

Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily

A Randomized Controlled Trial

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ACETAMINOPHEN IS A COMMON constituent of over-the-counter pain relievers. For management of moderate to severe pain, physicians often prescribe opioid and acetaminophen combination preparations. Such preparations have demonstrated benefit in pain relief and are regarded as safe when taken as directed.

During early clinical development of a novel combination product containing hydrocodone and acetaminophen, we observed a surprisingly high incidence of elevations in serum alanine aminotransferase (ALT) in participants receiving the combination product at total daily doses that contained 4 g daily of acetaminophen, the upper limit of recommended acetaminophen dosing (Purdue Pharma L.P., data available from authors on request). The study was stopped early because of the frequency and magnitude of ALT elevations in the active treatment groups vs the placebo group.

Because ALT elevations had generally not been reported in adults receiving recommended doses of acetaminophen, there was concern that opioids might increase susceptibility to acetaminophen liver toxicity.

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, Setting, and Participants A randomized, single-blind, placebo-controlled, 5-treatment, parallel-group, inpatient, diet-controlled (meals provided), longitudinal study of 145 healthy adults in 2 US inpatient clinical pharmacology units.

Intervention Each participant received either placebo (n=39), 1 of 3 acetaminophen/opioid combinations (n=80), or acetaminophen alone (n=26). Each active treatment included 4 g of acetaminophen daily, the maximum recommended daily dosage. The intended treatment duration was 14 days.

Main Outcomes Serum liver chemistries and trough acetaminophen concentrations measured daily through 8 days, and at 1- or 2-day intervals thereafter.

Results None of the 39 participants assigned to placebo had a maximum ALT of more than 3 times the upper limit of normal. In contrast, 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 (ratio of medians, 2.78; 95% confidence interval, 1.47-4.09; $P < .001$). Trough acetaminophen concentrations did not exceed therapeutic limits in any participant and, after active treatment was discontinued, often decreased to undetectable levels before ALT elevations resolved.

Conclusions Initiation of recurrent daily intake of 4 g of acetaminophen in healthy adults is associated with ALT elevations and concomitant treatment with opioids does not seem to increase this effect. History of acetaminophen ingestion should be considered in the differential diagnosis of serum aminotransferase elevations, even in the absence of measurable serum acetaminophen concentrations.

JAMA. 2006;296:87-93

www.jama.com

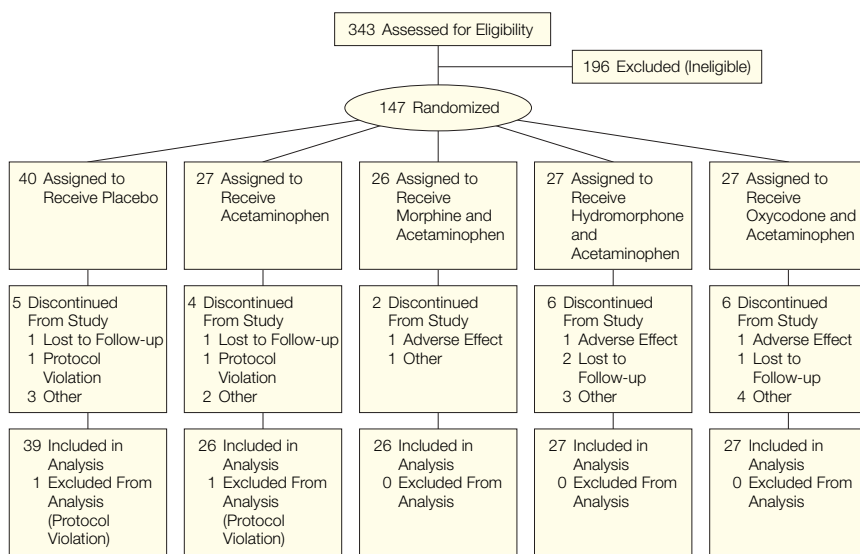
This study was therefore designed to investigate hepatotoxicity among participants receiving acetaminophen alone, opioid/acetaminophen combinations, or placebo.

