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10

Management of adverse effects of intrathecal opioids in acute pain

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Intrathecal opioids have been used for several decades in different clinical settings. They are easy to administer and provide many benefits in clinical practice, such as better quality of spinal anaesthesia, prolonged postoperative analgesia, decreased postoperative analgesic requirements and early mobilisation. Several lipophilic and hydrophilic opioids are available for intrathecal administration, either in combination with general anaesthesia or as adjuncts to local anaesthetics. Adverse effects after intrathecal lipophilic opioids administration are predominantly short-lived and benign. In contrast, intrathecal hydrophilic opioids may have potentially serious adverse effects, the most feared of which is respiratory depression. In this review, we will focus on the contemporary evidence regarding intrathecal hydrophilic opioids and present their adverse effects and how to manage them.

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Introduction

Since their introduction into clinical practice in the 1970s [1], intrathecal opioids have become popular for treating acute pain in various settings, such as caesarean section or lower limb joint arthroplasty. Intrathecal opioids can be used either in combination with general anaesthesia or as adjuncts to intrathecal local anaesthetics. The administration of intrathecal opioids is associated with postoperative benefits, such as improving the quality of spinal anaesthesia, decreasing postoperative analgesic requirements and facilitating early mobilisation after abdominal surgery [2]. As an example, analgesia may be prolonged up to 24 h after intrathecal morphine [2]. Further advantages of intrathecal opioids are a rapid and easy administration, associated with a low risk of technical complications and failure [3]. However, the administration of intrathecal opioids is accompanied by several adverse effects, which may preclude this effective analgesic technique in certain patients and clinical situations.

Two main categories of opioids are distinguished: lipophilic (e.g. fentanyl and sufentanil) and hydrophilic molecules (e.g. morphine, diamorphine and hydromorphone).

The pharmacokinetic properties of the specific molecules following intrathecal administration determine the adverse effects encountered in clinical practice (Table 1). Lipophilic opioids have a rapid onset, diffuse swiftly into surrounding tissues and thus have a short duration of action with limited rostral spread [4]. Therefore, they are mainly used to prolong the sensory block of the intrathecal local anaesthetics. In contrast, hydrophilic intrathecal opioids have a slower onset of effect, a prolonged rostral spread above the injection point and slow plasma reuptake, resulting in a wider covered area and a prolonged duration of action. They require up to 90 min to achieve a peak effect with a duration of action of up to 24 h [5]. Of note, intrathecal diamorphine, almost exclusively used in the United Kingdom, is 280 times more lipid soluble than morphine and therefore has a shorter onset time of action, although data supporting this are scarce [6].

Adverse effects with intrathecal lipophilic opioids are predominantly short-lived and benign [7,8]. In contrast, adverse effects after intrathecal administration of hydrophilic opioids may be more serious; understanding these consequences are critical to ensure safe and effective clinical use. In this review, we will focus on presenting contemporary evidence of adverse effects after the intrathecal administration of hydrophilic opioids and their management in the perioperative setting, with a particular focus on articles published in the last 10 years. Moreover, as data on hydromophone or diamorphine are limited, with only a few studies investigating the intrathecal route of these two drugs, most of the evidence presented here on hydrophilic opioids comes from data on intrathecal morphine.

What are the most important adverse effects of intrathecal opioids for acute pain therapy?

The most common adverse effect after the administration of intrathecal lipophilic opioids is pruritus, while other clinically relevant adverse effects are negligible [7,8]. All hydrophilic opioids share the same adverse effect profile after intrathecal administration and mimic those after systemic administration. The most common adverse effects are nausea and vomiting, pruritus, urinary retention, sedation and respiratory depression. In the following section, we discuss the recent evidence of these adverse effects. Fig. 1 summarises the overall evidence for hydrophilic opioids.

Nausea and vomiting

Two recent reviews on lipophilic opioids analysed the adverse effects of fentanyl or sufentanil when added to spinal local anaesthetics [7,8]. In 17 randomised trials with over 1000 patients, one

Table 1
Pharmacological properties of lipophilic and hydrophilic intrathecal opioids.

