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CASE REPORT

Two fatal and four surviving cases after accidental infusion of ropivacaine

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Abstract

Purpose In this paper, we describe six cases, where patients were falsely treated with pre-filled ropivacaine solution instead of medical saline solution for postoperative settings. Two of the patients died because of fatal concentrations of ropivacaine in blood, four survived with no further physical injury, and two of them showed typical intoxication symptoms. The collected blood and urine samples of the deceased, as well as the surviving patients, were analyzed in laboratory routine screening.

Methods Ropivacaine and its main metabolite 3-OH-ropivacaine were analyzed by gas chromatography–mass spectrometry.

Results All of the six cases showed positive blood results of ropivacaine. Due to the poorly secured sample material of the survived patients at hospital, the quantitative examination of 3-OH-ropivacaine could not be carried out. In one fatal case, there were ropivacaine and 3-OH-ropivacaine traceable in urine. In all cases, metamizole was found in blood and traces of piritramide in urine. The amount of metamizole was within the upper limits of therapeutical treatment values. Patients with lower blood concentrations of ropivacaine showed more physical symptoms as compared to those with higher concentrations of active substances.

Conclusions In the context of symptom development and intoxication, the speed of injection was a very important factor to cause fatal ropivacaine cases. To our knowledge, these are the first reported cases of fatal intoxication with ropivacaine.

Keywords Ropivacaine · 3-OH-ropivacaine · GC–MS · Analgesic · Malpractice · Fatal poisoning

Introduction

Optimal peri- and postoperative pain management operates on a multidisciplinary basis, combining individual patient-related variables with current management guidelines. In this context, the application of amide-type local anaesthetics through epidural or perineural catheters plays an important role [1, 2]. The amide-type local anaesthetics lidocaine, bupivacaine and ropivacaine are commonly used for pain control. These substances reversibly inhibit regional sensory nerve impulse conduction without affecting consciousness. As one possible and in some cases even severe side-effect, cardiotoxicity has been described in the medical literature [3, 4].

Because of several deaths after the use of bupivacaine and etidocaine, the development and search for drugs with less cardiotoxicity was necessary. Thus, ropivacaine was developed and introduced to the market as an alternative to bupivacaine [5]. It is a newer long-acting amide-local anaesthetic drug, which is available as an optically pure solution. Ropivacaine-hydrochloride is the hydrochloride salt of 1-propyl-2′, 6′-pipecoloxylidide and is prepared as a pure *S*-enantiomer. Because of the *N*-propyl-group, ropivacaine is less lipid-soluble than bupivacaine [6], but with a similar pharmacokinetic disposition for protein binding in plasma and blood/plasma concentration ratio. Studies showed that 94% of ropivacaine will be bound to plasma proteins [7]. In vivo, ropivacaine has shown less cardiotoxicity than equal concentrations of bupivacaine and lidocaine and had a significantly higher threshold for central nervous system (CNS) toxicity than bupivacaine [8]. The significantly lower cardiotoxicity could be explained by its faster dissociation from cardiac Na^+ channels and studies suggested, that the "*S*"-enantiomer was less toxic than the "*R*"- enantiomer [5, 9].

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Due to its good tolerance and low side-effects, ropivacaine has been a well-known drug, which is used in postoperative pain management for adults [8] and children [10].

The terminal elimination half-life ($t½$) of ropivacaine after epidural administration (regardless of dosage) ranges from 5–7 h, and the t ½ after intravenous administration is about 2 h [11]. After intravenous application, ropivacaine undergoes extensive hepatic metabolism, with only 1% of the drug being eliminated unchanged in urine [12].

There are different known biotransformations for ropivacaine, like oxidative metabolism and dealkylation. Based on urinary analysis in humans, 3-hydroxy-ropivacaine, 4-hydroxy-ropivacaine, 2,6-pipecoloxylidide, 3-hydroxy-2′,6′-pipecoloxylidide and 2-hydroxymethyl-ropivacaine have been identified as metabolites [12, 13]. The major metabolite of ropivacaine in urine is 3-hydroxy-ropivacaine. About 37% of the administered ropivacaine dose will be hydroxylated to this metabolite. Responsible for the formation of major and minor metabolites are two cytochrome P450 (CYP450) isoenzymes like CYP1A2 and CYP3A4 [12, 13]. 3-OH-ropivacaine has significantly less pharmacological activity than ropivacaine [14].

Typical symptoms for CNS-toxicity occur 2–8 min after infusion of ropivacaine. The most common symptoms are visual and hearing disturbances, dysarthria, tingling, perioral numbness, dizziness, paraesthesia, light-headedness, muscular twitching and muscular rigidity [15]. Also reported are nausea, vomiting, urinary retention and bradycardia [5, 12]. CNS symptoms of local anaesthetic toxicity occur before cardiovascular symptoms and signs [15].

