Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily
A Randomized Controlled Trial

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[NOTE: the most common over-the-counter brand name for acetaminophen is Tylenol; the most common opioid-acetaminophen combination is Vicodin.]

FROM ABSTRACT

Context
During a clinical trial of a novel hydrocodone/acetaminophen combination, a high incidence of serum alanine aminotransferase (ALT) elevations was observed.

Objective
To characterize the incidence and magnitude of ALT elevations in healthy participants receiving 4 g of acetaminophen daily, either alone or in combination with selected opioids, as compared with participants treated with placebo.

Design
Each active treatment included 4 g of acetaminophen daily, and treatment duration was 14 days.

Main Outcomes
Serum liver chemistries and trough acetaminophen concentrations.

Results
The incidence of maximum ALT of more than 3 times the upper limits of normal was 31% to 44% in the 4 treatment groups receiving acetaminophen, including those participants treated with acetaminophen alone.

Compared with placebo, treatment with acetaminophen was associated with a markedly higher median maximum ALT by 178% with a range of increase between 47% – 309%.

Conclusions
Initiation of recurrent daily intake of 4 g of acetaminophen in healthy adults is associated with ALT elevations.

THESE AUTHORS ALSO NOTE

Acetaminophen is a common of over-the-counter pain reliever.
“For management of moderate to severe pain, physicians often prescribe opioid and acetaminophen combination preparations.” [Like Vicodin]

During early clinical development of a product containing hydrocodone and acetaminophen, we observed a surprisingly high incidence of elevations in serum alanine aminotransferase (ALT) in participants receiving daily doses that contained 4 g daily of acetaminophen, the upper limit of recommended acetaminophen dosing.

This gives concerns that opioids with acetaminophen might increase susceptibility to liver toxicity.

This study was therefore designed to investigate hepatotoxicity among participants receiving acetaminophen alone, opioid/acetaminophen combinations, or placebo.

The participants in this study were healthy men and women volunteers, who were taking no medications.

Many of the active treatment group were assigned to take Extra Strength Tylenol.

Routine serum liver chemistries were performed on the group, including alanine aminotransferase (ALT).

“Exposure to any acetaminophen treatment was the single best predictor of elevated ALT response.”

COMMENT

“In this 5-group, single-blind, randomized, placebo-controlled study we found that each of the 3 opioid/acetaminophen treatments frequently produced ALT elevations.”

“We were surprised to observe that treatment with acetaminophen alone at the recommended maximal dose of 4 g per day also produced frequent ALT elevations.” [Very Important]

“Indeed, the ALT elevations produced by treatment with acetaminophen alone differed very little in frequency or magnitude from those produced by the opioid/acetaminophen combination treatments.”

“The data therefore do not support a role for opioids in the ALT elevations observed.” [meaning the elevated ALT was caused by the acetaminophen]

“We therefore conclude that the ALT elevations observed were the result of acetaminophen treatment at 4 g daily.” [Important]
“Prior literature supports our observations that a subset of healthy adult participants will develop ALT elevations when repeatedly treated with 4 g of acetaminophen daily.”

This study also suggests that Hispanics are more susceptible to injury by acetaminophen than other races evaluated in this study. [Important]

“The magnitude of the ALT elevations, and the concomitant elevation of AST and GST confirm the hepatic origin of these enzymes.”

“The frequency and magnitude of ALT elevations we observed would be considered a signal for potential liver safety concerns.”

“A clinically important observation was that ALT elevations occurred in the absence of plasma acetaminophen concentrations that would traditionally be considered hepatotoxic.”

“We conclude that initiation of treatment of healthy adults with acetaminophen taken at the maximum daily recommended dose of 4 g for 4 or more days frequently causes elevations in serum aminotransferases, which often persist when acetaminophen concentrations are no longer measurable.”

**KEY POINTS FROM DAN MURPHY**

1) Ingesting 4 g of acetaminophen daily has been considered to be safe.

2) Acetaminophen liver damage risk can be assessed by evaluating liver enzymes in the blood.

3) Important liver enzymes that indicate liver damage elevated more than 3 times the upper limits of normal in 31% to 44% of healthy volunteers given 4 g of acetaminophen (Extra Strength Tylenol) or 4 g of acetaminophen in a opioid combination [Vicodin] for a period of 4 – 14 days.

4) Treatment with acetaminophen alone at the recommended maximal dose of 4 g per day also produced frequent elevations of liver enzymes, indicating liver injury. [Very Important]

5) These authors conclude that the elevated liver enzymes observed were the result of acetaminophen treatment at 4 g daily. [Important]

6) Hispanics may be more susceptible to injury by acetaminophen than other races. [Important]