

Bupivacaine crystal deposits after long-term epidural infusion

Introduction

Of patients with metastatic cancer 10–15% suffer from severe pain despite systemic pain therapy with oral opiates and non-opiate analgesics [10]. Interventional pain therapy using long-term epidural catheters (EC) and neuraxial administration of local anesthetics (LA) and opiates has a better analgesic effect, is associated with reduction in some of the side effects of oral opiates and improves the quality of life in these patients [27].

Materials and methods

A 45-year-old male patient (body weight 52 kg, height 1.61 m and body mass index 20 kg m^{-2}) with a recurrent gastric adenocarcinoma suffered from severe upper quadrant abdominal pain due to

tumor infiltration into the retroperitoneal space. The only other relevant fact from the medical history was smoking-related chronic obstructive pulmonary disease (COPD). Initially the carcinoma was diagnosed as grade pT3pN2M0. After surgical excision of the carcinoma the patient had been asymptomatic until a recurrence of the tumor was found on follow-up computed tomography (CT) 1 year later. The patient suffered from upper quadrant abdominal pain and the initial analgesia with acetaminophen, oral morphine and a corticosteroid was inadequate. Subsequently ethanol neurolysis of the celiac plexus was performed, although this also failed to improve pain control. A tunnelled EC (Tuohy 18-G peridural needle and catheter, Perifix, Braun, Melsungen, Germany) was placed at thoracic spinal

level 7/8. The correct location of the EC was confirmed by injection of 3 ml lidocaine 2% with epinephrine (1:200,000) and the pin-prick method which resulted in a change in thoracic sensory level to the pin-prick from 4 to 12. The epidural infusion was started with a mixture of bupivacaine HCl 0.25% and morphine HCl 0.005% in a 1,000 ml bag via a portable, battery powered electronic pump at 6 ml h^{-1} [39]. The infusion solution was prepared from stock solution of bupivacaine by the hospital pharmacy of the Kantonsspital Lucerne. The solution was adjusted to pH 5.5–6.0 with NaOH. The daily administered doses amounted to 360 mg bupivacaine HCl and 7.16 mg morphine HCl. The daily infusion volume of the LA mixture was 144 ml. With this therapy the patient's pain severity was reduced so that only occasional mild

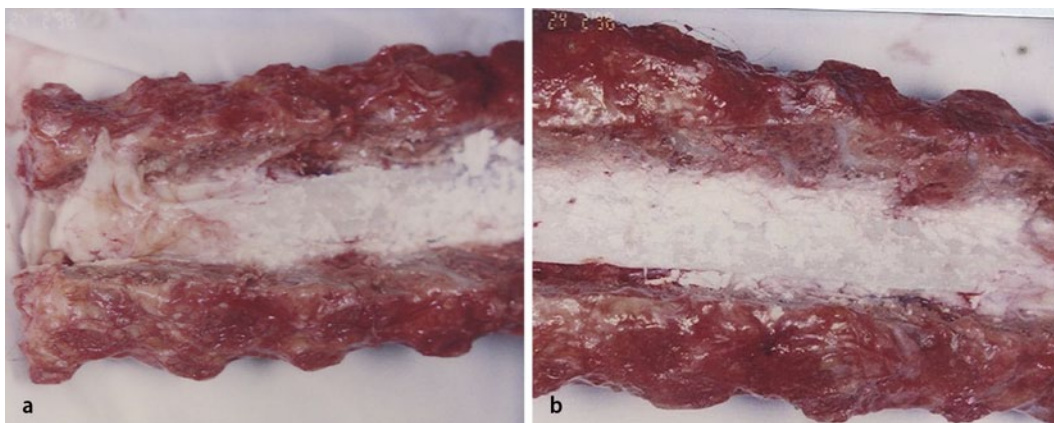


Fig. 1 ◀ a,b Autopsy of the thoracic spine (two different locations) showing white crystalline deposits in the epidural space

