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Propranolol and metoprolol: Two comparable drugs with very different post-mortem toxicological profiles

Pirkko Kriikku[a,b,*], Samu Pelkonen[b], Maija Kaukonen[c], Ilkka Ojanperä[b,a]

[a] Forensic Toxicology Unit, Finnish Institute for Health and Welfare, P.O. Box 30, 00271 Helsinki, Finland
[b] Department of Forensic Medicine, University of Helsinki, P.O. Box 40, 00014 Helsinki, Finland
[c] Finnish Medicines Agency (FIMEA), Helsinki, Finland

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ABSTRACT

Propranolol is a widely used beta-blocker mainly prescribed for the treatment of hypertension and other cardiac conditions. This medicine is also a frequent finding in drug screens, but little is known about its post-mortem toxicological profile. Our aim was to examine all post-mortem toxicology cases positive for propranolol in a three-year period, between 2016 and 2018 in Finland, and to compare these cases to those positive for metoprolol, another beta-blocker commonly used to treat cardiac diseases. There were 179 cases positive for propranolol and 416 for metoprolol in the study period. In the majority of propranolol cases (53%), the drug concentration in the blood was above the typical therapeutic range, but among the metoprolol cases this proportion was 18%. Propranolol was significantly more common than metoprolol in fatal poisonings, suicides and in cases with a history of drug abuse. Alcohol, benzodiazepines, antipsychotics and antidepressants were significantly more often detected in propranolol cases than in metoprolol cases. The deceased positive for propranolol were significantly younger than those positive for metoprolol. Cardiovascular diseases as the underlying cause of death were significantly more common among the metoprolol cases than among the propranolol cases. Our results showed significant differences between the propranolol group and the metoprolol group in post-mortem toxicology cases. The two drugs were used by two very different groups of people, with propranolol use being associated with psychiatric conditions.

1. Introduction

Propranolol is a beta-adrenergic receptor antagonist that initiated the use of beta-blockers in the treatment of cardiovascular diseases (CVD). The developer of the drug was the British scientist Sir James Black, who subsequently received a Nobel Prize in Medicine for his work [1]. Propranolol is a non-selective beta-blocker; it blocks both of the beta-adrenergic receptors, β1 and β2, for the action of adrenaline and noradrenaline and thus inhibits sympathetic effects that act through these receptors. Propranolol possesses no intrinsic sympathomimetic activity. Metoprolol, another beta-blocker well established in the treatment of various cardiovascular conditions, is a β1-selective adrenoceptor antagonist, which also lacks sympathomimetic activity. Propranolol is the most lipophilic of the beta-blockers, and thus its concentration in the brain is higher than that of other drugs used for the same indication [2].

Many of the therapeutic indications of the use of propranolol and metoprolol are the same. Currently, propranolol and metoprolol are both used to treat hypertension, angina pectoris, cardiac arrhythmias, thyrotoxicosis and in migraine prophylaxis. In addition, propranolol is used for the treatment of essential tremor and hypertrophic obstructive cardiomyopathy. Propranolol is also being used "off-label" to treat fear of social situations [3], panic disorder and other types of anxiety disorders [4].

Regarding the adverse effects of propranolol, the drug has been connected to depression [5–9], at least in patients susceptible to depression [10]. Psychotic episodes in connection with propranolol therapy have also been reported [11–17]. Propranolol has reportedly been misused for the purpose of self-medication for fear of social situations and stage fright [18,19].

Apart from some case reports, there is very little information in the literature on the toxicological profile of propranolol in relation to the cause of death. The aim of this study was to examine post-mortem (PM) cases positive for propranolol in terms of blood

* Corresponding author at: Forensic Toxicology Unit, Finnish Institute for Health and Welfare, P.O. Box 30, 00271 Helsinki, Finland.
E-mail address: pirkko.kriikku@thl.fi (P. Kriikku).

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Table 1
Details on PM cases positive for propranolol and metoprolol. Medians and ranges for the blood alcohol concentration (BAC) are calculated for cases in which alcohol was detected above the laboratory cut-off (0.2 g/kg).

