ROLE OF NALBUPHINE IN ANALGESIOLOGY

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Keywords

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Opiate analgesics provide the most effective pain relief of any class of agents and are a standard of care for control of mild to severe pain [1]. But even with , the side effects of mu-agonist analgesia are occasionally troublesome. The side effects most commonly encountered are pruritis, nausea/emesis, constipation, urinary retention, respiratory depression and undesirable sedation, and the development of tolerance and dependence. These can remain obstacles to optimally effective employment of opioid analgesia.

The use of the opioid mixed agonist—antagonist nalbuphine as an analgesic agent provides a number of advantages. Used as the sole opioid analgesic, it can satisfactorily cover mild to moderate pain with a low incidence of side effects. The ceiling effect of nalbuphine, which prevents it from supplying sufficient analgesia to cover the most severe discomfort, also prevents increasing sedation and respiratory depression as the dose is increased, potentially providing an increased safety margin in comparison to mu-agonists.

When nalbuphine is used concurrently with mu-agonists (e.g. morphine, hydromorphone, fen-tanyl), the benefits of both mu- and kappa-analgesia can be obtained, with simultaneously decreased incidence and severity of the common mu-agonist side effects (pruritis, nausea/emesis, constipation, urinary retention, respiratory depression and undesirable sedation). Data from animal studies also suggest that combined nalbuphine and mu-agonist administration may decrease the development of opioid tolerance and dependence.

In this article we review an alternative manner of providing opioid analgesia. This is the use, either singly or in combination with other opioid agents, of the mixed opioid agonist—antagonist nalbuphine. Nalbuphine has the potential to maintain or even enhance mu-opioid based analgesia while simultaneously mitigating the common mu-opioid side effects.

1. Introduction

Opiate analgesics provide the most effective pain relief of any class of agents and are a standard of care for control of mild to severe pain [1]. But even with , the side effects of mu-agonist analgesia are occasionally troublesome. The side effects most commonly encountered are pruritis, nausea/emesis, constipation, urinary retention, respiratory depression and undesirable sedation, and the development of tolerance and dependence. These can remain obstacles to optimally effective employment of opioid analgesia.

In this article we review an alternative manner of providing opioid analgesia. This is the use, either singly or in combination with other opioid agents, of the mixed opioid agonist—antagonist nalbuphine. Nalbuphine has the potential to maintain or even enhance mu-opioid based analgesia while simultaneously mitigating the common mu-opioid side effects.

2. Opioid receptors, and endogenous and exogenous ligands

There is a vast literature on opioid receptors, lig-ands, and binding; entire books are devoted to these topics (e.g. [9]). For present purposes several current summaries provide appropriate background in conjunction with more recent primary publications.

2.1.Opioid receptor types

It is generally agreed that there are three major classes of receptors mediating opioid-induced analgesia. These are the mu-, kappa-, and delta-opioid receptors . They are all blockable by naloxone, an opioid receptor-specific competitive antagonist. Roles for all three receptor types in the mediation of opioid analgesia have been proposed. At least the mu- and kappa-receptors, and probably all three, can be pharmacologically differentiated into subtypes. While some data suggest that there may be clinically useful distinctions among these subtypes , currently there are no commercially available agents that take advantage of subtype specificity .

There is also a receptor which binds opioids in a non-naloxone reversible fashion. It is usually referred to as the sigma opioid receptor, and it has no apparent role in mediating opioid-induced analgesia. It may mediate the psychotomimetic effects of some opioids, apparently related to its ability to bind phencyclidine (PCP). Neither opioids commonly used for clinical analgesia, nor nalbuphine, bind to the sigma receptor to any significant degree. The common clinically used opioid analgesics (e.g. morphine, hydromorphone, and fentanyl) bind most readily to the mu-receptor, less well to the kappa-receptor, and relatively poorly to the delta receptor. This implies that the main analgesic effects, as well as the undesirable side effects of these medications are likely to be mu-receptor-mediated. Data reviewed in the following are consistent with this notion.

Nalbuphine binds readily to both mu- and kappa-receptors. A key point in understanding the utility of nalbuphine is that while it binds readily to both the mu- and kappa-receptors, its actions on these populations are divergent. When nalbuphine binds to mu-receptors it serves only to competitively displace other mu-agonists from the receptor, without itself displaying any agonist activity itself. At mu-receptors, then, nalbuphine has only antagonist effects, similar to those of naloxone. When nalbuphine binds to kappa-receptors, however, it has an agonist, activating effect. This pattern of binding and effects defines nalbuphine as a mixed agonist—antagonist.

2.2 Opiate receptor populations mediating kappa-analgesic effects

Most clinically useful opioids achieve their analgesic effect through binding and activation of mu-opioid receptors. What is less well appreciated is that significant analgesia can be obtained through activation of the kappa-opioid receptor alone.