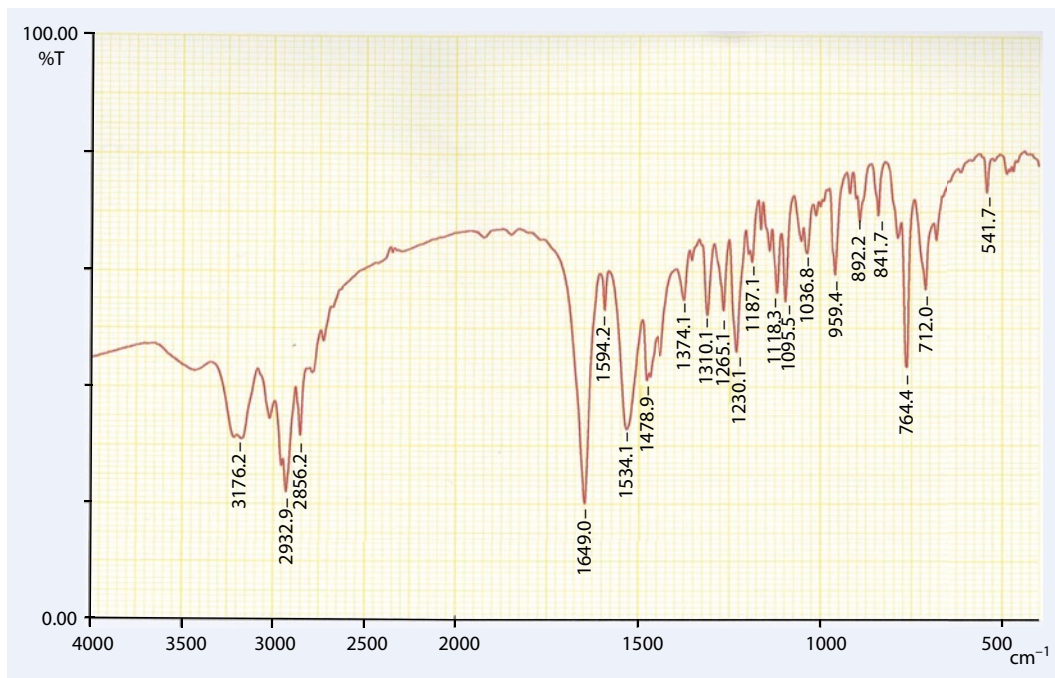


Fig. 2 ◀ Reference spectrum of bupivacaine base (red curve)

