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CASE REPORT

Acute fatal poisoning with pilsicainide and atenolol

W. Hikiji · K. Kudo · N. Nishida · T. Ishida · Y. Usumoto · A. Tsuji · N. Ikeda

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Abstract A fatal case of intentional poisoning with two antiarrhythmic agents, pilsicainide, a pure sodium channel blocker, and atenolol, a selective β1 blocker, is presented. A woman in her twenties was found dead at home and empty pill packages of pilsicainide, atenolol, and aspirin were found near by. Hesitation marks were found on the wrist, and strong fibrous degeneration was observed in the cardiomyocytes of the sinoatrial node. The blood concentrations of pilsicainide and atenolol were 7.83 and 4.94 μg/ml, respectively, both far above the reported therapeutic levels. According to these results, we concluded that death was due to cardiac arrhythmia caused by poisoning with pilsicainide and atenolol. This is the first report of fatal poisoning attributable to an overdose of the combination of these two antiarrhythmic drugs.

Keywords Pilsicainide · Atenolol · Poisoning · Cardiac arrhythmia

Introduction

Pilsicainide is a pure sodium channel blocking agent developed in Japan [1], prescribed for the treatment of re-entrant supraventricular and ventricular tachyarrhythmia. Atenolol is a selective β1 adrenergic antagonist, prescribed for the treatment of hypertension, ischemic heart disease, and certain dysrhythmias [2]. Both pilsicainide and atenolol have the potential to cause severe cardiac complications in overdose according to the literature [3–16], but no case of fatal poisoning has been previously reported for the combination of these two drugs. We present here a fatal case of combined, intentional poisoning of pilsicainide and atenolol in an adult female with a literature review.

W. Hikiji · K. Kudo · T. Ishida · Y. Usumoto · A. Tsuji · N. Ikeda (✉)
Department of Forensic Pathology and Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan
e-mail: norii@forensic.med.kyushu-u.ac.jp

W. Hikiji
e-mail: hikiji@forensic.med.kyushu-u.ac.jp

N. Nishida
Department of Legal Medicine, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan

Case history

A woman in her twenties with a medical history of depression was found at home in a state of cardiac pulmonary arrest and death was confirmed on arrival at hospital. Although she had no regular medication, packages of pilsicainide (12 tablets × 25 mg, total of 300 mg), atenolol (six tablets × 50 mg, total of 300 mg), and aspirin (eight tablets × 100 mg, total of 800 mg) were found empty in her room. It was suspected that she had taken the tablets from a medical clinic, where she worked as a clerical assistant. She had no prior history of either cardiovascular or cerebrovascular disease.

Autopsy findings

Gross findings

An autopsy was carried out 15 h after death. The decedent was 144 cm in height and weighed 44 kg. Three parallel superficial incisions were seen on the left wrist, which were considered to be hesitation marks. Five pill residues were

found in the stomach, and the legible letters written on the tablets suggested that they were aspirin. The heart weighed 186 g and the left ventricle was slightly dilated. The remainder of the external and internal examination revealed a healthy individual.

Microscopic findings

The cardiomyocytes of the sinoatrial node showed strong fibrous degeneration (Fig. 1). The coronary arteries were free of atherosclerosis and the lungs showed severe congestion and prominent edema, with collapse of alveolar spaces. The kidneys showed focal interstitial nephritis but no evidence of significant infectious destruction.

Toxicological examination

No alcohol or other volatile compounds in a blood specimen were revealed by head space-gas chromatography (GC) with a flame ionization detector. Drug screening for acidic, neutral, and basic drugs and chemicals by gas chromatography–mass spectrometry (GC–MS) and high performance liquid chromatography (HPLC) using whole blood and urine samples confirmed the presence of pilsicainide and atenolol. Concentrations of pilsicainide and atenolol in right and left heart blood and urine were determined by GC–MS and HPLC, respectively with slight modifications to previously published methods [17, 18]. The results are shown in Table 1. Post-mortem toxicology did not reveal any other toxic substances, including salicylate, a metabolite of aspirin.