Opioid	Lipophilic	Hydrophilic
Example	Fentanyl, sufentanil	Morphine, diamorphine, hydromorphone
Onset time (min)	10–20	60–90
Duration of action (hours)	1–3	18–24
Rostral spread	Minimal	Significant

Fig. 1. Summary of the overall evidence regarding the adverse effects following intrathecal administration of hydrophilic opioids. *No data on diamorphine or hydromorphone.

study found that intrathecal fentanyl reduced the incidence of nausea or vomiting with a risk ratio (95% CI) of 0.41 (0.24–0.70) and a number needed to treat of 6.5 [8]. On the other hand, the authors concluded that intrathecal fentanyl was associated with a higher rate of pruritus; indeed, the risk ratio (95% CI) was 5.89 (2.07–16.79), and the number needed to harm (NNH) was 13.5 [8]. Based on 10 randomised controlled trials with a total of 517 patients, another meta-analysis confirmed both findings with intrathecal fentanyl, while data on intrathecal sufentanil and nausea and vomiting were insufficient [7].

Several articles explored nausea and vomiting in patients receiving intrathecal morphine, but very few data exist on other hydrophilic opioids. A recent meta-analysis of 2500 patients undergoing abdominal surgery concluded that there was no increased risk of postoperative nausea and vomiting in patients receiving up to 400 μg intrathecal morphine [2]. This contrasts with another contemporary meta-analysis, including 1814 patients undergoing lower joint arthroplasty, which reported a rate of nausea and vomiting in the control and intrathecal morphine groups of 30% and 42%, respectively, with a risk ratio (95% CI) of 1.4 (1.3–1.6) [9]. In addition, the authors performed a sub-group analysis according to the dose of intrathecal morphine and concluded that rates of nausea and vomiting were similar between groups with doses up to 100 μg; this rate significantly increased with higher doses. This conclusion was reinforced by a retrospective study in 241 patients undergoing caesarean section where authors examined doses of 100 and 200 μg of intrathecal morphine, similarly reporting a lower incidence of nausea and vomiting with lower doses [10]. In addition, a recent meta-analysis by Sultan et al. analysed the effect of low dose (50–100 μg) versus high dose (>100–250 μg) of intrathecal morphine after elective caesarean section in 480 patients [11]. The authors found that nausea and vomiting occurred less in the low-dose group, with an odds ratio (95% CI) of 0.44 (0.27–0.73). Finally, another recent meta-analysis on 4400 obstetric patients receiving any intrathecal opioid (morphine; diamorphine; fentanyl; sufentanil; or pethidine, also called meperidine) found a similar rate of nausea and vomiting compared with the control group. Of note, the authors did not explore the dose–response effect of specific opioids [12]. Thus, intrathecal opioids are likely to increase the risk of postoperative nausea and vomiting in a dose-dependent manner in all types of surgery, but this effect might not be apparent following abdominal surgery. It may be that the risk of postoperative nausea and vomiting is high in patients having abdominal surgery regardless of intrathecal opioids, but this remains an area for further investigation.

Several pharmacological agents have been investigated to prevent nausea and vomiting associated with neuraxial opioids. These are similar to those used for nausea and vomiting after intravenous opioids. In an obstetric population, two narrative reviews concluded that ondansetron 4–8 mg, granisetron 1–3 mg, droperidol 0.5–1.25 mg and dimenhydrinate 50–100 mg all reduced the rate of nausea and vomiting [3,13]. In a systematic review with a meta-analysis including 1111 patients undergoing all types of surgery, Grape et al. demonstrated that intravenous dexamethasone reduced the rate of nausea and vomiting within 24 postoperative hours with a risk ratio (95% CI) of 0.42 (0.35–0.51) [14]. A subgroup analysis between low (2.5–5.0 mg) and moderate doses (6.0–10.0 mg) did not reveal any difference between groups [14]. Of note, all data available in the literature focused on the prevention but not on the treatment of established nausea and vomiting after intrathecal opioids.

In summary, the rate of nausea and vomiting after intrathecal morphine is dose-dependent in patients undergoing lower joint arthroplasty or caesarean section and significantly increases with doses beyond 100 μg. Consequently, a dose of less than 100 μg of intrathecal morphine may likely be a reasonable compromise to provide sufficient analgesia without increasing the risk of nausea and vomiting. Dexamethasone and 5-HT3 receptor antagonists are effective for preventing nausea and vomiting, while there are no data on the treatment of this adverse effect once established.