This paper describes the circumstances of two deaths and four intoxications and discusses the autopsy results and toxicological findings. The detection and quantification of ropivacaine and its main metabolite 3-OH-ropivacaine are presented in blood and urine with gas chromatography–mass spectrometry (GC–MS) as an analytical method.

Case histories

After orthopaedic surgeries, it is common practice that hospitalized patients receive analgesics metamizole and piritramide in the form of infusions. In cases of higher doses and multiple infusions, the medication is normally applied via intravenous catheters in medical saline solutions as a transporter. In the cases at hand, instead of using ineffective medical saline solutions, infusion with the active substance ropivacaine were applied. Instead of receiving the drug through controlled infusion pumps to avoid overdose, the patients were given it intravenously through solutions. Due to the visual similarity of the saline solution and ropivacaine-solution bags, a night nurse mistakenly gave 0.2 L bags with 0.2% (400 mg/bag) ropivacaine solution via venous infusion to suspected seven patients. In one case it was not possible to reconstruct which solution had been applied. Because of the high workload, time pressure, and understaffing, the nurse did not accurately register the time of medication. It could be reconstructed that the time interval of the infusion set up with ascertainment of wrongfully applied solution, and sampling was 4 h. During the night in question, two of these patients, a 62-year-old woman, and a 78-year-old man died. The remaining other patients (56–83 years old) survived. All six patients received intravenous ropivacaine solution as a carrier solution for metamizole as well as piritramide. The negative results of the toxicological analyses could exclude the possible seventh mistreatment (case 7, Table 3). In all cases, the examination of the applied ropivacaine bags was not possible. Venous blood samples and urine were immediately taken from all patients. Two of the surviving patients showed symptoms of poisoning like discomfort, racing heart, tachycardia, nausea, numbness, tingling of the skin, and near-death experience. After treatment with saline infusion and intensive observation, all surviving patients were free of ropivacaine symptoms and could be discharged from the hospital in accordance with their individual diagnosis and stage of healing. In both death cases, an autopsy was performed the following day.

A 78-year old man with a body length of 167 cm and a bodyweight of 81 kg (BMI: 29) was autopsied. He was operated on in the hospital for a hip prosthesis implantation a few days earlier. The deceased showed fresh injection marks in the cubital fossa of the right arm and on the back of the left hand. There were signs of slightly developed intracranial pressure (brain: 1280 g), haemorrhagic lung oedema (left lung: 790 g, right lung: 830 g) and a filled urinary bladder (ca. 400 mL). A hypertrophic heart was detected (heart: 460 g) with coronary arteriosclerosis and sclerotic changes on the aortic valve. A tumorous change was visible in the right kidney without any signs of metastasis. A clear cause of death could not be determined during autopsy. A toxicology analysis was requested.

A 62-year old woman with a body length of 156 cm and a bodyweight of 69 kg (BMI: 28.4) was autopsied. She suffered from breast tumour with metastasis with the thoracic vertebrae and from back pain. The deceased showed fresh injection marks in the cubital fossa of both arms. There were signs of intracranial pressure (brain: 1050 g) and haemorrhagic lung oedema (left lung: 585 g, right lung: 650 g). A moderately to strongly developed coronary arteriosclerosis was visible. Fibrotic changes in the liver could be detected (liver: 1470 g). A clear cause of death could not be determined during autopsy. A toxicology analysis was requested.

Due to the clear results of the toxicological analyses, no further examinations (such as histology) were ordered from the state attorney.

Materials and methods

Specimen collection at autopsies

Peripheral blood from the iliac vein and central blood from the inferior vena cava together with urine were collected from the male victim. However, it was difficult to collect urine from the female victim. Pericardial fluid, gastric contents, brain, and liver were also obtained from one case.

All specimens analyzed were collected during an autopsy at the Institute of Forensic Medicine of Ulm University. Blood and urine were taken from the five surviving patients for intoxication investigation. All collected samples were stored at 4 °C in plastic containers without preservative until analyzed.

Analytical methods

Routine toxicological analysis

In all cases, a comprehensive toxicological screening was requested. All collected samples were routinely screened for drugs, medications, ethanol and other volatile compounds with cloned enzyme donor immunoassays, GC–MS, liquid chromatography–tandem mass spectrometry and headspace–gas chromatography–flame ionization detection. Positive results were confirmed and quantified by specific techniques. For the urine samples, we did not use hydrolysis preparations; we only tried to analyze free 3-OH-ropivacaine in these samples.

