

Acetaminophen Levels 4 and 7 Hours After 2000 and 3000 mg Single Doses in Healthy Adults

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Abstract

Purpose: Therapeutic acetaminophen levels are not achieved at currently recommended doses. The purpose of this study is to determine acetaminophen levels in healthy adults after taking a single dose well in excess of the recommended dose.

Methods: 24 healthy adults received single 2 or 3 gram acetaminophen doses. Serum acetaminophen levels were drawn at 4 and 7 hours after the dose.

Results: The 2 gram doses (6 subjects) ranged from 23 to 40 mg/kg of body weight. The 3 gram single doses (18 subjects) ranged from 38 to 69 mg/kg of body weight. Mean 4-hour acetaminophen levels for 2 and 3 gram doses were 8.8 (SD 3.6, range 3-13) and 21.8 (SD 6.5, range 6-32) mcg/ml, respectively. Mean 7-hour acetaminophen levels for 2 and 3 gram doses were 1.5 (SD 1.4, range 0-3) and 7.7 (SD 4.6, range 0-17) mcg/ml, respectively.

Conclusions: Dosing by weight (i.e., mg/kg) appears to provide a more predictable dose-response relationship. Optimal adult dosing appears to be somewhere in the 20 to 30 mg/kg range based on the premise that the 4 hour level is a trough level that should be in the low therapeutic range.

Introduction

Acetaminophen (also known as paracetamol and APAP) is a frequently used antipyretic and analgesic in both children and adults. The currently recommended single doses are 650-1000 mg for adults and 10-15 mg/kg for children, with a maximum dose of 90 mg/kg per day.¹⁻³ Single doses greater than 140-150 mg/kg are recognized to have hepatotoxic effects. The current dosing recommendations are based on the serum level required to achieve an antipyretic effect, with therapeutic serum acetaminophen (APAP) levels of 10-20 mcg/mL (66-132 micromol/L).^{8,9} While analgesic acetaminophen levels have not been established, it is hypothesized that analgesic serum levels are greater than antipyretic levels.^{4,5} Several recent studies have found that therapeutic acetaminophen levels have not been reached at currently recommended doses.^{4-6,8-10}

The purpose of our study is to report serum acetaminophen levels, at 4 and 7 hours post-ingestion, in adults who received large doses of acetaminophen (2 or 3 times the oral maximum single recommended dose).

Methods

This study represents a sub-group analysis of a study to examine the effects of superactivated charcoal (SAC) administration on acetaminophen serum levels. Institutional review board (IRB) approval was obtained. This study is a randomized unblinded human experimental design trial to determine the efficacy of late administration of SAC given three hours after an acetaminophen dose. Healthy adult study subjects were recruited and paid \$50 for study participation. Subjects were randomized by a coin flip to SAC or no-SAC. Only the no-SAC subjects are described in this current report. A health screening questionnaire was used to exclude study subjects with 1) allergy to acetaminophen, 2) hepatic or renal disease, 3) heavy alcohol use, 4) chronic gastrointestinal disease, or 5) use of any medication within 24 hours of the study. The study protocol recommended a screening serum ALT (alanine transaminase) assay prior to the study to screen for occult liver disease. Written informed consent was obtained and following this, acetaminophen was administered as a single dose in the morning after an overnight fast. Serum acetaminophen levels were measured at 4 and 7 hours after the initial acetaminophen dose. The first 6 subjects received a 2 gram dose of acetaminophen. However, since most acetaminophen levels were found to be low, the protocol was revised to use a 3 gram dose of acetaminophen for the remainder of the study. Forty-eight subject runs of healthy adult volunteers were randomized to SAC (n=24) or no-SAC (n=24) groups.

Results

The results of the 24 no-SAC subject runs are described here. The mean age of participants was 27.4 years (SD 5.1). Mean weight was 61.6 kg (SD 11.9). Six participants were administered 2 grams acetaminophen under the initial protocol. The 2 gram single doses ranged from 23 to 40 mg/kg of body weight. 18 participants received a single 3 gram dose of acetaminophen under the revised protocol. The 3 gram single doses ranged from 38 to 69 mg/kg of body weight.

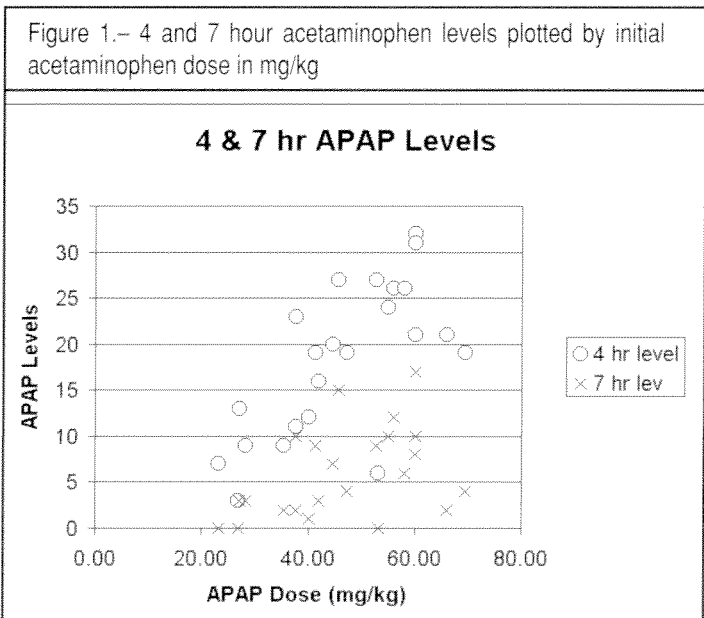
Mean 4-hour acetaminophen levels for 2 and 3 gram doses were 8.8 (SD 3.6, range 3-13) and 21.8 (SD 6.5, range 6-32) mcg/ml, respectively. Mean 7-hour acetaminophen levels for 2 and 3 gram doses were 1.5 (SD 1.4, range 0-3) and 7.7 (SD 4.6, range 0-17) mcg/ml, respectively. These results are further stratified in table 1. Table

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2 stratifies levels by mg/kg acetaminophen dosing groups. The actual 4 and 7 hour levels by acetaminophen dosing in mg/kg are graphed in figure 1.

