

Commentary on: Borrows DL, Hagardorn AN, Harlan GC, Wallen EDB, Ferslew KE. A fatal drug interaction between oxycodone and clonazepam. *J Forensic Sci* 2003;48(3):683–86.

Sir:

We read with interest the paper by Burrows, et al. describing a reported fatal drug interaction between oxycodone and clonazepam (Klonopin®) (1). We believe that the classification of this death as a lethal drug interaction between oxycodone and clonazepam is not the most appropriate interpretation of the data presented.

The designation of a fatality as a lethal drug interaction is a diagnosis of exclusion; other plausible causes of the death must be ruled out, leaving the alleged interaction as the most likely explanation. The concept of a drug interaction implies that a pharmacokinetic or pharmacodynamic effect has occurred that would not occur with either drug alone. We believe that the data presented do not meet these criteria and therefore do not support the conclusion.

The authors seem to base their statement of a fatal drug interaction on a metabolic interaction between oxycodone and clonazepam. They state that the oxycodone concentration reported appears to exceed what would be expected from a normal therapeutic dose as a result of the inhibition of its metabolism by the concomitant ingestion of clonazepam. Specifically, they suggest the competitive inhibition of CYP3A4 by clonazepam as the possible mechanism resulting in increased oxycodone concentrations.

Enzyme inhibition may depend on many factors including the concentrations of both substrate and inhibitor, K_m and K_i . We were unable to locate any reports indicating clonazepam is a CYP3A4 inhibitor. It is not known if inhibiting CYP3A4 increases oxycodone concentration, even if clonazepam is an effective inhibitor of the enzyme at the concentrations reported. It is not even established that CYP3A4 mediates the metabolism of oxycodone (the authors cite only an unreferenced internet editorial as support for this statement). It was shown in 1998 that inhibition of CYP2D6, the primary enzyme involved in the conversion of oxycodone to oxymorphone, did not significantly alter the pharmacodynamic effects of oxycodone (2). Therefore, it is even less likely that inhibition of a proposed minor metabolic pathway would have a fatal outcome. Further, the hepatic pathology described for the decedent suggests that the metabolic capacity of any CYP450 isozyme may well have been diminished at baseline. There are no data, new or published, to support enzyme inhibition as a mechanism of toxicity in the present case.

The authors report that the oxycodone concentration in the decedent exceeded that which is expected from a normal therapeutic dose of the drug. However, it is also stated that the decedent was a drug abuser. As such, she would likely be able to tolerate much higher concentrations of oxycodone than a narcotic-naïve individual. Empiric correlation of blood concentration with an alleged fatal pharmacodynamic effect without considering this crucial part of the history is inappropriate.

Multiple blood specimens as well as vitreous humor were obtained during autopsy of the decedent. However, the results for each sample were not presented. The authors state that the concentrations reported for clonazepam and oxycodone accurately reflect antemortem concentrations because femoral blood was used in the analysis. This may not be the case. Published data demonstrate that oxycodone concentrations in heart blood may be higher, lower or roughly the same as femoral blood oxycodone concentrations (3,4). No reports exist in which human antemortem and postmortem concentrations of oxycodone were correlated and no specific conclusions regarding pharmacologic effects can be drawn solely from the measured concentrations.

The simultaneous abuse of benzodiazepine and opioid medications is a common toxicologic problem. Pharmacologic depression of the central nervous system from these medications is well established. In fact, this combination of drugs is exploited in conscious sedation and to induce general anesthesia. Further, it is known that persons receiving treatment with opioids and benzodiazepines together can die if improperly managed. However, this represents the direct result of intended pharmacologic effects of the medications, not a drug interaction.

The simple effects of each drug alone are easily sufficient to account for this patient's demise. This conclusion is supported by previous publications. Drummer reported nine deaths alleged to be secondary to oxycodone poisoning (5). All nine cases had other drugs present in addition to oxycodone including three in which benzodiazepines were also found. Anderson reviewed 27 cases of oxycodone deaths determined to be of OxyContin use (3). Six of the cases also involved benzodiazepines while in only two of the 27 cases oxycodone was the sole medication detected. Two other cases had oxycodone present in addition to both benzodiazepines and trazodone.

Finally, the reader should be aware that the statement: "Six billion prescriptions were written for OxyContin in the year 2000..." is incorrect. According to the United States Census Bureau, the population of Earth in the year 2000 was only 6.1 billion people (6). According to Purdue Pharma, the manufacturer of OxyContin®, 5,932,981 prescriptions for this drug were written in the year 2000 (7).

We agree that it is likely that the drug ingestions were responsible for this patient's death. However, it is not necessary to hypothesize that a drug interaction occurred. Indeed, the existing data and previous reports indicate that this is not the case. We believe the readers of the *Journal of Forensic Sciences* should not conclude that there is an established drug interaction between oxycodone and clonazepam.

References

1. Burrows DL, Hagardorn AN, Harlan GC, Wallen EDB, Ferslew KE. A fatal drug interaction between oxycodone and clonazepam. *J Forensic Sci* 2003;48:683–6. [PubMed]
2. Heiskanen T, Olkkola KT, Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther* 1998;64:603–11. [PubMed]
3. Anderson DT, Fritz KL, Muto JJ. Postmortem case examples involving Oxycontin®. Society of Forensic Toxicologists (SOFT) Annual Meeting 2001; New Orleans, LA.
4. Dalpe-Scott M, Degouffe M, Garbutt D, Drost M. A comparison of drug concentrations in postmortem cardiac and peripheral blood in 320 cases. *Can Soc Forensic Sci J* 1995;28:113–21.
5. Drummer OH, Syrjanen ML, Phelan M, Corder SM. A study of deaths involving oxycodone. *J Forensic Sci* 1994;39:1069–75. [PubMed]
6. US Census Bureau: Total Midyear Population for the World: 1950–2050. <http://www.census.gov/ipc/www/worldpop.html> 2003.
7. Schnoll S. Personal Communication. Stamford, CT: Purdue Pharma, LP, September 2, 2003.

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