

Safety Analysis of Acetaminophen (APAP)-Associated Hepatotoxicity Office of Drug Safety Analysis

Nonprescription Drugs Advisory Committee Meeting

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Overview of Presentations

- **National estimates of APAP-associated overdoses**
- **Review of literature and Poison Control data**
- **Summary of Spontaneous Reports of APAP-associated hepatotoxicity**

Background

- **APAP-associated hepatotoxicity has been reported with**
 - **intentional overdose (suicide)**
 - **unintentional overdose (e.g., therapeutic misuse)**
 - **recommended doses (rarely)**

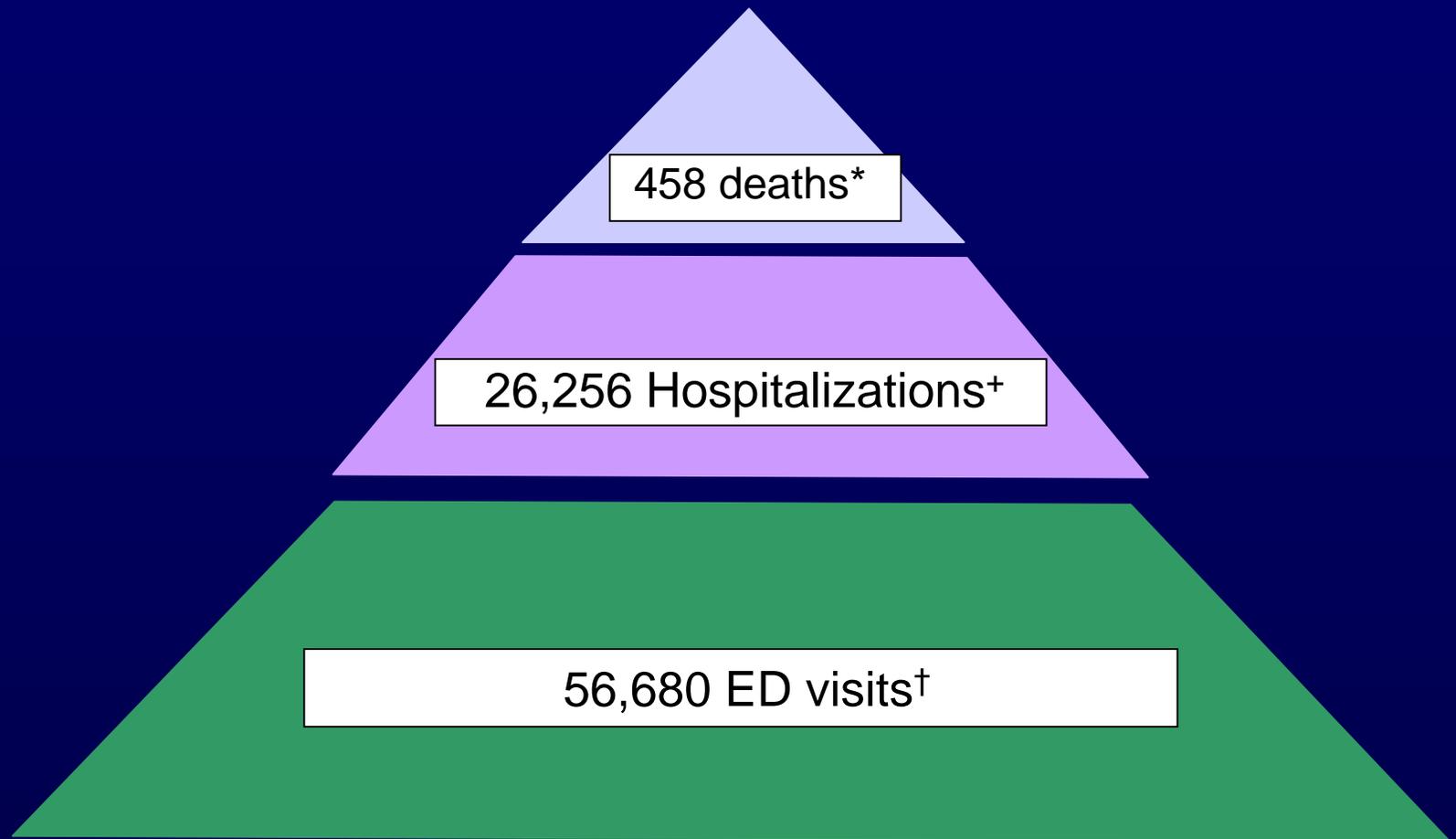
Objective

- **To estimate the number of overdoses associated with APAP, particularly unintentional overdoses**

Sources of Data

- **National Hospital Ambulatory Care Survey: Emergency Department (ED) Component**
- **National Electronic Injury Surveillance System**
- **National Hospital Discharge Survey**
- **Multiple Cause of Death Files**

Annual APAP-Associated Overdoses in U.S.