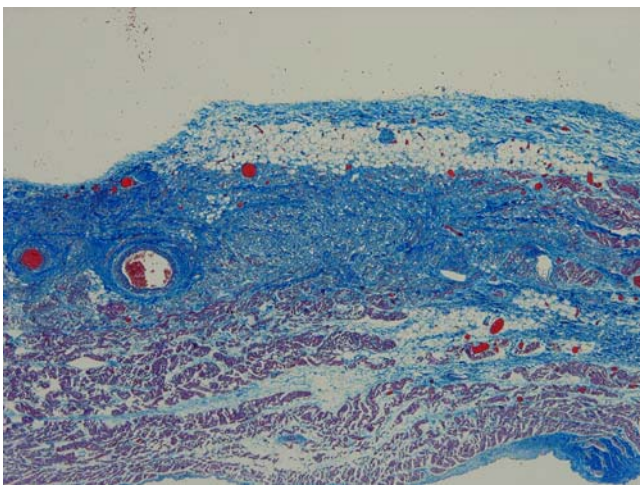

Fig. 1 High-power view of the fibrous changes in the cardiomyocytes of the sinoatrial node (Elastica–Masson staining ×40)

Table 1 The concentrations of pilsicainide, atenolol, aspirin (μg/ml) detected in this case

	Pilsicainide	Atenolol	Aspirin
Right cardiac blood	7.83	4.94	–
Left cardiac blood	8.01	5.58	–
Urine	8.33	4.55	–

Discussion

Antidepressants are often selected for intentional poisonings for their accessibility [19] and cardiovascular drugs are not commonly associated with suicides in general. However, poisoning with cardiovascular drugs is often associated with significant morbidity and mortality [20].

Pilsicainide is a tertiary amine pyrrolizine analogue of lidocaine [21], produced by the Biomedical Institute of Suntory Limited, Japan. Therefore, to date, clinical data regarding this drug have been limited to investigations in Japan. It is considered highly effective and safe as it specifically blocks sodium channels without interfering with other channels [22]. Pilsicainide inhibits depolarization of non-nodal cardiomyocytes, slowing down the regeneration and transmission of action potentials between cells and reducing the conduction velocity of the heart. As a result, it suppresses isolated ectopic beats and prolongs the atrial effective refractory period to pharmacologically terminate atrial fibrillation [22, 23]. Previous studies reported that pilsicainide prolonged PQ and QRS intervals in a dose-dependent manner [24]. In the few reported clinical cases of pilsicainide intoxication, common electrocardiographic changes, such as PQ, QRS, and QTc prolongation, some of them leading to atrioventricular dissociation, Brugada syndrome such as ST-segment elevation, and idioventricular rhythm, have been observed [3–5].

Atenolol is a selective β1 adrenergic antagonist. The very high blood concentration of the β-blocking agents decreases sinoatrial node function, as well as automaticity, contractility, and conduction velocity of the heart by depressing membrane stability and blocking not only β receptors but also sodium channels [25, 26], although these phenomena are more prominent in lipophilic agents such as propranolol than in hydrophilic agents including atenolol. As a result, various cardiovascular dysfunctions, including bradycardia, hypotension, high-degree blocks, junctional rhythms, and intraventricular conduction delays, can be present with increasing toxicity [27], which can result in asystole.

The blood specimens in this case were obtained from cardiac blood which could have been influenced by the agonal flow towards the large vessels and the redistribution

of basic lipophilic molecules from lung parenchyma and stomach content [28]. However, no significant postmortem change was seen in neither femoral nor cardiac blood concentrations of atenolol, metoprolol, and propranolol in the study by Pelissier-Alicot et al. [29]. It is therefore considered that the blood concentrations of both pilsicainide and atenolol at death are not significantly different to the values obtained in our laboratory, 15 h postmortem.

The pathological findings of the decedent, including congested and edematous lungs and the cardiac abnormalities, are consistent with death attributable to drug poisoning. The fibrous degeneration of the sinoatrial node is most likely to be congenital, as the decedent had no regular medication to cause such a change and it does not result from acute antiarrhythmic drug poisoning. However, it may have contributed to the outcome such as hastening the death. Tablet residues of aspirin were found in the gastric content but had no effect on the death as neither the original drug nor the metabolites were detected in blood or urine of the decedent. It is therefore suspected that the decedent ingested aspirin tablets shortly before death, several hours after the ingestion of pilsicainide and atenolol.

