Treatment of Amatoxin Poisoning: 20 year retrospective Analysis

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Introduction

- Amanita Poisoning Review:
  - Incubation stage
  - Gastrointestinal phase
    - Vomiting, diarrhea, abdominal pain
  - Hepatotoxic phase
    - Hepatic damage with progressive coagulopathy
  - Hepatorenal syndrome
    - Hemorrhages, seizures, renal injury, fulminant hepatic failure (and probably death)
Introduction

- Toxin responsible are amanitins ($\alpha, \beta, \gamma$)
- Bicyclic peptides bridged by sulfur atom
- Use the transport system for biliary acids to reach the liver
- Inhibits RNA polymerase II
  - This prevents transcription
  - So no new mRNA
  - Protein synthesis is limited
Silymarin Complex
- **Silybin** major compound
- Animal studies have shown treatment benefit
- Competes for $\alpha$-amanitin cellular uptake by the bile salt transport systems of the hepatocyte membrane
- Radical scavenger
- Anti inflammatory effects
- Stimulates liver cell metabolism and growth.
- Side effects: nausea, headaches, pruritus, urticaria
Methods

- A review of cases in literature of human amanita mushroom poisonings from North America and European countries from the last 20 yrs.
- 2108 cases included with 32 liver transplants
  - Herculean effort shows in pages of tables....
- Most frequent implicated mushrooms were *A. phalloides, bisporigera, magnivelaris, ocreata, verna and virosa*
Statistical analysis

- Cases were separated into 11 modes of care
  - Supportive care only
  - Detoxication* (oral, extra-corporeal)
  - Benzylpenicillin (PCN)
  - N-acetyl cysteine (NAC)
  - Silybin
  - Silybin/PCN, PCN/antioxidant, PCN/steroid, PCN/thioctic acid
  - PCN/(X_1+X_2+...)+Silybin, PCN/(X_1+X_2+...)-Silybin

- Detoxication procedures were ignored for assignment of the various modes.
Analysis

Rates of drug therapy use:
- Benzylpenicillin (86.5%),
- Silybin (38.2%)
- Steroids (27.6%)
- Thiocytic acid (27.1%)
- NAC (11.8%)
Analysis

- Overall survival was 89.7%
- Mortality rates broken into: transplant included (LTi), and transplant excluded (LTe)
  - LTi counted Liver transplants as mortalities
  - LIe removed Liver transplants from numerator and denominator
- The highest mortality rate was in the supportive measures only group (47.3%).
- Detoxication had a mortality rate of 10.4%
  - Not statistically different than the pooled drug treatment groups.
Analysis

- The lowest mortality rates were seen in (no difference between them)
  - Silybin*
  - NAC
  - Silybin/PCN*
  - PCN/(X_1+X_2+...)+Silybin

- Unless grouped with Silybin, PCN did not demonstrate any benefit.

*Significantly different than detoxication only group only for LTe
Discussion

Although no adjustments were made for multiple comparisons, co-morbidities, treatment location, age, detoxication therapies, conclusions made were:

- Benzylpenicillin (PCN) did not demonstrate any treatment benefit.
- Silybin is beneficial in decreasing mortality
- NAC is beneficial in decreasing mortality
Take home points

- Overall survival was 89.7%
- The lowest mortality rates were seen in the silybin groups and the NAC monotherapy group
- “..Silymarin \([\text{Silybin}]\), and...NAC play a crucial role in the recovery of amatoxin-poisoned patients.”
- “Clinical data......do not show benzylpenicillin \([\text{PCN}]\) to be an effective drug”