BALTIC MEDICO-LEGAL ASSOCIATION

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Olanzapine: challenges in toxicological results interpretation

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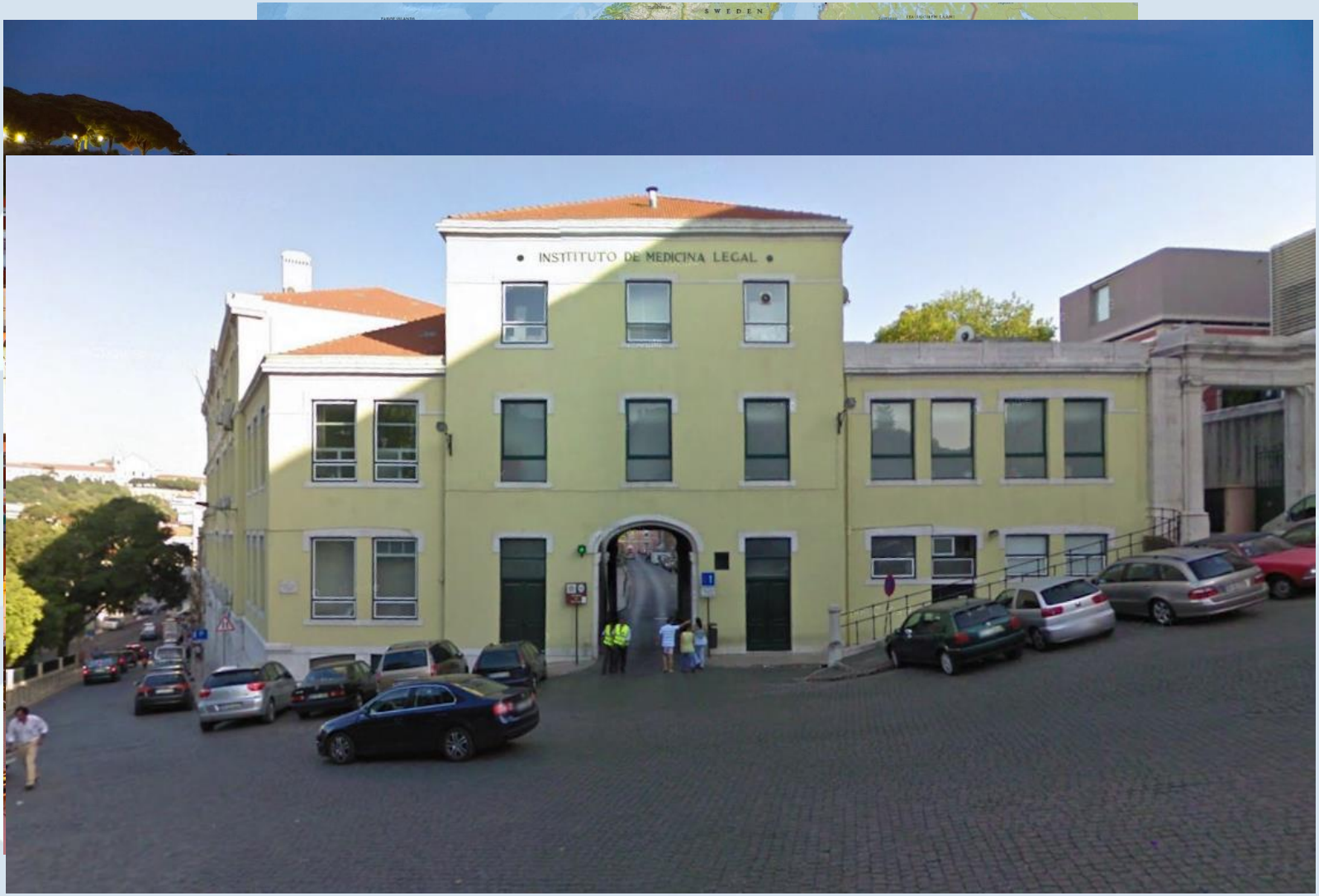


