugs.](#)
- Miyashita T, Kimura K, Fukami T, Nakajima M, Yokoi T.
- Drug Metab Dispos. 2013 Oct 8. [Epub ahead of print]

A. Hypo 1 was found to be toxic, so the chemists came up with Hypo 2. You have been asked to predict whether 2 will be more or less toxic than 1, or about the same. Ignore the changes in bond angles, it's my mistake. Back up your answer with chemistry. (10 points)

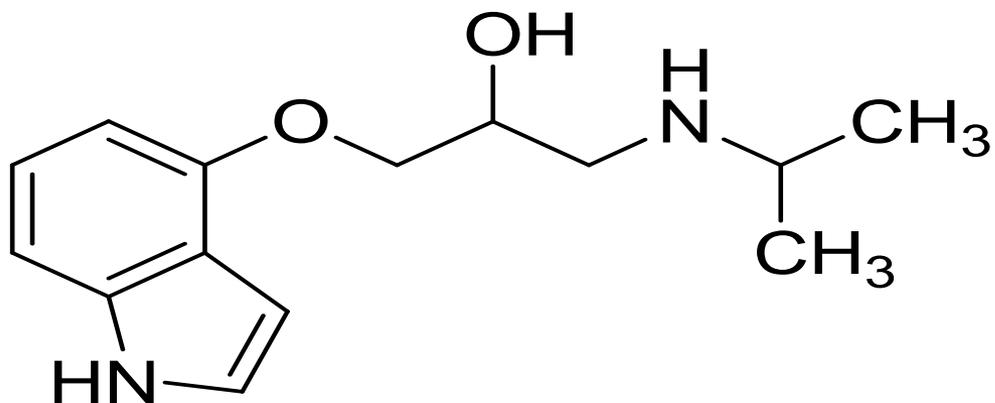


Boxed structures are common; arrows indicate potential metabolism to electrophiles

Show mechanism and all products for formation of a phenol, i.e. initial oxidation product and final products



Show mechanism and all products for formation of isopropylamine, i.e. initial oxidation product and final products



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