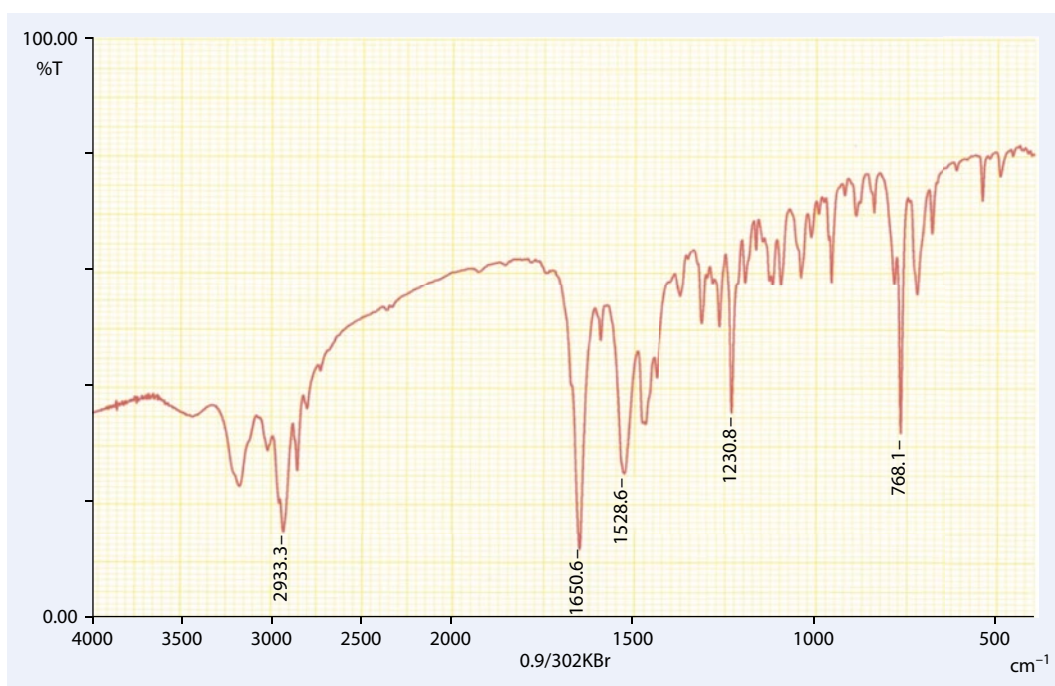


Fig. 3 ◀ Infrared spectrum of the crystalline deposits (red curve) in the thoracic epidural space

abdominal pain occurred and the patient was discharged and treated as an outpatient. However, 3 months later the severity of the pain increased and infusion concentrations were doubled to bupivacaine HCl 0.5% and morphine HCl 0.01% and the infusion rate halved to 3 ml h⁻¹ (daily infusion volume 72 ml); therefore the administered total daily dose remained the same (bupivacaine HCl 360 mg and morphine HCl 7.13 mg). The patient died 6

months after initiation of epidural anesthesia with the EC still in place. An autopsy was performed to examine the spinal canal. The total administered dose over 6 months (192 days) amounted to 69 g of bupivacaine HCl and to 1.37 g of morphine HCl. The EC provided effective pain relief and the patient did not report any adverse neurological symptoms or other complications from the epidural analgesia during this period. The EC was

never changed but the catheter insertion site was regularly inspected and was free from any skin reaction or infection.

Results

The autopsy revealed extensive large white crystalline deposits in the epidural space extending from thoracic level 4 to 8 (■ Fig. 1a,b).

These deposits and the reference bupivacaine base (derived from commercial bupivacaine HCl, Schweizerhall, Basel, Switzerland) were analyzed by infrared spectrometry (infrared spectrometer: Paragon 500 FT-IR, Perkin Elmer, Schwerzenbach, Switzerland). The analysis was performed on potassium bromide pellets. The spectrum of bupivacaine base derived in the pharmacy laboratory from commercial bupivacaine HCl served as the reference (■ Fig. 2).

The spectrum of the crystalline deposits is presented in ■ Fig. 3.

Both spectra in the same picture (■ Fig. 4) illustrate strong similarities.

The correlation coefficient between both spectra was automatically calculated by the infrared spectrometer and showed a high correlation (coefficient 0.973) which indicated that the crystalline deposits could be identified as bupivacaine base.

The spectrum of morphine base derived in the pharmacy laboratory from commercial morphine HCl (Hänseler, Herisau, Switzerland) served as the reference (■ Fig. 5).

There was no similarity between the spectrum of bupivacaine base deposits and the spectrum of morphine base (■ Fig. 6).

No morphine base or morphine HCl could be detected either by infrared spectrometry or by thin-layer chromatography (TLC).

A histological examination was performed and ■ Fig. 7 gives an overview showing the crystalline deposits as a bright pink eosinophilic material on the left side surrounded by soft tissue and mainly by fat tissue (dark pink) on the right side.

The soft and fat tissue contained some calcified tissue corresponding to splintered bone fragments. Crystals with double light refraction could not be seen in the polarised light. A detail image of necrotic adipocytes within the crystalline material is shown in ■ Fig. 8. Nerve tissue could not be differentiated from the crystalline tissue and was not identified within or without the crystalline deposits (■ Fig. 8).

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Abstract

The case of a 45-year-old male patient (body weight 52 kg, height 1.61 m) with a locally invasive gastric carcinoma infiltrating into the retroperitoneal space is reported. Because of severe cancer pain a tunnelled thoracic epidural catheter (EC) was placed at thoracic spinal level 7/8 and a local anesthetic (LA) mixture of bupivacaine 0.25% and morphine 0.005% was infused continuously at 6 ml h⁻¹. To optimize pain therapy the concentration was doubled (bupivacaine 0.5%, morphine 0.01%) 3 months later but the infusion rate was reduced to 3 ml h⁻¹ thus the total daily dose did not change. The patient died 6 months after initiation of the epidural analgesia from the underlying disease. The total amount of bupivacaine infused was 69 g and of morphine 1.37 g. The patient never report-

ed any neurological complications. The autopsy revealed large white crystalline deposits in the thoracic epidural space which were identified as bupivacaine base by infrared spectrometry. Morphine could not be detected. A histological examination showed unreactive fatty tissue necrosis within the crystalline deposits but nerve tissue could not be identified. It is concluded that the bupivacaine crystalline deposits arose due to precipitation but the clinical significance with regard to sensory level and neuraxial tissue toxicity is unknown.