METHODS

In this study (2-center, randomized, single-blind [participants were blinded to treatment assignment], placebo-controlled, 5-treatment, parallel group,

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Figure 1. Study Disposition Diagram

longitudinal design), eligible participants were healthy men and women volunteers of non-childbearing potential of any ethnic or racial group 18 to 45 years of age. Participants were considered to be healthy based on medical history, physical examination, electrocardiogram results, and clinical laboratory measures (including negative urine drug screen, hepatitis B surface antigen, and hepatitis C antibody results). No participants entered the study on concomitant medications. Race/ethnicity was self-reported; country of origin was not recorded.

Protocol was approved by the institutional review board for each study center. Participants gave written informed consent before entering the study and were housed in 1 of 2 clinical research facilities for the entire study.

Participants received 1 of the 5 treatment regimens (defined in the next section) administered orally every 6 hours for up to 14 days (56 doses), according to a randomization schedule in a 1:1:1:1:1.5 ratio. Participants were assigned to treatment according to a centrally generated randomization schedule using a block size of 11 participants (FIGURE 1).

Description of Specific Treatments

Treatment 1: Percocet, 2 tablets (7.5 mg of oxycodone/500 mg of acetaminophen; commercial product; lot number, 320481NV) plus 2 placebo tablets (lot number, CB26-06).

Treatment 2: Dilaudid, 2 tablets (2 mg of hydromorphone; commercial product; lot number, 03DLT21004) Extra Strength Tylenol, 2 caplets (500 mg of acetaminophen; commercial product; lot number, EDA041).

Treatment 3: Two morphine tablets (15 mg; commercial product; lot number, 356926A) Extra Strength Tylenol, 2 caplets (500 mg of acetaminophen; commercial product; lot number, EDA041).

Treatment 4: Two placebo tablets (lot number: CB26-06) Extra Strength Tylenol, 2 caplets (500 mg of acetaminophen; commercial product; lot number, EDA041).

Treatment 5: Two placebo tablets (lot number, CB26-06) plus 2 placebo tablets (lot number, CB-2003-01).

Routine serum liver chemistries (bilirubin, aspartate aminotransferase [AST], ALT, alkaline phosphatase) and serum alpha glutathione S-transferase (α GST), a measure of hepatocellular injury, were measured daily through day

8. After day 8, chemistries were measured on alternate days or daily in participants with elevations ($>1 \times$ the upper limit of normal [ULN]). The protocol required discontinuation of treatment for any participants with ALT or AST concentrations more than 120 U/L ($3 \times$ ULN).

Study evaluations included adverse events, laboratory tests, vital signs, and pharmacokinetics. End-of-study evaluations included laboratory tests, physical examinations, and vital signs.

Pharmacokinetics

Plasma acetaminophen concentrations were measured daily in all participants at morning trough as well as over a single 6-hour dosing interval on day 3 of therapy (48-54 hours on therapy). The participant's acetaminophen concentration time series was used to estimate the area under the concentration curve (48-54 hours), peak concentration (48-54 hours), and time-to-peak concentration (48-54 hours) by noncompartmental methods using validated pharmacokinetic software WinNonLin (Pharsight Corp, Mountain View, Calif).

Diet

Participants' diets consisted solely of catered, standardized, whole-food meals provided as breakfast, lunch, dinner, and nighttime snack. Participants did not have access to foods or beverages other than those provided. Food diaries were not collected.

Statistical Analysis

Analysis of the impact of opioids on risk of acetaminophen hepatotoxicity was performed on a modified intention-to-treat basis and focused on longitudinal ALT, AST, and total bilirubin values provided by a central laboratory. A 2-sided $P < 0.05$ was considered significant. All analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

Descriptive and inferential methods were applied to summary end points: (1) LabMax (each participant's maximum posttreatment value); (2) LabRatio (ratio of LabMax to base-

line value); (3) LabTmax (time to maximum observed value); (4) binary indicators of LabMax > K with K = 1, 2, 3, 5 or 8 ULN for ALT and AST, and K = 1 or 1.5 for total bilirubin.

