

Hepatic Events

Paul B. Watkins, MD

Director, General Clinical Research Center

Professor of Medicine

Professor Pharmacology

University of Michigan

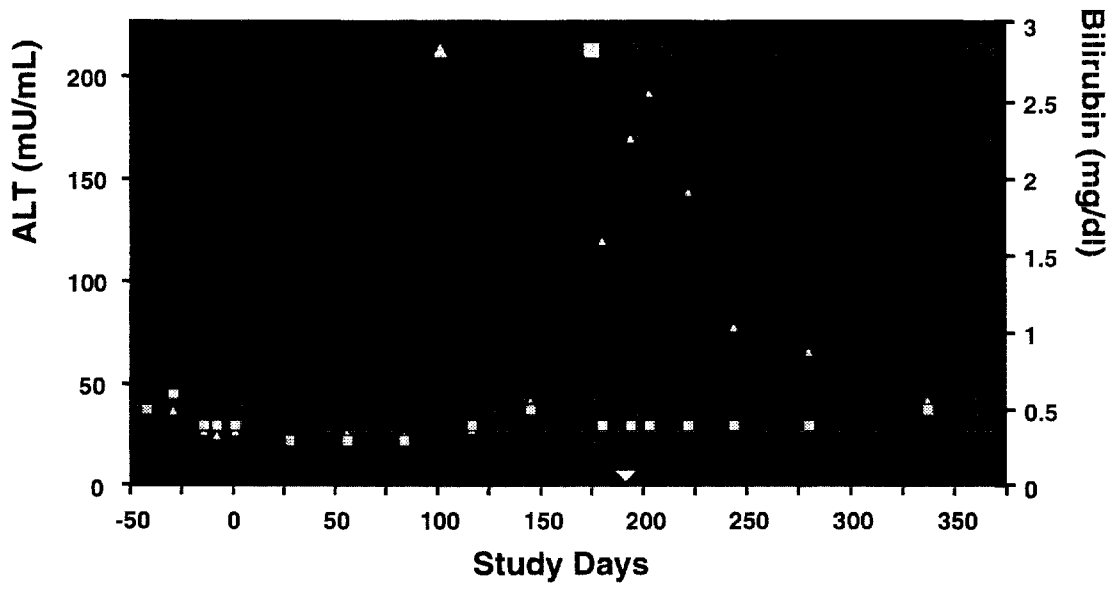
Active Consulting Contracts

- Abbott
- Pfizer
- Roche
- TAP
- Warner-Lambert/Parke-Davis
- FDA

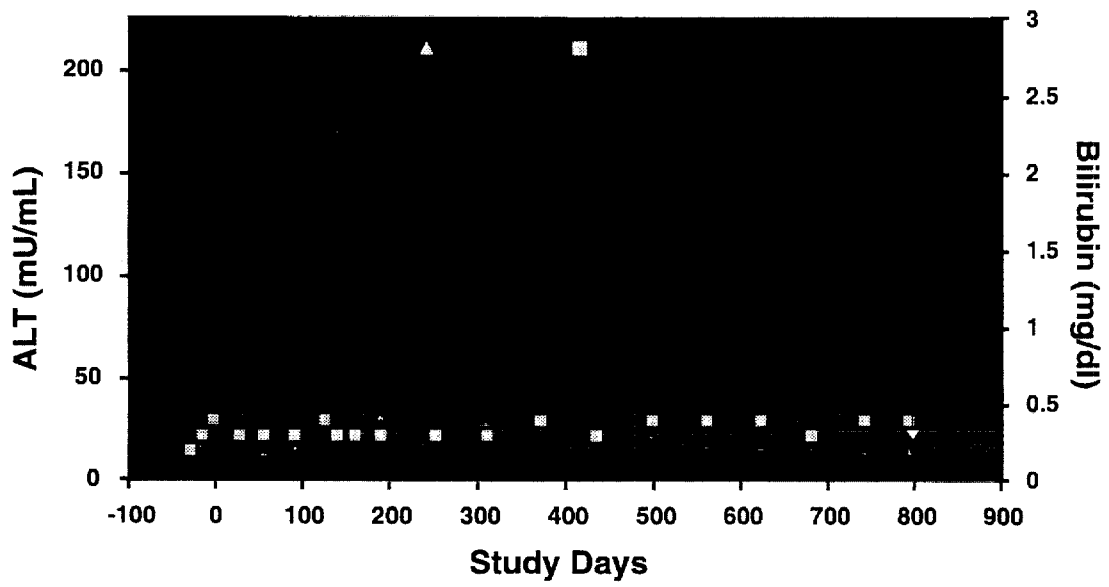
Hepatocellular Injury

- Liver cell is globally injured
- Elevations in serum ALT
- Height of ALT correlates with extent of injury
- ALT > 3x ULN = "Clinically Significant"
- Jaundice = severe injury

Clinical Trial Patient (ALT/Bilirubin)



Clinical Trial Patient (ALT/Bilirubin)



Approach to Review of Spontaneous Cases

- Reviewed all Med Watch liver events on a weekly basis
- Formation of independent review board
- Periodic review of complex cases with other hepatologists

Background Liver Disease in Type 2 Diabetes

- Non-alcoholic steatohepatitis (NASH)
- Hepatitis C

Cases of Acute Liver Failure in 13 US Medical Centers 1994 -1996

	Number	
Acetaminophen overdose	60	20%
Cryptogenic / NANBNC	43	15%
Drug reactions	34	12%
Hepatitis B	30	10%
Hepatitis A	20	7%
Wilson's Disease	19	6%
Autoimmune hepatitis	18	6%
Misc categories	71	24%
Total	295	100%