	N		Median (range) age		BAC ≥ 0.2 g/kg N (%)		Median (range) BAC (g/kg)		Suicides N (%)		Implicated in fatal poisoning N (%)		History of drug abuse N (%)	
Propranolol	**all**	**179**	**51****	**(19–94)**	**78**	**(44)***	**1.20**	**(0.27–4.70)**	**60**	**(34)****	**54**	**(30)****	**26**	**(15)****
	male	102	51**	(20–94)	46	(45)*	1.20	(0.27–4.70)	26	(25)**	21	(21)**	18	(18)**
	females	77	50**	(19–79)	32	(42)*	1.25	(0.29–4.20)	34	(44)**	33	(43)**	8	(10)**
Metoprolol	**all**	**416**	**71**	**(19–95)**	**120**	**(29)**	**1.40**	**(0.20–4.10)**	**28**	**(6.7)**	**11**	**(2.6)**	**6**	**(1.4)**
	male	255	69	(19–93)	86	(34)	1.30	(0.20–3.50)	18	(7.1)	4	(1.6)	5	(2.0)
	females	161	75	(24–95))	34	(21)	1.75	(0.37–4.10)	10	(6.2)	7	(4.3)	1	(0.6)

*Indicates statistically significant difference ($p < 0.05$) between propranolol and metoprolol group
**Indicates statistically significant difference ($p < 0.001$) between propranolol and metoprolol group

concentrations, cause and manner of death and demographics of the deceased, and to compare these with cases positive for metoprolol during the same period of time. A comparative analysis of the causes of death and toxicology findings between propranolol and metoprolol cases during a three-year period in 2016–2018 is presented.

2. Material and methods

The Finnish medico-legal system for determining the cause of death is described elsewhere [20]. In brief, according to the Finnish legislation, a medico-legal investigation into the cause of death is performed whenever the death is not known to be due to illness or when the deceased has not been treated by a doctor during his or her last illness; the death was caused by an accident, suicide, crime, poisoning, occupational disease or treatment or there is reason to suspect one of them; or the death has otherwise happened unexpectedly. In about 16% of all deaths, the Police orders a forensic autopsy that is performed by a forensic pathologist, and in most cases the investigation includes PM toxicology.

In the medico-legal investigation, the forensic pathologist determines the cause and manner of death based on background information, autopsy findings and additional investigations. In suspected poisoning cases the forensic pathologist may consult a forensic toxicologist to assess the significance of the toxicological findings in the event of death. The relevant substances are then recorded in the death certificate as the ones implicated in the cause of death.

For this study, data was extracted from the forensic toxicology database, maintained by the Finnish Institute for Health and Welfare (THL), in which all results of the PM toxicological analyses in medico-legal investigations nationwide, as well as information from the death certificates, are collected. The study material consisted of the forensic pathologist's referral, toxicology laboratory results and information extracted from the death certificate. The death certificate, issued by the forensic pathologist who performed the autopsy, included the cause and manner of death, substances implicated in fatal poisoning with the principal finding separately indicated, a short description of the circumstances of death and the autopsy findings.

Propranolol or metoprolol, or both, were quantitatively determined in PM femoral venous blood from deceased who had died between 1 January 2016 and 31 December 2018. A method based on ultra-high-performance liquid chromatography with two consecutive detectors, a photodiode array detector and a corona charged aerosol detector (UHPLC-DAD-CAD), was used for the analysis of the studied drugs as a part of a comprehensive toxicology panel. The method has been described in detail elsewhere [21]. The limit of quantification was 0.05 mg/L for both propranolol and metoprolol.

All statistical analyses were carried out using IBM SPSS software (version 25). As the frequency distributions of the blood concentrations and the age of the deceased were not normally distributed, medians were used to characterise the data. The analysis was performed using the Mann–Whitney *U* test for independent samples. Comparisons between groups were performed using Kruskall–Wallis ANOVA on ranks and then the Dunn-Bonferroni test if a significant difference in groups were identified. A p value < 0.05 was regarded as statistically significant.

3. Results

During the three-year period 2016–2018, there were 179 PM cases positive for propranolol and 416 for metoprolol. In two cases, both propranolol and metoprolol were detected. Median (range) propranolol concentration in the PM blood was 0.32 (0.02–16) mg/L, and median (range) metoprolol concentration was 0.20 (0.05–76) mg/L. In the propranolol group, in 53% (N = 95), the concentration