Log transformed values of LabMax and LabRatio were analyzed using an analysis of covariance model with fixed effects for treatment, center, and pre-dose value (day 1). The results from the fitted model were used to obtain unbiased statistical estimates (with confidence intervals). This was done by exponentiating least square means (and their 95% confidence limits).

The models for LabRatio and LabMax also provided a test of the overall null hypothesis that stated the mean response (log scale) to acetaminophen is invariant to concomitant administration of the opioids studied. More generally, the models provided tests for all pairwise comparisons among the 5 treatment regimens. Analyses of LabMax included computation of confidence intervals for the difference between treatment-specific arithmetic means. In support of these model-based analyses, sensitivity analyses relying on nonparametric methods were performed. Diagnostic procedures, auxiliary analyses, and exploratory analyses were also performed.

Secondarily, multivariable linear regression models were used to explore the predictive value of independent variables including treatment, baseline ALT, body mass index (calculated as weight in kilograms divided by height in meters

squared), race/ethnicity, center, other baseline and demographic measures, and interactions among these. Principal components analysis was used to explore relationships among the study variables.

Estimates of ALT elevation rates were obtained by tabulation of treatment-specific counts (for elevations to >1 ×, >2 ×, >3 ×, >5 ×, and >8 × the ULN). For completeness, Fisher exact test procedure was applied to the evaluation of association between treatment regimen and ALT elevation.

RESULTS

Of 343 participants screened, 147 were randomized. Two randomized participants were given single doses of study medication on study day 1 before they were withdrawn because of positive urine drug screen results. The remaining 145 participants comprised the modified intent-to-treat population.

Among the 145 participants in the modified intent-to-treat population, the treatment groups were similar in demographic characteristics (TABLE 1).

Meaningful differences in the magnitude and incidence of ALT elevations were not detected among the active treatment regimens. There were no statistically significant differences in log LabMax ALT among the active treatment groups. In contrast, the mean response to placebo was statistically significantly different from that of each of the active treatments. The null hypothesis that the active treatments do not differ from pla-

cebo was rejected ($P < .001$). In exploratory analyses, exposure to any acetaminophen treatment was the single best predictor of elevated ALT response.

Only 1 of 39 participants (3%) taking placebo experienced ALT more than 2 times the ULN at any time during the study, and no placebo participants experienced ALT more than 3 times the ULN (TABLE 2). In contrast, more than 19% of participants experienced ALT more than 5 times the ULN in each of the 4 active treatment groups. A similar pattern of ALT elevations by treatment is noted when participants' peak ALT elevations were normalized by their baseline ALT values (TABLE 3). Only 1 of 39 (3%) participants using placebo experienced peak ALT more than 5 times the baseline, while 29 of 106 (27%) of participants in the active treatment groups experienced peak ALT more than 8 times the baseline.

Individual participant and group mean ALT values over time are shown for the placebo group, the acetaminophen-only treatment group, and composite of the 3 opioid/acetaminophen treatment groups in FIGURE 2. The temporal patterns of ALT elevations were similar in all the active treatment groups, including the acetaminophen-alone group. Elevation of ALT to more than 3 times the ULN (120 U/L) was not observed prior to day 3 in any of the treatment groups. After discontinuation of dosing due to ALT elevations to more than 3 times the ULN, the ALT continued to increase for

