REPEATED SUPRATHERAPEUTIC ACETAMINOPHEN (PARACETAMOL) USE RESULTING IN A FATALITY

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Abstract. In the United States acetaminophen (paracetamol) is the most commonly used nonprescription analgesic. In addition to its nonprescription use, acetaminophen is also a common ingredient of prescription opioid combination products. This case report describes an acetaminophen-related fatality that occurred as a consequence of an unintentional overdose of a prescribed hydrocodone/acetaminophen product. While these deaths are uncommon, they can be prevented if the prescriptions for these products are written and dispensed properly and if patients are warned not to exceed the proper dosage recommendations.

Keywords: acetaminophen, overdose, mortality

Introduction

In the United States acetaminophen (paracetamol) is the most commonly used nonprescription analgesic. In addition to its nonprescription use, acetaminophen is also a common ingredient of prescription opioid combination products. One such product is the combination of hydrocodone and acetaminophen (e.g., Anexsia, Co-gesic, Loracet, Lortab, Norco, Panacet, Vicodin, Zydone) which is the most commonly prescribed generic drug product in the United States, with approximately 120 million prescriptions annually [1]. Typically, these products contain hydrocodone 2.5-10 mg and acetaminophen 325-750 mg per dosage unit. Given the relative safety of acetaminophen, iatrogenic overdosage and supratherapeutic dosing excursions by the patient are not usually associated with either morbidity or mortality. However, this case report describes an acetaminophen-related fatality that occurred as a consequence of an unintentional overdose of a prescribed hydrocodone/acetaminophen product.

Case Report

A previously healthy 38 year old female was admitted to the hospital with acute renal and hepatic failure. Four days prior to admission she underwent bunion surgery. Vicodin ES (hydrocodone 7.5 mg and acetaminophen 750 mg/tablet), one to two tablets every four to six hours as needed, was prescribed for post-operative pain. She experienced some initial intolerance to the hydrocodone/acetaminophen product and received Darvocet N 100 (propoxyphene napsylate 100 mg and acetaminophen 650 mg/tablet) for one to two doses before resuming the hydrocodone/acetaminophen product. Primarily in the form of hydrocodone/acetaminophen, the patient self-administered 18.25-18.9 gm of acetaminophen over 48 hours, plus an additional 750 mg four to eight hours later. The amounts ingested were verified by the medical examiner by counting the remaining doses of medication and through a medication log kept by the patient. While at home, she developed nausea, vomiting, itching, lethargy, confusion, jaundice and decreased urine output. Her initial laboratory values were: ALT 8,579 IU/L, AST 12,915 IU/L, creatinine 4.1 mg/
function tests were abnormal following the extended concentrations that exceeded five times the upper limit of normal and more than 19% had ALT concentrations that exceeded three times the upper limit of the reference range. However, more than 33% of the acetaminophen-treated subjects had the therapeutic concentration. However, more than the trough acetaminophen concentrations exceeded intermittently over the 14 day study period. None of the acetaminophen and acetaminophen concentrations were obtained 14 consecutive days. Serum liver function tests of medications and placebo were administered over daily acetaminophen total dose of four grams. The study was a double-blind, placebo-controlled, parallel-group design with the three dosing regimens (oxycodone, hydromorphone, morphine). Each treatment arm included the ingestion of acetaminophen 1,000 mg every six hours (the actual prescription indicated that the ingestion of more than four grams of acetaminophen in a 24-hour period of time) of acetaminophen may cause hepatotoxicity of varying degrees. Even maximum therapeutic daily doses of four grams for a prolonged period of time have been associated with liver function aberrations (but not clinical toxicity).

Watkins, et al. conducted a randomized, single-blind, placebo-controlled, parallel five treatment group longitudinal study of 145 healthy adults [2]. The researchers were alarmed at the high incidence of unintentional overdosage and the fact that even therapeutic daily doses that did not exceed four grams resulted in acute hepatic failure. Contrary to the Watkins study, no patients had AST or ALT values that exceeded two times the upper limit of the reference values [3]. The same research group performed a retrospective analysis of patients who received acetaminophen for the treatment of osteoarthritis in seven clinical trials [4]. The patients (1,039) received 1,950-4,000 mg daily for periods of four weeks to 12 months. There were no reports of symptomatic hepatotoxicity, but 17.4% of patients had an ALT value that exceeded the upper limit of the reference range. However, the validity of the patient histories must be considered and it is unlikely that the doses of acetaminophen were reported accurately.