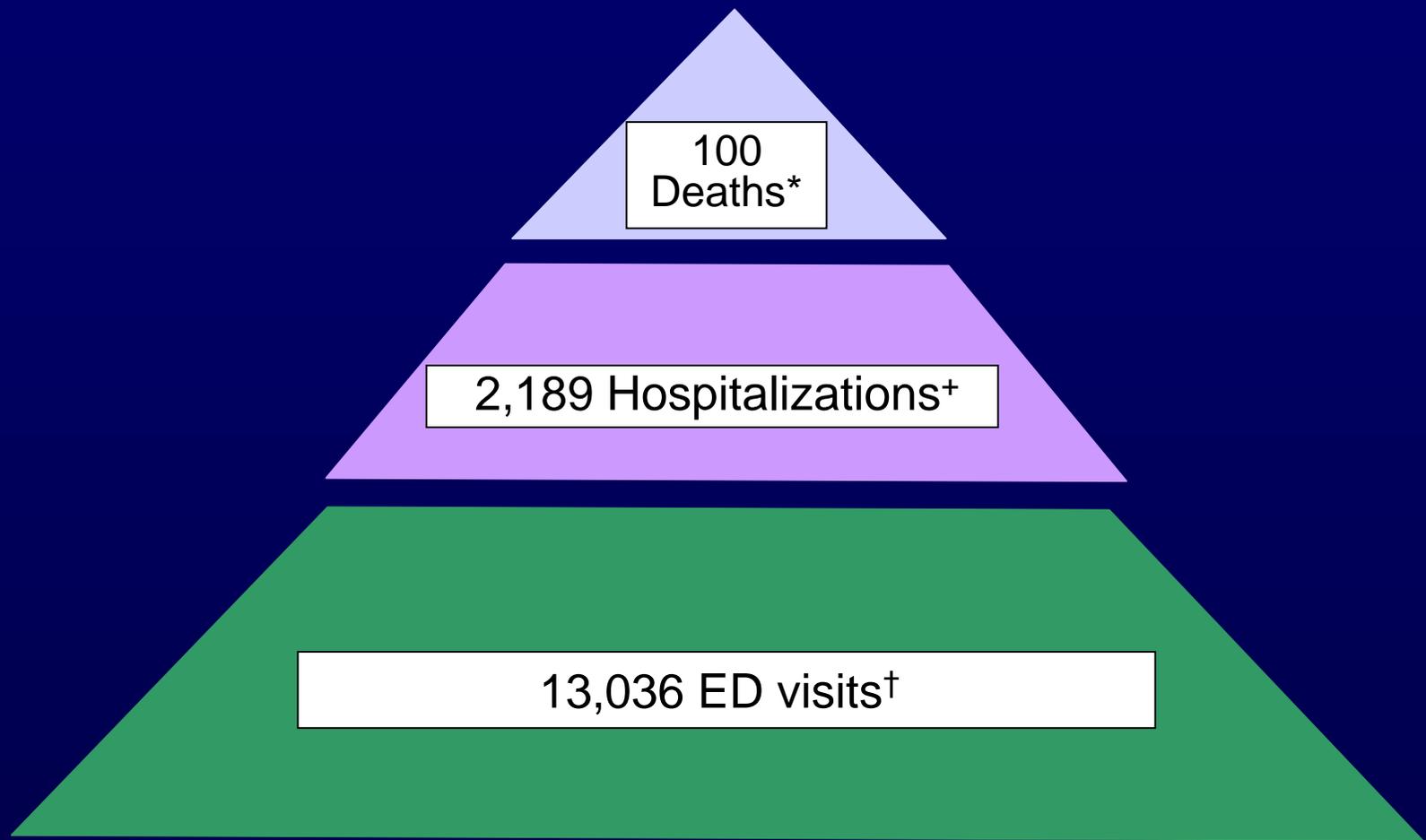
*Multiple cause of death, 1996-1998; ⁺NHDS data, 1990-1999;

[†]NEISS, 2000; NHAMCS, 1993-1999

Definitions of Intentionality

- **NHDS and Mortality - ICD-9 codes used:**
 - intentional: suicide or overdose due to other substances
 - unintentional: **accidental overdose by APAP** AND no indication of:
 - suicide
 - overdose due to other substances
 - depressive disorder
- **Emergency Department**
 - reviewed the comments fields
 - intentional: mentions of suicide or suicide ideation
 - unintentional: mentions of **accidental ingestion or therapeutic misuse**;
 - children <6 are classified as accidental ingestion, unless stated otherwise

Annual Unintentional APAP-Associated Overdoses in U.S.