Table 1. Characteristics of the Study Population by Treatment Group

	Placebo	Acetaminophen	Oxycodone plus Acetaminophen	Hydromorphone plus Acetaminophen	Morphine plus Acetaminophen	Total	P Value*	P Value†
Participants, No.	39	26	27	27	26	145		
Sex, No. (%)								
Men	32 (82)	18 (69)	24 (89)	22 (81)	17 (65)	113 (78)	.20	.46
Women	7 (18)	8 (31)	3 (11)	5 (19)	9 (35)	32 (22)		
Age, mean (range) y	32.8 (18-45)	34.0 (18-45)	36.7 (20-45)	32.6 (19-44)	33.5 (21-44)	33.8 (18-45)	.31	.64
Race/ethnicity, No. (%)								
African American	5 (13)	3 (12)	4 (15)	3 (11)	4 (15)	19 (13)	.99	.99
Hispanic American	23 (59)	15 (58)	16 (59)	14 (52)	14 (54)	82 (57)		
White American	11 (28)	8 (31)	7 (26)	10 (37)	8 (31)	44 (30)		
Body mass index mean (range)‡	25.8 (18.1-31.0)	25.8 (18.9-29.8)	26.0 (19.8-30.0)	25.4 (18.9-29.7)	25.2 (19.9-29.9)	25.7 (18.1-31.0)	.86	.84

*Comparison across all 5 treatment groups.

†Comparison across 3 groups (placebo, acetaminophen only, and acetaminophen plus opioid).

‡Calculated as weight in kilograms divided by height in meters squared.

0 to 4 days (median 2 days) and remained more than 3 times the ULN for 1 to 11 days (median 6.5 days). The highest ALT observed was 636 U/L ($\approx 16 \times$ ULN) in a participant receiving hydromorphone plus acetaminophen. The highest ALT observed in the acetaminophen alone group was 575 U/L ($\approx 14 \times$ ULN).

TABLE 4 displays statistical estimates of treatment differences for the LabMax ALT. The results show statistically significant elevation in median LabMax ALT in the opioid/acetaminophen combination treatments or the acetaminophen-alone treatment compared with the placebo treatment. The median LabMax ALT values for the active treatments were 2.57 to 3.08 times higher than the placebo value. There were no statistically significant differences in median LabMax ALT among the active treatment groups. These findings were supported by comparable results in a nonparametric analysis.

AST elevations were generally smaller than those of ALT, but followed a simi-

lar time course. Levels of α GST rose relative to predose values in those participants with elevations in ALT and also followed a similar time course (data available upon request). Peak ALT and peak α GST levels were highly correlated (Pearson correlation coefficient of determination = 0.89; data available upon request). There were no abnormalities or consistent trends in total bilirubin or alkaline phosphatase and all participants with ALT elevations were asymptomatic. All significant ALT elevations resolved after treatment was stopped with the exception of a participant in the morphine plus acetaminophen group who was lost to follow-up after day 19 (ALT was 194 on day 18 and 168 on day 19).

To identify participant characteristics that might be associated with increased susceptibility to ALT elevations, exploratory analyses were performed using stepwise multivariable linear regression for log LabMax ALT. Independent variables selected for the final model in order of decreasing nominal statistical significance were

treatment group, baseline log ALT, and race/ethnicity. Potential predictors that were rejected included other demographic and baseline characteristics. Results of an exploratory principal components analysis were consistent with the linear model results.

Among all participants in any treatment group receiving acetaminophen, the relative risk of maximum ALT more than 3 times the ULN for Hispanic Americans vs non-Hispanics was 1.9 (95% confidence interval, 1.1-3.3).

Mean acetaminophen area under the concentration curve from 48 to 54 hours and peak concentration of 48 to 54 hours across all active treatments were similar and ranged from 39.0 to 47.2 $\mu\text{g}\cdot\text{h}/\text{mL}$ and from 12.6 to 16.7 $\mu\text{g}/\text{mL}$, respectively. No difference was detected in mean acetaminophen trough levels, peak concentration, or area under the concentration curve between those participants exhibiting ALT elevations (to $>1 \times$ ULN or $>3 \times$ ULN) and those who did not (data available upon request). In participants with ALT elevations to more

Table 2. Incidence of Peak Alanine Aminotransferase Elevations by Multiples of Upper Limit of Normal*

