REFINING KNOWLEDGE ON PROPRANOLOL OVERDOSING THROUGH AN AUTOPSY CASE SERIES

Celine Gys[1], Sofie Abrahams[1], Machteld Philipsen[1], Babette van Rafelghem[2], Eline Baetens[2], Vidija Soerdjbalie-Maikoe[2], Werner Jacobs[2], Adrian Covaci[1]

1 University of Antwerp, Toxicological Centre celine.gys@uantwerpen.be

2 UZA

The International Association of Forensic Toxicologists, Established 1963

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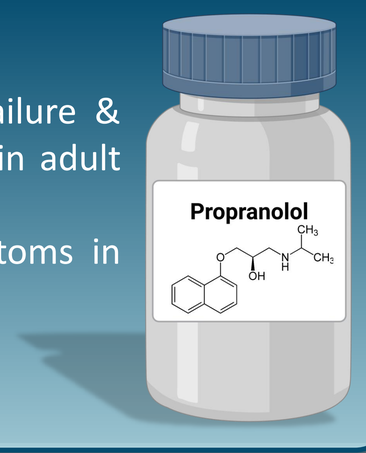
BACKGROUND

- **Propranolol** (1-7)**:**
  - non-selective, first generation β-adrenergic receptor antagonist
  - LogP = 3.48: highly lipophilic, passage blood-brain barrier (BBB)
  - V_d = 3-5 L/kg
  - pKa = 9.5
- **Overdosing:**
  - High risk of potentially fatal poisoning due to powerful cardiac effects & swift onset of action
- **Use** (7) **:**
  - Registered (BE): treatment of hypertension, cardiac failure & angina, secondary prevention of myocardial infarction in adult patients
  - Off-label (BE): prophylaxis of migraine, physical symptoms in anxiety or panic disorders (palpitations, tremor)
  - Oral administration of propranolol.HCl
  - Dose 10 – 320 mg per day depending on the indication



AIMS

- Report on post-mortem concentrations & autopsy findings from potentially fatal propranolol overdoses
- Describe a series of four independent post-mortem cases of polydrug intoxication, all including propranolol overdosing

METHODS

- Forensic autopsy including histopathology & toxicological analysis
- Propranolol measurement in post-mortem samples using LLE & LC-MS/MS
- Other medication and drugs (of abuse) were identified and/or quantified using validated analytical methods based on chromatography & mass spectrometry

RESULTS & DISCUSSION

Cases (n = 4, 2022)

1/ Man, 62
2/ Man, 21
3/ Man, 36, CPR without intubation
4/ Woman, 48, CPR with intubation

- Multiple (partially) **intact** propranolol **tablets** in oesophagus, stomach contents and/or duodenum found in cases 1-3
- High levels of propranolol in stomach contents in all cases
- Propranolol preparations ingested:
  1/ 40 mg
  2/ 40 mg
  3/ not known
  4/ 160 mg, slow release

Polydrug intoxication in all cases

- Frequent occurrence involving propranolol (3)
- Concomitant use of other medication and/or drugs of abuse:

1/ zolpidem, alprazolam, dosulepine, lorazepam
2/ ethanol, cocaine, paracetamol
3/ amisulpride, paliperidone, nordazepam
4/ amitriptyline, diazepam, tramadol