A study that was conducted by Schiødt, et al. examined the medical records of all patients who were hospitalized for the management of excessive acetaminophen ingestion [7]. Seventy-one patients met the study criteria and 50% were identified as having poisoned themselves accidentally with acetaminophen. Histories were available in 81% of those with the unintentional overdoses. Their mean dose was 11 gm and three patients ingested four grams or less in a 24-hour period. They had a mean peak ALT concentration of 2557 IU/L and a mean

Discussion

This patient interpreted the prescription literally and initiated self-therapy with two tablets of the hydrocodone/acetaminophen product every four hours (the actual prescription indicated that the patient should take ‘1-2 tablets every 4-6 hours as needed’). Over a 48-hour period she ingested 18.25-18.9 gm of acetaminophen, plus an additional 750 mg four to eight hours later--significantly in excess of the maximum recommended daily dose of four grams. While fatalities such as this are uncommon, there is a growing body of evidence that the repeated supratherapeutic ingestion (defined as the ingestion of more than four grams of acetaminophen in a 24-hour period of time) of acetaminophen may cause hepatotoxicity of varying degrees. Even maximum therapeutic daily doses of four grams for a prolonged period of time have been associated with liver function aberrations (but not clinical toxicity).

Watkins, et al. conducted a randomized, single-blind, placebo-controlled, parallel five treatment group longitudinal study of 145 healthy adults [2]. The research subjects received a placebo, acetaminophen, and each of three acetaminophen-opioid combinations (oxycodone, hydromorphone, morphine). Each treatment arm included the ingestion of acetaminophen 1,000 mg every six hours, with a daily acetaminophen total dose of four grams. The medications and placebo were administered over 14 consecutive days. Serum liver function tests and acetaminophen concentrations were obtained intermittently over the 14 day study period. None of the trough acetaminophen concentrations exceeded the therapeutic concentration. However, more than 33% of the acetaminophen-treated subjects had ALT concentrations that exceeded three times the upper limit of normal and more than 19% had ALT concentrations that exceeded five times the upper limit of normal. None of the subjects developed overt hepatotoxicity, but it is significant that liver function tests were abnormal following the extended use of acetaminophen in maximal therapeutic doses.

Temple and colleagues studied aminotransferase activity in 37 (36 completed the study) healthy subjects who received acetaminophen doses of 4 gm, 6 gm, and 8 gm daily for three days [5]. The study was a double-blind, placebo-controlled, parallel-group design with the three dosing regimens. AST and ALT concentrations were measured at multiple times. The hepatic aminotransferases remained within the normal reference value range throughout the study.

Larson, et al. conducted a multi-center prospective analysis of 662 patients who developed acetaminophen-induced acute liver failure [6]. Within the cohort, 275 patients met the study criteria and 131 of the patients (48%) were identified as having ingested the acetaminophen excess unintentionally. The patients in the unintentional overdose category ingested a mean total dose of 20 gm and an average daily dose of 7.5 gm. Nineteen (7%) of the patients reported that they had not exceeded daily doses of four grams and 16 had ALT concentrations that were in excess of 1,000 IU/L. Approximately 63% had ingested an acetaminophen/opioid combination product. The researchers were alarmed at the high incidence of unintentional overdosage and the fact that even therapeutic daily doses that did not exceed four grams resulted in acute hepatic failure. However, the validity of the patient histories must be considered and it is unlikely that the doses of acetaminophen were reported accurately.
peak AST of 7,430 IU/L. Approximately one-third of the unintentional group ingested acetaminophen in the form of an acetaminophen/opioid product. The study attempted to establish an association between the use of alcohol and acetaminophen overdosage, but this could not be validated.