Introduction

- Fatal intoxications are a massive challenge for pathologists all over the world
- Difficulty to determine if and which drug(s) caused the death
- International reference tables
  - Presence of other substances and little statistical expression
  - Kinetic phase of the substance
  - *Post mortem* redistribution and instability of substances

Introduction

Olanzapine:

- Atypical antipsychotic
- Treatment of schizophrenia and bipolar disorder
- Multiple receptors (antagonism to dopaminergic D1, D2, D4, serotoninergic 5-HT2A, 5-HT2C, histaminergic H1, cholinergic M1-5, and a1-adrenergic receptors)

Introduction

- Olanzapine intoxication - anticholinergic symptoms and central nervous system depression, miosis and unpredictable fluctuations between somnolence/coma and agitation/ aggression

- Half-life, after oral administration – 30h

- Lipophilic molecule with large volume of distribution (10-20 L/kg)

- Instability in *post mortem* blood

Aim of the study

- To characterize forensic fatal cases with positive blood levels for the antipsychotic Olanzapine

- To correlate the concentrations of this drug with the manner of death and the cause of death attributed in the reports

Material and methods

- Authorization by the Ethics committee of the National Institute of Legal Medicine
- Retrospective, observational and descriptive study
- Reports of forensic autopsies where Olanzapine was detected by toxicological blood examinations (peripheral blood)
- South Branch of the National Institute of Legal Medicine and Forensic Sciences, in Lisbon, Portugal
- 2013 – 2015
  - 2700 autopsies;
  - 1860 toxicological exams – 1805 therapeutic drugs

Material and methods

- Data base - IBM® SPSS Statistics®

- Variables - sex, age, place of death, death confirmation date, autopsy date, clinical history, signs of putrefaction, cause of death, manner of death, and ancillary tests performed, namely toxicological [Forensic Chemistry and Toxicology Service at the South Branch of the National Institute of Legal Medicine – gas chromatography - mass spectrometry (GC-MS)] and histological exams

- Descriptive and inferential statistical analysis

RESULTS

- 53 cases
- Mean age: 53.66 years (minimum: 26 years; maximum: 86 years)
- 35 men (66%) and 18 women (34%)
- Mean of 2.55 days between death confirmation and autopsy
- Psychiatric clinical history unknown in 25 cases

RESULTS

Place of death				
		Frequency	Percent	Cumulative Percent
Valid	Health Institution	10	18.9	18.9
	Prison	3	5.7	24.5
	Residential Care Home	4	7.5	32.1
	Own residence	24	45.3	77.4
	Public place	11	20.8	98.1
	Working place	1	1.9	100.0
	Total	53	100.0	

RESULTS

Signs of putrefaction				
		Frequency	Percent	Cumulative Percent
Valid	Discoloration changes	9	17.0	17.0
	Advanced putrefaction changes	1	1.9	18.9
	No visible putrefaction changes	43	81.1	100.0
	Total	53	100.0	

RESULTS

Causes of death		
	Frequency	Percent
Undetermined	2	3.8
Asphyxia by hanging	6	11.3
Asphyxia by choking	3	5.7
Asphyxia by carbon monoxide	1	1.9
Traumatic injuries	9	17
Drowning	1	1.9
Natural causes	13	24.5
Fatal intoxications	13	24.5
Asphyxia by hanging and fatal intoxication	1	1.9
Traumatic injuries and fatal intoxication	2	3.8
Asphyxia by choking and fatal intoxication	1	1.9
Acute myocardial infarction and fatal intoxication	1	1.9
Total	53	100.0

RESULTS

Manner of death				
		Frequency	Percent	Cumulative Percent
Valid	Natural death	15	28.3	28.3
	Accident	4	7.5	35.8
	Suicide	20	37.7	73.6
	Homicide	1	1.9	75.5
	Undetermined	13	24.5	100.0
	Total	53	100.0	