Treatment*	No.	No. (%)				
		$>1 \times$ ULN	$>2 \times$ ULN	$>3 \times$ ULN†	$>5 \times$ ULN	$>8 \times$ ULN
Placebo	39	15 (38)	1 (3)	0	0	0
Acetaminophen	26	21 (81)	13 (50)	10 (38)	6 (23)	1 (4)
Acetaminophen + opioid						
Oxycodone + acetaminophen	27	20 (74)	14 (52)	11 (41)	5 (19)	1 (4)
Hydromorphone + acetaminophen	27	21 (78)	15 (56)	12 (44)	10 (37)	4 (15)
Morphine + acetaminophen	26	19 (73)	14 (54)	8 (31)	6 (23)	2 (8)
All active drugs combined	106	81 (76)	56 (53)	41 (39)	27 (25)	8 (8)

Abbreviation: ULN, upper limit of normal.

*ULN = 40 U/L.

†Relative risk is greater than 4.9 (95% confidence interval, 4.91-infinity; $P = .002$).

Table 3. Incidence of Peak Alanine Aminotransferase Elevations by Multiples of Participant's Baseline Alanine Aminotransferase*

Treatment*	No.	No. (%)				
		$>1 \times$ BL	$>2 \times$ BL	$>3 \times$ BL	$>5 \times$ BL	$>8 \times$ BL
Placebo	39	37 (95)	11 (28)	4 (10)	1 (3)	0
Acetaminophen	26	26 (100)	21 (81)	15 (58)	12 (46)	7 (27)
Acetaminophen + opioid						
Oxycodone + acetaminophen	27	25 (93)	19 (70)	18 (67)	12 (44)	6 (22)
Hydromorphone + acetaminophen	27	27 (100)	21 (78)	18 (67)	15 (56)	8 (30)
Morphine + acetaminophen	26	26 (100)	23 (88)	16 (62)	13 (50)	8 (31)
All active drugs combined†	106	104 (98)	84 (79)	67 (63)	52 (49)	29 (27)

Abbreviation: BL, baseline.

*Alanine aminotransferase value, predose day 1.

†When comparing all active drugs combined vs placebo, the relative risk for greater than 3 times the baseline is 6.2 (95% confidence interval, 2.4-15.8).

than 3 times the ULN during treatment, acetaminophen concentrations fell quickly when dosing was stopped. As a result, acetaminophen was often undetectable while ALT remained elevated. FIGURE 3 shows the time courses of acetaminophen, ALT, and AST concentrations in the participant in the acetaminophen-only group with the highest ALT elevation.

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. 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.

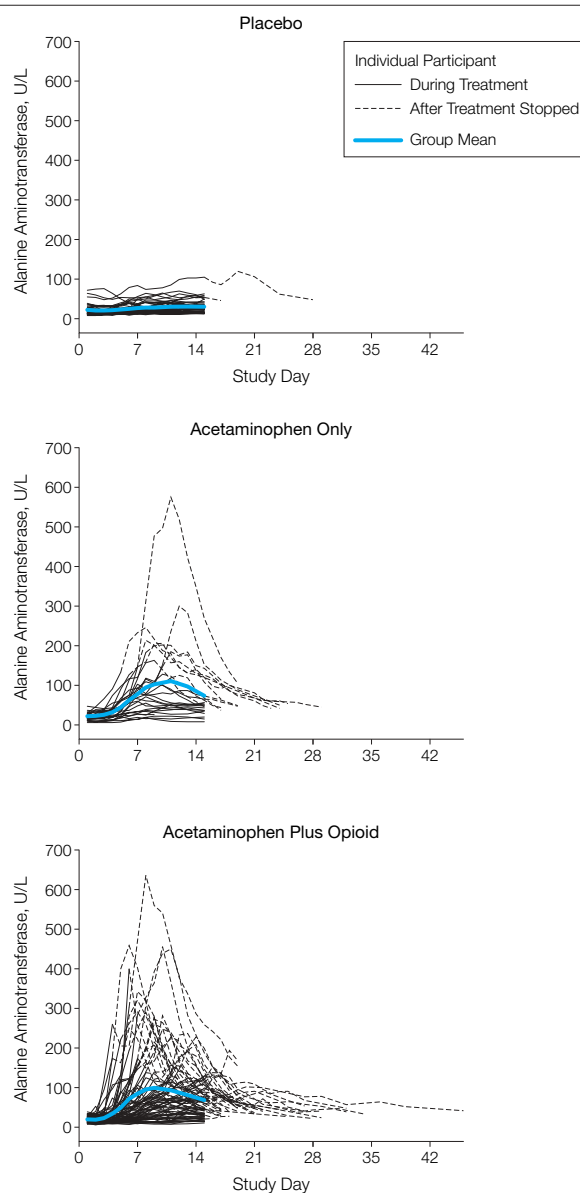
Causes for ALT elevation other than acetaminophen were not evident. To minimize extraneous sources of variability, all participants were confined to clinical pharmacology units during the study, sharing living space, and receiving standardized catered meals. Elevations in ALT have been previously observed in healthy adults receiving placebo¹ and this has been attributed to changes in diet, specifically with change from a standard diet to a high-carbohydrate, high-calorie diet.² However in this study, diet is an unlikely explanation for the differences in ALT elevations observed among treatment groups because the same meals were served to all participants. An infectious or environmental factor causing ALT elevations is also unlikely given the relatively small number of ALT elevations in the concurrent placebo group. Finally, the continued elevation in ALT for 1 to several days after discontinuing therapy, and the subsequent rapid fall in ALT are consistent with liver toxicity observed after an acute overdose of acetami-

