K41 Determination of Clozapine and Desmethylclozapine in the Postmortem Blood of a Schizophrenic Patient

Nikolas P. Lemos, PhD, Michelle Moreton, BSc, Jennifer S. Button, BSc, Terry D. Lee, and David W. Holt, DSc, Forensic Toxicology Service, St. George's Hospital Medical School, London, England SW17 0RE, United Kingdom*

Attendance at this presentation will enable the participant to study a toxicological case involving the determination of clozapine and its metabolite, desmethylclozapine, in the blood of a schizophrenic patient who suddenly collapsed and died after recently switching to this medication. The presentation will also enable the participant to learn how such cases are processed by the Forensic Toxicology Service in London, UK.

This presentation is important to the toxicological and analytical community as it is the first such case in our London Service involving a possible toxicological involvement of clozapine. Our determination of clozapine and metabolite in the case blood specimen levels appears to be in agreement with previously published data on the significant postmortem redistribution of clozapine. Our findings, when considered in the light of data from the drug manufacturer's therapeutic drug monitoring scheme, do not support the hypothesis that clozapine was directly involved in this death, despite the apparently high concentrations of the drug and its metabolite, probably due to the significant post-mortem redistribution.

The Forensic Toxicology Service offers a screening and quantification toxicology service to most of Her Majesty's Coroners and Forensic Pathologists in London as well as various Police Forces and one branch of the Armed Forces. As a result, we are required to screen for a large number of prescribed and illicit drugs in post-mortem specimens followed by quantification of those detected. All analyses must be completed and our final report must be submitted to the Courts within 15 business days of the arrival of the case at the Service. This case was presented to the Service in November 2002 and involved a 40-year-old Caucasian female with a history of schizophrenia who was committed under the UK's Mental Health Act. The deceased collapsed and died only 15 days after switching to this medication under medical supervision.

We were requested to analyze an unpreserved post-mortem blood specimen from the deceased using our standard alcohol and illicit drug screens, in order to facilitate HM Coroner in his Inquest into this woman's unexplained death. No other biological specimens were available.

Using appropriate calibrators, the case blood specimen was screened for alcohol and determined to be negative. Similarly, paracetamol (i.e., acetaminophen) and salicylates were not detected. Using our standard liquid-liquid drug extraction scheme for basic (i.e., alkaline) drugs followed by gas chromatography – mass spectrometry (GC-MS), we were able to identify clozapine and its major metabolite, desmethylclozapine, in the blood sample. When quantified by GC-MS using appropriate calibrators and controls, blood clozapine was determined to be 0.8 mg/L and blood desmethylclozapine measured 0.3 mg/L. Using our benzodiazepine screen by HPLC-MS-MS no benzodiazepines or metabolites were detected in the blood specimen. No amphetamines, methadone, opiates or cocaine were detected in the sample.

Clozapine is prescribed in the United Kingdom as an antipsychotic drug to treat schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs. It is prescribed in tablet form (25 or 100 mg) under the trade name Clozaril®. Patients on clozapine must be closely supervised and must participate in a therapeutic drug monitoring scheme sponsored by the drug manufacturer. Amongst clozapine's side effects are cardiac disorders such as arrhythmia, pericarditis, myocarditis, delirium and tachycardia.

After reviewing the scientific literature, it became apparent that it is most unusual for a patient to collapse and die within 15 days of switching to clozapine therapy. Although the measured concentrations of clozapine and its metabolite initially appeared relatively high, it is now well established that these substances undergo significant post-mortem redistribution and their concentrations increase several-fold after death (Flanagan et. al., 2003). Our case is important to the toxicological and analytical community as it is the first such case in our London Service involving a possible toxicological involvement of clozapine. Our determination of clozapine and metabolite in the case blood specimen levels appears to be in agreement with previously published data on the significant post-mortem redistribution of clozapine. Our findings, when considered in the light of data from the drug manufacturer's therapeutic drug monitoring scheme, do not support the hypothesis that clozapine was directly involved in this death, despite the apparently high concentrations of the drug and its metabolite, probably due to the significant postmortem redistribution.

Clozapine, Desmethylclozapine, GC/MS

 ** Presenting Author*