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Reference values of lithium in postmortem femoral blood

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ABSTRACT

Introduction: The main recipients of lithium, people diagnosed with bipolar disorder, show an increased mortality in both natural and unnatural causes of death. Based on international data persons diagnosed with bipolar disorder comprise 2.3–9.6% of all suicidal deaths. In cases of suicide among those suffering from bipolar disorder, 17–53% are due to fatal intoxications. Diagnosing fatal intoxications is often challenging, particularly when the reference information needed to interpret the concentration of a drug is lacking or scarce.

Aim: The aim of this study was to establish postmortem femoral blood reference concentrations of lithium, providing both fatal and "normal" postmortem concentrations, as well as to investigate the impact of the mode of intoxication and to study the co-detection of lithium and antidepressant drugs in intoxications and controls.

Method: In Sweden, forensic autopsies are performed in unnatural and obscure deaths. This study included all autopsies in which lithium was found during the study period (1992–2010). Lithium was not included in the regular drug screen, but analysed upon request using flame photometry, ion-selective electrode detection or atomic absorption spectrophotometry. Each case was evaluated according to an established strategy, with strict inclusion and exclusion criteria followed by a multi-observer manual review (Fig. 1, Table 1). The cases included were classified as single intoxications (group A), multi-drug intoxications (group B) or controls (group C). The control group only included cases where death by intoxication and antemortem incapacitation by drugs could be ruled out.

Results and discussion: During the study period, lithium was found in 124 cases. After application of inclusion and exclusion criteria and the subsequent manual review, 21 cases were classified as group A (n = 4), group B, (n = 7) and group C (n = 10). The femoral blood lithium concentrations in group A (median 2.69 mmol/l) and group B (median 2.10 mmol/l) were significantly different (p = 0.01) compared to group C (median 0.2 mmol/l). There were however no statistically significant difference between the concentrations in groups A and B. The most common mode of death in intoxications was acute-on-chronic (n = 10), but the impact of chronic use on the fatal blood concentrations could not be evaluated since there was just one case without previous use. There was no difference in the proportion of co-detections of lithium and antidepressants between intoxication cases and controls.

1. Introduction

Patients diagnosed with bipolar disorder, the main recipients of lithium, display increased mortality with respect to natural causes of death [1]. In addition, studies from different countries show that these patients comprise 2.3–9.6% of all suicidal deaths [2–5] and may have a more than 20-fold increase in suicide rate compared to the general population [6]. In cases of suicide among those suffering from bipolar disorder, 17–53% are due to fatal intoxications [7]. One study has shown an increased rate of suicidal attempts in bipolar patients receiving antidepressant treatment, alone or in combination with lithium, compared with lithium alone [8], however there is currently no consensus as to if bipolar patients prescribed antidepressants are at higher risk for suicide than those not receiving antidepressants [9].

In the clinical setting it is known that intoxications with lithium have a mortality rate of up to 10% [10,11]. The acute symptoms of intoxication are predominantly neurological with reduced consciousness or even coma in serious cases [11–14]. Symptoms

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associated with increasing body lithium levels, consist mainly of fine tremor, vomiting, diarrhea and nausea and may serve as early, although not specific, signs of intoxication [14]. In addition, studies suggest that the mode of intoxication plays an important role in the severity of lithium intoxications, with the symptoms in acute intoxications being less severe than those in chronic intoxications [15–18].

However, making the diagnosis fatal intoxications postmortem is a complicated task. Postmortem redistribution of drugs, bacterial metabolism and sample site variations complicates the interpretation of postmortem blood drug levels [19,20], and for lithium not much such information is available. However, even more important is of course information about the "normal" postmortem blood concentrations of lithium in patients prescribed this drug, to be compared to the concentrations found in certified fatal intoxications. Although a number of publications have provided data on blood lithium levels, most of these are case reports, or small series of cases, gathered in a clinical setting [21–28]. Hence it is difficult to determine whether or not a postmortem blood lithium concentration is "elevated" and possibly fatal using literature data on blood concentrations only.

