Case Report

รายงานผู้ป่วย

Death from midazolam and atracurium poisoning: A case report

การตายจากไมด้าโซแลมและอะทราคิวเรียม: รายงานการชันสูตรพลิกศพหนึ่งราย

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บุญศักดิ์ หาญเทอดสิทธิ์ พ.บ.

ภาคสาขาวิชานิติเวชศาสตร์ กลุ่มงานเวชศาสตร์ฉุกเฉินและนิติเวช โรงพยาบาลมหาราช นครราชสีมา, นครราชสีมา 30000, ประเทศไทย

Abstract

The author reports a nurse anesthetist who died from self-injected intravenous midazolam with atracurium. Reported suicides committed by this method have been performed by knowledgeable persons with easy access to these medicationsม, however, the combination of midazolam with atracurium has not been reported in Thailand. The high index of restriction for taking these drugs will reduce the possibility of suicide by this method.

Keywords: midazolam, atracurium, suicide

บทคัดย่อ

ผู้เขียนได้รายงานการตายของวิสัญญีพยาบาลซึ่งฉีดยาที่มีส่วนผสมของไมด้าโซแลมและอะทราคิวเรียมเข้าเส้นเลือดเพื่อฆ่าตัวตาย โ ดยการตายลักษณะนี้เคยมีรายงานมาบ้างซึ่งมักกระทำโดยบุคลากรผู้มีความรู้และสามารถเข้าถึงยาได้ง่าย ดังนั้น การป้องกันการเข้าถึงยาและการใช้ยาอย่างเข้มงวดจะช่วยลดการฆ่าตัวตายโดยวิธีนี้ได้

คำสำคัญ: การเป็นพิษจากไมด้าโซแลมและอะทราคิวเรียม, ฆ่าตัวตาย

Introduction

Midazolam and atracurium are widely used in the anesthetic department and should be used under supervision of anesthesiologist or a special physician. Deaths from intravenous injection of midazolam with other medication have been reported. The manner of death was either suicide1, 2, an accident3 or even murder4. Atracurium has also been reported as the cause of death from suicide5. However, there is no report of death from intravenous midazolam in combination with atracurium. We report an

anesthetic nurse who died from self-injected midazolam with atracurium, and overview of previously reported cases.

Case report

A 30-year-old anesthetic nurse was found death in her room at about one a.m. in January. The scene investigation showed that the body was lying face-up in the bed. She was dressed in pajamas with the lower half of her body covered with a blanket. Her right arm was wrapped loosely with fabric. There was a syringe (5 ml) with a needle contained 0.2 ml of pale red fluid, two blood stained needles (gauge 25), three needles (gauge 18) without blood stained, and one empty syringe (5 ml) labeled “dormicum 1 mg/ml” on the right side of her body (on the bed). Multiple dry blood stained cotton buds, and rat killer named “Sed-Ar” were also found on the right side of the body. On the left side of the body, there were two mobile phones and one empty teflon-topped glass ten ml container. There was a small amount of alcohol in a bottle of alcoholic beverage and a suicide note on the table near the bed. According to the police investigation, the room was closed with latch from inside and there were no signs of foul play. The initial body examination at the scene showed multiple recent injection marks on the dorsum of both hands and dorsum of the right foot. There were recent multiple contusions on the lower extremities and dry fine frothy fluid in both nostrils. The estimated time of death was approximately 24-36 hours before the body was found. There was no history of drug allergy. An autopsy was performed ten hours after the body was discovered. The body was a thin female, 163 cm in length with shoulder-length hair. There were four recent injection marks on the dorsum of the right hand, six recent injection marks on the dorsum of the left hand, and four recent injection marks on the dorsum of the right foot. There were non-patterned recent multiple contusions, one to five centimeters in diameter, on the anterior aspect of the left thigh, right knee, and anterior aspect of both legs. The internal examination showed no evidence of injury to the vital organs. The brain had no pathological lesion (1,200 gm). The thyroid gland was normal shape and size. The airways showed no edema or foreign body obstruction, but the trachea was filled with fine frothy fluid. Both lungs showed a moderate degree of edema without any lesions or masses. There was no pulmonary thrombo-embolism. The right and the left lung weighed 450 g and 430 g, respectively. The heart had a normal shape and size. All major coronary arteries were widely patent. Neither valvular abnormality nor congenital anomaly was observed. There was no vegetation on the heart valves. The heart and lungs had a mild degree of putrefaction. There was no evidence of peritonitis. The liver, spleen, small bowel, large bowel, kidneys adrenal glands and pancreas had no significant gross pathologic abnormality. No evidence of acute pyelonephritis was detected. The retroperitoneal region had no blood collection. The pelvic organs

showed no significant gross lesions. The uterus and ovaries were of normal size and shape. There was 20 milliliters of turbid brownish liquid in the stomach. The gastric mucosa showed generalized severe gastritis. The femoral blood, inferior vena cava (IVC) blood, gastric contents, urine, and "Sed-Ar" (rat killer) were submitted for toxicological analysis at the Regional Medical Science Center, Chiang Mai province. The bloody fluid content in the syringe which was recovered at the scene and femoral blood were submitted for toxicological analysis at the Forensic Department, Faculty of Medicine, Chiang Mai University, Chiang Mai Province. The results of the toxicological analysis were presented in Table 1. According to the hospital investigation, the midazolam and atracurium were stolen from her work place.