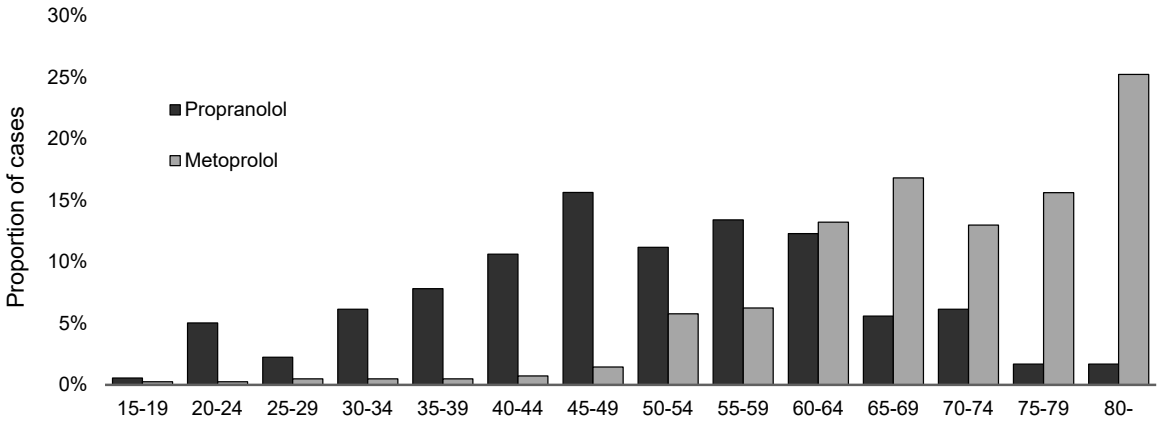

Fig. 1. Age distribution in PM cases positive for propranolol and metoprolol.

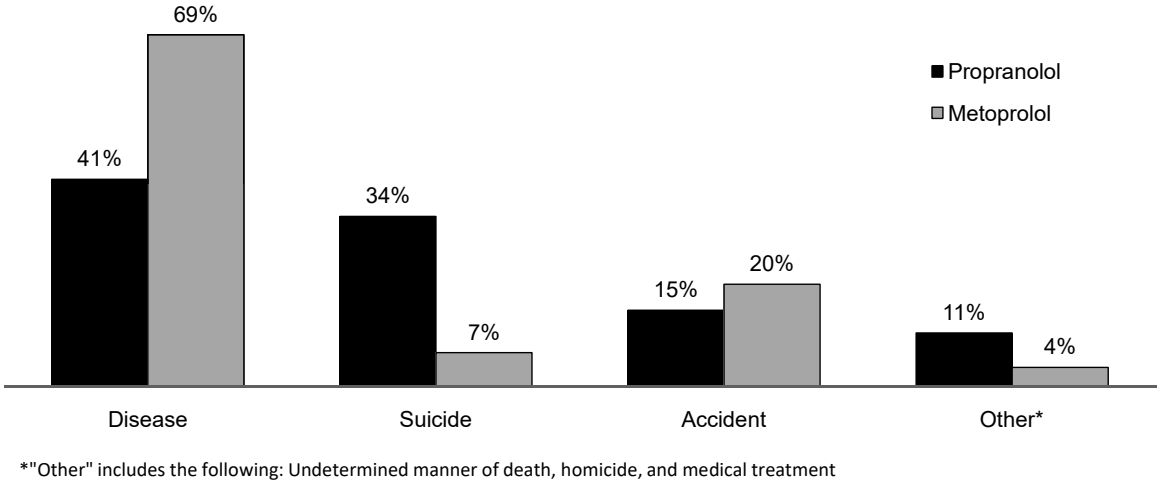

Fig. 2. Proportion of each manner of death in PM cases positive for propranolol and metoprolol.

was over the upper limit of the typical therapeutic plasma concentration of living individuals. In the metoprolol group, the corresponding percentage was 18% (N = 76).

Details of the gender and age distributions are given in Table 1. As illustrated in Fig. 1, the deceased in the propranolol group were significantly younger than those in the metoprolol group ($p < 0.001$). The proportion of females was 57% and 61% in propranolol and metoprolol groups, respectively. The difference in the proportion of females was not significant ($p > 0.05$).

The two cases in which both propranolol and metoprolol were detected were both self-poisoning cases, in which the primary intoxicant was propranolol.

As seen in Table 1, alcohol was detected proportionally more often in the propranolol group than in the metoprolol group, and the difference was significant ($p = 0.002$). History of drug abuse was significantly more common in the propranolol group than in the metoprolol group ($p < 0.001$). In the propranolol group, benzodiazepines were detected in 65% (N = 117), antipsychotics in 32% (N = 57) and antidepressants in 40% (N = 72) of cases. In the metoprolol group, benzodiazepines were detected in 25% (N = 105), antipsychotics in 12% (N = 50) and antidepressants in 21% (N = 86). All of these pharmacological groups were significantly more frequently detected in the propranolol group than in the metoprolol group ($p < 0.001$).

