J Forensic Sci, May 2004, Vol. 49, No. 3
Paper ID JFS2003344
Published 7 April 2004
Available online at: www.astm.org

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:

This letter is in response to information published within a case report written by David L. Burrows et al. in the May 2003 issue of *J Forensic Sci* (1). We credit the authors for bringing to light the potentially fatal consequence of the concomitant abuse of two central nervous system (CNS) depressant drugs, such as oxycodone and clonazepam, as there may be an under-appreciation of such a risk. The risk of fatal overdose is indeed substantially increased when opioids are abused in combination with other CNS active drugs (2). However, in the article, titled "A fatal drug interaction between oxycodone and clonazepam," the authors provide a table with OxyContin® (oxycodone HCl controlled-release) pharmacokinetic and dosage information (Table 1) that is inaccurate and potentially misleading.

In Table 1, the authors state that the maximum daily dose of OxyContin is 20–23^0 mg/day (20–23^0 mg/day?), depending on formulation given or opioid tolerance, and that therapeutic plasma concentrations are 0.01–0.16 μg/mL. However, as stated in the professional prescribing information for OxyContin, with pure opioid agonist analgesics, like oxycodone, there is no defined maximum dose. Rather, the dose is titrated to analgesic effectiveness, with unmanageable side effects sometimes being the dose-limiting factor. The more serious side effects may include somnolence and respiratory depression. Like with all pure opioid agonist analgesics (morphine, hydromorphone, oxycodone, fentanyl), with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics (3).

Taking into consideration that there is no maximum daily dose for OxyContin tablets and the wide range of factors that can affect analgesia in a patient (tolerance, severity of pain, disease progression), suggesting a maximum daily dose is inaccurate. The reported daily doses during OxyContin clinical trials ranged from 20 mg to 1360 mg in patients with both cancer and noncancer pain (3,4).

The authors also listed the therapeutic plasma concentration of oxycodone as 0.01–0.16 μg/mL and the toxic plasma concentration as 0.2–5.0 μg/mL in Table 1. As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance (3). As such, an accurate estimate of therapeutic or toxic plasma oxycodone concentrations cannot be determined.

The authors also state in Table 1 that the lethal plasma concentration of OxyContin is 4.3–14 μg/mL (0.4–2.7 μg/mL when combined with other CNS depressants). Given the information stated above regarding a lack of a maximum daily dose for oxycodone, it would be as impossible to determine a lethal plasma concentration, as it would a therapeutic or toxic plasma concentration. In several published reports where only oxycodone was found at autopsy, the reported femoral or peripheral oxycodone concentrations ranged from 0.12–8.0 mg/L (μg/mL) (5–7). In cases of polysubstance abuse, where oxycodone is a contributing factor, the range is <0.10 mg/L to 15.00 mg/L (5–8). Thus, the lethal concentration of oxycodone cannot be accurately determined due to several factors, including interpatient variability of analgesic doses, sampling site, degree of tolerance to respiratory depressant effects of opioids, intake of concomitant drugs or alcohol and postmortem redistribution. In the case series mentioned above (2), blood oxycodone concentrations were significantly higher in single drug deaths, as compared with multiple drug deaths (7).

The points presented here highlight the complexity of interpreting antemortem and postmortem oxycodone concentrations as therapeutic, toxic, or lethal. Multiple factors besides postmortem plasma concentrations should be considered when determining which substance or substances were the causes of a drug abuse death.

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