Specimens	Analytical techniques	Results
NaF tube (grey-top)	GC-HS (Varian space autosampler: Varian	Methanol 19.4 mg%
(no preservative)	Spectrophotometry (UV-Vis Spectrophotometer: Jasco	Cholinesterase activity 4,756 IU/mL
(no preservative)	LC/MS/MS (Ion Trap), Model Bruker Esquir HCT Extraction method: Blood 1 ml adjust pH 9-10 with buffer 1 ml, extract with BuCl 8 ml, dissolve with MeoH 200 uL, inject to LC/MS/MS	Negative for benzodiazepines
EDTA tube (purple-top)	HPLC (solvent delivery sytem varian 9012Q; UV-Vis detector ProStar: Varian 9050; Method I: column C18 250 x 4.6 mm, 5µm (Ascentis guard column C18 Method II : column C8 125 x 4.6 mm, (Luna phenomenex and guard column C8; Bond Elut-C18, 500 mg 3 mL (Varian))	(sensitivity 1,600 ng/mL)
Gastric contents	Thin layer chromatography (Silica gel 60 F254: MERCK	organochlorine, carbamate, in coumatetaryl, warfarin, coumarin
	Gutzeit's test	Negative for Zinc phosphide
	Reinsch's test	Mercury, bismus
Urine 20 ml	Thin layer chromatography (Silica gel 60 F254: MERCK	Negative for MA, Morphine
Rat killer named "Sed-Ar"	Thin layer chromatography (Silica gel 60 F254: MERCK	organochlorine, carbamate, coumatetaryl, w

Specimens	Analytical techniques	Results
Fluid content in syringe	HPLC (solvent delivery sytem varian 9012Q; UV-Vis detector ProStar: Varian 9050; Method I: column C18 250 x 4.6 mm, 5µm (Ascentis guard column C18 Method II : column C8 125 x 4.6 mm, (Luna phenomenex C8; Bond Elut-C18, 500 mg 3 mL (Varian))	(sensitivity 1,600 ng/mL)
	REMEDi HS (Automated HPLC)	Found Atracurium; sensitivity 47 ng/mL

Table 1. Results of toxicological analysis

Discussion

Midazolam is a short-acting benzodiazepine which is widely used in the anesthetic department as pre-medication in the surgical patient. It is also use for treatment for status epilepticus. In Thailand, midazolam is available as a 0.5 percent solution, in ampules of one ml (5mg/ml) and three ml (15 mg/3 ml) of midazolam hypochloride, for intravenous administration. The dosage for intravenous pre-medication ranges between 0.1-0.3 mg/kg6 and should be injected slowly. In general, the sedative and hypnotic dose is 1-2 mg. The onset of action is about 30 seconds depending on rate of intravenous injection. After IV administration, peak effect is seen within two to three minutes and the duration of retrograde amnesia is 20 to 30 minutes7. The duration of action is about 15–20 minutes. Midazolam is three to four more times more potent than diazepam7. Although midazolam-related death is very rare because of wide therapeutic ranges (table 2) death from rapid intravenous injection of midazolam have been reported due to respiratory depression4, 8, 9 and anaphylactic reaction10. However, prompt detection and treatment are the important factor of death prevention in clinical practice11, 12. The postmortem diagnosis for anaphylaxis and allergic reaction are more difficult than clinical diagnosis because it base on serology and skin tests. Serum tryptase and histamine may helpful as indicators of anaphylactic reactions, but delayed postmortem interval blood sampling may have some influence on postmortem tryptase concentrations13.

Note	Sex	Age (yr.)	Occupation	Medication	Method, dose	Result	Postmortem blood level/ Method for detection	COD	MOD	Ref.
-	NA	NA	NA	Amitriptyline, perphenazine, and midazolam	NA	Dead	NA	probably resulted from drug cardiotoxicity	S (depression)	1
-	NA	NA	Nurse from the anaesthesiology department	Ultiva (2 mg) and Dormicum (1 mg/mL)	IV	Dead	metabolite of remifentanil midazolam by GC/MS-EI	NA	NA	2
Pre-mortem blood 2800 ng/ml	M	63	unknown	Midazolam	10 mg (2 ml) IV	Dead	2400 ng/ml (HPLC)	Respiratory depression	A	3
-	F	48	unknown	Midazolam + cyanide	Probably rapid IV bolus	Dead	Midazolam 20 ng/mL, cyanide 0.2 µg/mL (GC/MS, HPLCDAAD)	Probably respiratory depression	H	4
Therapeutic range	M	66	unknown	Midazolam	Probably rapid IV bolus	Dead	30 ng/mL (GC/MS, HPLCDAAD)	Probably respiratory depression	H	4
Therapeutic range	M	69	unknown	Midazolam	Probably rapid IV bolus	Dead	40 ng/mL (GC/MS, HPLCDAAD)	Probably respiratory depression	H	4
-	M	45	Anesthesiologist	Atracurium	IV	Dead	Laudonosine 500 ng/ml (GC-NPD for screening, GC-MS for confirmation)	Atracurium overdose	S	5

