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Morphine spinals and the evidence for safety

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History

Josef Wang first described the use of intrathecal morphine in 1977.[1] He injected 8 rats (weighing between 400–500 g) with 25 µg intrathecal morphine. The tail-flick response was monitored. He concluded that intrathecal morphine might become a predictable modality of pain relief. Yaksh followed on 2 years later with a study looking at the use of intrathecal morphine in parturition in rats and rabbits.[2] Gravid rats and rabbits had intrathecal catheters inserted. After the initiation of nest building, the rats were injected with 15, 45 and 100 µg of intrathecal morphine and the rabbits with 80 µg. Analgesia was tested in the rats with a hot plate as well as a tail flick test. In rabbits it was tested with a hot probe. The animals were well analgised and there was no difference compared to controls with the onset of delivery as well as the percentage of pups alive after 150 minutes. Alper in the editorial of the same journal in which Yaksh's article was published described intrathecal morphine as "potentially revolutionary".[3] He also made mention of how Josef Wang was now looking at the use of intrathecal morphine for the treatment of intractable pain of inoperable cancer.[4]

Pharmacology

Opioid receptors are found in the brain (periaqueductal grey matter, rostral ventral medulla and medial thalamic limbic system. In addition, opioid receptors are also found in the spinal cord (Rexed laminae II or V and substantia gelatinosa).

Opioids can be classified according to their solubility. Morphine is a hydrophilic opioid, which remains in the cerebrospinal fluid for longer than the lipophilic opioids (fentanyl and sufentanil). This is advantageous as it allows the drug to remain in the intrathecal space because it crosses the dura poorly. This results in a prolonged duration of action.

Effectiveness

There is no doubt that morphine provides 12–24 hours of effective postoperative analgesia.[5]

Adverse Effects

Adverse effects include pruritus, nausea and vomiting and respiratory depression.[5] Of these, respiratory depression is the most feared. The difficulty in reviewing the literature is that the term "respiratory depression" has no clear definition.[6] Consequently determining the exact incidence is not a perfect science.

The reported incidence of respiratory depression ranges from 0–0.9%.[7]

The incidence of respiratory depression correlates with the dose of intrathecal morphine. Meta-analysis indicates a reduced frequency of hypoxaemia when lower doses (vs. higher doses) of single-shot intrathecal opioids are used.[8] The optimal dose (balancing effective analgesia and a low incidence of adverse effects) is most probably between 75–150 µg.[9]

In one study, neither 100 µg nor 250 µg intrathecal morphine affected minute ventilation or the ventilator responses to CO_2, whereas both measurements were depressed for 3 hours after 8 mg subcutaneous morphine.[10]

Bailey et al. explored the effects of 300 µg of intrathecal morphine versus 0.14 mg per kilogram of body weight on ventilator drive.[11] He found that the depression of the ventilator response to hypoxia after the administration of intrathecal morphine is similar in magnitude to, but longer lasting than, that after an equianalgesic dose of intravenous morphine.

The mechanisms of respiratory depression include[7]:

- Vascular uptake by the epidural or subarachnoid venous plexuses and circulation to brainstem respiratory center;
- Arachnoid penetration and movement into the spinal cord;
- Rostral spread via the aqueous cerebrospinal fluid to the brainstem;
- Rostral spread via direct perimedullary vascular channels.

Patients At Risk[7]

- Obstructive sleep apnoea
- Morbid obesity

- Elderly
- Cardiopulmonary disease
- Preoperative opioid tolerance
- Hypermagnesemia (in obstetric patients)

Guidelines

The American Society of Anesthesiologists has published guidelines for the postoperative monitoring of patients who have had intrathecal monitoring.[8] This should be done hourly for the first 12 hours and then 2 hourly for the next 12 hours. Monitoring should include respiratory rate as well as level of consciousness. Pulse oximetry is not more sensitive than clinical monitory. Capnography is sensitive but has severe practical limitations.

Conclusions

Intrathecal morphine has the advantages of:

1. Simplicity
2. Reliability
3. Prolonged duration without a catheter in situ

With all interventions in anaesthesia, one must weigh up the benefits versus the risk. The most dreaded risk of intrathecal morphine is that of respiratory depression. This risk is dose-dependent. Doses of 100 µg are effective for analgesia with very little risk of respiratory depression. However, respiratory depression is potentially fatal. Therefore, the patient at risk for respiratory depression must be recognised and adequate monitoring put in place. Over-sedation and respiratory depression should be proactively treated. However, the same holds true for patients receiving opioids systemically.

Sound evidence-based medicine must be followed as opposed to dogma.

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