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Clinical toxicology of propranolol and metoprolol overdose in adults

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Abstract

Beta-adrenergic receptor antagonists potentially risk causing fatal poisoning when taken over the daily recommended doses. The aim of this study is to investigate the differences and potential dose-related effects of propranolol and metoprolol toxicity depending on their selectivity. This 7-year-long retrospective cohort study was conducted among on 43 adult patients who received overdose propranolol (n= 22) and metoprolol (n= 21). Patients were divided into groups, with a daily overdose ≥ 240 mg/day for propranolol, ≥ 200 mg/day for metoprolol, and toxic dose ≥ 400 mg/day for both drugs. The groups were compared in terms of admission symptoms, heart rate, blood pressure, electrocardiography findings, cardiovascular effects, toxicity severity scores, treatment, follow-up times, and outcomes. Thirty-four (79.1%) of the patients who exceeded the daily dose were female, and there were no statistically significant differences between the groups in terms of gender (p= 0,281). The mean age was 29 (18-72) years, and there were no statistically significant differences between groups in terms of mean age (p= 0.192). When the vitals of the patients who exceeded the daily dose was examined, it was found that 23 (54.8%) patients had bradycardia, and 20 (46.5%) patients had hypotension. 65.2% of the bradycardia patients and 70% of the hypotensive patients were in the propranolol overdose group (p= 0.030 p= 0.021, respectively). Mean dose of symptomatic propranolol overdose patients (n= 12) was found as 1256 (280-2000) mg, mean dose of symptomatic metoprolol overdose patients (n= 11) was found as 559 (250-1000) mg. When toxic dose (≥ 400 mg) intakes were compared, more cardiovascular effects were observed in the propranolol group (p= 0.014). As a result, it was determined that Propranolol overdose has more cardiovascular effects than metoprolol overdose and there is a linear dose-symptom relationship for Propranolol.

Keywords: Beta blocker poisoning, propranolol, metoprolol, emergency medicine

1. Introduction

Due to their blood pressure and heart rate lowering effects, beta-adrenergic receptor antagonists (B-blockers) are commonly used in adults in the treatment of hypertension, tachycardia, cardiac angina, and heart failure (1). They have a risk of causing bradycardia, hypotension, bronchospasm, myocardial infarction, heart failure, and potentially fatal toxicity when taken above the daily recommended doses (2).

The cellular toxicity of B-blockers depends on their membrane stabilizing activities (MSA), lipophilicity, and intrinsic sympathomimetic activities (ISA). Agents with high MSA (Propranolol, Carvedilol, Acebutolol, Betaxolol, and Oxprenolol) inhibit fast sodium channels and cause a wide QRS range. Agents with high lipid solubility (Propranolol, Penbutolol, Metoprolol, and Betaxolol) cross the blood-brain barrier quickly and cause neurological side effects such as seizures and delirium. Agents with ISA (Pindolol, Penbutolol, Acebutolol, and Carteolol) have partial antagonist properties. They activate or block receptors depending on the situation; however, this protective effect of ISA does not completely prevent cardiovascular toxicity at toxic doses (3).

Propranolol is one of the first generation classical non-selective B-blockers with MSA, high lipid solubility, no ISA and a half-life of 3-5 hours. On the other hand, metoprolol is a second-generation B1-selective blocker with MSA, moderate lipid solubility, no ISA and a half-life of 3-7 hours (4–6).

In National Poison Solidarity Centre (UZEM) 2018 report, among the first 50 human health agents the cases were exposed to (according to ATC name), metoprolol ranked 39th (n=865, 0.56%), while propranolol ranked 45th (n=817, 0.53%) (7). In the American Association of Poison Control Centre (AAPCC) National Poison Data System (NPDS) 2020 report, 3,328 (86.0%) drug-related death cases were reported. Of these deaths, 263 occurred due to cardiovascular drugs (82 Amlodipine, 24 Metoprolol, 17 Propranolol, 15 Digoxin, 15 Verapamil, 14 Diltiazem, 11 Carvedilol, 10 Verapamil) (8).