There were significantly more fatal poisonings by drugs, alcohol or carbon monoxide in the propranolol group than in the metoprolol group ($p < 0.001$). Propranolol was detected in 87 fatal poisonings and implicated (alone or together with other drugs) in 54 fatal poisonings. For metoprolol, the numbers were 35 and 11, respectively. There were significantly more fatal poisonings by the particular beta-blocker in the propranolol group than in the metoprolol group ($p < 0.001$). Of the propranolol poisonings, 70% (N = 38) were suicides; whereas for metoprolol, the percentage was 82% (N = 9). In the remaining cases, the manner of death was undetermined in 20% (N = 11) of the propranolol poisonings and 9.1% (N = 1) of the metoprolol poisonings, and accident/unintentional overdose in 9.3% (N = 5) of the propranolol poisonings and 9.1% (N = 1) of the metoprolol poisonings. Two of the accidental poisonings by propranolol were related to abuse of illegal drugs.

As seen in Table 1, suicides in general were more common in the propranolol group than in the metoprolol group, and the difference was significant ($p < 0.001$). The other manners of death in PM cases positive for propranolol and metoprolol are illustrated in Fig. 2.

There were 11 suicide cases in which propranolol alone had caused the fatal poisoning. The median (range) blood concentration in the cases was 6.1 (3.4–13) mg/L. Two of these suicides were related to abuse of illegal drugs. For metoprolol, the number of single poisonings among suicides was four and the median (range) blood concentration 11 (6–25) mg/L.

The studied cases were also examined in terms of CVD as the cause of death. The following ICD-10 codes were used when extracting the data: I00-I09 (rheumatic heart diseases), I10-I15 (hypertensive diseases), I20-I25 (ischemic heart diseases), I26-I28 (pulmonary heart disease and other diseases of pulmonary vessels), I30-I52 (other forms of heart disease), I60-I69 (cerebrovascular diseases), I70-I79 (diseases of arteries, arterioles and capillaries), and I80-I99 (other diseases of the circulatory system). The list of ICD-10 codes is the same as Statistics Finland uses for the official mortality statistic on CVD.

In 46% of the studied cases (N = 270), the underlying cause of death was a CVD. This corresponds to 75% of the cases in which the manner of death was disease. The two by far most common causes of death by CVD were chronic ischemic heart disease (I25) (N = 175, 65% of the CVD cases) and hypertensive heart disease (I11) (N = 48, 18% of the CVD cases). Of the cases in which the underlying cause of death was CVD, 11% (N = 30) were positive for propranolol and 90% (N = 242) for metoprolol.

Of the studied cases, CVD was significantly more common as the underlying cause of death among the metoprolol cases (58%) than among the propranolol cases (17%) ($p < 0.001$).

About half of the diseases other than CVS (N = 91) were connected to excessive use of alcohol, such as alcohol abuse or addiction or alcoholic liver disease. The other half consisted of various causes of death; among them the most common were diabetes mellitus and various types of gastric ulcers.

Of the deceased positive for propranolol, 17% died of alcohol related diseases. For metoprolol the percentage was 3.6%.

In 16% (N = 17) of the drug toxicity deaths in which propranolol or metoprolol was detected, CVS was recorded as a contributing cause of death. Among these were seven fatal poisonings in which propranolol was implicated and three in which metoprolol was implicated.

4. Discussion

Of these two comparable drugs used mainly for the treatment of hypertension, propranolol was significantly more often detected than metoprolol above the blood levels representing a typical therapeutic range, in drug abuse cases, together with alcohol, benzodiazepines, antipsychotics and antidepressants, in fatal poisonings

and in suicides. In addition, the deceased positive for propranolol were significantly younger than those positive for metoprolol. On the other hand, only a relatively small proportion of the deceased positive for propranolol died of CVD (17%) whereas these were the most common causes of death among the metoprolol cases (58%).

The typical range of therapeutic plasma concentrations in the treatment of CVD is 0.02–0.30 mg/L for propranolol and 0.035–0.50 mg/L for metoprolol [22]. In 2019, more than 12 million defined daily doses (DDD) of beta-blockers were sold in Finland. For propranolol the number was 4.5 million doses and for metoprolol 20 million doses [23]. This makes metoprolol the second most used beta-blocker after bisoprolol, and propranolol the third most used. According to WHO, DDD for propranolol and metoprolol is 160 mg and 150 mg, respectively [24].

Metoprolol was a more prevalent finding in PM toxicology than propranolol but not as much as expected. The DDD values of metoprolol in the study period were more than 4-fold when compared to those of propranolol; whereas, PM detections of metoprolol in the study period were only about 2.3-fold. In part, this may be due to the significantly higher prevalence of confounding substances, such as alcohol, in propranolol cases that may have contributed to death either directly or by inducing conditions that have led to death. In addition, it is likely that most deceased on beta-blocker medication are not directed to medico-legal autopsy. The higher prevalence of sudden and unexpected death in the propranolol group may be due to co-ingested psychiatric and/or abused drugs and psychiatric indications for propranolol, all of which are associated with a higher incidence of fatal poisoning and suicide.