We have previously published postmortem reference values for a variety of drugs [29], and subsequently assessed particular groups of drugs such as antidepressants [30], sedatives and hypnotics [31] and antipsychotics [32]. In all these studies, we have used a standardized method for collection, handling and analysis of samples, as well as data evaluation, which together with access to a large number of cases, allows for more reliable information about postmortem reference concentrations of pharmaceutical drugs than previously available [29]. The purpose of this study was to use the same strategy to evaluate postmortem femoral blood concentrations of lithium in certified intoxications and in postmortem control cases in order to assist in postmortem investigations of lithium-positive cases. In addition, we also wanted to study the mode of intoxication and the concurrent presence of antidepressant drugs in intoxications and controls in our forensic material.

2. Methods

2.1. Study population

In Sweden all doctors have an obligation to report a death to the police whenever there is a suspicion of an unnatural cause of death (homicide, suicide, accident or undetermined), unknown identity, medical malpractice or unclear circumstances surrounding death. In most of these cases the police will request a forensic autopsy. At autopsy, femoral blood samples are consistently collected and subjected to toxicological screening for alcohols and drugs at the Swedish national forensic toxicology laboratory. Some drugs, including lithium, are analyzed at external laboratories. All forensic medicine departments in Sweden and the national forensic toxicology laboratory use data management systems for the routine casework. Both systems are developed to serve as real-time databases, in which all relevant data about the autopsy findings, the circumstantial information from the police, medical history (when available) and the toxicological results are stored and easily retrieved by automatized searches [33]. This study included all autopsy cases in which lithium (ATC group N05AN01) was detected in femoral blood during the study period (1992–2010).

2.2. Sampling procedures

All femoral blood samples were collected according to a standardized procedure, as described previously [31]. Potassium fluoride was added to each sample at the time of collection in order to counteract bacterial growth. All samples were stored at 4 °C until analyzed, however during transport (1–3 days) to the laboratories the samples may have been exposed to room temperature.

2.3. Analytical method

Lithium was not included in the regular screening program at the National forensic toxicology laboratory in Linköping during the study period, but instead at external laboratories running this analysis on an everyday basis. Lithium was analyzed only upon request by the forensic pathologist, either when suspicion of lithium intoxication was raised, or to exclude lithium toxicity.

In most cases lithium was analyzed with atomic absorption spectroscopy [34], offering a high specificity and a reasonably low limit of detection of 0.05 mmol/l. During different time periods, the analyses were instead performed with ion-selective electrode methodology or flame photometry, but with similar sensitivity and high specificity.

2.4. Selection of postmortem control cases (group C)

The selection procedure has been described in detail previously [32]. In brief, cases in which lithium was found were subjected to a set of inclusion and exclusion criteria based on ICD-9 codes (see Tables 1 and 2). The selection aimed to produce a body of cases in which the subject had an ability to act immediately prior to death, i.e. was not incapacitated by drugs. Following this semi-automated selection procedure an independent manual review by at least two of the authors was performed to identify potential errors or unclear cases. Cases were only included on consensus among the authors.

Drownings were included only if they were witnessed suicidal jump into water; all other cases of drowning, e.g. bodies found dead in a bath tub, were excluded since incapacitation due to drugs could not be ruled out. Cases with suicidal sharp force injuries exclusively to smaller blood vessels were excluded because of the

Table 1
Inclusion criteria for group C based on ICD-9 codes (with supplementary suffices).[a]

Manner of death	Cause of death	Definition
	800–959	Trauma and extraneous bodies in upper and lower airway
	410K	Acute myocardial infarction
	441A	Dissecting aortic aneurysm
	441B, 441D	Ruptured abdominal aortic aneurysm
	994B[b]	Drowning
E953		Suicide, hanging, asphyxiation or suffocation
E955		Suicide, firearms or explosive substances
E956		Suicide, sharp force injuries
E958		Suicide, without further specification

[a] Certain suffices are supplements to the ICD-9 codes defined by the Swedish Medico-legal Society and used by the Swedish forensic pathologists to provide more detailed and specific diagnoses.
[b] Cases of drowning were only included in the study if they were witnessed suicidal jumps into a body of water.