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B-blocker exposures are generally reported as case reports or case series. There are limited numbers of studies that investigated the comparison of clinical toxicity of propranolol and metoprolol. The present study was designed to investigate the differences and potential dose-related effects of propranolol and metoprolol toxicity depending on their selectivity.

2. Materials and methods

2.1. Patients and data collections

The files of patients older than 18 years of age who were evaluated with suspicion of B-blocker toxicity in the Emergency Department (ED) of Ondokuz Mayıs University Medical Faculty were analyzed retrospectively. This study was approved by The Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (Decision number. 2014/920). Of the 57 patients who were suspected of B-blocker intoxication, 43 were included in the study. In multiple drug intakes, patients who had taken cardiovascular drugs (antihypertensive-antiarrhythmic) together with B-blockers were excluded from the study. Two patients who had taken multiple drugs, including propranolol, were excluded since they had not exceeded the daily propranolol dose (120-240 mg). Other B-blockers (Carvedilol, Nebivolol, and Bisoprolol) were excluded from the analysis. Patients with a history of severe cardiac arrhythmia, renal and hepatic dysfunction, and those who left the hospital voluntarily or without permission while their follow-up was continuing, were also excluded (Fig. 1).

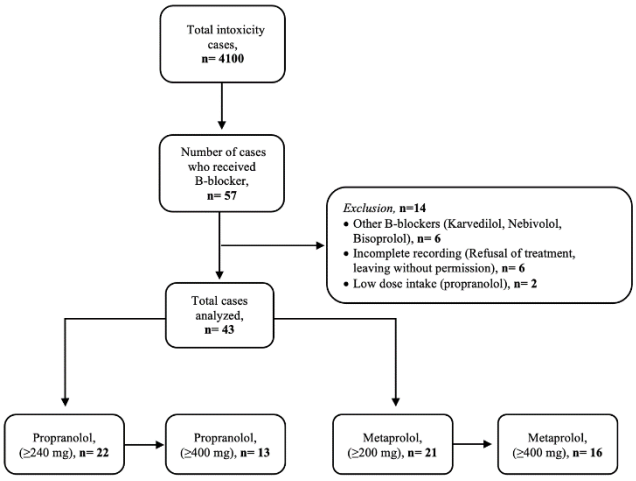

Fig.1. Flowchart

Patients were divided into groups, with a daily overdose of≥ 240 mg/day for propranolol, ≥ 200 mg/day for metoprolol, and a toxic dose of≥ 400 mg/day for both drugs (9). Heart rate (beat/min), PR interval (ms), QRS width (ms), QT distance (ms), and corrected QT (QTc) time (ms) (Bazett formula; QTC= QT/√RR) were calculated from the patients' ECGs. A PR interval of ≥ 200 ms was considered as a first-degree atrioventricular (AV) block, a QRS time of ≥100 ms was considered as interventricular conduction delay, and when patients' QTc values were calculated according to heart rate, ≥ 440 ms was considered as prolonged QT. Patients with systolic blood pressure (SBP) of ≤ 90 mmHg and a mean arterial pressure of [MAP= (SBP + 2DKB)/3] ≤ 70 mmHg at the time of admission to the hospital were considered hypotensive. A heart rate of ≤ 60 beats/minute measured at the time of admission to the hospital was considered bradycardia. The treatment of patients according to their current clinic, intoxication severity scores (o; no symptoms, 1; mild symptoms, 2; moderate symptoms, 3; severe symptoms, 4; death), the time between drug intake and hospital admission, and hospital stay were recorded.