Note	Sex	Age (yr.)	Occupation	Medication	Method, dose	Result	Postmortem blood level/ Method for detection	COD	MOD	Ref.
-	NA	NA	NA	sufentanil and midazolam	NA	NA	Sufentanil in blood 1.1 ng/mL (GC/MS), midazolam in blood 50 ng/mL (HPLC +GC/MS)	intoxication	S	8
-	M	31	patient	Morphine 50 mg + Midazolam 50 mg	Rapid IV injection within 10 min	Alive, hypotension, treatment with IV crystalloid until recover	No	-	-	9
-	M	39	unknown	1 mg of Midazolam	IV	Alive	-	hypersensitivity	A	10
-	M	68	unknown	Midazolam 10 mg + Atropine 0.5 mg	IM	Alive, no complication	-	-	A	11
-	M	45	unknown	Midazolam 20 mg + Atropine 0.5 mg	IM	Alive, no complication	-	-	A	11
probably from given drugs (no other causes)	F	44	unknown	50 + 50 μg of fentanyl IV	Oral and IV	Alive, apnea for an hour	No blood test	-	A	12
-	F	45	Nurse in surgical clinic	Laudanosine, unknown amount	IV injection on the wrist	Dead	Cardiac blood 917 ng/ml	Therapeutic dose without mechanical ventilation	S	16

Note	Sex	Age (yr.)	Occupation	Medication	Method, dose	Result	Postmortem blood level/ Method for detection	COD	MOD	Ref.
-	M	53	unknown	Midazolam	Oral (drug smuggled)	Dead	whole blood was estimated to be 163 ng/ml. (LOD: 300 pg/ml by HPLC/ FAB-MS)	Strangulation	H	18

Table 2. Overview of case reports

a Cause of death

b Manner of death: S=suicide, A=accident, H=homicide

c Not available

d Intravenous

e Intramuscular

Atracurium is a non-depolarizing muscle relaxant which is usually used in anesthetic department for endotracheal intubation and surgery. In Thailand, atracurium is available as a one percent solution, in ampules of 1, 2.5 and 5 ml of the besylate salt, for intravenous administration. The normal dose is 0.5-0.6 mg/kg with slow intravenous injection (more than 10-20 seconds). The onset of action is 3-5 minutes and duration is 20-45 minutes14. Atracurium may cause hypotension due to blocking the acetylcholine at the sympathetic ganglia14 and by the mechanism of histamine release, depending on the dose especially more than 0.5 mg/kg15. Laudanosine, a tertiary amine, is an active metabolite of atracurium's Hofmann elimination (A spontaneous non-enzymatic chemical breakdown occurs at physiological pH and temperature) and has been associated with central nervous system excitation, resulting in the precipitation of seizures15. Anaphylaxis and anaphylactoid reaction induced by atracurium have been reported (non-dose-related) 14, 15. In this case, the only positive finding for toxicological analysis was midazolam and atracurium in the syringe recovered from the scene. Undetected midazolam and atracurium in blood specimens might result from small amount of the drugs which might cause death due to anaphylaxis and rapid self-injection or from limitations of the detection method. In addition, laudanosine is the major active metabolite of atracurium and is more stable in vitro, so this should be the focus of evaluations16. That the post-mortem degradation of drug in blood samples is time-dependent and causes decreased drug concentration should also be considered. A previous study showed that blood midazolam has high post-mortem stability at room

temperature17 which indicates that undetected midazolam in blood samples is caused mainly by a very low level of midazolam, not caused by post-mortem degradation. High sensitivity method for detection of small amount of midazolam18 may be helpful. Multiple recent injected wounds on the body indicated a high intention to die with several attempts. The tissue around the sites of injection may be helpful for toxicological analysis of suspected drugs. In conclusion, the cause of death in this case was presumed that the rapid venous injection of midazolam in combination with atracurium by the mechanism of respiratory depression and may have been combined with an allergic reaction. The syringe that contained midazolam and atracurium is only the significant clue for the conclusion of the cause of death; therefore the scene investigation is very important for suspected poisoning. The manner of death was concluded as suicide based on scene investigation, external body examination, autopsy findings, and toxicological analysis. The high level of control system is very important for prevention of misuse of anesthetic drugs, especially in the hospital. According to the Thai law, midazolam is considered in the second class of controlled psychotic drugs and substances which must be possessed by permission19, 20.

Conflict of interest

This research complies with the current laws of Thai and has no conflict of interest.

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