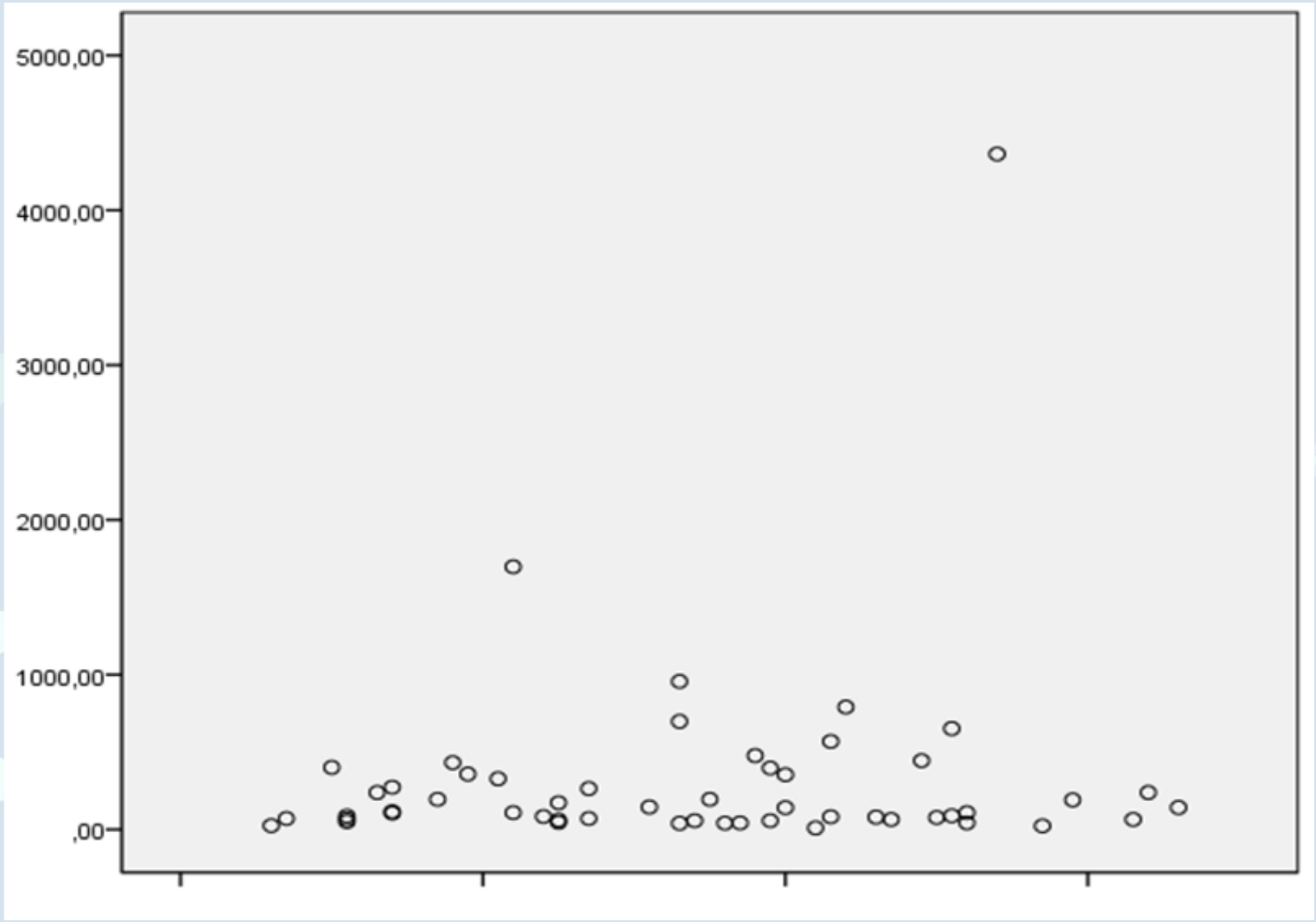
RESULTS

Descriptives				
			Statistic	Std. Error
Olanzapine concentration (ng/ml)	Mean		318.6	87.7
	95% Confidence Interval for Mean	Lower Bound	142.6	
		Upper Bound	494.6	
	5% Trimmed Mean		212.9	
	Median		116.0	
	Std. Deviation		638.5	
	Minimum		10.0	
	Maximum		4363.0	