Cardiovascular involvement was defined as:
An SBP of <90 mm Hg or a heart rate of <60 beats/min,
Symptoms suggestive of decreased end-organ perfusion (e.g., decreased consciousness, syncope, myocardial infarction) and
The need for a therapeutic intervention involving cardioactive drugs (e.g., atropine, glucagon, catecholamines) other than treatments with intravenous fluids alone
The patients who could not meet all three of the above criteria were considered as patients who did not have cardiovascular involvement.

2. 2. Statistical analysis

The statistical analyses were performed with IBM SPSS v.23. The normality of the continuous variables was analyzed with the Shapiro Wilk test. Pearson Chi-square test was used to compare the categorical variables, Mann Whitney U test was used to compare non-parametric qualitative data, and the T-test was used to compare the normally distributed data. The results were presented as mean ± standard deviation, median (min-max), frequency, and percentage. The level of significance was considered as $p < 0.05$.

3. Results

This 7-year-long retrospective cohort study was conducted among 43 adult patients who received overdose propranolol (n= 22) and metoprolol (n= 21). During the study period, 1.40% (57/4100) of adult poisoning cases were due to B-blocker intoxication. Thirty-four (79.1%) of the patients with overdose were female, and there were no statistically significant differences between the groups in terms of gender (p= 0,281). The mean age was 29 (18-72) years, and there were no statistically significant differences between groups in terms of mean age (p= 0,192). When the patients were examined according to the drugs they took, it was found that 20 (46.5%) patients had taken only B-blocker (propranolol or metoprolol), while 23 (53.5%) had taken more than one drug (multiple drugs). Antidepressants (31.0%), nonsteroid anti-inflammatory drugs (20.7%), analgesics (17.3%), and other drugs (31.0%) were the drugs most commonly taken together. When the vitals of the patients who exceeded the daily dose

was examined, it was found that 23 (54.8%) patients had bradycardia and 20 (46.5%) cases had hypotension. 65.2% of the bradycardia patients and 70% of the hypotensive patients were in the propranolol overdose group (p= 0,030 p= 0,021, respectively). No significant difference was found between groups in terms of cardiovascular involvement criteria (p= 0,151). Mean dose of asymptomatic patients (n= 20, 46.5%) was found as 734 (200-2000) mg, mean dose of asymptomatic propranolol overdose patients (n= 10) was found as 468 (240-1000) mg and mean dose of asymptomatic metoprolol overdose patients (n= 10) was found as 1000 (200-2000) mg. Mean dose of symptomatic patients (n= 23, 53.5%) was found as 923 (250-2000) mg, mean dose of symptomatic propranolol overdose patients (n= 12) was found as 1256 (280-2000) mg and mean dose of symptomatic metoprolol overdose patients (n= 11) was found as 559 (250-1000) mg. No statistically significant difference was found in terms of treatment and symptoms (Table 1).

