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Case Report

Lethal suicide attempt with a mixed-drug intoxication of metoprolol and propafenone — A first pediatric case report

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ABSTRACT

Introduction: The β1 adrenergic receptor blocker metoprolol is often prescribed together with the antiarrhythmic drug propafenone. Both are metabolized by cytochrome P450 2D6 and propafenone is also an inhibitor of this enzyme. We present a pediatric case showing metoprolol and propafenone intoxication in combination.

Case: A 14-year-old girl was admitted to a local emergency department after ingestion of metoprolol (probably 1 g) and propafenone (probably 1.5–3 g) in a suicide attempt. She developed cardiogenic shock with cardiac arrest and was fully resuscitated. Veno-arterial femorofemoral extracorporeal membrane oxygenation was started immediately. High serum levels of both drugs were detected approximately 10 h after ingestion (2630 ng/mL metoprolol and 2500 ng/mL propafenone). Other serial samples for the monitoring of the levels of metoprolol and its metabolite alfa-hydroxymetoprolol were obtained between days 2 and 4 after admission. The metoprolol/alfa-hydroxymetoprolol ratio on the 2nd day was 36.1, indicative of a poor metabolizer phenotype. The elimination half-life of metoprolol was prolonged to 13.2 h and the clearance decreased by about 70%. The patient condition gradually worsened, brain edema and intracerebral hemorrhage occurred, and on the 6th day, the patient died.

Conclusion: We document a pediatric case report of death due to a mixed drug overdose of metoprolol and propafenone, along with data regarding serum metoprolol, alfa-hydroxymetoprolol, and propafenone levels.

1. Introduction

Metoprolol, a commonly prescribed selective β1 adrenergic receptor blocker, is widely used to treat patients with various cardiovascular diseases. Blockade of the β1 receptor in the heart reduces the heart rate and myocardial contractility. It also blocks β-adrenergic receptors in the kidney and reduces plasma renin activity. Orally administered metoprolol is almost completely absorbed, although first-pass metabolism reduces its systemic availability by about 50%. Its lipophilicity and a low degree of binding to plasma proteins (about 12%) facilitate extensive distribution in and penetration into the central nervous system. After extensive hepatic metabolism via cytochrome (CYP) P450 2D6, metoprolol is excreted primarily as inactive metabolites. Total body clearance ranges between 43.2 and 92.4 L/h and elimination half-life is usually 3–4 h [1]. Metoprolol has a dose-dependent effect which increases with increasing daily doses up to complete β1 blockade at plasma concentrations >107 ng/mL. 30% of the maximum effect is necessary for a clinically significant effect; this limit was observed at a metoprolol plasma concentration of 12 ng/mL [2]. Metoprolol is involved in acute accidental intoxication or self-poisoning cases, including fatalities. The overdose-related toxic effects are mainly due to heart failure and severe respiratory problems [3]. Metoprolol levels resulting in toxicity were reported by Dupuis et al. [3] as 650 ng/mL and by Repetto and Repetto [4] as 1000 ng/mL, while lethal concentrations range between 3600–19800 ng/mL. However, there are a few case

Abbreviations: Cl, clearance; CYP, cytochrome P450; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; EM, extensive metabolizer; ICU, intensive care unit; IM, intermediate metabolizer; MR, metabolic ratio; PM, poor metabolizer; $t_{1/2}$, elimination half-life; UM, ultrarapid metabolizer.

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reports of successfully treated metoprolol intoxication with doses up to 50 g and concentrations higher than 10,000 ng/mL (Table 1) [5–11]. Propafenone is a well-known antiarrhythmic drug which is also metabolized through CYP2D6-mediated pathways, and it acts as an enzyme inhibitor [12,13]. The drug blocks sodium channels and also exhibits β-adrenergic and calcium channel-blocking activities. Stoschitzky et al. [14] classified propafenone as both a Class Ic and Class II antiarrhythmic agent, and the dosage currently recommended for cardioversion of paroxysmal atrial fibrillation results in clinically significant β-blockade. The drug can cause a number of electrocardiogram (ECG) changes, and overdosing may lead to congestive heart failure, conduction disturbance, hypotension and seizure. Few case reports of propafenone poisoning have been documented in the literature, and intoxication, particularly in amounts greater than 4 g, may be fatal [15–21]. Propafenone intoxication is uncommon in children and young people. However, it is frequently used by adults, a fact which makes propafenone an accessible drug [22]. Successful treatment of a young patient (17-year-old male) after ingestion of 3 g propafenone in a suicide attempt has been presented by Wożakowska-Kapłon and Stępień-Walek [23]. Another pediatric survival case (16-year-old girl) after intoxication with 6 g of propafenone has been described by Saz et al. [22] which was similar to a case reported by Ardiç et al. [24] in which a 17-year-old male ingested about 6 g of propafenone. The successful recovery of a young patient (18-year-old female) who ingested extremely large doses of propafenone (9 g) and captopril (1 g), both of which are known to have severe cardiac side effects, has been reported by Avci et al. [25] However, blood propafenone levels were not measured in these cases. Drug levels resulting in toxicity have been reported by Repetto and Repetto [4] as 2000 ng/mL, and lethal/postmortem levels as 7700 ng/mL (in children 800 ng/mL). The highest lethal drug concentration (12,000 ng/mL) was documented by Maxeiner and Klug [19] in a 20-year-old female who ingested 6 g of propafenone. We present, to our knowledge, the first pediatric case showing metoprolol and propafenone intoxication in combination, along with data regarding serum metoprolol, alfa-hydroxymetoprolol, and propafenone levels.