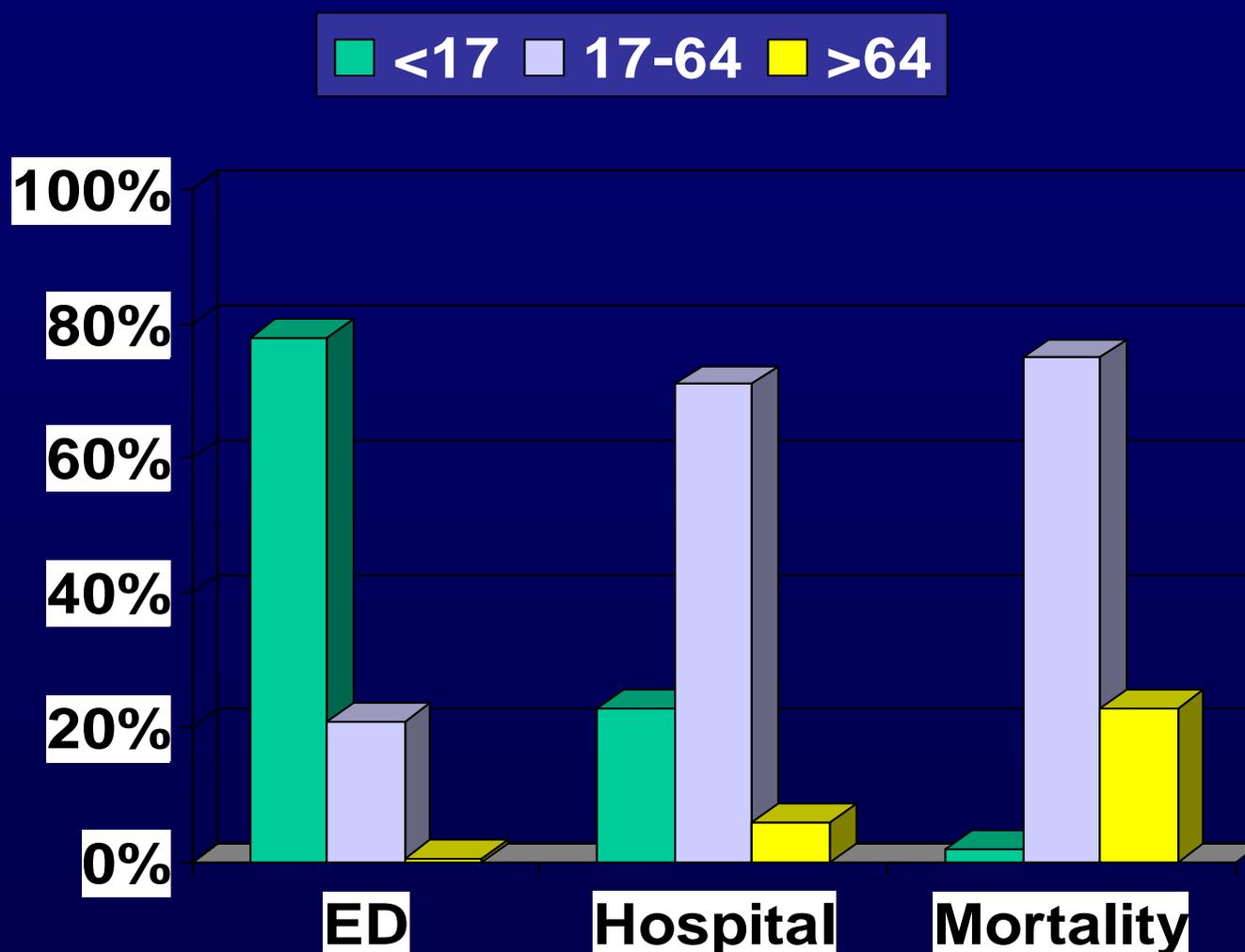
*Multiple cause of death, 1996-1998; + NHDS data, 1990-1999;