	2 gram dose	3 gram dose
At 4 hours:		
Mean level	8.8	21.8
Level <10 (subtherapeutic)	4 of 6 (67%)	1 of 18 (6%)
Level 10-20 (therapeutic)	2 of 6 (33%)	5 of 18 (28%)
Level >20	0	12 of 18 (67%)
At 7 hours:		
Mean level	1.5	7.7
Level <10 (subtherapeutic)	6 of 6 (100%)	11 of 18 (61%)
Level 10-20 (therapeutic)	0	7 of 18 (39%)

Acetaminophen dose range (mg/kg)	20-29	30-39	40-49	50-59	60-70
Number of subjects	4	3	6	6	5
At 4 hours:					
Mean level	8.0	14.3	18.8	22.2	24.8
Level <10 (subtherapeutic)	3	1	0	1	0
Level 10-20 (therapeutic)	1	1	5	0	1
Level >20	0	1	1	5	4
At 7 hours:					
Mean level	1.5	4.7	6.5	7.8	8.2
Level <10 (subtherapeutic)	4	2	5	2	3
Level 10-20 (therapeutic)	0	1	1	4	2



Discussion

All participants received an acetaminophen dose greater than the currently recommended doses. In both the 2000 mg and 3000 mg groups, only about 30% of subjects had serum acetaminophen levels in the therapeutic range at 4 hours post ingestion. The 2000 mg dose was subtherapeutic in most instances, while the 3000 mg dose was above the upper limit of the therapeutic range, suggesting much higher peak levels. While the 2000 mg dose appears to be too low, and the 3000 mg appears to be too high, a 2500 mg dose would not necessarily be just right since there is substantial overlap in the distribution. The average weight of the study cohort (61 kg) suggests that the study subjects are relatively small, which would result in acetaminophen levels higher than what is to be expected in larger individuals (since the dose per kg would be smaller). Thus, the low levels found in this group are likely to be even lower in larger subjects.

Dosing by weight (i.e., mg/kg) appears to provide a distribution which more consistently reflects a dose-response relationship. Optimal dosing appears to be somewhere in the 20 to 30 mg/kg range based on the premise that the 4 hour level is a trough level that should be in the low therapeutic range. Pediatric dosing is currently recommended at 10-15 mg/kg every 4 hours^{1,2} although there are higher dosing recommendations.^{4,10}

Complicating this matter further is that the 4 and 7 hour levels obtained in this study were based on a single dose of acetaminophen prior to which, the study subjects had an acetaminophen level of zero. If adult patients are to take acetaminophen every 4 hours to maintain a therapeutic level, then their initial dose may have to be in the 20 to 30 mg/kg range, but their subsequent doses would have to be lower since they would now be giving the second dose on top of a trough level that is in the low therapeutic range instead of zero. This would make optimal dosing more complex and poor patient compliance would be expected.

Dosing acetaminophen every 6 hours for the first and second dose is not supported by this study since 7 hour levels were almost always very low unless the initial dose was greater than 40 mg/kg.

Route of Administration: Several studies have found that therapeutic acetaminophen levels are not achieved at currently recommended rectal doses in neonates, children, and adults.^{4,6,8-10} Therapeutic acetaminophen levels were achieved in studies in which the administered doses were higher than those currently recommended, and there was no evidence of accumulation.^{4,6,11-14} There appears to be no age-related differences in plasma acetaminophen elimination between neonates, children, and adults (young and elderly), despite age-related differences in metabolism.^{4,6,7} Most studies have found that orally administered acetaminophen results in predictable serum levels, while rectally administered acetaminophen has a greater variation in absorption and thus serum acetaminophen. A study by Montgomery, et al, found that 45 mg/kg rectal dose of acetaminophen resulted in peak plasma concentrations comparable with those resulting from recommended oral doses at three hours after suppository insertion in children.¹⁴ However, a recent study by van der Marel, et al, found no significant difference in serum acetaminophen levels between those with 20 mg/kg doses administered rectally and those who received oral doses.¹⁵

Our data were obtained at 4 and 7 hours post ingestion, and subsequent studies should be measured more frequently to deter-

mine peak acetaminophen concentrations. Furthermore, a single dose was used, and the effects of multiple doses must also be investigated. It is likely that acetaminophen dosing would be more optimal if a larger loading dose was used, followed by smaller maintenance doses, similar to the dosing method of other drugs.

While our study was performed in a cohort of healthy adults, the data and conclusions do not apply to patients with abnormal liver function and those with other conditions or medications which interact with the pharmacokinetics of acetaminophen metabolism and excretion.

In summary, dosing by weight (i.e., mg/kg) appears to provide a more predictable dose-response relationship. Optimal initial dosing appears to be somewhere in the 20 to 30 mg/kg range based on the premise that the 4 hour level is a trough level that should be in the low therapeutic range. Subsequent doses should probably be lower, but our study does not address this.

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