A prospective poison center study by Daly, et al. of 277 (249 met the study criteria) consecutive patients who ingested supratherapeutic (defined as greater than four grams per 24 hours) doses of acetaminophen revealed that an average daily dose of as little as 9.6 grams for a median duration of 48 hours was capable of producing hepatotoxicity [8]. At initial presentation 18.9% had AST concentrations of 50-1,000 IU/L (mean dose = 11.7 gm; range 9.6-13.8 and in 7.2% the AST exceeded 1,000 IU/L. The AST was less than 50 IU/L in 50.6% of patients, but one-half of those patients also received acetylcysteine therapy which may have influenced their outcome by reducing morbidity.

Dart and Bailey conducted a systematic review of the medical literature to determine the occurrence of liver failure in subjects who participated in prospective trials that involved the repeated use of therapeutic doses of acetaminophen (30,865 subjects) and compared the data to retrospective case reports (9,337 patients) involving the same type of acetaminophen use [9]. In the prospective trials 0.4% had an aminotransferase activity that exceeded the upper limit of normal and there were no cases of hepatic failure or death. In the retrospective cohort, 1% had elevated transaminases, 0.01% (1 patient) had a liver transplant and 0.06% (6 patients) died. A limitation of the retrospective series may have been inaccurate reporting of the ingested dose.

Supratherapeutic doses of acetaminophen have been used in double-blind, randomized, placebo-controlled trials for the management of body temperature in stroke victims [10,11]. The standard protocol incorporated the administration of acetaminophen 1,000 mg six times per day for five days. Liver function abnormalities were reported in six of 26 patients, but the actual AST and ALT values were not reported [11]. A prospective study by den Hertog and colleagues evaluated the use of acetaminophen in 697 stroke patients who received acetaminophen 6000 mg daily for three days [12]. None of the patients experienced liver enzyme disturbances and there were no cases of acute liver failure.

It is apparent from these studies that the prolonged use of maximal therapeutic doses of acetaminophen may be associated with aberrations in aminotransferase concentrations, but overt hepatotoxicity appears to be a rare phenomenon. However, as illustrated by this patient, supratherapeutic acetaminophen ingestion can be associated with grave consequences. This is supported by the growing body of evidence that indicates that unintentional supratherapeutic dosing may increase the risk of symptomatic hepatotoxicity. The supratherapeutic ingestion may be the consequence of misprescribing of the drug by a physician, failure of the pharmacist to identify the potential toxicity of the prescription as written or the misuse of an acetaminophen-hydrocodone prescription by the patient.

To prevent unintentional acetaminophen-induced hepatotoxicity from the supratherapeutic ingestion of acetaminophen-opioid combination products, a number of proactive steps should be taken. Physicians must be aware of the dose of acetaminophen in the opioid combination products and write the prescriptions properly to insure that the patient does not self-administer in excess of four grams of acetaminophen daily. When a prescription is written for the patient to take one-two tablets every four to six hours as needed for pain, it gives the patient the prerogative of using two tablets every four hours. To rectify that, each prescription should include the maximum number of doses that may be taken during any 24 hour period. For example, “Take 1-2 tablets every 4-6 hours as needed for pain, not to exceed 5 tablets per 24-hour period.” The United States Food and Drug Administration (FDA) notified healthcare professionals that it has asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit [13]. This should reduce the risk of inadvertent acetaminophen toxicity. Furthermore, both the physician and pharmacist should inform the patient that the pain-reliever contains acetaminophen and that no other acetaminophen-containing products should be used while taking the acetaminophen-opioid combination product. When the prescription is written improperly, the pharmacist should alert the physician that the prescription as written allows for a potential overdose of acetaminophen and recommend that it be amended and clarified to protect the patient.

**Conclusions**

This patient died from a supratherapeutic ingestion of acetaminophen that was contained in an acetaminophen/hydrocodone combination product. While these deaths are uncommon, they can be prevented if the prescriptions for these products are written and dispensed properly and if patients are warned not to exceed the proper dosage recommendations.
References


