



Disturbances of glucose metabolism associated with the use of psychotropic drugs: A post-mortem evaluation



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ABSTRACT

Treatment with atypical antipsychotic agents and tetracyclic antidepressants has been associated with impaired glycemic control. Reported complications have included new-onset diabetes mellitus, life-threatening diabetic ketoacidosis and, rarely, death. The study presented herein focuses on biochemical investigations of glucose metabolism in a series of medico-legal cases that revealed the presence of atypical antipsychotic agents (clozapine, olanzapine, quetiapine and risperidone) or mirtazapine at toxicology. Two different approaches were used. In one, 55 forensic autopsy cases (characterized by the presence of clozapine, olanzapine, quetiapine, risperidone and mirtazapine toxicologically identified) were retrospectively selected. In the second approach, 20 forensic autopsy cases that had a cause of death attributed to diabetic ketoacidosis were retrospectively selected. The combination of the results obtained from the first and second approaches allowed only one case of possibly drug-induced glucose metabolism disturbance (in one individual treated with mirtazapine who was not known to suffer from diabetes mellitus) to be identified. Though our results could raise the question of the benefit of systematizing postmortem biochemical investigation in situations of sudden death involving individuals treated with psychotropic drugs, the study stresses the importance of investigating all potentially relevant data (including the overall knowledge of medication history) in order to formulate appropriate hypotheses concerning the cause and pathogenesis of death.

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1. Introduction

Treatment with atypical antipsychotic agents (such as clozapine, olanzapine, quetiapine and risperidone) and tetracyclic antidepressants (such as mirtazapine) has been associated with impaired glycemic control. Reported complications have included insulin resistance, impaired glucose tolerance, new-onset diabetes mellitus, life-threatening diabetic ketoacidosis and, rarely, death [1–15].

Mechanisms postulated to account for drug-induced glucose metabolism impairment would include sympathetic nervous system dysregulation and insulin resistance secondary to drug-induced weight gain. Indeed, even at low doses quetiapine treatment has been associated with significant weight gain and metabolic syndrome. Risperidone may also cause weight gain and/or associated metabolic problems, though less frequently than clozapine, olanzapine and quetiapine. Furthermore, acute

pancreatitis and new-onset diabetes mellitus that may have been associated with mirtazapine therapy have been described in clinical trials and case reports [2,3,16–21].

A review of relevant forensic literature revealed a certain number of fatalities due to diabetic ketoacidosis in diabetic and nondiabetic individuals receiving antipsychotic drugs, including some suggestive of medication-associated ketoacidosis [4,22–24].

However, apart from the study by Ely et al. [4] pertaining to 17 deaths with hyperglycemia and ketoacidosis in the setting of antipsychotic therapy, most reports concern single or few cases with postmortem biochemical investigations mainly limited (though not systematically) to vitreous glucose, blood ketone and blood glycosylated hemoglobin measurements.

The study presented herein focuses on biochemical investigations of glucose metabolism in a series of medico-legal cases that revealed the presence of atypical antipsychotic agents (clozapine, olanzapine, quetiapine and risperidone) or mirtazapine at toxicology. Our aim was to identify possible situations of drug-induced glucose metabolism disturbances so as to ascertain the relevance of the observed biochemical results in the pathogenesis of death.

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2. Materials and methods

2.1. Study design and study populations

The present study was performed during 2010–2015 and was designed as a retrospective study. All cases collected for the study underwent medico-legal autopsies as requested by local inquiring authorities. Biochemical investigations and toxicology were performed as part of medico-legal investigations.

Two different approaches were used. In one, 55 forensic autopsy cases (34 male subjects and 21 female subjects between 24 and 69 years of age) were retrospectively selected. All had undergone medico-legal autopsies, toxicology and biochemistry. Postmortem interval was defined as the interval between death and peripheral blood/vitreous humor sampling and ranged between 12 and 48 h. The presence of clozapine, olanzapine, quetiapine, risperidone and mirtazapine (and/or their metabolites) in femoral blood and/or urine was toxicologically identified (each substance considered individually or in combination, irrespective of the measured concentration).

In the second approach, 20 forensic autopsy cases of death attributed to diabetic ketoacidosis (11 male subjects and 9 female subjects between 26 and 67 years of age), were retrospectively selected at the same time as the first. In accordance with previous observations, diabetic ketoacidosis was determined to be the cause of death when blood beta-hydroxybutyrate levels were higher than 2500 $\mu\text{mol/l}$, vitreous glucose concentrations above 10 mmol/l and alternative causes of death/alternative causes of increased ketone body production were excluded based on all postmortem investigation findings.