Table 1. Clinical toxicity data in case of daily overdose

		Total, n=43	Propranolol, (≥ 240 mg), n= 22	Metoprolol (≥ 200 mg), n= 21	p
Female, n (%)		34 (79.1)	19 (55.9)	15 (44.1)	0.281[b]
Age, median (min-max)		29 (18-72)	28 (18-62)	30 (18-72)	0.192[a]
Drug dose, (mg), median (min-max)		640 (200-2000)	800 (240-2000)	500 (200-2000)	0.607[a]
Admission time, (min)		60(15-600)	60 (30-600)	60 (15-520)	0.307[a]
Drug intake, n (%)	Multiple drugs	23 (53.5)	12 (52.2)	11 (47.8)	0.887[b]
	Single drug	20 (46.5)	10 (50.0)	10 (50.0)	
Heart rate, (beats/min), median (min-max)		60 (46-92)	58 (48-80)	64 (46-92)	0.193[a]
Bradycardia, (≤ 60 beats/min), n (%)		23 (54.8)	15 (65.2)	8 (34.8)	**0.030***
Systolic BP, (mmHg), median (min-max)		100 (40-140)	90 (40-110)	100 (70-140)	**0.021[a]**
Hypotension, (≤ 90 mmHg), n (%)		20(46.5)	14 (70.0)	6 (30.0)	**0.021***
MAP, (mmHg), median (min-max)		73 (20-102)	70 (20-90)	73 (50-102)	**0.028[a]**
MAP, (≤ 70 mmHg), n (%)		21 (48.8)	15 (71.4)	6 (28.6)	**0.009***
PR distance, (ms), mean±SD		166.65 ± 32.72	173.64 ± 31.39	159.33 ± 33.22	0.154**
Long PR, (≥ 200 ms), n (%)		8 (18.6)	6 (75.0)	2 (25.0)	0.240[b]
QRS distance, (ms), median (min-max)		88 (70-172)	90 (70-106)	88 (72-172)	0.480[a]
QRS (≥ 100 ms), n (%)		6 (14.0)	3 (50.0)	3 (50.0)	0.999[b]
QTc, (ms), median (min-max)		400 (350-550)	400 (370-460)	410 (350-550)	0.642[a]
QTc, (≥ 440 ms), n (%)		8 (18.6)	3 (37.5)	5 (62.5)	0.457[b]
Cardiovascular involvement, n (%)		17 (39.5)	11 (64.7)	6 (35.3)	0.151*
Gastric lavage, n (%)		38 (88.4)	20 (52.6)	18 (47.4)	0.664[b]
Activated carbon, n (%)		38 (88.4)	20 (52.6)	18 (47.4)	0.664[b]
Therapeutic intervention, n (%)		17 (39.5)	11 (64.7)	6 (35.3)	0.151*
Atropine		15 (34.9)	9 (60.0)	6 (40.0)	0.396*
Dopamine		8 (18.6)	6 (75.0)	2 (25.0)	0.240[b]
Glucagon		3 (7.0)	2 (66.7)	1 (33.3)	0.999[b]
Symptomatic, n (%)		23 (53.5)	12 (52.2)	11 (47.8)	0.887*
Vomiting		6 (14.0)	2 (33.3)	4 (66.7)	0.412[b]
Dizziness		12 (27.9)	8 (66.7)	4 (33.3)	0.206*
Somnolence		5 (11.6)	2 (40.0)	3 (60.0)	0.664[b]
Chest pain		7 (16.3)	2 (28.6)	5 (71.4)	0.240[b]
Syncope		2 (4.7)	2 (100.0)	0	0.488[b]

*MAP; Mean Arterial Pressure, QTc; Corrected QT, a Mann Whitney U, * The Chi-square statistic, ** T test, b Fisher's Exact test*

When single-time overdose (≥ 400 mg) drug intakes were compared, more cardiovascular involvement was observed in the group that received propranolol, and it was statistically signification (p= 0,014). As expected, it was found that the group that received propranolol needed more therapeutic intervention (p= 0,014) (Table 2).

In terms of intoxication severity classification, 2 (4.7%) of the cases in the "severe" group had taken high dose propranolol. Both cases were symptomatic (syncope, chest pain), hypotensive (OAB= <40 mmHg) and had bradycardia (<40 beats/min). All of the cases were followed and treated in the ED, and they were discharged with recovery (Table 3).

Table 2. Clinical toxicity data in case of toxic overdose (≥ 400 mg)