Pilsicainide reaches average plasma peak concentrations of 0.65 μg/ml within 1–2 h of a single oral dose of 100 mg, whereas atenolol reaches 0.16 μg/ml within 2–3 h of a dose of 50 mg in humans without renal dysfunction, according to previous reports [30, 31]. The right cardiac blood level of each drug in our decedent was 7.83 and 4.94 μg/ml, respectively, which were both clearly consistent with an overdose, and implied that she had taken at least all the tablets left in her room at once. The concentrations of pilsicainide and atenolol in urine were 8.33 and 4.55 μg/ml, respectively, both close to those in blood. This indicates that the victim was alive for several hours until both drugs were absorbed, reaching an early stationary phase and then excreted in the urine, as the average peak blood concentrations are reached 1–2 h after the ingestion of pilsicainide and 2–3 h after the ingestion of atenolol [32, 33]. We therefore concluded that death was due to cardiac arrhythmia caused by the combined intoxication with pilsicainide and atenolol.

The presented case is the first reported fatal poisoning attributable to the combination of the two antiarrhythmic drugs mentioned. Although there is a wide variability in patient responses to antiarrhythmic drugs, it is indicated that both pilsicainide and atenolol are potentially fatal in overdose situations, even in young people.

References

1. Kumagai K, Nakashima H, Tojo H et al (2006) Pilsicainide for atrial fibrillation. Drugs 66:2067–2073
2. Hoffman BB, Lefkowitz RJ (1996) Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Goodman LS, Gilman A, Hardman JG, Limbird LE (eds) Goodman & Gilman's the pharmacological basis of therapeutics, 9th edn. McGraw Hill, New York, pp 199–248
3. Nakata K, Moriwaki R, Yamaguchi A, Takenouchi S, Mato T, Tsutsumi H (2006) Case in which magnesium sulfate effectively treated ventricular tachycardia due to overdose of pilsicainide hydrochloride. Chudoku Kenkyu 19:49–53
4. Horita Y, Kanaya H, Uno Y et al (2004) A case of the toxicity of pilsicainide hydrochloride with comparison of the serial serum pilsicainide levels and electrocardiographic findings. Jpn Heart J 45:1049–1056
5. Ozeki S, Utsunomiya T, Matsuo S, Yano K (1999) Pilsicainide intoxication in a patient with dehydration. Jpn Circ J 63:219–222
6. Petrov D, Sardowski S, Geshava M (2007) 'Silent' Prinzmetal's ST elevation related to atenolol overdose. J Emerg Med 33:123–126
7. Love JN, Elshami J (2002) Cardiovascular depression resulting from atenolol intoxication. Eur J Emerg Med 9:111–114
8. Snook CP, Sigvaldason K, Kristinsson J (2000) Severe atenolol and diltiazem overdose. J Toxicol Clin Toxicol 38:661–665
9. Pertoldi F, D'Orlando L, Mercante WP (1998) Electromechanical dissociation 48 hours after atenolol overdose; usefulness of calcium chloride. Ann Emerg Med 31:777–781
10. Delima LG, Kharasch ED, Butler S (1995) Successful pharmacologic treatment of massive atenolol overdose: sequential hemodynamics and plasma atenolol concentrations. Anesthesiology 83:204–207
11. Stinson J, Walsh M, Feely J (1992) Ventricular asystole and overdose with atenolol. BMJ 305:693
12. Saitz R, Williams BW, Farber HW (1991) Atenolol-induced cardiovascular collapse treated with hemodialysis. Crit Care Med 19:116–118
13. Abbasi IA, Sorsby S (1986) Prolonged toxicity from atenolol overdose in an adolescent. Clin Pharm 5:836–837
14. Freestone S, Thomas HM, Bhamra RK, Dyson EH (1986) Severe atenolol poisoning: treatment with prenalterol. Hum Toxicol 5:343–345
15. Weinstein RS, Cole S, Knaster HB, Dalbert T (1985) Beta blocker overdose with propranolol and with atenolol. Ann Emerg Med 14:161–163
16. Montgomery AB, Stager MA, Schoene RB (1985) Marked suppression of ventilation while awake following massive ingestion of atenolol. Chest 88:920–921
17. Ishida T, Kudo K, Inoue H, Tsuji A, Kojima T, Ikeda N (2006) Rapid screening for and simultaneous semiquantitative analysis of thirty abused drugs in human urine samples using gas chromatography–mass spectrometry. J Anal Tox 30:468–477
18. Venkatesh G, Ramanathan S, Mansor SM et al (2007) Development and validation of RP-HPLC-UV method for simultaneous determination of buparvaquone, atenolol, propranolol, quinidine and verapamil: a tool for the standardization of rat in situ intestinal permeability studies. J Pharm Biomed Anal 43:1546–1551
19. Drasch G, Dahlmann F, von Meyer L, Roider G, Eisenmenger W (2008) Frequency of different anti-depressants associated with suicides drug deaths. Int J Legal Med 122:115–121
20. Watson WA, Litovitz TL, Rodgers GC Jr et al (2005) 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 23:589–666
21. Miyano S, Sumoto K, Satoh F et al (1985) New antiarrhythmic agents. N-aryl-8-pyrrolizidinealkamides. J Med Chem 28:714–717
22. Hattori Y, Hidaka T, Aisaka K, Satoh F, Ishihara T (1988) Effects of SUN 1165, a new potent antiarrhythmic agent, on the kinetics