All these cases had undergone medico-legal autopsies, toxicology and biochemistry. Postmortem interval was defined in the same way as in the first approach. The interval between death and peripheral blood/vitreous humor sampling ranged between 14 and 50 h. The aim was to assess whether these cases were also characterized by the presence of clozapine, olanzapine, quetiapine, risperidone and/or mirtazapine (and/or their metabolites) in femoral blood and/or urine (each substance considered individually or in combination, irrespective of the measured concentration).

All cases selected for this study originated from forensic practice with deaths occurring outside the hospital. Medical records and clinical histories of the deceased as well as police reports were consistently reviewed before conclusions were made.

Case inclusion criteria for both studied groups included the presence of both postmortem biochemistry and toxicology results as well as availability of all biological samples (vitreous humor, femoral blood and postmortem serum from femoral blood).

2.2. Postmortem investigations

Death and medico-legal autopsy intervals ranged between 14 and 50 h. Medico-legal autopsies, histology, toxicology and biochemistry were performed in all cases. Medical records and clinical histories as well as police reports pertaining to each case were consistently reviewed before conclusions were made.

Conventional autopsies were carried out jointly by two forensic pathologists (at least one board-certified) as in accordance with both local standards and international guidelines for medico-legal autopsies.

Peripheral blood from the femoral veins, cardiac blood, vitreous humor, urine, bile, cerebrospinal and pericardial fluids as well as gastric contents, hair and samples of certain tissues (liver, brain and skeletal muscle) were systematically collected for toxicological and biochemical analyses.

Conventional histology was systematically performed and included hematoxylin–eosin (HE) stain of brain, heart, lung, liver and kidney samples.

Systematic toxicological analysis based on the use of chromatographic techniques and mass spectrometry was systematically carried out.

In all cases, biochemical investigations included determination of vitreous glucose, femoral blood glycated hemoglobin, acetone and beta-hydroxybutyrate.

2.3. Vitreous humor, femoral blood and postmortem serum from femoral blood collection

Undiluted vitreous humor samples (between 1 and 3 ml) were obtained by aspiration using a sterile needle and syringe. Right and left vitreous samples were collected through a scleral puncture at the lateral canthus, aspirated from the center of each eye, pooled in the same syringe and mixed together. After collection, vitreous samples were immediately centrifuged at $3000 \times g$ for 15 min. The separated supernatant was collected and stored in preservative-free tubes. All samples were transferred to the laboratories immediately after collection. When analyses were delayed, samples were stored at -20°C .

Peripheral blood from the femoral veins was systematically collected for toxicological and biochemical analyses prior to autopsy. Femoral blood samples were collected by aspiration with sterile needles and syringes from the femoral vein(s). Blood samples were drawn after clamping the vein(s) at the proximal end and keeping the lower limb(s) raised for several minutes. Samples were transferred to the laboratories immediately post collection. When analyses were delayed, samples were stored at -20°C .

2.4. Postmortem biochemistry investigations

Glucose was analyzed in vitreous humor on the Roche Modular P clinical chemistry system (glucose hexokinase method, Roche Diagnostic, Mannheim, Germany).

Beta-hydroxybutyrate concentrations were determined on a Cobas Mira Plus (Roche Diagnostics, Switzerland) by an enzymatic photometric method adapted in house from the technique described by Ruell and Gass. Refrigerated or frozen femoral blood samples were thawed overnight at 4°C and deproteinized with perchloric acid. Supernatant was used for analysis.

Blood acetone values were routinely determined by the use of headspace gas chromatography coupled to flame ionization detector (HS-GC-FID) on an Agilent 1888 headspace and a 6850 GC (Palo Alto, CA, USA). Blood samples were incubated over 20 min at 80°C and were injected into GC. Analyses were performed on blood stored in tubes containing sodium fluoride.

Glycated hemoglobin was determined on whole blood samples (stored in tubes containing EDTA) by ion-exchange high-performance liquid chromatography (HPLC) (Bio-Rad D-10 Dual Program, Hercules, CA, USA).

2.5. Ethics

All relevant ethical issues were identified and discussed with the local Ethical Committee. All cases included in this study underwent medicolegal autopsies as requested by the inquiring authorities. Biological fluids and tissue samples are routinely collected during autopsy for toxicological and/or biochemical purposes in our facility. Moreover, toxicology and biochemistry are routinely performed as part of medicolegal investigations. All analyzed samples were anonymized prior to analysis. Approval by the ethics committee to perform toxicology and biochemistry in the selected subjects was therefore unnecessary.

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