



U.S. Food and Drug Administration

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# Hepatotoxicity through the Years Impact on the FDA

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# Hepatotoxicity = Toxicity #1

Through the years, hepatotoxicity has been the most common single adverse effect causing major drug problems, including withdrawals and refusals to approve.

## **Withdrawal**

Marsilid (iproniazid)	1956
Ticrynafen	1979
Benoxaprofen	1982
Bromfenac	1998
Troglitizone	2000

## **Non-Approval**

Ibufenac (Eur)	1920's
Perhexiline (Fr)	1980's
Dilevalol (Port, Ir)	1990
Tasosartan	1998

# Hepatotoxicity through the Years Impact on the FDA

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Hy's Law and Current Practice: A hypothesis  
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Needs

# **Hepatotoxicity through the Years Impact on the FDA**

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# Needs

## 1. Better data on current practice

Sensitivity and specificity of signals; complete accounting of positive cases, sample of negatives

- Hy's Law: Elevated rate TA and some elevated bilirubin (sensitivity probably high but specificity unstudied)
- Impact of magnitude of TA elevation as signal (3X, 5X, 10X)
- TA signal alone: how large a sample is reassuring re bilirubin elevation (again, sensitivity and specificity)

## 2. Potential for other information

- Relevant structural clues, animal data -could influence sample size
- Other tests of value

# Hepatotoxicity

In addition to NA's and withdrawals, many drugs are explicitly second-line or bear serious warnings because of liver toxicity, including (partial list)

## **Second Line**

Pemoline  
Tolcapone  
Trovafloracin  
Felbamate

## **Moderate W/P**

Zileuton  
Tacrine  
Labetalol  
Diclofenac

## **Strong Warning**

Valproic Acid  
Ketoconazole  
Nicotinic Acid  
Acetaminophen  
Chlorzoxazone  
Isoniazid  
Dantrolene  
Rifampin



# **Hepatotoxicity = Toxicity #1**

**Through the years, hepatotoxicity has been the most common single adverse effect causing major drug problems, including withdrawals and refusals to approve.**

## **Withdrawal Non-Approval**

**Marsilid (iproniazid) 1956 Ibufenac (Eur) 1920's**

**Ticrynafen 1979 Perhexiline (Fr) 1980's**

**Benoxaprofen 1982 Dilevalol (Port, Ir) 1990**

**Bromfenac 1998 Tasosartan 1998**

**Troglitizone 2000**

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# Hy's Law and Current Practice: A hypothesis in use

Therefore consider:

1. Adequacy of sample size (if 1000 relevant exposures, can rule out only rate  $> 1/300$  or  $1/3000$  serious injury)
2. If there is TA signal, need enough exposure to rule out too high a rate of bilirubin elevation. Depends on what drug is for. A sample of, say, 15,000 (large, simple safety study) rules out a rate of  $1/5000$  TA/bili or  $1/50,000$  serious injury
3. Note exposures  $< 4$ -6 weeks may not be useful

# Needs

## 1. Better data on current practice

**Sensitivity and specificity of signals; complete accounting of positive cases, sample of negatives**

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## 2. Potential for other information

- **Relevant structural clues, animal data -could influence sample size**
- **Other tests of value**

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# Other Toxicity (partial list)

Only a few other kinds of toxicity have been as important:

## **Hematologic**

- WD: nomifensine (H.A.), phenylbutazone (AA),  
temafloxacin
- NA: aprindine (agran)
- Limits: ticlopidine, clozapine, felbamate,  
chloramphenicol, procainamide, tocainide, Ptu

## **Cardiovascular (QT, inotropes, pro-arrhythmia)**

- WD: terfenidine, cisapride, astemizole, grepafloxacin  
(QT)
- Na: lidoflazine, sertindole (QT); milrinone,  
vesnarinone, flosequinan, emoximone
- Limits: Bepridil, sotalol, dofetilide, quinidine, type 1a, 1c  
antiarrhythmics, milrinone, dobutamine,  
ziprasidone

# Other Toxicity

## **Sclerosing syndromes (various organs)**

WD: None

NA: Practolol, aminorex

Limits: Methysergide, appetite suppressants,  
amiodarone

## **Sporadic, unique**

Fenfluramine valvulopathy

Suprofen ARF

Aminoglycoside nephrotoxicity, auditory, vestibular

Thalidomide/Accutane - teratogenicity

NSAID's - GI bleeding

Phenformin/metformin - lactic acidosis

Zomepirac - anaphylaxis

OC/estrogen - thromboembolism

Estrogen - endometrial Ca

Antipsychotics - tardive dyskinesia

# Personal Experience

Iproniazid gave my grandmother fatal acute hepatic necrosis

Ticrynafen - As director, cardio-renal division in 1988 signed off on major hepatotoxin, perhaps despite premarketing clue

