J Anesth (2011) 25:442–445
DOI 10.1007/s00540-011-1125-4

CLINICAL REPORT

Successful treatment of ropivacaine-induced central nervous system toxicity by use of lipid emulsion: effect on total and unbound plasma fractions

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Received: 28 January 2011 / Accepted: 2 March 2011 / Published online: 16 March 2011

Abstract A 24-year-old man underwent surgery for a fractured left clavicle and received an interscalene brachial plexus block for intraoperative and postoperative analgesia. After injection of 40 ml 0.5% ropivacaine and confirmation of analgesia, general anesthesia was induced and maintained with propofol. Although the operation was completed uneventfully, the patient was restless and there was limb twitching during emergence from anesthesia. Ropivacaine-induced toxicity was suspected, and a dose of 100 ml 20% lipid emulsion was infused intravenously. The symptoms of toxicity disappeared, and there was full recovery of consciousness within 5 min. Plasma concentrations of total and protein-unbound ropivacaine measured 2 h 20 min after local injection were 1.99 and 0.13 μg/ml, respectively. After infusion of lipid emulsion, the ropivacaine concentrations decreased to 1.72 and 0.05 μg/ml, respectively. The patient had no pain, and neurological examination revealed sensory loss around the clavicle. The patient was discharged without any complications.

Keywords Local anesthetic · Ropivacaine · Toxicity · Peripheral nerve block · Lipid emulsion

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Introduction

After the first report of successful treatment of local anesthetic-induced toxicity by use of lipid emulsion [1], its use has increased so widely that it has become almost a standard procedure [2–7]. However, the detailed mechanism of its action as an antidote is unknown [8, 9]. Only a few clinical studies have examined the effect of lipid emulsions on the plasma concentrations of local anesthetics [2, 3]. We report here a case of ropivacaine-induced central nervous system (CNS) toxicity treated with lipid emulsion. We measured the plasma concentrations of both total and protein-unbound (unbound) ropivacaine before and after administration of lipid emulsion to elucidate the mechanism by which lipid reduces CNS toxicity.

Case description

An otherwise healthy 24-year-old man (height 167 cm, weight 66 kg) was scheduled for elective open reduction and internal fixation of a fractured left clavicle. An interscalene brachial plexus block was performed with an insulated short-beveled needle connected to a nerve stimulator. The brachial plexus was localized on the first attempt, without any difficulty, by eliciting deltoid stimulation at 0.6 mA. Once the plexus was located, 40 ml 0.5% ropivacaine was injected in 5 ml increments with gentle aspiration between doses. The motor response to stimulation disappeared promptly after injection of the first few milliliters of solution. At no time was any blood aspirated, nor did he report pain or paresthesia. Verbal contact was maintained with the patient throughout the procedure, and there were no early signs of systemic toxicity. His vital signs remained unchanged throughout the administration of

ropivacaine. After 5 min, sensory block was assessed with cold test, and established in his left shoulder and the clavicular area. Immediately after confirmation of the block, general anesthesia was induced and maintained with propofol using a target-controlled infusion pump to produce an estimated plasma concentration of 3.0 μg/ml. Fentanyl (100 μg) was added on induction of general anesthesia. A laryngeal mask airway was inserted, and the lungs were ventilated mechanically. Flurbiprofen (50 mg) was used for postoperative analgesia. The operation lasted approximately 1.5 h; the total dose of propofol was 980 mg. No arrhythmias were noted throughout the course of anesthesia.

Soon after discontinuation of propofol, the laryngeal mask airway was removed. The patient was awake with his eyes open, and he responded to verbal commands. However, he was restless, incoherent, talkative, inarticulate, and his speech was slurred and irrational. Twitching of his limbs, except for his left arm, was observed. He did not complain of nausea, palpitations, dizziness, or headache. His vital signs were normal. At that time, the estimated plasma concentration of propofol was 1.0 μg/ml. After 10 min of observation, we gave 100 ml 20% lipid emulsion over 10 min based on diagnosis of ropivacaine-induced CNS toxicity. Just before lipid administration, an arterial blood sample was obtained for measuring blood gases and ropivacaine concentration. Analysis of the blood sample gave the results: pH 7.358, $PaCO_2$ 44.8 mmHg, PaO_2 278.9 mmHg, glucose 101 mg/dl, and Hb 11.4 g/dl.

All neurological derangements disappeared and consciousness recovered within minutes. He remained hemodynamically stable without any arrhythmia or QRS prolongation. There was no evidence of complications, for example allergic reactions or phlebitis, secondary to the administration of lipid emulsion. Immediately after completion of the lipid emulsion infusion, a second arterial blood sample was obtained to measure ropivacaine concentrations. The sensory and motor block totally disappeared by the next morning. The patient had no further symptoms and was discharged without sequelae.