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Risk Factor Analysis

- **Limited information available on risk factors**
 - **underreporting or no reporting of some variables of interest (e.g., hepatotoxicity)**
 - **sample size too small for exploring subgroups**

Age Distribution of Unintentional Cases



NEISS, 2000; NHDS data, 1990-1999; Multiple cause of death, 1996-1998

Percent of Liver Disease Reported Among Fatal APAP Overdose Cases, Mortality Data, 1996-1998

| Liver Disease Reported | Unintentional (N=235) | Intentional (N=1,010) |
|--|----------------------------------|----------------------------------|
| Chronic alcohol | 13% | 1% |
| Other chronic liver disease | 42% | 8% |

Limitations

- **Misclassification of data**
 - **type of liver disease may be misclassified**
 - alcohol-related liver disease as other liver disease
 - some diseases may be acute but identified as chronic
 - **suicidal cases may be misclassified as unintentional overdose to “protect” the patient’s family from stigma**
- **Detection bias**
 - **the contributing cause of death may be investigated more with unintentional APAP overdoses than when the cause of death is known to be suicide, thus liver diseases may be reported more often**

Conclusions

- **Children account for at least 22% of the hospitalized cases of unintentional overdoses**
- **The observed association of chronic alcohol and chronic liver disease with unintentional APAP overdose suggests that pre-existing liver disease may increase the morbidity and mortality from APAP-associated hepatotoxicity.**

Overview of Presentations

- **National estimates of APAP-associated overdoses**
- **Review of literature and Poison Control data**
- **Summary of Spontaneous Reports of APAP-associated hepatotoxicity**

Objectives

- **To identify case series of APAP-associated hepatotoxicity in published literature**
 - to describe the demographic characteristics, intentionality, dose, and outcomes
- **To study the extent of APAP-associated fatalities reported to the Poison Control Database**

Literature Review

- **MEDLINE search to identify APAP-associated hepatotoxicity literature**
- **Restricted to U.S. case series (at least 10 cases) published in the U.S. literature in the last 10 years**

Case Series - Data Sources

- **8 published case series were identified**
 - 4 hospital medical chart reviews
 - 2 hospital medical chart reviews and published cases
 - 1 registry
 - 1 transplant center consortium

Case Series - Demographic Characteristics

- **Number of cases per series- 47 to 73**
- **Age -**
 - **2 pediatric**
 - **range - 5 weeks to < 19 years**
 - **6 largely adult**
 - **range - 23 to 88 years**
- **Gender -**
 - **6 reported gender**

APAP Dose in the Unintentional Group

| | Dose (gm/day) | Total | Number with Dose \leq 4gm/day |
|-----------|---------------|-------|---------------------------------|
| Johnston | 1.3-20 | 53 | 9 |
| Schiødt | 2-30 | 21 | 3 |
| Zimmerman | <4->15 | 67 | 27 |
| Whitcomb | 3.5-25 | 21 | None |
| Broughan | 15.9* | 8 | None |

*Mean

Comparison of Deaths & Serious Outcomes in Unintentional & Intentional Groups

| | Unintentional | Intentional |
|-----------|------------------|------------------|
| | Serious or Death | Serious or Death |
| Johnston | 17 | NA |
| Schiødt | 11 | 4 |
| Zimmerman | 13 | NA |
| Whitcomb | 5 | NR |
| Broughan | 2 | None |

NA: Not applicable; NR: Not Reported;
Serious Outcomes: Hepatic coma; Liver Tx

Methods - APAP in TESS

- **TESS - Toxic Exposure Surveillance System is the poisoning database of AAPCC**
- **Annual reports from 1995-1999 were reviewed**
 - **only cases that listed APAP as the primary (first) agent were included**

Summary of Calls

- APAP-related calls represents 10% of all 1999 calls to PCCs
- Calls slightly decreased from 111,175 in 1995 to 108,102 in 1999
- In 1999
 - about 50,000 (46%) calls were treated in health care facilities
 - 1,768 (2%) of the calls had major effect*
 - >50% calls in children (\leq 19 years)

*Signs or Symptoms occurring as a result of the exposure were life threatening or resulted in significant residual disability

Root Cause Among Children, 1999

- **Of all APAP related calls in children under 6 years (N=40,105)**
 - **8,634 (22%) involved children under 6 years of age who ingested adult formulations**