		Total, n:29	Propranolol, (≥ 400 mg), n:13	Metoprolol (≥ 400 mg), n:16	p
Female, n (%)		22 (75.9)	11 (50.0)	11 (50.0)	0.410[b]
Age, median (min-max)		36 (18-65)	33 (19-62)	37 (18-65)	0.537[a]
Drug dose, (mg), median (min-max)		1000 (500-2000)	11000 (640-2000)	775 (500-2000)	0.036[a]
Admission time, (min)		60 (15-600)	60 (30-600)	0 (15-520)	0.288[a]
Drug intake, n (%)	Multiple drugs	15 (51.7)	6 (40.0)	9 (60.0)	0.588[b]
	Single drug	14 (48.3)	7 (50.0)	7 (50.0)	
Heart rate, (beats/min), median (min-max)		58 (48-92)	55 (48-60)	63 (48-92)	**0.031[a]**
Bradycardia, (≤ 60 beats/min), n (%)		19 (65.5)	12 (46.2)	7 (36.8)	**0.003[b]**
Systolic BP, (mmHg), median (min-max)		95 (40-120)	90 (40-110)	00 (70-120)	**0.015[a]**
Hypotension, (≤ 90 mmHg), n (%)		15 (51.7)	10 (66.7)	5 (33.3)	**0.014***
MAP, (mmHg), median (min-max)		70.86 ± 15.71	63.92 ± 16.02	76.50 ± 13.41	**0.029****
MAP, (≤ 70 mmHg), n (%)		15 (51.7)	10 (66.7)	5 (33.3)	**0.014***
PR distance, (ms), mean±SD		166 (110-242)	166 (116-242)	157 (110-240)	0.417[a]
Long PR, (≥ 200 ms), n (%)		6 (20.7)	4 (66.7)	2 (33.3)	0.364[b]
QRS distance, (ms), median (min-max)		88 (70-172)	88 (70-106)	6 (72-172)	0.481[a]
QRS (≥ 100 ms), n (%)		4 (13.8)	1 (25.0)	3 (75.0)	0.606[b]

QTc, (ms), median (min-max)	400 (350-550)	390 (370-440)	410 (350-550)	0.342[a]
QTc, (≥ 440 ms), n (%)	4 (13.8)	1 (25.0)	3 (75.0)	0.606[b]
Cardiovascular involvement, n (%)	15 (51.7)	10 (66.7)	5 (33.3)	**0.014***
Gastric lavage, n (%)	25 (86.2)	11 (44.0)	14 (56.0)	0.999[b]
Activated carbon, n (%)	25 (86.2)	11 (44.0)	14 (56.0)	0.999[b]
Therapeutic intervention, n (%)	15 (51.7)	10 (66.7)	5 (33.3)	**0.014***
Atropine	14 (48.3)	9 (64.3)	5 (35.7)	**0.042***
Dopamine	6 (20.7)	5 (83.3)	1 (16.7)	0.064[b]
Glucagon	3 (10.3)	2 (66.7)	1 (33.3)	0.573[b]
Symptomatic, n (%)	18 (62.1)	10 (55.6)	8 (44.4)	0.249[b]
Vomiting	6 (20.7)	2 (33.3)	4 (66.7)	0.663[b]
Dizziness	9 (31.0)	6 (66.7)	3 (33.3)	0.226[b]
Somnolence	3 (10.3)	2 (66.7)	1 (33.3)	0.573[b]
Chest pain	5 (17.2)	1 (20.0)	4 (80.0)	0.343[b]
Syncope	2 (6.9)	2 (100.0)	0	0.192[b]

*MAP; Mean Arterial Pressure, QTc; Corrected QT, a Mann Whitney U, * The Chi-square statistic, ** T test, b Fisher's Exact test*

Table 3. Intoxication severity and patient follow-up times in case of daily overdose

		Total, n=43	**Propranolol, (≥ 240 mg), n= 22**	**Metoprolol, (≥ 200 mg), n= 21**
Intoxication severity, n (%)	0 (no symptoms)	20 (46.5)	10 (50.0)	10 (50.0)
	1 (mild)	14 (32.6)	8 (57.1)	6 (42.9)
	2 (moderate)	7 (16.3)	2 (28.6)	5 (71.4)
	3 (severe)	2 (4.7)	2 (100.0)	0
	4 (death)	0	0	0
Follow up time, n (%)	24 hours	11 (25.6)	5 (45.5)	6 (54.5)
	24-48 hours	15 (34.9)	6 (40.0)	9 (60.0)
	48-72 hours	16 (37.2)	11 (68.8)	5 (31.3)
	72-96 hours	1 (2.3)	0	1 (100.0)

4. Discussion

The indications (angina pectoris, cardiac arrhythmias, thyrotoxicosis and migraine prophylaxis) for the use of these two B-blocker drugs, which are mainly used in the treatment of hypertension, are similar. In addition to being used in the treatment of essential tremor, hypertrophic obstructive cardiomyopathy, propranolol is also used “off-label” to treat fear of social situations, panic disorder and types of other anxiety disorders (10).