nophen.³ We therefore conclude that the ALT elevations observed were the result of acetaminophen treatment at 4 g daily.

An association between therapeutic dosing of acetaminophen and elevations in ALT has not been previously reported. Several studies⁴⁻⁸ have measured serum ALT between days 5 and 30 after starting therapy with acetaminophen and have expressly stated that no or only very minor ALT elevations were observed. These studies have involved a variety of patient populations

that were generally elderly. We could find only 3 published studies where healthy young adults were treated with acetaminophen daily and serum ALT was monitored after 5 days of treatment. In one study,⁹ ALT was monitored "at least biweekly" while 20 healthy adult volunteers received 4 g of acetaminophen daily. A single participant asymptotically experienced ALT of more than 4 times ULN and AST of more than 15 times ULN at day 16. Although the individual labo-

Figure 2. Serum Alanine Transferase vs Time on Study



ratory values for the other participants were not given, a figure in the manuscript appears to indicate an increase in mean ALT from day 4 to day 11, peaking at about 1.5 times the ULN. In the second study,¹⁰ 15 healthy participants received 3.9 g of acetaminophen daily for 7 days and “minor transaminase rises (less than twice normal) were noted . . .” In the third study,¹¹ 20 healthy men were given 4.0

g of acetaminophen daily and serum ALT was monitored twice weekly. Although changes in serum ALT are described as “overall . . . minor,” 2 participants were noted to have ALT elevation exceeding 4 times their baseline and 1 was withdrawn from the study on this basis (ALT ≈ 4 × ULN). Hence, the prior literature supports our observations that a subset of healthy adult participants will develop ALT el-

evations when repeatedly treated with 4 g of acetaminophen daily.

The incidence of ALT elevations we observed in our studies of healthy adults is higher than previously reported in similar studies.⁹⁻¹¹ This may, in part, relate to the relatively high proportion of Hispanic individuals in our study since our exploratory analysis suggested that Hispanic origin is associated with increased susceptibility to ALT elevations. Ethnic and racial differences in acetaminophen pharmacokinetics have been reported,^{12,13} but we are unaware of studies examining acetaminophen metabolism differences between Hispanics and others. Hispanics have been reported to have higher baseline ALT levels than white individuals¹⁴ and this may relate to a higher incidence of fatty liver disease among Hispanics.¹⁵ Although it is possible that a fatty liver is more susceptible to injury by acetaminophen, body mass index, which is typically elevated in patients with fatty liver, was not correlated with ALT elevations in this study. However it should be noted that the maximum body mass index among participants in this study was 31, and therefore the full effect of this variable may not have been evident. Nonetheless, it seems unlikely that fatty liver accounts for much variation in susceptibility in our population.