Fatalities

- **Total number of deaths in 1995 was 76; increased to 141 in 1999**
- **APAP-associated fatalities represented 16% of the total (873) fatalities in 1999**

Intentionality Among Fatalities, 1999

- **92 (65%) had suicidal intent**
- **43 (30%) unintentional**
- **6 (4%) reason unknown**

Root Cause Among Unintentional Fatalities, (N=43), 1999

- 28 (65%) took single OTC ingredient
- 4 (9%) took one Rx APAP product
- 11 (26%) took >1 APAP product simultaneously including
 - OTC + Rx
 - 2 Rx
 - 2 Rx + 1 OTC
 - 2 OTC

Limitations

- **Underreporting may be extensive**
 - serious cases may go directly to EDs and may not be captured by PCCs
- **Chronic users may not be captured by PCCs**

Conclusions

- **There are published cases of hepatotoxicity at recommended doses of APAP**
 - some are linked to risk factors such as alcohol use and/or fasting
- **Unintentional cases are associated with serious outcomes including deaths**

Conclusions - 2

- **Use of adult formulations of APAP in young children account for 22% of calls to PCCs involving children < 6**
- **Among unintentional fatalities, 26% were due to use of > 1 APAP products simultaneously**

Overview of Presentations

- National estimates of APAP-associated overdoses
- Review of literature and Poison Control data
- Summary of Spontaneous Reports of APAP-associated hepatotoxicity

Objective

- **To describe the circumstances which led to hepatotoxicity in individuals who ingested at least one APAP-containing product**
- **Review of Adverse Event Reporting System (AERS) reports**
 - **focus on cases without apparent suicidal intent**

Case Selection

- **Inclusion criteria of AERS* Cases**
 - U.S. cases
 - received by FDA b/n Jan 1998 to Jul 2001
 - at least one APAP-containing product
 - hepatotoxicity
 - cases without apparent suicidal intent
 - **Reviewed - 307 of 633 reports**
 - 25 pediatric cases
 - 282 adult cases (>12 years)
- * AERS is an FDA database of spontaneously reported adverse drug events

General Summary Information

Pediatric Cases (n=25)

- **Ages: range < 1 day to 8 years**
 - (median 2 years, mean 1 year)
- **Gender**
 - male - 17, female - 7, unknown - 1
- **Outcomes**
 - severe, life threatening liver injury - 15
 - death - 10
 - hospitalization - 21
 - emergency room - 2
- **Dose (n=10) range 106 to 375 mg/kg/day**

APAP Product Data Among Pediatric Cases

- **Number of APAP products**
 - 22 (88%) 1 APAP product
 - 3 (12%) > 1 APAP product
- **APAP products involved (n=30)**
 - single ingredient - 16 (53%)
 - concentrated drops (100mg/mL) - 7
 - unspecified APAP product - 12 (40%)
 - OTC combo and Rx/APAP - 2 (7%)

Factors leading to Hepatotoxicity among Pediatric Cases

- **Medication Errors - 20 cases* (80%)**
 - Errors from product confusion (7)
 - Misinterpretation of product label or instructions (5)
 - Use of > 1 APAP-containing product (3)
 - Other events - 10
- **Unknown - 5 cases (20%)**

*More than 1 error possible

Additional Factors in Pediatric Cases

- **Co-suspect medications - 6**
 - azithromycin (2), iron, ibuprofen, ranitidine, amoxicillin/clavulanic acid, cocaine (used by mother), and amoxicillin
- **Possible underlying liver disease - 4**
 - prior h/o TPN induced liver changes
 - enzyme deficiency
 - Hepatitis C antibody in infant
 - Hepatitis B in mother

General Summary Information

Adult Cases (n=282)

- **Ages - 15 to 85 years**
 - (median 42, mean 44)
- **Gender**
 - male - 100, female - 175, unknown - 7
- **Outcomes**
 - severe, life threatening liver injury - 169
 - death - 124
 - liver transplant - 7
 - hospitalization - 229

Indication for APAP Use (Intentionality)

- **199 (71%) therapeutic indication, primarily analgesia**
- **74 (26%) unknown use**
- **9 (3%) abuse**

APAP Product Information in Adult Cases

- **Type of product**
 - 138 (38%) - unspecified product
 - 122 (33%) - Rx combination with narcotic
 - 76 (21%) - single ingredient product
- **500mg strength reported most**
- **70 (25%) reported use of >1 APAP product**
 - more often included use of a Rx product in combination with an OTC product