RESULTS

Percentiles								
		Percentiles						
		5	10	25	50	75	90	95
Weighted Average	Olanzapine concentration (ng/ml)	24.4	41.4	65.0	116.0	356.0	679.6	1178.3

RESULTS


Olanzapine concentration
5000,00
4000,00
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Results

Manner of death * Cause of death Crosstabulation							
Count							
		Cause of death					Total
		Fatal intoxication	Asphyxia by hanging and Fatal intoxication	Traumatic injuries and Fatal intoxication	Acute myocardial infarction and Fatal intoxication	Asphyxia by choking and Fatal intoxication	
Manner of death	Accident	0	0	0	0	1	1
	Suicide	6	1	1	0	0	8
	Homicide	1	0	0	0	0	1
	Undetermined	6	0	1	1	0	8
Total		13	1	2	1	1	18

DISCUSSION

- There was no statistically significant difference:
  - Between the different signs of putrefaction observed, with respect to Olanzapine concentration (p=0.210)
  - Between the different manners of death, with respect to Olanzapine concentration (p=0.0331)
- After operationalization of variable “cause of death” into 2 groups, fatal and non fatal intoxication, there was statistically significant difference with respect to Olanzapine concentration (p=0.001)

DISCUSSION

- 13 cases were classified as fatal intoxications:
  - In 5 multi-drug-related cases, Olanzapine was not considered responsible for the cause of death (Olanzapine concentration: mean – 82.0ng/ml; Std – 69.1)
  - In 8 multi-drug-related cases, other drugs were present in sufficient concentration that Olanzapine was not solely responsible for the cause of death (Olanzapine concentration: mean – 1222.6ng/ml; Std – 1346.4); after removing the outlier: mean: 773.4ng/ml; std – 481,2)

DISCUSSION

- In 5 cases, other causes besides fatal intoxication contributed to death:
  - 2 cases of traumatic injuries and fatal intoxication, but just one related with Olanzapine (Olanzapine: 273ng/ml)
  - Asphyxia by hanging and fatal intoxication related with Olanzapine (Olanzapine: 569ng/ml)
  - Acute myocardial infarction and fatal intoxication related with Olanzapine (Olanzapine: 354ng/ml)
  - Asphyxia by choking and fatal intoxication related with Olanzapine (Olanzapine: 397ng/ml)

DISCUSSION

- Fatal *post mortem* concentrations of Olanzapine from the study of Christopher Vance and Ian M. McIntyre, were found to be in the range of 1400ng/ml-6200ng/ml, in peripheral blood

- Concentrations of Olanzapine associated with fatal intoxication were:
  - 1238ng/ml in blood, from Stephens and co-workers;
  - 4900ng/ml in blood, from Elian and colleagues;
  - 980ng/ml in blood, from Levine and co-workers

CONCLUSIONS

- Fatal intoxications are in many occasions a diagnosis of exclusion
- Importance of circumstantial information
- *Post mortem* Olanzapine blood concentrations may not represent true *ante mortem* or *peri mortem* levels and should be interpreted cautiously

CONCLUSIONS

- There was no statistically significant difference between the different types of manner of death, with respect to Olanzapine concentration

- There was statistically significant difference between the groups of cases classified as fatal and non fatal intoxications, with respect to Olanzapine concentration

CONCLUSIONS

- The limitations of the international reference tables suggests the need to create a reference table with local casuistic (a percentile table)

- In our study, based on our casuistic, fatal *post mortem* concentrations of Olanzapine should be considered above the 90th percentile (679.6ng/ml)

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