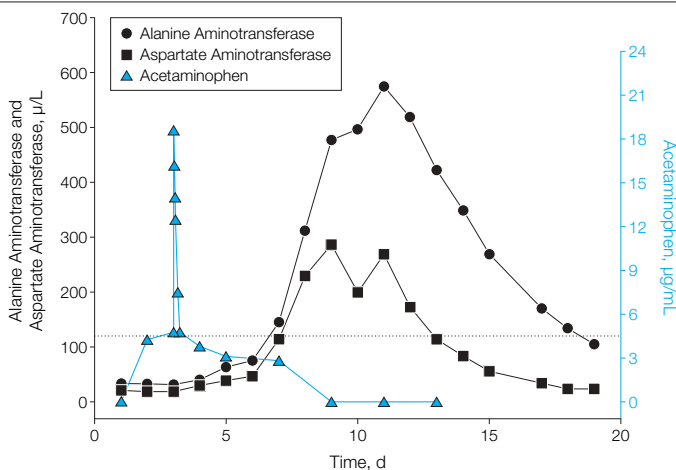
It is unclear why more than minor ALT elevations have not been reported in studies involving patient populations treated with 4 g daily of acetaminophen. In addition to a possible age effect, we speculate that prior recurrent treatment with acetaminophen may reduce the likelihood of ALT elevations during subsequent acetaminophen treatment. A similar phenomenon has been reported with the drug tacrine. Patients who developed ALT elevations during treatment with tacrine were found to have reduced ALT response on rechallenge, even when treatment was initiated many weeks after discontinuation of therapy.¹⁶ The mechanisms underlying this long-lasting “adaptation” are not known,¹⁷ but we speculate that this could account for reduced incidence of ALT el-

Table 4. Comparison of Treatments in Terms of Maximum Alanine Aminotransferase (LabMax for Alanine Aminotransferase)

The 2 Treatments Being Compared in Terms of Mean Response	Estimate of the Ratio of the 2 Means (95% Confidence Interval for the Ratio)
Active treatments vs placebo	
Acetaminophen vs placebo	2.78 (1.47-4.09)*
Hydromorphone + acetaminophen vs placebo	3.08 (1.64-4.52)*
Morphine + acetaminophen vs placebo	2.67 (1.40-3.94)*
Oxycodone + acetaminophen vs placebo	2.57 (1.37-3.77)*
Acetaminophen + opioid vs acetaminophen alone	
Hydromorphone + acetaminophen vs acetaminophen	1.11 (0.53-1.69)
Morphine + acetaminophen vs acetaminophen	0.96 (0.45-1.47)
Oxycodone + acetaminophen vs acetaminophen	0.93 (0.45-1.41)
Acetaminophen + opioid between group comparisons	
Hydromorphone + acetaminophen vs morphine + acetaminophen	1.15 (0.54-1.76)
Hydromorphone + acetaminophen vs oxycodone + acetaminophen	1.20 (0.58-1.82)
Morphine + acetaminophen vs oxycodone + acetaminophen	1.04 (0.49-1.59)

*Statistically significant, *P* < .001.

Figure 3. Concentrations in Participant Randomized to Acetaminophen Alone Group Who Had Highest Peak Alanine Aminotransferase Concentration



Plasma acetaminophen and serum alanine aminotransferase and aspartate aminotransferase concentrations in the participant randomized to acetaminophen alone group with highest peak alanine aminotransferase. A 6-hour pharmacokinetic study was performed on day 3; other acetaminophen concentrations are trough levels. Acetaminophen treatment was discontinued when the serum alanine aminotransferase exceeded 3 times the upper limit of normal (dotted line) per protocol.

elevations among patient populations vs healthy study participants.