Medication or drug found in toxic concentration in blood

Propranolol in urine (ng/mL)
1/ 3140
2/ 6370
3/ 6500
4/ 945

t ½ = 3 – 6 h

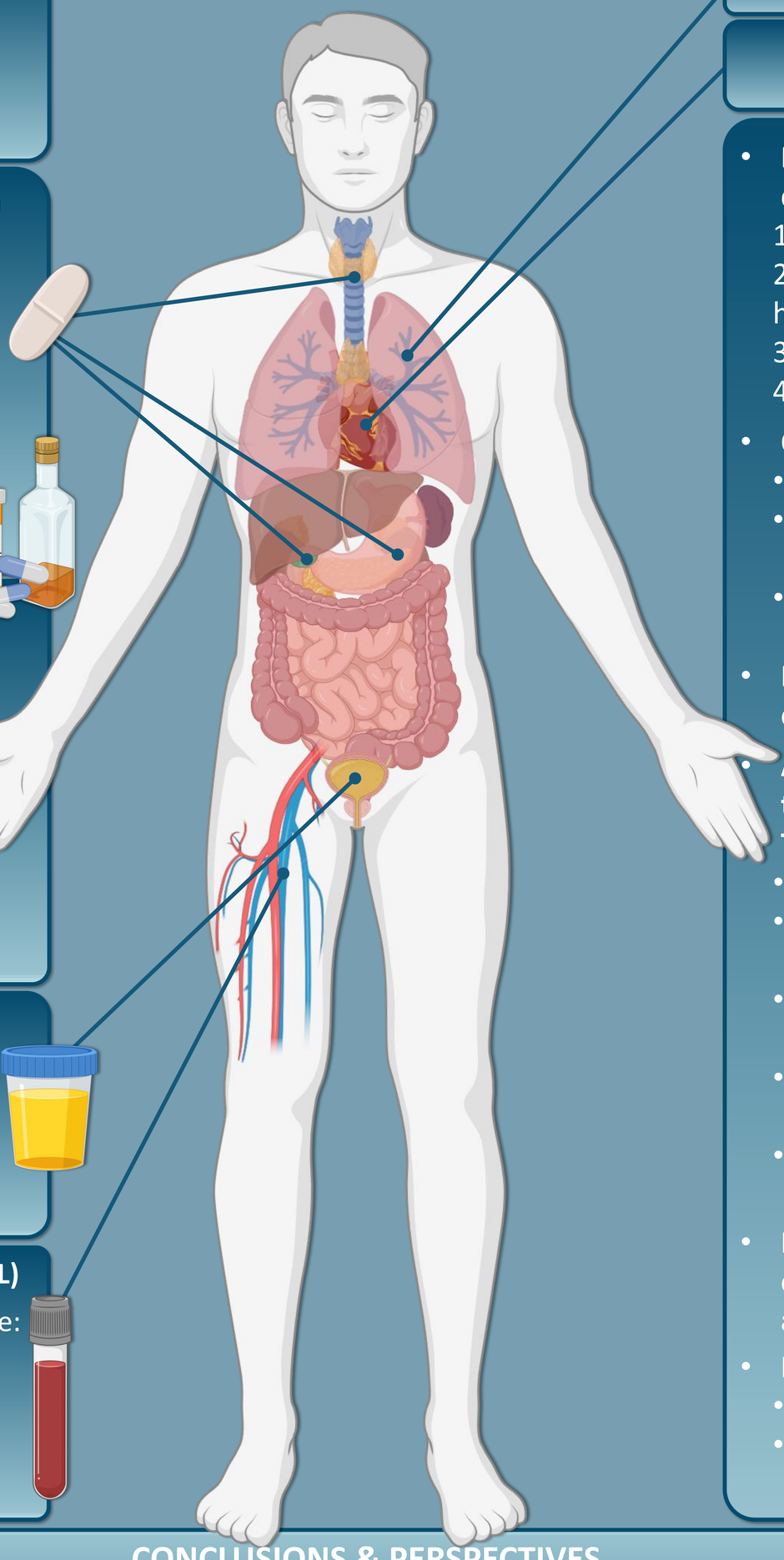
Reported levels in fatal cases (ng/mL)
900-2000 (6)

Propranolol in whole blood (ng/mL)
(NaF, femoral vein)
1/ 5980
2/ 6140
3/ 9150
4/ 1490

Reported levels (ng/mL)

Recovery after overdose:
1540-2800 (4)

Post-mortem:
3400-13000 (3)
2900-29000 (5,6)



Pulmonary oedema in all cases

Myocardial infarction due to coronary atherosclerosis in case 4

- **Polydrug use/intoxications result in several drug interactions:**
  1/ increased sedation
  2/ increased dysregulation blood pressure & heart rhythm
  3/ prolongation QT interval
  4/ increased sedation & serotonin level
- **Only in case 4 therapeutic use of propranolol**
  - (secondary) prevention myocardial infarction
  - lowest detected levels of propranolol in blood and urine
  - possibly artificially elevated concentration due to post-mortem redistribution
- **Possible (self-)medication for mediation of cardiovascular effects of cocaine use in case 2**
- **All measured blood concentrations > typical therapeutic plasma levels in living individuals**(3)
- **Toxicity** (1-6)**:**
  - Within 2 h of ingestion, as early as 20 min(1)
  - Sinus bradycardia, hypotension, hypoglycaemia
  - Membrane stabilising properties: widened QRS leading to arrhythmia in overdose
  - Passage BBB: altered level of consciousness, hallucinations, seizures
  - Severe cases: heart failure, cardiogenic shock, coma
- **Pulmonary oedema & high propranolol concentrations in urine indicate prolonged agonal phase**
- **Registered cause of death:**
  - Propranolol (mixed) overdose: cases 1-3
  - Ischemic myocardial infarction due to severe coronary atherosclerosis: case 4

CONCLUSIONS & PERSPECTIVES

- All four cases presented polydrug intoxication – common for propranolol overdosing
- Three cases showed several intact tablets in the digestive system, all showed high levels of propranolol in the stomach contents
- Propranolol (or mixed) intoxication was considered the cause of death in 3/4 cases
- Myocardial infarction was determined the cause of death in the only case where propranolol was used therapeutically
- Pulmonary oedema & high propranolol concentrations in urine in all cases, indicating a prolonged agonal phase
- Analysis of more cases in the future, including detection of various (active) metabolites of propranolol for interpretation

References

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