Buprenorphine-Related Deaths: Low Levels may be Significant

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AIMS: Buprenorphine is a partial mu-opioid receptor agonist, and is used for the treatment of moderate to severe chronic pain, but has also been introduced as an alternative to methadone in opiate substitution therapy. Some years after its introduction on the Swedish market, illegal use of buprenorphine started, and several deaths involving buprenorphine have been documented in Sweden. The aim of this study was to explore the femoral blood and urine levels in buprenorphine-positive cases, and to compare these concentrations with those observed in driving under the influence cases (DUI).

METHODS: A slightly modified previously published LC-MS/MS method (Kronstrand et al, JAT 2003;27:464-70) was used to determine buprenorphine on both postmortem cases and DUI cases where subjects either were prescribed buprenorphine, or when abuse was suspected.

RESULTS: The mean ± SD buprenorphine concentrations in postmortem femoral blood (all cases, n = 32) and in blood from DUI cases (n = 94) were 3.1 ± 4.7 and 1.6 ± 1.8 ng/g, respectively. The overlap was substantial both for buprenorphine and norbuprenorphine levels. Additionally, in four postmortem cases, where intoxication was ruled out (causes of death: hanging = 2, pulmonary embolism = 1 and severe liver cirrhosis = 1), the mean (median) concentration was 7.8 (4.3) ng/g. Hence it seems impossible to define a fatal level. It may be argued that buprenorphine was actually not involved at all in any of these deaths, explaining these toxicological results. However, in at least eleven of the intoxication cases, buprenorphine was apparently the most suspected drug based on circumstances, and the yet the mean ± SD were only 2.0 ± 2.0. Further, these subjects typically presented with massive pulmonary edema with lung weights averaging 1394 ± 312 g as compared to 1142 ± 297 g in postmortem controls (hangings, n = 1,979), and often with froth in the airways, suggesting that an overstimulation of the mu-opioid receptors in the brain stem resulting in respiratory depression as the basic mechanism for their demise. No other opioid drugs were present in their blood. The ratio norbuprenorphine to buprenorphine in postmortem cases (mean 1.15) was similar to that in DUI cases (mean 1.55), but in 20 of the postmortem cases the buprenorphine concentration was higher than that of norbuprenorphine suggesting recent intake. In addition, urine analysis indicated a period of abstinence before the last dose.

CONCLUSIONS: In eleven postmortem cases effects of buprenorphine was considered the main cause of death even though the blood concentrations were comparable to those of DUI cases and postmortem controls. This corroborates the notion that interpretation of postmortem levels of opioid drugs warrants caution and comprehensive review of each case.

Keywords: Buprenorphine, Intoxication, Postmortem