Reagents and materials

Ropivacaine, 3-OH-ropivacaine and internal standards (IS) (methadone-d_9 and fentanyl-d_5) were purchased from LGC Standards (Teddington, UK); Tris(hydroxymethyl)aminomethane (THAM) for buffer solution, dichloromethane, and ethyl acetate from MERCK (Darmstadt, Germany). Blank blood and urine samples were used for the development and validation of the method. For preparing quality controls, the specimens were obtained from healthy volunteers with obtaining informed consent. Blank blood and urine were screened for drugs and medications (including ropivacaine). They were all negative. Biological material was stored at + 4 °C before analysis.

Standard, calibrator and quality control preparations

Stock solutions of ropivacaine and 3-OH-ropivacaine (both 1 mg/mL in methanol) were stored at − 22 °C. Calibrators were prepared in 200 µL of drug free blood and 100 µL urine samples by spiking them with ropivacaine and 3-OH-ropivacaine to obtain concentrations at 0.1, 0.2, 0.5, 1.0 and 2.0 mg/L and 0.020, 0.050, 0.1, 0.25, 0.5 mg/L, respectively. Before each analysis series, quality control samples were prepared at 0.150 and 0.750 mg/L for ropivacaine and 0.150 and 0.450 mg/L for 3-OH-ropivacaine in addition to negative blood and urine controls. Spiking solutions of methadone-d_9, for the quantification of ropivacaine, and fentanyl-d_5, for the quantification of 3-OH-ropivacaine, were prepared for use as ISs at the concentration of 0.100 mg/L.

Extraction, chromatographic and spectrometric conditions

Twenty or ten microliters of 1 mg/L methanolic solution of methadone-d_9 (IS) and fentanyl-d_5 was added to the different samples (200 µL blood and 100 µL urine, respectively), and placed in an Eppendorf vial together with 100 µL Tris-buffer (0.2 M THAM solution pH 9, adjusted with hydrochloric acid). After dichloromethane (500 µL) was added, the sample was vortexed for 2 min, followed by centrifugation at 13,000 rpm for 6 min. Then, the organic phase was transferred to a 2 mL glass vial and evaporated under a stream of nitrogen at 38 °C. Next, we added 30 µL acetic anhydride and 20 µL pyridine, and incubated for 20 min at 65 °C. After cooling, we evaporated again and the dry residue was reconstituted in 50 µL ethyl acetate and transferred to the glass insert. One microliter (splitless) of each extract was injected into the Agilent GC-MSQQQ 7000A system (Agilent, Santa Clara, CA, USA) to attain separation and identification. A 30 m, 0.25 mm diameter and 0.25 µm film thickness analytical column (VF-5 ms; Agilent) was used with helium as the carrier gas (1.0 mL/min). The inlet temperature of the gas chromatograph was 250 °C, and oven temperature was initially 100 °C (hold 2 min), ramped at 20 °C/min up to 250 °C (hold for 12 min). The mass selective detection transfer line was 280 °C.

The GC–MS controlled by Masshunter software (agilent) was used in the selected ion monitoring (SIM) mode. Under these conditions, the ropivacaine and 3-OH-ropivacaine retention times were 11.6 and 16.3 min, respectively. The total chromatography time per injection was 21.1 min.

Ions monitored for ropivacaine and 3-OH-ropivacaine included *m/z* 126*, 120 and 84 and *m/z* 127, 126* and 98, respectively, while those for ISs methadone-d_9 and fentanyl-d_5 included *m/z* 78*, 226 and 303 and *m/z* 250*, 194 and151, respectively (*quantifier ions).

Results

The methods for ropivacaine and 3-OH-ropivacaine were validated in accordance with the recommendation for the validation of new methods [16]. The validation results are

Table 1 Validation data for the quantification of ropivacaine and 3-OH-ropivacaine in blood

Parameter	QC level	Ropivacaine	QC level	3-OH-ropivacaine
Linear concentration range [mg/L]		0.1–2.0		0.02–0.5
LOD [mg/L]		0.004		0.002
LOQ [mg/L]		0.02		0.02
Coefficient of determination [R^2]		0.999		0.998
Intraday precision [RSD %]	0.150 mg/L	5.1	0.150 mg/L	3.1
	0.750 mg/L	1.9	0.450 mg/L	2.8
Intraday accuracy [% bias]	0.150 mg/L	1.5	0.150 mg/L	0.9
	0.750 mg/L	0.7	0.450 mg/L	1.5
Interday precision [RSD %]	0.150 mg/L	5.1	0.150 mg/L	4.8
	0.750 mg/L	3.2	0.450 mg/L	3.1
Interday accuracy [% bias]	0.150 mg/L	1.6	0.150 mg/L	− 2.9
	0.750 mg/L	2.3	0.450 mg/L	3.6
Recovery [%]	0.150 mg/L	106	0.150 mg/L	88.5
	0.750 mg/L	112	0.450 mg/L	92.1