This study investigated propranolol and metoprolol toxicity in adults regardless of the intention of being exposed. Previous studies showed that propranolol is responsible for more exposure than other B-blockers and is associated with more deaths (1,3,9). In our study, it was found that propranolol and metoprolol did not differ in terms of the number of individuals exposed, gender and age.

It was found that the patients did not differ in terms of intoxication severity, frequency and distribution of symptoms following exposure. No optimal threshold at which patients became symptomatic was found for both drugs. The mean dose was found as 1256 (280-2000) mg for patients who took propranolol and as 468 (240-1000) mg for asemptomatik patients. While patients became symptomatic as the dose increased with propranolol, it was not the same with metoprolol. We could not answer with the available data whether this linear dose-response for propranolol was the class effect of B-blockers.

Neurological symptoms (seizure, delirium, somnolence, vomiting) have been reported due to high lipophilic propranolol and moderate lipophilic metoprolol, although B-blockers do not have strong sedative properties (9,11). Although there were no patients who had seizures in our study, somnolence, dizziness, and vomiting can be considered the symptoms of central nervous system depression. In terms of these symptoms, no difference was observed between groups in terms of overdose. Prominent symptoms were mainly bradycardia and hypotensive blood pressure measurements. There were more patients with bradycardia and hypotension in the propranolol group.

In a study investigating B-blocker cardiotoxicity, cardiotoxicity was found to be associated with notable ECG changes in most symptomatic patients. Negative dromotropic effects such as first-degree AV block and interventricular conduction delays were observed most frequently. Bradycardia (a negative chronotropic effect) was reported to be a less common manifestation (12). In our study, no difference was found between drug groups in terms of ECG findings. In terms of cardiovascular involvement, a statistically significant difference in favour of propranolol was found for intakes of >400 mg (p= 0,014). MSA characteristics of propranolol can be responsible for cardiovascular effects. Metoprolol is known to have high doses of MSA characteristics (5, 6).

Intravenous fluid (10-20 ml/kg saline) was started on all our patients regardless of their admission vitals. While 39.5% of the patients who exceeded the daily dose needed therapeutic intervention (atropine and/or dopamine), 51.7% of the overdose (≥ 400 mg) patients needed therapeutic intervention. A statistically significant difference in favour of the propranolol group was found in terms of atropine administration for overdose (p= 0,042). While there is weak evidence for the useful effects of glucagon, glucagon recommended in resistant shock was used only in three of our patients (13).

In our study, approximately half of the cases were symptomatic, but no deaths occurred. Groups were not found to differ significantly in terms of symptoms and intoxication severity. While there was a correlation between dose and symptoms for propranolol, there was no such correlation for metoprolol. Propranolol shows more cardiovascular effects

than metoprolol in overdose.

One of our study's limitations is that B-blocker doses were recorded according to patient reports without actual measurement of blood concentrations. For this reason, the reported doses were only predictions of potential exposure. Admission findings of the patients were obtained from records. To the best of our knowledge, there are no studies which make associations between and confirm intoxication severity and serum levels. Daily follow-up data of patients whose treatment processes started at admission were not included in the present study.

Conflict of interest

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Authors' contributions

Concept: F.Ö., M.A., C.K., Design: F.Ö., M.A., Data Collection or Processing: F.Ö., M.A., C.K., Analysis or Interpretation: F.Ö., M.A., Literature Search: F.Ö., M.A., C.K., Writing: F.Ö., M.A.

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