Keywords

Epidural catheter · Local anaesthetic agent · Bupivacaine · Precipitation · Pain therapy

Bupivacainkristalle nach epiduraler Langzeitinfusion

Zusammenfassung

Berichtet wird über einen 45-jährigen Patienten (Körpergewicht 52 kg, Körpergröße 1,61 m) mit lokal invasivem, das Retroperitoneum infiltrierendem Magenkarzinom. Wegen starker Tumorschmerzen wurde ein tunnelter Epiduralkatheter auf der Höhe Th7/8 zur kontinuierlichen Infusion (6 ml/h) einer lokalanästhetisch wirkenden Kombination aus 0,25%igem Bupivacain und 0,005%igem Morphin gelegt. Zur Therapieoptimierung wurden 3 Monate später die Konzentration verdoppelt (0,5%iges Bupivacain und 0,01%iges Morphin) und die Infusionsrate halbiert (3 ml/h), sodass sich die tägliche Dosis nicht veränderte. Sechs Monate nach Beginn der Epiduralanalgesie verstarb der Patient an seiner Grunderkrankung. Insgesamt waren 69 g Bupivacain und 1,37 g Morphin infundiert worden. Zu keiner Zeit hatte der Patient neurologische

Komplikationen angegeben. In der Autopsie fanden sich großflächige weiße kristalline Ablagerungen im thorakalen Epiduralraum, infrarotspektrometrisch erwiesen sich diese als aus Bupivacain bestehend. Morphin konnte nicht nachgewiesen werden. Die histologische Untersuchung zeigte eine nichtreaktive Fettgewebsnekrose innerhalb der Bupivacainkristalle; Nervengewebe ließ sich nicht identifizieren. Es wird davon ausgegangen, dass die Bupivacainkristalle durch Präzipitation entstanden sind. Nicht bekannt ist ihre klinische Bedeutung auf sensorischer Ebene und hinsichtlich einer neuroaxialen Gewebetoxizität.

Schlüsselwörter

Epiduralkatheter · Lokalanästhetikum · Bupivacain · Präzipitation · Schmerztherapie

Discussion

Of cancer patients 10–15% fail to achieve sufficient analgesia from oral medications mainly due to tolerance to the analgesic effect of opioids and the occurrence of opioid-related side effects following dose escalation. At this point interventional pain therapy, such as epidural analgesia can be introduced with much greater efficacy [12]. Tissue toxicity to LA has been

documented in animal studies particularly at higher concentrations [2, 3, 4, 6, 7, 8, 11, 13, 14, 15, 16, 17, 18, 19, 20, 25, 29, 31, 32, 33, 34, 37, 38] but seldom observed using the recommended clinical concentrations in humans [1, 15, 22, 23, 24, 26, 28, 31].

Analgesia provided by LA agents administered neuraxially can often be augmented by the addition of adjuvants, such as opioids (morphine) and alpha agonists (clonidine; [12]). Different LA mixtures or