of rate-dependent block of Na channels and ventricular conduction of extrasystoles. J Cardiovasc Pharmacol 11:407–412
23. Kanki H, Mitamura H, Takatsuki S et al (1998) Postrepolarization refractoriness as a potential anti-atrial fibrillation mechanism of pilsicainide, a pure sodium channel blocker with slow recovery kinetics. Cardiovascular Drugs and Therapy 12:475–482
24. Satoh S, Watanabe J, Keitoku M et al (1989) Effects of N-(2,6-dimethylphenyl)-8-pyrrolizine acetamide hydrochloride hemihydrate on the ventriculo-atrial conductivity of accessory pathways. Arzneimittel-Forschung Drug Res 39:908–911
25. Holstege CP, Eldridge DL, Rowden AK (2006) ECG manifestations: the poisoned patient. Emerg Med Clin North Am 24:159–177
26. Reith DM, Dawson AH, Epid D, Whyte IM, Buckley NA, Sayer GP (1996) Relative toxicity of beta blockers in overdose. J Toxicol Clin Toxicol 34:273–278
27. Delk C, Holstege CP, Brady WJ (2007) Electrocardiographic abnormalities associated with poisoning. Am J Emerg Med 25:672–687
28. Moriya F, Hashimoto Y (1999) Redistribution of basic drugs into cardiac blood from surrounding tissues during early-stages postmortem. J Forensic Sci 44:10–16
29. Pelissier-Alicot AL, Gaulier JM, Dupuis C et al (2006) Postmortem redistribution of three beta-blockers in the rabbit. Int J Legal Med 120:226–232
30. https://www.daiichisankyo.co.jp/med/contents/di/sr1/if/pdf/if_sr_cap_0801_06.pdf
31. Ishizaki T, Oyama Y, Suganuma T et al (1983) A dose ranging study of atenolol in hypertension: fall in blood pressure and plasma renin activity, beta-blockade and steady state pharmacokinetics. Br J Clin Pharmacol 16:17–25
32. Maeno K, Ikeda T, Takada S, Kobayashi K, Bunko H, Hisada K (1990) The effect of oral SUN-1165 on hemodynamics at rest and during exercise in patients with ischemic heart disease. Jpn Pharmacol Ther 18:4051–4057
33. Baselt RC (ed.) (2002) Disposition of toxic drugs and chemicals in man, 7th ed. Biomedical Publications, Foster City, CA, pp 87–88