2. Materials and methods

A 14-year-old Caucasian girl (weighing approximately 55 kg) with no prior history of cardiac disease was admitted to the emergency department of a local hospital having ingested probably 1 g of metoprolol (Vasocardin 50 mg tablet, oral use, Zentiva, Slovakia) and about 1.5–3 g of propafenone (Rytmonorm 150 mg film-coated tablet, oral use, BGP Products Czech Republic) in a suicide attempt. However, the precise amount of each drug and the exact time of ingestion were unknown. She showed loss of consciousness, seizures, and widening of the QRS-complex on an ECG; spontaneous breathing was observed. Clinical signs and symptoms of intoxication were recorded in the patient chart. High serum levels of metoprolol (2630 ng/mL) and propafenone (2500 ng/mL) were measured approximately 10 h after ingestion. Other serial samples for the monitoring of metoprolol and its metabolite alfa-hydroxymetoprolol were obtained between the 2nd and the 4th day of hospitalization, and were analyzed by high-performance liquid chromatography with fluorescence detection at 230 and 300 nm by Perinova et al. [26] with minor modification. Metoprolol, α-hydroxymetoprolol and the internal standard nadolol were extracted from 200 μL of serum with 50 μL 1 M NaOH following by extraction with 1.5 mL of dichloromethane. Chromatographic separations were performed on the reversed-phase column Supercosil^{TM} LC-18 (15 cm × 3 mm, 5 μm) with the mobile phase consisting of acetonitrile: metanol: water: triethylamine (14:5:81:0.05, pH 3.8) at a flow rate of 0.7 mL/min. The total analysis lasted 12 min. The retention time was 2.04 min for α-hydroxymetoprolol, 3.02 min for nadolol and 9.04 for metoprolol. The limit of detection was 3 ng/mL and the limit of quantification 5 ng/mL for both metoprolol and α-hydroxymetoprolol. The intra-assay and inter-assay coefficients of variation were less than 7.2% and the recovery values were observed between 98.2–103.0%. The calibration curve was linear over a concentration range of 5–500 ng/mL for both compounds [26]. Pharmacokinetic analysis of metoprolol levels was performed using software MWPharm version 3.30 and interpreted by a clinical pharmacologist. Ethics Committee approval was obtained for publication.

3. Results

After admission, the clinical condition of the patient deteriorated rapidly. She developed cardiogenic shock including severe hypotension (65–85/45–50 mmHg) and bradycardia (50 beats per minute). At this time, electromechanical dissociation with circulatory arrest occurred. The patient was fully resuscitated, ventilated, and high doses of catecholamines and β-mimetic drugs (adrenaline and isoprenaline) were administered. Glucagon (a β-blocker antidote) and activated charcoal were also administered. An attempt at external temporary cardiac paging using an endovascular electrode introduced through the internal jugular vein into the right ventricle was made. However, the stimulation

Table 1
Metoprolol plasma levels in intoxications with lethal or reversible outcome [5–11,27].

Reference	Number of subjects	Lethal intoxication Reversible intoxication	Quantity ingested (g)	Plasma levels (ng/mL) Lethal intoxication	Plasma level (ng/g or ng/mL) Reversible intoxication
Moller [5]	1	0			
		1	10		12,200
Sire [6]	1	0			
		1	Unknown		13,100
Wallin and Hulting [7]	1	0			
		1	50		18,000
Stajić et al. [8]	1	1	Unknown	4700	
		0			
Rohrig et al. [9]	1	1	Unknown	19,800	
		0			
Takahashi et al. [10]	1	0			
		1	2		680
Kinoshita et al. [11]	1	1	Unknown	3600	
		0			
Page et al. [27]	1	0			
		1	5		13,570