LOD limit of detection, *LOQ* limit of quantification, *RSD* relative standard deviation, *QC* quality control

summarized in Table 1. For validation, calibration curves (each measured six times) and quality control samples (low 0.15 mg/L and high 0.45 and 0.75 mg/L), with spiked blood were analyzed. The recovery rate was between 112 and 88.5%. Statistical evaluation of the data was carried out using Valistat 2.0 GTFCh (Jena, Germany). The validation of the method covered linearity, the limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, and recovery.

Both analytes calibration curves showed good linearity over the validated concentration range of 0.1–2.0 mg/L and 0.02–0.5 mg/L with coefficient of determination (R^2) value as high as 0.999 for ropivacaine and 0.998 for 3-OH-ropivacaine.

The interday and the intraday precision and accuracies ($n = 6$ each, 8 days) were checked at concentrations of 0.15 and 0.75 mg/L for ropivacaine. For the metabolite, we used concentrations of 0.15 and 0.45 mg/L. Over a time period of 24 h, we checked the stability for both analytes after processing. The results indicated that both analytes are stable during this time period.

The validated analytical ropivacaine method for examinations in blood was applied to all samples from the two postmortem as well as the intoxication cases.

All samples were tested for common drugs, medication, and for alcohol as ordered by the public prosecutor. Alcohol was not detected in either of the cases and the concentration of metamizole was within the upper limit of therapeutic values for pain treatment. Piritramide was only detectable in urine.

Ropivacaine was detected in six cases (Tables 2, 3). Because of the low amounts of retrieved biological material in the surviving patients, we could not quantify 3-OH-ropivacaine in blood.

In case 7 (Table 3), we could only find 3-OH-ropivacaine in urine. In this case, the patient did not show any symptoms and there was also a low level of creatinine. The analytic results could prove that the medication was given in medical saline solutions as a transporter and not in a ropivacaine-bag. Thus, the detection of 3-OH-ropivacaine in urine could be explained by the medication given during his operation one day before; thus, the case 7 was excluded.

Table 2 Ropivacaine and 3-OH-ropivacaine concentrations in two fatal cases

Case No.	Age	Sex	Medication	Autopsy findings	Detected conc [mg/L]			Detected conc. [mg/L]			Creatinine mg/dL	pH
					Ropivacaine			3-OH-ropivacaine				
					hb	pb	Urine	hb	pb	Urine	Urine	
1	78	m	Piritramid, metamizole	Pulmonary and brain edema	11.6	2.91	Positive	0.15	0.02	Positive	69	6.5
2	62	f	Piritramid, metamizole	Pulmonary edema	13.1	4.3	n.dm.	0.41	0.03	n.dm.	n.dm.	n.dm.

Concentrations above the calibration curves are determined after dilution of samples

hb heart blood, *pb* peripheral blood, *m* male, *f* female, *n.dm.* not determined

Table 3 Ropivacaine and 3-OH-ropivacaine concentrations in five supposed intoxication cases

Case no	Age	Sex	Medication	Symptoms after medication	Detected conc. [mg/L]				
					Ropivacaine		3-OH-ropivacaine	Creatinin [mg/dL]	pH
					pH	Urine	Urine	Urine	
3	69	m	Piritramid, metamizole	No symptoms	0.69	Positive	Positive	134	6.0
4	78	m	Piritramid, metamizole	Near-death-experience, hearth arrhythmia	0.38	Positive	Positive	63	7.8
5	56	f	Piritramid, metamizole	Nausea, heart arrhythmia, dyspnoea, prickling	0.87	Positive	Positive	62	7.5
6	67	m	Piritramid, metamizole	No symptoms	1.21	Positive	Positive	167	7.0
7	83	m	Piritramid, metamizole	No symptoms	n.dt.	n.dt.	Positive	49	8.4

n.dt. not detectable

The concentration of ropivacaine in peripheral blood was higher in the autopsy than in the surviving cases (Tables 2, 3), but close to intoxication levels.

In both fatal cases, the concentrations of ropivacaine and 3-OH-ropivacaine were lower in peripheral blood than in heart blood. Postmortem distribution was investigated calculating the mean ratios of heart to peripheral blood concentrations, which was 3.5 for ropivacaine probably due to the postmortem redistribution.

