K23 Bupropion and Its Metabolites in Twenty-Nine Postmortem Cases

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This presentation will impact the forensic community and/or humanity by assisting forensic pathologists and toxicologists in evaluation of postmortem concentrations of bupropion and its metabolites.

Bupropion is a unique antidepressant unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitors or other antidepressant agents. It is also widely prescribed at low doses for smoking cessation. Bupropion is extensively metabolized via hydroxylation of the tert-butyl side chain to morpholinol-bupropion (M), and via reduction of the carbonyl group to the amino-alcohol isomers, threohydrobupropion (Threo) and erythrohydrobupropion (Erythro). Animal studies have demonstrated the morphinol and the amino-alcohol metabolites have approximately 50% and 20% the antidepressant activity of bupropion, respectively. Postmortem toxicological finding have been reported in only a few overdose cases.

We present the postmortem blood and liver bupropion and bupropion metabolite toxicology findings in 29 deaths: 10 cases of massive ingestion of bupropion where the drug was considered a major contributor to fatal drug overdose; 13 cases of fatal mixed drugs intoxication where there was little indication of excessive bupropion ingestion; and 6 cases of death by natural causes where the decedent was receiving bupropion. Bupropion and its metabolites were isolated from alkalized blood and liver specimens by liquid/liquid extraction with n-butyl chloride/ether mixture. Extracts were back-extracted into acid, extracted with hexane for cleanup and following sample alkalization isolated with butyl chloride. The residues were then analyzed by GC/MS with separation in a DB-5MS column (15m x 0.25mm id x 25 *u*m film thickness) at the following temperatures: initial, 70ºC; ramp, 15ºC/min; finial 250ºC; yielding retention times: bupropion, 7.13; Erythro, 7.87; Threo, 7.98; M, 8.89 and alphaprodine (IS), 8.73 min. Ions monitored for bupropion, Erthyro, and Threo were 44/100/139 m/z; for M, 44/116/224 m/z; and IS, 172/187 m/z. Typical calibrations for all bupropion analytes were from 0.20 - 4.0mg/L. Heart or aorta bupropion and metabolite blood values are given in Table 1 and liver values in Table 2. Femoral blood or other blood specimens from peripheral sites were also analyzed.

Table 1. BLOOD Mean, mg/L (Range, mg/L)

	Bupropion	Erythro	Threo	Morpholinol
Overdose	2.7 (0.28-7.4)	1.4 (0.5-2.8)	11 (2.5-27)	3.1 (1.7-4.2)
Incidental	0.37 (0.1-0.65)	0.43 (0.27-1.1)	2.1 (0.34-5.6)	0.79 (0.57-1.4)
Natural	0.43 (0.26-0.60)	0.51 (0.39-0.75)	2.6 (1.8-4.1)	0.65 (0.51-0.77)

Table 2. LIVER Mean, mg/Kg (Range, mg/Kg)

	Bupropion	Erythro	Threo	Morpholinol
Overdose	5.6 (1.3-16)	6.6 (6.4-15)	81 (40-160)	18 (3.7-61)
Incidental	2.0(0.6-5.4)	2.6 (1.0-4.5)	12 (3.6-50)	4.4 (0.73-17)
Natural	0.59 (0.3-0.7)	2.4 (1.4-4.6)	15 (7.0-17)	2.5 (1.0-5.9)

Only one of the overdose cases was due to bupropion as a single agent. In the other nine bupropion overdose cases, at least one other drug was present in significant toxic amounts; 8 cases involved other antidepressants and 1 involved opiates. Obviously, other drugs were present in the 13 bupropion incidental cases; 9 involved at least one opiate. Comparing blood bupropion data from heart/aorta with peripheral sites revealed no significant postmortem redistribution in these cases. In general, parent bupropion values in blood and liver are good indicators of overdose. Additionally, liver Threo concentrations provide a good discriminater between overdose and therapeutic use. In fatal poisoning, bupropion is seldom encountered as the single causative agent.

Bupropion, Bupropion Metabolites, Fatal Poisoning

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