Pruritus

Pruritus following administration of intrathecal opioids occurs in 30–60% of patients undergoing general surgery [15] or orthopaedic surgery [9] and in up to 100% of patients undergoing caesarean section [16]. Seki et al. concluded in their review that all intrathecal opioids – fentanyl, sufentanil, pethidine (meperidine), and morphine – significantly increased the incidence of pruritus, with the exception of diamorphine [12]. However, the conclusion regarding diamorphine is probably a

confounder as studies investigating this drug were prone to performance bias and imprecision, with an overall low level of evidence. A recent meta-analysis of 2500 patients receiving intrathecal hydrophilic opioids for abdominal surgery concluded a risk ratio (95% CI) of 4.3 (2.5–7.5) [2]. Moreover, the authors demonstrated dose-dependency between 100 and 800 μg of intrathecal morphine. In another meta-analysis including 3338 patients undergoing a range of surgery, Pöpping et al. concluded that the risk of pruritus was similarly increased with an NNH (95%CI) of 4 (3–5) [17]. Threshold doses for most intrathecal opioids are unknown except for morphine. Indeed, Sultan et al. showed in a meta-analysis with 480 patients that morphine doses above 100 μg caused significantly more pruritus than lower doses with an odds ratio (95% CI) of 0.34 (0.20–0.59) [11]. While the duration of pruritus after intrathecal morphine seems to be considerably longer than after the administration of other intrathecal opioids [13], it is reassuring that only a minority of patients require treatment for this adverse effect [3].

Different drugs have been studied for the management of intrathecal opioid-induced pruritus, such as 5-HT3 receptor antagonists, opioid agonist/antagonist and dexamethasone [16]. Data demonstrate that intravenous ondansetron 4 or 8 mg, tropisetron 5 mg, granisetron 3 mg or dolasetron 12.5 mg are effective for both prevention and treatment of pruritus [16,18]. The opioid agonist/antagonist pentazocine may also be effective at a dose of 15 mg [15], while dexamethasone 2.5–10 mg does not prevent the occurrence of this side effect [14].

In summary, pruritus is a frequent and dose-dependent side effect of intrathecal opioids [2,19], especially when morphine is used at doses above 100 μg. Pruritus is generally self-limiting and can be prevented and treated with 5-HT3 receptor antagonists, treated with opioids agonist/antagonist, whereas dexamethasone is ineffective for preventing this adverse effect.

Urinary retention

While urinary retention is a side effect often observed after intravenous opioid administration, the data following intrathecal administration is less clear. In a study on healthy volunteers, intrathecal opioids interfered with bladder function by causing dose-dependent suppression of detrusor muscle contractility and a reduction in sensations of urge [20]. Several meta-analyses focusing on adverse effects of intrathecal opioids could not draw robust conclusions about urinary retention, as a restricted number of trials specifically sought this outcome, and as many patients undergoing extensive surgery have urinary catheters in situ [2,7,8]. As an example, a recent meta-analysis did not find any difference between patients receiving intrathecal fentanyl and sufentanil or not [7]; this is potentially due to their relatively short duration of action. That said, a meta-analysis of 3338 patients concluded that intrathecal morphine increased the risk of urinary retention in patients undergoing minor surgery, with an NNH of 6.5 [17]. Additionally, a meta-analysis of 1814 orthopaedic patients concluded a risk ratio (95% CI) for urinary retention of 1.4 (1.1–1.8) in patients receiving intrathecal morphine compared to a control group [9]. When established, acute urinary retention following intrathecal hydrophilic opioids is likely to resolve spontaneously. Patients who still present urinary retention after 6–8 h with no other detectable cause may require urethral catheterisation [21,22]. In these patients, in–out urinary catheterisation and subsequent observation for recurrence are usually appropriate; patients suffering from benign prostatic hyperplasia or neurological disease might require an indwelling urinary catheter for 24 h [21,22].

In summary, the limited literature presents conflicting evidence regarding an increased risk of urinary retention with intrathecal hydrophilic opioids. When present, no specific treatment is usually needed.

Sedation

Soon after the routine introduction of intrathecal opioids into clinical practice, physicians noticed that sedation was a common and dose-dependent side effect occurring with all types of intrathecal hydrophilic opioids [23], while this side effect is not reported with lipophilic opioids [7,8]. Most studies investigated morphine [24,25], and older reports demonstrated that clinically relevant sedation occurred in all patients after administration of 2.5 mg of intrathecal morphine and in over 50% of

patients after 1.0 mg [26]; sedation develops over 2–4 h after injection and often leads to profound respiratory depression [26]. On the other hand, the risk of sedation with morphine doses of ≤500 μg is either not increased [2] or without clinical significance as it does not require treatment [9]. With contemporary doses of intrathecal opioids, the risk of sedation is so rare that it is no longer reported individually but only as a risk marker for clinically relevant hypoxaemia or respiratory depression [27].