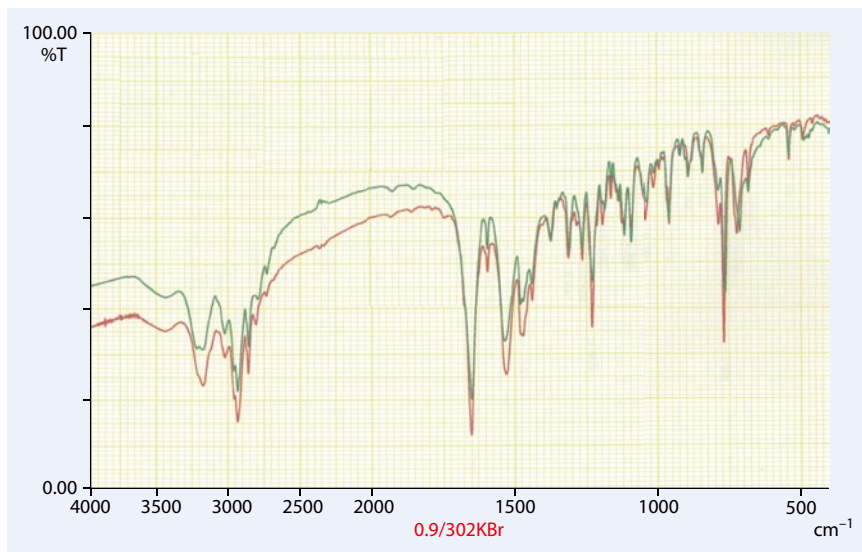


Fig. 4 ▲ Infrared spectrum of bupivacaine base (green curve) serves as the reference and infrared spectrum of the crystalline deposits (red curve) correlates highly with the reference (correlation coefficient 0.973)

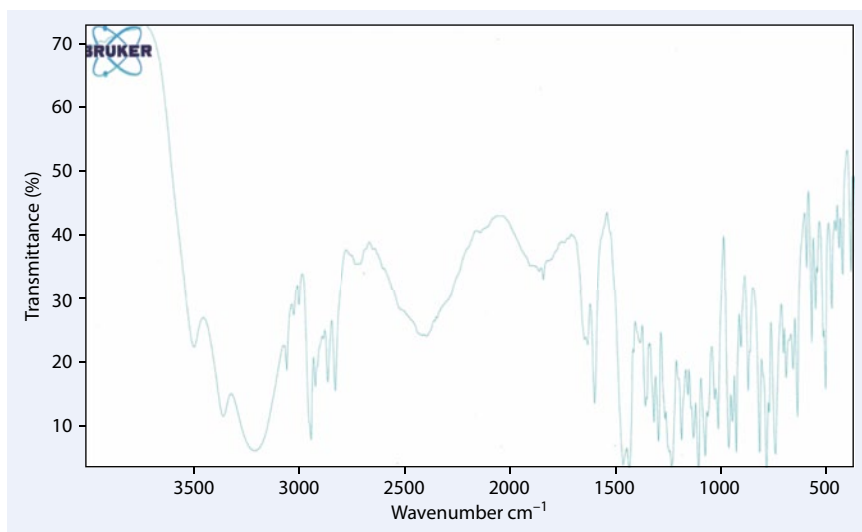


Fig. 5 ▲ Infrared spectrum of morphine base (blue curve)

LA without supplements have not been extensively examined for local tissue damage in humans [31] apart from a few case reports [1, 15, 22, 23, 24, 26, 28]. To explain the mechanism of tissue toxicity various pathophysiological pathways of LA or LA mixtures in different human and animal tissues, such as skin, soft tissue, muscle and neurological tissue are discussed but the pathogenesis has not been elucidated in detail [1, 13, 19, 20, 29, 32, 33, 34, 35, 36, 37, 38]. Particularly, only limited information is available on the extended epidural administration of continuous infusion of LA or LA mixtures for weeks and months.

The location of crystalline deposit seen at autopsy corresponds to the catheter tip, where the highest concentration of LA is to be expected. In a similar case, bupivacaine morphine deposits were found in the soft tissue after catheter dislodgement and epidural analgesia therapy of 8 weeks duration [1]. To elucidate the mechanism for the formation of bupivacaine base deposits, several considerations must be made: (1) bupivacaine is a weak base with pKa 8.05. (2) To provide a stable solution the bupivacaine base is dissolved in HCl to form the salt bupivacaine HCl. To maintain a stable solution