An Australian study [25] compared the relative toxicity of beta-blockers in overdose by using clinical data from patients presenting to hospital with self-poisoning, coroner's data and prescription data from 1987 to 1995. The investigators found that propranolol was over-represented in beta-blocker poisoning when prescription data were also examined, and propranolol was the only beta-blocker associated with death. Furthermore, propranolol was taken by a younger age group. Another study, reviewing beta blocker-related exposure data and fatality case abstracts reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System during 1985–1995 [26], found that propranolol was responsible for the greatest number of exposures and implicated as the cause of death in a disproportionately high percentage of fatalities. Interestingly, the patients were generally young women. In a more recent German study on beta-blocker poisonings, no fatalities were observed with single-substance exposures. The researchers found some differences in the toxic symptoms, such as seizures associated with propranolol poisoning, but the severity of poisoning did not differ substantially among the studied drugs [27].

In the present study, the concentration of propranolol was three times more often over the upper limit of the typical therapeutic plasma concentration of living individuals than the concentration of metoprolol. This result is in line with a recent paper reporting summary statistics for PM drug concentrations representing all causes of death, in which the median PM concentration obtained for both propranolol and metoprolol were within the typical therapeutic range of each drug in living individuals, but the upper percentile PM concentrations were much higher for propranolol than for metoprolol [28].

PM drug redistribution refers to the changes that occur in drug concentrations after death due to the redistribution of drugs between blood and other body compartments, such as the lungs, liver, and myocardium. For most drugs, at least some concentration changes are likely to occur, but the extent of these changes varies greatly depending on the pharmacological properties of the drug. Mantinieks et al. studied the PM and ante-mortem (AM) blood concentrations in cases in which both sample matrices were available for the same individual [29]. For propranolol, the PM/AM ratio was 1.4, which was similar to other cardiovascular drugs, indicating that at least some increase in the drug concentration after death is likely.

Based on the available information on the drug, it is unlikely that the differences between fatalities related to propranolol and metoprolol are linked to the intrinsic toxicological properties of the drugs but rather to differences between patient groups using the drug and associated co-ingested substances. Previous research in Finland has shown that the fatal toxicity index (FTI) that illustrates the relevance of a particular drug in fatal poisonings in relation to its consumption is indeed much higher for propranolol than for metoprolol [30]. In that study, propranolol was recognised as the only cardiac drug associated with particularly high toxicity, and its FTI was comparable with many antidepressants and antipsychotics, such as bupropion, sulpiride, clomipramine, quetiapine and trazodone [30].

Given the differences between the pharmacology of propranolol and metoprolol, it was expected that there would be differences in the fatalities related to these two drugs. The magnitude of these differences was, however, larger than expected. Although the main indication of both of these drugs is the treatment of cardiac diseases, propranolol is also used to treat symptoms like tremor and palpitations and to lower the pulse in patients in drug and alcohol rehabilitation, which can explain at least a part of the differences seen in this study. Although medico-legal investigations are very comprehensive in Finland, covering nearly 20% of all deaths in each year, many of the patients using beta blockers for cardiac issues may not end up being investigated medico-legally, if their death was caused by a disease and was not unexpected. This may also complicate any conclusions drawn from our study.

5. Conclusion

Propranolol was significantly more common than metoprolol in fatal poisonings, suicides, and in the deceased with a history of drug abuse. Alcohol, benzodiazepines, antipsychotics and antidepressants were significantly more often detected in the propranolol cases than in the metoprolol cases. The deceased with a propranolol finding were significantly younger than those with a metoprolol finding. CVD as the underlying cause of death was significantly more common among the metoprolol cases than among the propranolol cases. In our study material, the propranolol users represented a very different group of individuals than the metoprolol users. It is likely that in a considerable proportion of propranolol deaths the drug was not taken for the treatment of cardiac issues but rather for psychiatric indications, such as the physical symptoms in panic or anxiety disorder, or in alcohol or drug rehabilitation.

CRediT authorship contribution statement

Pirkko Kriikku: Conceptualization, Formal analysis, Writing – original draft, Visualization. **Samu Pelkonen:** Investigation, Writing – review & editing. **Maija Kaukonen:** Data curation, Writing – review & editing. **Ilkka Ojanperä:** Conceptualization, Writing – review & editing, Project administration, Supervision.

Conflict of interest.

None of the authors have any interests to declare.

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