Plasma concentrations of ropivacaine were measured by liquid chromatography–mass spectrometry as described previously [10] with minor modifications. The unbound fraction was measured after ultrafiltration by use of a membrane (YM-30; Millipore, Billerica, MA, USA). Plasma concentrations of total ropivacaine were 1.99 and 1.77 μg/ml, and the unbound fractions were 0.13 and 0.05 μg/ml, before and after lipid infusion, respectively.

Discussion

In our case, a 100-ml bolus dose of 20% lipid emulsion immediately abolished the CNS symptoms induced by ropivacaine. Although we could not establish a causal relationship between lipid infusion and recovery of consciousness, the remarkable decrease of the unbound plasma concentration together with the rapid recovery of consciousness and disappearance of CNS symptoms suggest that the effect was because of the lipid emulsion.

The mechanism of the reversal of the toxic effects of local anesthetics by lipid emulsion is still unclear. One theory is that it creates a lipid plasma phase that essentially extracts the highly lipid-soluble local anesthetic molecules from the aqueous plasma phase [8, 9]. Consequently, reduction of the unbound local anesthetic concentration in the aqueous plasma phase increases the diffusion gradient between intoxicated tissue and plasma, thereby facilitating efflux of local anesthetics from the tissue to plasma, leading to prompt disappearance of their toxic effects. If this theory is correct, the systemic toxicity of local anesthetics would be directly related to their unbound rather than their total plasma concentration, as reported previously [11]. This was also suggested by our animal experiments showing that the concentration of unbound local anesthetics in plasma was comparable with that in cerebral extracellular fluid, and the latter concentration determined the degree of CNS toxicity [12, 13]. As far as we are aware, this is the first clinical report to show a relationship between unbound plasma concentrations of a local anesthetic and CNS symptoms before and after treatment with lipid emulsion.

In this case, the unbound plasma concentration was 0.13 μg/ml 2 h 20 min after administration of ropivacaine. The unbound plasma concentration should have been much higher during the operation, because the estimated time to peak concentration after brachial plexus block is 30–60 min [14, 15]. Although the mean value of the unbound plasma concentration of ropivacaine at the maximum tolerated dose is 0.56 μg/ml [11], there are large variations in this value among individuals, and CNS toxicity can be induced even at a free concentration of 0.08 μg/ml [16]. After administration of the lipid emulsion, the unbound plasma concentration of ropivacaine rapidly decreased to 0.05 μg/ml, lower than the level required for CNS toxicity. This abrupt decrease is not explained by the pharmacokinetic changes reported previously [14, 15, 17]. In contrast with the unbound fraction, there was little decrease in the total plasma concentration of ropivacaine after lipid infusion in our patient. Other studies also showed a small decrease in total plasma concentrations of various local anesthetics after infusion of lipid emulsion [2, 3].

The dose of ropivacaine used in this case is quite common for a brachial plexus block. A negative aspiration test, prompt onset of analgesic effect, and the lack of signs of toxicity just after injection of ropivacaine exclude the

possibility of inadvertent intravascular injection. The delayed onset of systemic toxicity reflects slow absorption from the brachial plexus, probably because of the absence of richly vascularized tissue [18, 19]. Because there were no blood gas abnormalities, acidosis or hypoxia did not affect the toxicity. Although the CNS toxicity was resolved by the lipid emulsion, the analgesic effect was not affected. These differential effects can be explained by a rapid decrease of the plasma concentration of unbound ropivacaine and a sustained high concentration in the brachial plexus because of low vascularity. The potential effect of concomitant general anesthesia must be taken into consideration. It might mask severe signs of CNS toxicity because of its anticonvulsive effect [20].

Because propofol contains 10% lipid emulsion and is used for treating convulsions, it might be useful against local anesthetic-induced toxicity. However, our case suggests that use of propofol as an antidote for local anesthetic-induced toxicity is limited, because CNS symptoms appeared even after administration of a total of 98 ml propofol for approximately 1.5 h. In sharp contrast, 100 ml 20% lipid emulsion quickly abolished CNS toxicity.

There are many reports describing successful resuscitation from severe systemic toxicity of local anesthetics using lipid emulsion [1–5]. One major concern was the potential harmful effects of lipid overload. Certainly, the bolus infusion of a large dose of lipid emulsion may have adverse effects [21], and several case reports do not support the early use of lipid emulsion [22, 23]. In recent reports, however, the time from onset of anesthetic-induced toxicity to administration of lipid emulsion has decreased [4, 5, 24], and it would not be prudent to wait until there was cardiac toxicity before administering lipid emulsion. Once signs of local anesthetic toxicity are manifest, accumulating evidence supports the early use of lipid infusion to attenuate progression of the toxicity.

In summary, we report a case of ropivacaine-induced CNS toxicity treated successfully by lipid emulsion. Because the plasma concentration of unbound ropivacaine decreased rapidly, whereas the total concentration was not greatly affected by lipid infusion, reversal of the toxicity may have been because of the rapid trapping of unbound ropivacaine by the lipid.

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