the pH has to be kept well below the pKa, usually between 5.5. and 6.0. (3) When a bupivacaine HCl solution is infused the body buffering capacity (protein, bicarbonate) adjusts the pH close to the physiological range of $\text{pH } 7.4 \pm 0.05$ which predisposes bupivacaine HCl to precipitate [39]. Contrary to lidocaine the in vitro titration of bupivacaine to a higher pH is very critical and results invariably in precipitation of the drug [1, 21, 39]. Considering these facts there are several situations in which the precipitation of bupivacaine in vivo may arise: (1) the pH of the LA solution rapidly changed to a higher pH value after infusion into the epidural space. (2) The underlying disease (cancer) could have altered the solubility of the bupivacaine-morphine solution with regard to tissue pH, tissue buffer capacity and protein binding [16]. The cancer could have diminished the proportion of protein-bound drug and thus made it more prone to precipitation. (3) The EC as a foreign body in the epidural space could serve as a facilitator of precipitation. (4) In the second period of pain therapy the concentrations were doubled to bupivacaine HCl 0.5%, morphine HCl 0.01% and the infusion rate halved to 3 ml h^{-1} . The lower infusion rate and the higher concentration of the drug could possibly lead to a more rapid adjustment of the tissue to pH 7.4 thereby favoring precipitation. Taken together, the type of drug, the concentration, composition, the physicochemical properties of the drug, interactions with human tissue, the interaction of the EC as foreign body in human tissue, the speed of infusion into the epidural space and the long-term administration of the LA mixture could favor precipitation with subsequent tissue damage [1]. In this case morphine base or morphine HCl in the crystals could not be detected by infrared spectrometry (because the quantity was too small or due to complete resorption). In a similar case morphine HCl could be demonstrated by chemical analysis in such LA mixture deposits [1]. Morphine does not alter the pH or solubility of LA mixtures [5, 16]. The stability and compatibility of such LA mixtures are proven to be safe in infusion systems [5, 9, 14, 16, 30] and safe when used clinically [14]. On the contrary this case and another

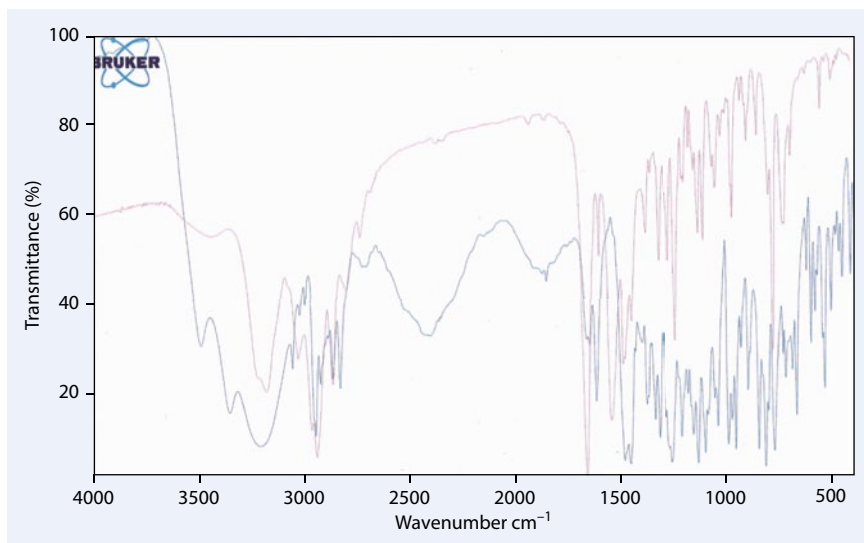


Fig. 6 ▲ Spectrum of bupivacaine base (upper or violet curve) showing no similarity to the spectrum of morphine base (lower or blue curve). Both spectra were derived with the infrared spectrum software (OPUS 6.5, FT-IR Alpha-T, Bruker Optics, Billerica MA)