The clinical importance of the ALT elevations observed in our study is also unclear. The magnitude of the ALT elevations, and the concomitant elevation of AST and α GST confirm the hepatic origin of these enzymes. An ALT of more than 3 times the ULN is typically considered clinically significant and if confirmed, is generally considered justification for further evaluation for liver disease. Indeed, there are few approved drugs known to produce ALT elevations with a magnitude and incidence comparable with those observed in this study (ie, more than one third of acetaminophen-treated participants experienced ALT elevations to $>3 \times$ ULN). In other contexts, the frequency and magnitude of ALT elevations we observed would be considered a signal for potential liver safety concerns. However, acetaminophen clearly has a remarkable safety record when taken as directed, and chronic treatment with 4 g daily has been confirmed to be safe.^{8,18-21} Our observations, therefore, illustrate that there is uncertainty regarding the ability of aminotransferase elevations to predict potential for serious liver injury in some instances. We suspect that the ALT elevations we observed would have resolved with continued administration of acetaminophen, but this should be investigated in future studies.

A clinically important observation was that ALT elevations occurred in the absence of plasma acetaminophen concentrations that would traditionally be considered hepatotoxic. Indeed, at the time of the highest ALT elevation, acetaminophen concentrations were frequently near or below the limits of assay detection. Plasma acetaminophen concentrations would therefore be of limited value in determining whether ALT elevations were due to therapeutic doses of acetaminophen.

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. A history of recurrent acetaminophen ingestion should therefore be sought when evaluating otherwise unexplained elevations in serum aminotransferase observed in clinical practice or during clinical trials.

Author Contributions: Dr Watkins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Watkins, Kaplowitz, Slattery, Harris, Colonnese.

Acquisition of data: Harris, Colonnese.

Analysis and interpretation of data: Watkins, Kaplowitz, Slattery, Colucci, Stewart, Harris, Colonnese.

Drafting of the manuscript: Watkins, Colucci, Harris, Colonnese.

Critical revision of the manuscript for important intellectual content: Watkins, Kaplowitz, Slattery, Colucci, Stewart, Harris, Colonnese.

Statistical analysis: Watkins, Colucci, Stewart, Harris, Colonnese.

Obtained funding: Slattery, Harris.

Administrative, technical, or material support: Colonnese.

Study supervision: Harris.

Financial Disclosures: Drs Watkins, Kaplowitz, and Slattery report having served as paid consultants to Purdue Pharma L.P. during the planning and execution of the study but were not paid for the preparation of this article. The manufacturers of Tylenol, Dilaudid, and Percocet are McNeil, Knoll, and Endo Labs, respectively. Drs Watkins, Kaplowitz, and Stewart report that they have never had financial relationships with these companies. Dr Slattery reports having served as a consultant for McNeil. Morphine is a generic drug with several manufacturers with information that we have not included in this article. This information can be provided on request.

Independent Statistical Analysis: Paul Stewart, PhD, professor of biostatistics at the University of North Carolina School of Public Health, had access to all of the data used for the primary analyses reported. He performed an independent verification of the calculations and interpretations presented in those primary analyses (ie, the primary test of the null hypothesis of no differences among the active treatment regimens along with all of the computations in all 3 tables in the article, which comprise all of the main results discussed in the abstract, results section, and comment section of the paper). As a result of this check, there were some minor corrections made to the findings reported in the article. In addition, based on review of the study protocol documents, and the inventory of all data collected in the study, Dr Stewart confirmed that the set of analyses presented in the paper are appropriate and sufficient. Dr Stewart was not compensated directly for this analysis; however, with ongoing studies in the UNC GCRC in this area, the GCRC's Scientific Advisory Committee agreed that this work by Dr Stewart should be considered an appropriate part of his efforts that are funded by the GCRC's grant (RR000046).

Funding/Support: The study was entirely funded by Purdue Pharma L.P. and was conducted at 2 contract research organizations. The handling and interpretation of the data was shared among all authors. Dr Stewart's efforts were supported by National Institutes of Health grant RR-000046.

Role of the Sponsor: The originally submitted manuscript went through the standard publication review process at Purdue Pharma, but no changes were suggested.

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