Summary of APAP Dosing in Adults (N=282)

- **132 (47%) had information to estimate daily dose (gm/day)**
 - range 0.65 to 30 (mean and median dose 6.5 and 5)
 - 65 with severe liver injury (mean and median dose 7.1 and 6)
 - 23 cases \leq 4 gm/day
 - higher in individuals that took $>$ 1 APAP product
- **43 (15%) with qualitative dosing information**
 - 2/3 suggest $>$ recommended doses
- **107 (38%) no dose information**

Alcohol Use

- **Alcohol use - 116 (41%) with history**
 - alcoholism or alcohol abuse - 64
 - regular, daily, or moderate use - 23
 - occasional use - 10
 - previous use - 6
 - not described - 13
- **86 (74%) developed severe liver injury**
- **Mean dose (gm/day) lower for users vs. non-users**

| Category of Liver Injury | Alcohol users | Non-users |
|--------------------------|---------------|--------------|
| All (N=132) | 5.6gm (N=53) | 6.9gm (N=79) |
| Severe only (N=65) | 6.0gm (N=38) | 8.6gm (N=27) |

Liver Disease

- **History of liver disease - 70 (25%) with h/o or underlying disease**
 - 20 alcohol-related
 - 23 viral hepatitis
 - all others - 27
- **49 (70%) developed severe liver injury**
- **Mean dose (gm/day) lower for for liver disease vs. non-disease**

| Category of Liver Injury | Liver disease | No disease |
|--------------------------|---------------|--------------|
| All (N=132) | 5.4gm (N=36) | 6.8gm (N=96) |
| Severe only (N=65) | 5.7gm (N=23) | 7.8gm (N=42) |

Additional Factors

- **Co-suspect medication use - 93**
 - 63 labeled for hepatotoxicity
- **Fasting or malnutrition**
 - information often not captured
 - small number reported malnutrition or decreased oral intake

Severe Liver Injury with Low Dose Ingestion

- 23 reported \leq 4gm/day
- 18 with risk factors* (11 with >1 RF)
 - 15 with alcohol history
 - alcoholism or alcohol abuse - 10
 - regular use - 3
 - occasional use - 2
 - 13 with liver problems
 - alcoholic liver disease - 4
 - viral hepatitis - 4
 - others: hepatomegaly - 2, chronic liver disease - 2, inc transaminases - 1
 - 3 with poor nutrition status

*More than one risk factor possible

Severe Liver Injury with Low Dose Ingestion

- **Circumstances unclear in 5 cases with no reported risk factors.**
 - **other possible contributors**
 - **concomitant use of inducers of cytochrome P-450 isoenzymes: phenytoin (1)**
 - **sepsis - 2**

Limitations

- **Dosing information may be unreliable**
- **No certainty that all cases were unintentional**
- **No certainty that the drug caused the event**
- **Lack accurate numerator and denominator**
- **Subject to under-reporting, only 1 to 10% of adverse events reported to FDA ^{1,2}**

1. Arch Intern Med 1988; 148: 1596-1600.

2. R I Med J 1987; 70: 311-6.

Conclusions

- **Circumstances that led to hepatotoxicity**
 - errors related to product confusion (children)
 - too much APAP (overuse or abuse)
 - use of multiple APAP-containing products
 - risk factors (alcohol use, liver disease)

Questions Remain

- **Do users lack knowledge?**
 - of the potential for hepatotoxicity
 - of the symptoms of hepatotoxicity
- **What is the role of malnutrition/fasting?**
- **What is the contribution of concomitant hepatotoxic medication?**
- **What additional factors place a small number of individuals at risk for severe hepatotoxicity at/or slightly > recommended doses?**

ODS Overall Conclusions

- **Unintentional APAP-associated overdoses are associated with**
 - large numbers of ED and hospital admissions
 - an estimated 100 deaths each year
- **Unintentional APAP-associated overdoses are preventable**

ODS Overall Conclusions - 2

- **Multi-factorial problem**
 - **product**
 - presence of APAP in multiple Rx and OTC products
 - multiple oral formulation strengths
 - **knowledge**
 - lack of knowledge related to APAP potential for toxicity
 - **risk factors**
 - alcohol, underlying liver disease, fasting

Next Steps

- **A variety of risk management and communication interventions should be considered to address unintentional APAP-associated overdoses leading to hepatotoxicity**