Respiratory depression

Respiratory depression is the most feared complication as it may occur up to 24 h after intrathecal opioid administration [28]. When discussing this adverse effect, we should bear in mind that a standard definition of respiratory depression does not exist. In practice, many surrogates have been used, such as decreased respiratory rate; oxygen saturation <92%; need for oxygen therapy or airway intervention; sedation requiring more than verbal stimulation to rouse the patient and need for opioid antagonists.

With intrathecal lipophilic opioids, there is no evidence that the risk of respiratory depression increases [7,8]. Indeed, two meta-analyses reported risk ratios (95% CI) of 3.20 (0.38–27.26; $p = 0.29$) [8] and 0.76 (0.25–2.34; $p = 0.64$). Regarding hydrophilic opioids, studies from the 1980s concluded that the rate of respiratory depression was up to 100%, with doses of intrathecal morphine between 0.3 and 2.5 mg [26]. Analysing studies published between 1985 and 2007, a meta-analysis concluded that the odds ratio (95% CI) for respiratory depression in patients who received intrathecal morphine was 7.9 (1.5–40.3) [29]. Over the following years, intrathecal opioid doses were gradually reduced, and respiratory depression was less frequently observed.

Respiratory depression after administration of intrathecal hydrophilic opioids with contemporary doses has been specifically studied in two different settings: obstetrics and joint arthroplasty. As these two represent probably the most common fields of clinical usage, the specific evidence is worth summarising. Retrospective evidence of 5036 obstetric patients highlights the absence of respiratory depression with intrathecal morphine doses below 150 μg [30]. A recent review of the literature on respiratory depression with contemporary doses of neuraxial morphine (intrathecal dose: ≤150 μg; epidural dose ≤3 mg) or diamorphine (intrathecal dose: ≤400 μg; epidural dose: ≤5 mg) after caesarean section included 78 articles and 18,455 patients, and concluded that the risk of respiratory depression ranged from 1.08 to 1.63 per 10,000 women [31]; this complication occurred with intrathecal morphine only. Of note, only 9 of the 78 studies (just 284 patients) investigated neuraxial diamorphine, preventing any meaningful conclusion [31].

In the domain of orthopaedic surgery, a recently published meta-analysis with 1814 patients and high-quality evidence concluded that intrathecal morphine was not associated with an increased risk of respiratory depression or hypoxaemia. Of note, intrathecal morphine doses analysed in this review ranged from 35 μg to 500 μg, with the most frequently investigated dose being 100 μg [9]. Another systematic review of 18 trials with patients undergoing total joint arthroplasty reached a similar conclusion [19]. A recent randomised controlled trial investigated the respiratory impact of 100 μg of intrathecal morphine on the first postoperative night with respiratory polygraphy in an elderly population of 60 patients undergoing hip arthroplasty [32]. The primary outcome was the apnoea–hypopnoea index, which is the number of apnoeic and hypopnoeic episodes per hour. The authors concluded that the index was similar between groups with 22.8 (95% CI 12.3–33.4) events. h^{-1} in the control group, and 16.1 (6.6–25.6) events. h^{-1} in the group receiving 100 μg of intrathecal morphine ($p = 0.30$) [32]. Of note, over 40% of these patients had a preoperative index of 15 events. h^{-1}, while the mean body mass index was 27 kg m^{-2} [32].

In summary, respiratory depression after intrathecal morphine is a dose-dependent adverse effect. A dose of 100 μg or less of morphine does not produce respiratory depression after surgery, even in an elderly population, in patients at risk of apnoea or in obstetric patients. With higher doses, specific monitoring for 24 h is recommended.

Does the choice of intrathecal opioid influence adverse effects?

As previously mentioned, all hydrophilic opioids have similar pharmacokinetic properties, and consequently, the same adverse effect profile after intrathecal administration. There is no robust

evidence to favour one over another to reduce the rate of adverse effects. The most well-described hydrophilic intrathecal opioid remains morphine; a dose in the range between 75 and 150 μg seems to be a reasonable compromise between analgesic efficacy and reduced adverse effects. Data on the adverse effects following the intrathecal administration of other hydrophilic opioids are scarce.

