K37 Postmortem Ropivacaine (Naropin) Concentrations

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After attending this presentation, attendees will understand postmortem concentrations of ropivacaine in biological fluids and tissues of an accidental overdose during a routine surgery involving an axillary block.

To report the concentrations of ropivacaine found in post-mortem tissue and fluid samples from a patient who died after being administered ropivacaine in a surgical setting. This is to provide post-mortem concentrations in the literature for ropivacaine, a drug that thus far has not been reported in this context.

Introduction: Ropivacaine is a local anesthetic indicated for surgical and acute pain management. It is manufactured by AstraZeneca

under the name Naropin® and received FDA approval in late 1996. Ropivacaine is an amide local anesthetic, belonging to the same group as mepivacaine and bupivacaine, and is supplied as the enantiomerically pure *S*-isomer in isotonic solutions (0.2-1.0 % w/v) of the hydrochloride salt. Ropivacaine has similar potency and duration of action to bupivacaine but has less central nervous system (CNS) and cardiovascular toxicity. Ropivacaine is used as an epidural injection for surgery, obstetric procedures, and postoperative pain. Additionally, it is used in the technique of peripheral nerve block and local infiltration for surgical procedures.

A case study is presented to document the post-mortem concentrations of ropivacaine found in an individual who was to undergo open reduction and external fixation surgery on his left hand. The deceased, a 32-year-old, healthy, male Caucasian, was administered midazolam and fentanyl for sedation prior to entering the Operating Room (OR). Once in the OR, he was given ropivacaine (30 mL of a 0.5% solution; 150 mg) via an axillary block whereupon he began to seize and subsequently die in the recovery room despite 2 hours of resuscitative work, which included bicarbonate, epinephrine, and electrical shocks.

Methods and Results: Ropivacaine was extracted from the samples by liquid-liquid extraction with *n*-butyl chloride: ether (4:1) after basifying the matrix with ammonium hydroxide. Extracts were back-extracted with 1M sulfuric acid, which was further washed with hexane. After re-basifying the aqueous phase, ropivacaine was extracted with *n*-butyl acetate. The extracts were analyzed by electron ionization gas chromatography/mass spectroscopy, operating in the selected ion monitoring mode, utilizing lidocaine as the internal standard. The following groups of ions (*126*, 84, 98) and (*86*, 120, 91) were monitored for ropivacaine and lidocaine, respectively, with a calibration curve ranging from 0.1-2 mg/L.

The results of the toxicological analyses performed for ropivacaine are shown in the table below. The method of standard addition (SA) was utilized for the liver and bile. The central blood was also found to contain therapeutic concentrations of midazolam (0.05 mg/L) but fentanyl was not detected. The empty vial of ropivacaine HCl used in the OR and an unopened bottle (0.5 %) of the same lot number were also submitted for toxicological analysis. The results of the pharmacy samples were positive for ropivacaine and 4400 mg/L ropivacaine, respectively, as expected.

Source of Sample	Aorta	Femoral	Liver (SA)	Vitreous Humor	Bile (SA)
Ropivacaine	2.4 mg/L	2.0 mg/L	4.4 mg/kg	1.4 mg/L	1.9 mg/L

Discussion: Ropivacaine was developed in response to the incidence of death from several accidental intravascular injections of bupivacaine. The rationale for developing ropivacaine (the propyl analog of bupivacaine) was a drug of lower lipid solubility to bupivacaine would be less cardiotoxic. Unintended intravenous injection may, however, still cause severe CNSand cardiac toxicity. Systemic plasma concentrations of ropivacaine depend on the total dose and concentration of drug administered, the route of administration, and the vascularity of the administration site. The recommended dose of ropivacaine is between 75-300 mg for most surgical anesthesia (epidural and major nerve block).

CNS symptoms of ropivacaine toxicity occur before cardiovascular symptoms and include numbness of the tongue, lightheadedness, visual disturbances, muscular twitching, tinnitus, and more seriously, convulsions and coma. Cardiovascular toxicity is a result of depressed cardiac conduction due to inhibition of inward flow of sodium ions, which may lead to ventricular arrhythmias and cardiac arrest. The greater tolerance to ropivacaine compared to other local anesthetics, however, may hide the early warning signs of toxicity. In two human studies (n=24) of continuous intravenous infusions of ropivacaine at a rate of 10 mg/min up to a maximum dose of 160 mg, symptoms of CNS toxicity occurred at plasma concentrations between 0.5 and 3.2 mg/L. Minimal cardiovascular effects were observed during these studies and included increased heart rate and arterial pressure.

The concentrations of total ropivacaine found in the post-mortem whole blood specimens of the deceased were consistent with those reported (1.0-6.0 mg/L; medium 3.5 mg/L) from the peripheral venous

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plasma samples (taken at various time intervals, 7-150 minutes, after administration) in six cases where inadvertent intravascular injection of ropivacaine during surgical procedures caused convulsions and cardiovascular toxicity. In addition, ropivacaine is highly protein bound (94%) and the whole blood concentrations reported here will, therefore, be more dilute compared to plasma concentrations. The patients in all the reported cases recovered. During surgical procedures, negative aspirations for blood and CSF fluid alone are not enough to ensure that inadvertent intravascular injection has not occurred; incremental administration and constant communication with the patient is essential to prevent accidental overdose.

In the absence of a history of illness, especially epilepsy and cardiovascular disease, and the timing of the seizure in relation to the administration of ropivacaine, it is probable that the levels reported here are indicative of fatal ropivacaine levels seen in post-mortem fluids and tissues due to inadvertent intravascular injection of the drug. These levels can be used in toxicological interpretations as to possible cause of death in subsequent investigations.

Ropivacaine, Local Anestheisa, Toxicity

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