Liver Transplantation and Surgery, 5:29,1999

Jaundice and Deaths with Hepatocellular Injury

Drug	Jaundice	Death	%	Reference
INH	114	13	12%	Gastroenterology 69:289,1975
Ketoconazole	18	1	6%	Gastroenterology 86:503,1985
Pimoline	43	1	2%	Gastroenterology 99:1517,1990
Diclofenac	90	7	7%	Hepatology 22:820,1995

U.S. Reports of Jaundice in Rezulin Treated Patients

Total number of cases	290
Unlikely / unrelated	96
Probable / Possible / Insufficient data	194
Predicted deaths	~ 20

As of 3/5/99.

US Deaths/ Transplants

Total # of reported cases	75	
Probable	16	28
Possible	12	

Confounding Factors in the 28 Probable/Possible Deaths/Transplants

Preexisting liver disease	7
Hepatitis B -	3
Cirrhosis -	2
NASH -	1
CMV -	1
Known Hepatic Drugs	9
No Factors Present	12

US Deaths/ Transplants

Total # of reported cases	75		
Probable	16] 28] 40
Possible	12		
Insufficient data	12		
Unlikely/Unrelated	35		

FDA Count Equals 35

In Worldwide Clinical Trials

(n=15,591)

- 2 deaths - “probably related”
- 4 jaundiced patients - ~20 predicted
- Could there have been something unusual about the two patients who died?

Clinical Trial Patient (#1-NIH)

- Flu-like prodrome while ALT < 3x ULN
- CMV IgM antibodies
- Inclusion body observed in liver biopsy
- Necrotic colon discovered at surgery

Letter Dated 6/10/98 to Dr. Genuth

“Conclusion: Accordingly the committee concludes that hepatic necrosis in this case was probably caused by troglitazone and believes that an important contributory role in the fatal outcome may have been played by bowel necrosis, a lesion for which the CMV infection is speculatively incriminable.”

Neil Kaplowitz, MD
Professor of Medicine
University of Southern California

Hyman J. Zimmerman, MD
Professor of Medicine, Emeritus
George Washington University

Anthony Tavill, MD
Director, Friedman Center
for Digestive and Liver Disorders
Cleveland, Ohio

Clinical Trial Patient (#2)

- “12 beers daily for 20 years”
- AST > ALT consistent with alcoholic hepatitis
- Height of AST / ALT not consistent
- Liver histology not obtained

Summary of Patient Cases

- Troglitazone contributed to the liver injury in each patient
- Both patients probably had underlying liver disease that reduced the ability to survive the drug related injury

Cases Considered “Rapid Risers”

Mechanisms of Hepatotoxicity Unknown

- No animal or in vitro model available

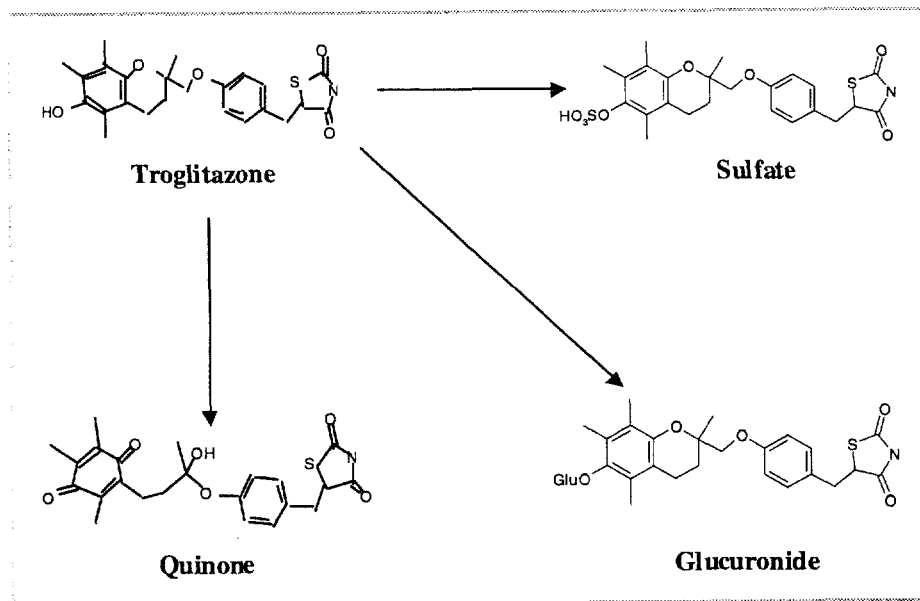
Potential Mechanisms of Hepatotoxicity

Quinone metabolite

CYP3A4 induction

PPAR γ activation in liver

Metabolism of Troglitazone



Potential Mechanisms of Hepatotoxicity

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Other Drugs Induce CYP3A4

- Rifampin
- Phenytoin
- Carbamazepine
- Glucocorticoids

Potential Mechanisms of Hepatotoxicity

Quinone metabolite

CYP3A4 induction

PPAR γ activation in liver

Conclusions

- Acute Liver Failure due to troglitazone is rare and idiosyncratic
- Assessment of many cases is not straightforward
- The agreed number of U.S. reported deaths / transplants due to drug is 35
- The mechanisms involved in troglitazone hepatotoxicity are unknown