After analyses, all samples were stored in a frozen state at − 20 °C for one year. Then we repeated the analyses for ropivacaine. Ropivacaine was stable in all samples (maximum storage time: 1 year). Due to insufficient quantity, we could not repeat the analyses for 3-OH-ropivacaine.

Discussion

The use of ropivacaine as an analgesic and as a local anaesthetic during a variety of surgical procedures has been studied extensively. All studies and case reports agreed upon the necessity of clinically controlled treatments. Thus, the proper way of ropivacaine-solution administration is to use infusion pumps to avoid overdose. However, very little is known about fatal threshold concentrations. Until now, there are reported therapeutic and toxic blood/plasma concentrations for ropivacaine, but no reported comatose/fatal threshold concentrations [17]. In one toxicity study with animals, ropivacaine concentrations of 9.8 mg/L were applied to dogs with one fatal outcome [18]. In addition to blood concentration, the manner of ropivacaine administration also plays an important role in terms of its toxicity. Several animal studies suggest electrocardiographic and blood pressure alterations by intravenous ropivacaine application [19–21].

In clinical experiences from 60 studies involving 3000 patients with ropivacaine dosages, there were six reports of probable accidental intravascular injections with given amounts of ropivacaine (intravenous 75–200 mg). In these cases, only one patient showed signs of cardiotoxicity, and no signs of CNS toxicity were recorded [22].

Ruetsch et al. [3] described seizure and serve cardiac arrhythmia after accidental intravascular injection of 225 mg ropivacaine in a short time with measured concentrations of 3.6 and 0.69 mg/L for total and free ropivacaine, respectively. These concentrations for total and unbound ropivacaine were clearly over the range of the experimental human threshold for CNS toxicity symptoms [15, 23].

Another accidentally intravascular application was described by Pfeiffer et al. [24]. Their drawn conclusion of different studies [15, 23] was, that CNS-symptoms occur at arterial blood levels of 0.34–0.85 mg/L and that neurological symptoms start after concentrations of 5 mg/mL ropivacaine, depending on the injection speed and concentration [24].

In our cases, six patients received low concentration ropivacaine bags (0.2% 200 mL) intravenously without a controlled infusion pump. Two of the patients died and only two of the survived patients complained about typical symptoms. It seems that the proclaimed symptoms do not correlate with the detected amount of ropivacaine in peripheral blood, especially because all patients received the same amount.

One essential factor for this phenomenon seems to be firstly the speed of injection because the rapid infusion results in more free ropivacaine reaching the target molecules to exert its toxic effects. This could partly explain the lack of a clear correlation between drug concentration in blood and the occurrence of symptoms.

Furthermore, the amounts of serum binding proteins including α_1-acid glycoprotein [25, 26], which are variable in different individuals, are the second factor for the manifestation of toxic symptoms. The combination of the speed of ropivacaine infusion and the amounts of binding protein(s) in blood seems to cause quite different outcomes (fatal to surviving without toxic symptoms, Tables 2, 3) even under similar ropivacaine exposure conditions.

To our knowledge, ropivacaine has been considered the safest long-acting local anaesthetic [5] and no fatal cases of

ropivacaine intoxication have been reported. However, we have presented two fatal cases of ropivacaine with its blood concentrations in this article. The doctors and nurses should be more cautious upon handling ropivacaine-solution bags.

In the cases at hand, the hospital management reacted with obligatory training courses for nursing staff and extra labelling of the ropivacaine-solution bag. At the request of the public prosecutor's office, the court issued a penalty order for negligent homicide in two cases and for negligent bodily harm in three cases against the nurse. She was sentenced to 1-year probation and had to pay a fine.

Conclusions

For postoperative pain treatment, intravenous 0.2% ropivacaine is recommended. In the cases at hand, the application of ropivacaine was unintentional and thus not monitored.

Even though ropivacaine is considered to be a safe pain medication drug, it should always be administered in a controlled environment, independently from the concentration of the applied ropivacaine solution.

In case of overdose, typical symptoms might not necessarily be present. Thus, in suspicious cases, patients should be treated immediately according to reliable treatment guidelines [27] and if blood results are negative for ropivacaine, its main metabolite 3-OH-ropivacaine can be analyzed in urine to prove previous administration.

It should be stressed, that when ropivacaine solution is administered intravenously, relatively slow infusion is essential to assure its safety.

The presented report is the first demonstration of fatal cases of ropivacaine together with their blood concentrations of ropivacaine and its metabolite.

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Availability of data and material All data were determined in the Institute of legal law Ulm.

Declarations

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval All analytical experiments were conducted at the request of judicial authorities. Informed consent was not necessary. The identities of all people are completely concealed.

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