Postoperative monitoring routines

Concerning the lipophilic opioids fentanyl and sufentanil, side effects are short-lived and mostly self-limiting, the most frequent being pruritus. Consequently, no specific monitoring is necessary.

Postoperative monitoring after lipophilic opioids is limited to 2 h after the injection due to their pharmacokinetic profile [33]. After intrathecal administration of hydrophilic opioid, postoperative monitoring is mainly aimed at detecting respiratory depression. Again, most monitoring recommendations are focused on intrathecal morphine and diamorphine.

In 2016 the ASA published 'Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration' [33]. These guidelines apply to any patient undergoing any surgery involving neuraxial opioids. In these guidelines, monitoring of respiration and level of consciousness after neuraxial morphine administration is advised every hour for the first 12 h and then every 2 h for the next 12 h for at least 24 h [33]. Subsequent monitoring is then tailored to the patient's clinical condition and medication. For example, patients suffering from obstructive sleep apnoea or obesity and receiving sedative medication may warrant continuous monitoring for a more extended period.

Given the rarity of clinically relevant sedation or respiratory depression with low doses of intrathecal opioids, the American Society for Obstetric Anesthesia and Perinatology (SOAP) has issued less restrictive guidelines, with the dual objective of avoiding physicians from withholding intrathecal morphine administration in case of absence of monitoring availability and avoiding overuse of the intermediate care unit. Their consensus statement published in 2019 addressed patients undergoing Caesarean section, the majority of whom are young and healthy and receive a single dose of neuraxial morphine with no concurrent sedatives [34]. No additional monitoring is proposed with doses of intrathecal morphine of 50 μg or below. For doses above 50 μg up to 150 μg, the task force recommends monitoring of respiratory rate and sedation every 2 h for 12 h [34]. For doses above 150 μg of morphine, the task force recommends following the ASA guidelines summarised above.

Also for obstetric patients, the UK National Institute for Health and Care Excellence (NICE) published their evidence review entitled 'Monitoring after intrathecal or epidural opioids for caesarean birth' in 2021 [35]. As morphine is rarely used in the UK, this review gives specific advice for monitoring after intrathecal diamorphine, which is thought to cause less respiratory complications than morphine because of its higher lipid solubility. However, it is essential to reinforce that no robust data support this. As no cases of clinically relevant respiratory depression related to the administration of intrathecal diamorphine in healthy patients were identified by the authors, the guidelines recommend no monitoring, with the exception of women specifically at risk of respiratory depression (obesity, obstructive sleep apnoea). But even in these patients, hourly monitoring for 12 h is deemed sufficient because the respiratory depression caused by diamorphine is unlikely to occur after this period. PROSPECT guidelines also recommend using intrathecal morphine at doses up to 150 μg in the obstetric setting but do not specifically recommend any monitoring requirements [36]. Of note, in the absence of a sufficient number of high-quality studies, these recommendations were based on expert consensus.

Conclusions

Intrathecal administration of hydrophilic opioids provides satisfactory analgesia after a wide range of surgical procedures. The most investigated drug is morphine; the literature demonstrated that a dose of 100 μg represents a threshold dose for nausea and vomiting and does not produce respiratory depression while providing satisfactory analgesia. There is no evidence to highlight a threshold dose for pruritus and urinary retention. While the former is typically mild and self-limiting, the latter might require standard treatment.

Practice points

- Clinically relevant adverse effects occur frequently after the administration of intrathecal opioids.
- Intrathecal lipophilic opioids are associated with pruritus.
- The most common adverse effects of intrathecal hydrophilic opioids are nausea and vomiting, pruritus, urinary retention, sedation and respiratory depression, with a clear dose-dependency.
- A dose of up to 100 μg of intrathecal morphine seems a reasonable compromise to ensure optimal analgesia with limited adverse effects. Specifically, 100 μg of intrathecal morphine does not produce respiratory depression, even in an elderly population, in patients at risk for apnoea and in obstetric patients.
- Specific guidelines exist for monitoring respiratory depression after different doses of intrathecal morphine.

Research agenda

- Investigate the threshold doses for intrathecal hydrophilic opioids other than morphine regarding the adverse effects of nausea and vomiting, pruritus, urinary retention, sedation and respiratory depression.
- Investigate drugs for treating established nausea and vomiting related to intrathecal opioids.
- Issue guidelines for monitoring respiratory depression after intrathecal opioids based on contemporary evidence.

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