- Focus on deaths, adverse dropouts (7 vs. 0)
- Importance of hepatitis testing (7/7 possible exposure)
- Duration exposure  $\geq$  4-6 weeks needed

Dilevalol - NA based on 2-3 modest bilirubin elevation plus TA elevation 2-3%

Tasosartan - NA based on 3%  $>$  3 X ULN plus one modest bilirubin elevation

# Myths

## 1. Relation to Pre-existing Liver Disease

“A stubborn [misconception] has been the view that patients with pre-existing hepatic disease are more likely than others to suffer hepatic injury on exposure to drugs that cause liver damage. There is virtually no evidence for this view [except for rifampin].” (Zimmerman, 1978)

2. “Idiosyncratic,” maybe, but probably not allergic. Seems to be dose-related, at least sometimes, and usually takes a month or so to occur. Rechallenge exaggerated but not instantaneous

# Metabolism

Many hepatotoxins (acetaminophen, INH, others) are metabolized by CYP450 enzymes, probably form active intermediate epoxide, yielding free radicals that attack macromolecules. To date, no good animal model, although there is one for acetaminophen

Questions:

- Could these drugs' toxicity be predictable by animals?
- Could SH prevent?
- Could at risk patients be identified?
- Could particular drugs needing special scrutiny be identified by structure?

Answer: Not yet



# What Do We Do Now?

Faced with this history of hepatotoxicity, what do we do? We measure liver 'function' and interpret the results

A. Measure:

1. What we measure
  - Transaminases - hepatocellular liver injury
  - AP - liver obstruction
  - Bilirubin - liver excretory function
  - Evidence of viral hepatitis if LFTs very abnormal
2. How often
  - No real standard, but probably every 2-4 weeks; longer intervals in extensions, shorter if concern (would we learn more if intervals were longer?)

# What Do We Do Now? (Cont'd)

## B. Interpret

1. Compare rates of transaminase abnormality with control, abnormality defined as some multiple of the ULN, typically 3x, 5x, 8x, etc
2. Don't always need control (can interpret extension periods) if abnormalities are frequent enough or large enough. E.g., several fold (3x) elevations at a 3% level do not occur often in control groups; 8-10x elevations at any rate are very unusual in control groups
3. Look at markedly abnormal individual cases (8-10x and greater)
4. Normalization with continued use does not give reassurance (INH, troglitazone)

# What Do We Do Now? (Cont'd)

Current “best” evidence of hepatotoxic trouble is:

1. Increased rate of TA elevation (elevation meaning 3X ULN or more)
2. Evidence of injury in some patients sufficient to give elevated bilirubin (does not need to be many) without evidence of obstruction, i.e., elevated AP

# Why TA plus Bilirubin

1. Theory: hepatocellular injury sufficient to impair bilirubin excretion must be extensive
2. Observation: "Hy's Law"  
About 10% of patients with elevated TA and jaundice will have serious/fatal hepatic necrosis
3. Cases:
  - a. Liver injury: isoniazid, iproniazid, dantrolene, ticrynafen, troglitizone, bromfenac, dilevalol
  - b. No liver injury: aspirin, tacrine (no bilirubin)

# Hy's Law and Current Practice: A hypothesis in use

If elevated TA to, say, 2-3% or greater,  
look at rate of bilirubin elevation to, say  
 $\geq 1.5 \times \text{ULN}$

Assume rate of this combination is about  
0.1 X rate of serious injury (Ballpark for  
bromfenac, troglitizone, isoniazid, etc)

# Hepatotoxicity

**In addition to NA's and withdrawals, many drugs are explicitly second-line or bear serious warnings because of liver toxicity, including (partial list)**

**Second Line Strong Warning**

**Pemoline Valproic Acid**

**Tolcapone Ketoconazole**

**Trovafloxacin Nicotinic Acid**

**Felbamate Acetaminophen**

**Chlorzoxazone**

**Moderate W/P Isoniazid**

**Zileuton Dantrolene**

**Tacrine Rifampin**

**Labetalol**

**Diclofenac**

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# Hy's Law and Current Practice: A hypothesis in use

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**NA: aprindine (agran)**

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**Na: lidoflazine, sertindole (QT); milrinone, vesnarinone, flosequinan, emoximone**

**Limits: Bepridil, sotalol, dofetilide, quinidine, type 1a, 1c antiarrhythmics, milrinone, dobutamine, ziprasidone**

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**2. “Idiosyncratic,” maybe, but probably not allergic. Seems to be dose-related, at least sometimes, and usually takes a month or so to occur. Rechallenge exaggerated but not instantaneous**

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**Assume rate of this combination is about  $0.1 \times$  rate of serious injury (Ballpark for bromfenac, troglitizone, isoniazid, etc)**

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