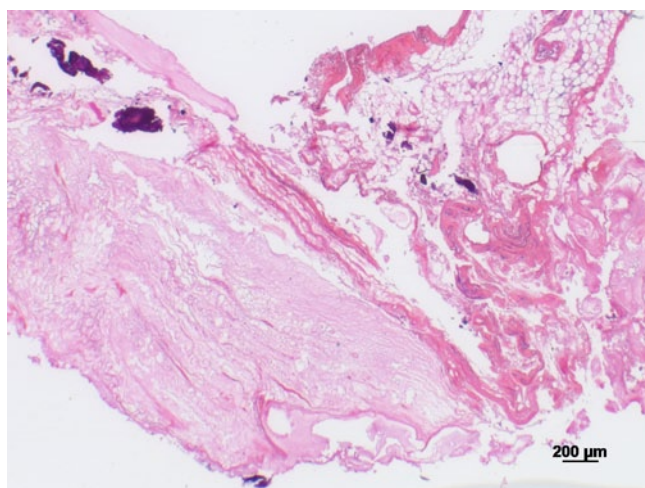


Fig. 7 ◀ Histological section of epidural space, thoracic level 4 to 8. Amorphous, pale eosinophilic material is seen on the left (crystalline deposits) beside the fat and soft tissue (dark pink) on the right side of the picture. There was no substantial inflammatory reaction (HE staining, magnification $\times 25$)

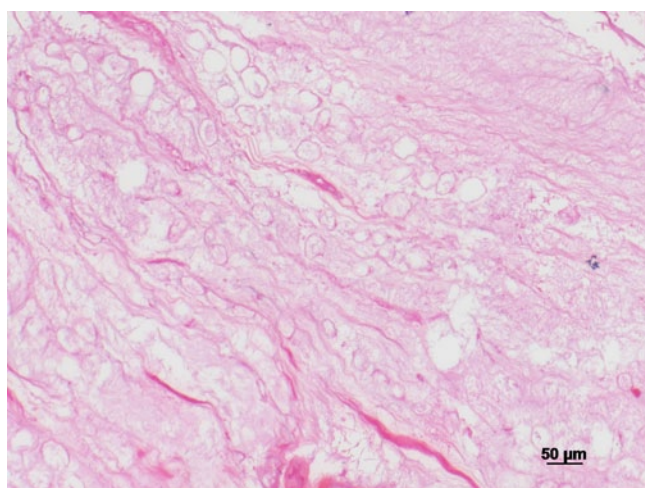


Fig. 8 ◀ Histological section of epidural space, thoracic level 4 to 8. Individual partial image areas show fatty tissue necrosis within the pale eosinophilic material (HE staining, magnification $\times 100$)

er case report [1] discovered bupivacaine deposits with unreactive necrosis in dif-

ferent human tissues (e.g. epidural space, skin, subcutaneous tissue, muscle and soft

tissue) after long-term continuous infusion of bupivacaine-morphine mixtures. In this case, the histological examination revealed fatty tissue necrosis within the bupivacaine deposits. Nerve tissue within or outside the deposits could not be identified. In the formerly published case [1] soft tissue necrosis developed after dislocation of the thoracic EC into the paraspinal space with continued inadvertent administration of bupivacaine-morphine solution [1]. After removal of the EC the same initial thoracic sensory level 4–12 on both sides persisted until the patient died several weeks later. As the CT scan of the thoracic spine showed no signs of myelon compression, it can be speculated that this terminally-ill patient had paraspinal tissue necrosis with crystalline bupivacaine deposits in addition to epidural deposits similar to the ones found in this case. These deposits could possibly maintain segmental analgesia in these patients. A nerve tissue damage by long-term epidural application of LA or LA mixtures cannot be excluded. If the patient would have lived for a longer period and the epidural analgesia continued, it could be speculated that compression of the myelon due to crystalline growth or direct toxic effects on nerve tissue could occur. To the best of the authors' knowledge, there is presently no information on using imaging techniques to detect similar epidural deposits. It is not known how common such small deposits are during long-term epidural infusion, whether they are specific for bupivacaine and how they affect epidural analgesia.

Conclusions

A mixture of bupivacaine and morphine may cause crystalline precipitation and result in tissue damage or unreactive necrosis. Damage of nervous tissue by these LA crystal deposits after long-term use cannot be excluded. Local tissue inflammation in addition to a foreign body, such as an EC might induce small local deposits of the LA mixture, to serve as a nidus for crystalline formation. The exact time period after which the LA deposits start to form is unknown but could be important for predicting the safety margin of long-term LA use.

The possibility of LA precipitation in the neuraxial space or other tissue should also be considered.

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Conflict of interest. The corresponding author states that there are no conflicts of interest.

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