Fatal Pain Relief

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Local anesthetics, intrathecal morphine

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Abstract
This case discusses a synergistic pharmacodynamic interaction between morphine and bupivacaine, resulting in death. This drug pair eliminated both central and peripheral respiratory drive.

Case

A 72-year-old woman was being evaluated for implantation of an intrathecal morphine pump. She had chronic back pain secondary to osteoporosis, numerous old compression fractures of the thoracic and lumbar spines, degenerative disk disease, and spinal stenosis. She was taking oral morphine (60 mg BID) and oxycodone (5 mg every 6 h for breakthrough pain as needed).

On the morning of the intrathecal morphine trial, the patient rated her pain 8 on a 10-point pain scale. She received an intrathecal morphine injection (600 mcg) through an indwelling, lumbar intrathecal catheter. Four hours later, she rated her pain at 6/10. She was given another intrathecal injection (300 mcg). Two hours later, she still rated her pain at 6/10. Her vital signs were normal with a respiratory rate of 20 breaths per minute. A third intrathecal injection of morphine (300 mcg) with bupivacaine (3.25 mg) was administered.

Immediately after the third injection, the patient reported total pain relief and rated her pain at 0/10. Thirty minutes later, the patient was pain-free still and was able to ambulate with adequate motor strength in her lower limbs. Fifteen minutes later,

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resting comfortably in bed, the patient's pulse oximeter saturation decreased to less than 85%. Oxygen by nasal cannulae (4 L/min) was started. Her vital signs were normal, with a respiratory rate of 10 to 12 breaths per minute.

Thirty minutes later, the patient was found unresponsive and pulseless. Attempts at resuscitation were unsuccessful. She was pronounced dead 75 minutes after her last intrathecal injection. An autopsy showed normal heart, lungs, and brain. The pathologist ascribed the cause of death to opioid-induced respiratory depression.

Discussion

This is an example of a pharmacodynamic drug–drug interaction(DDI).

More specifically, this is an example where abolishing pain with local anesthetic may eliminate the respiratory stimulus and unmask the respiratory depression effects of opiates.

Respiratory depression is a well-recognized complication of intrathecal opioid administration.[1] However, patients taking opioid therapy long term are generally resistant to this adverse effect because tolerance develops against the effects of the opioid medication. In this case, respiratory depression did not appear until the administration of a local anesthetic.

Often, a low dose of bupivacaine is added to intrathecal morphine to improve the quality of pain relief.[2] Devoid of respiratory muscle paralysis, intrathecal bupivacaine administration *per se* does not depress respiration. Pharmacokinetic interaction between morphine and intrathecal bupivacaine is minimal and clinically insignificant. However, an established therapeutic principle states that pain is a physiologic antagonist of opioid analgesia.[3]

Substance P, a strong respiratory stimulant, has effects on respiration opposite to those of morphine and endorphin.[4,5] It enhances the rhythmogenesis of brainstem motorneurons and increases the tidal volume and minute ventilation. On the other hand, substance-P antagonists, applied to the ventral surface of the medulla, blunt the ventilatory response to hypoxia, hypercapnia, and somatosensory-induced stimulation.[6] Laboratory studies show that substance P binding to its receptor (NK1) is inhibited by local anesthetics at concentrations reached in the cerebrospinal fluid after intrathecal injection.[7]

It appears that in this case, the stimulating effect of pain on respiration was abolished by administration of a local anesthetic. Intrathecal morphine administered nearly 7 hours earlier, along with long-term oral opioid ingestion, had predisposed

the patient to respiratory depression. Abolishing the pain that was sustaining her respiratory drive probably resulted in respiratory arrest. Similar catastrophic respiratory arrests have been reported after various analgesic techniques that abolish pain in patients who were opioid–dependent long term.[8]

Take-Home Points

- Pain is an important respiratory stimulant for patients who are opioid–dependent long term.
- Abolishing pain may eliminate the respiratory stimulus in these patients and unmask the respiratory depression effects of opiates.
- Respiratory functions should be monitored carefully for patients with long-term opioid dependency who undergo analgesic or anesthetic interventions that abolish pain.

Summary

Interaction: pharmacodynamic
Substrates: morphine and bupivacaine
Mechanism of action: synergy of pain relief (peripheral and central) and opioid-induced respiratory depression
Clinical effect: severe respiratory depression, culminating in death

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