Kappa-opioid receptors are distributed throughout brain and spinal cord areas involved in nociception. The greatest concentrations of kappa-receptors in nociceptive regions are in laminae I and II of Rexed in the spinal cord dorsal horn, as well as in the spinal nucleus of the trigeminal nerve (substantia gelatinosa). Nalbuphine binds avidly to kappa-receptors in these areas and when the kappa-antagonist is given intraventricularly or intrathecally, the antagonism is 10 times more potent. These data suggest that nalbuphine acts primarily at the level of the first synapse in the nociceptive systemin producing analgesia.

3. Efficacy of kappa-agonist based analgesia: ceiling effect of nalbuphine

There is ample evidence that kappa-agonists produce useful analgesia in humans when administered as a sole opioid agent, or when given in combination with a mu-agonist. Post-hysterectomy and post-myomectomy pain are adequately treated by nalbuphine; in fact, there is no difference in the adequacy of analgesia between nalbuphine and morphine treated patients. Intrathecal nalbuphine satisfactorily treats pain after total hip replacement or Caesarean section. Discomfort from dental extractions is also adequately treated by bolus intravenous nalbuphine. But while nalbuphine given alone can produce useful and adequate analgesia for many purposes, it does not produce as potent analgesia as do mu-agonists, and nalbuphine analgesia alone can be insufficient for some situations. For example, nalbuphine given via lumbar epidural for post-thoracotomy pain control is ineffective at doses of 10 and 20mg, while only 5mg of morphine provides adequate analgesia. Similarly, nalbuphine, given either by intravenous bolus or PCA, can be inadequate for covering pain from vasoocclusive crisis of sickle cell disease. Intravenous nalbuphine also may not cover pain after sternotomy for coronary artery bypass grafting, although it has been

used successfully by others for this purpose.

The problems that nalbuphine, like other mixed agonists—antagonists, exhibits a ceiling effect. That is, increasing doses of drug produce increasing intensity of analgesia only up to a point; beyond that point, further increases in dose do not result in increased intensity of analgesia. This analgesic ceiling effect can be a significant limitation of nalbuphine. Since it is not always possible to obtain the same maximum degree of analgesia with nalbuphine as with mu-agonists (e.g. morphine), the situations in which nalbuphine is used as a sole opioid agent must be chosen carefully.

4. Use of nalbuphine for labor analgesia

While epidural analgesia employing local anesthetics is the current standard for relief of labor pain, intravenous opioids are still widely used. Nalbuphine has been studied more for labor analgesia than for any other clinical use. Several reports show that acceptable labor analgesia can be obtained with PCA-delivered, intravenous bolus, or intramuscular bolus nalbuphine. Inevitably, though, the issues are more complex.

First, studies on the usefulness of nalbuphine for labor analgesia generally compare it to meperidine (pethidine), which has long been used for this purpose. In brief, studies that compare bolus (intravenous or intramuscular) administration of nalbuphine and meperidine at the usual clinical doses fail to show any clear advantage of nalbuphine: there is generally no better pain relief, no decrease in overall maternal side effects, nor a decreased incidence of fetal/neonatal adverse effects. Further, bolus meperidine appears to have an advantage when compared with bolus nalbuphine in that fetal heart rate tracings are not as frequently affected by meperidine at the doses commonly used, thus simplifying intrapartum evaluation of fetal well-being.

The issue of fetal/neonatal well-being is obviously a central concern in the issue of opioid selection. Transplacental transfer of nalbuphine occurs relatively rapidly whether it is given intravenously or intramuscularly. Nalbuphine may or may not affect baseline fetal heart rate and spontaneous variability, although it does not diminish the usefulness of fetal acoustic stimulation. Two reports totaling three cases describe newborns with bradycardia, cyanosis, and hypotonia requiring either supplemental oxygen therapy or brief mechanical ventilation; one of the affected neonates, however, had Apgar scores of 9, 10, and 10. It should be noted here that the ceiling effect on respiratory depression that is proven for adults has not been examined in children, infants, or neonates; neonates may not be protected from excessive respiratory depression by the use of nalbuphine.

In contrast to intravenous or intramuscular bolus administration, when PCA-delivered nalbuphine is compared to PCA-delivered meperidine, nalbuphine provides more effective maternal analgesia than does meperidine, without adverse fetal/neonatal effects.

Additionally, a study comparing PCA-delivered nalbuphine against intravenous bolus nalbuphine found that while both methods produced effective pain relief, more satisfactory analgesia was obtained when PCA delivery was used; again, no adverse fetal/neonatal events were reported. The finding that nalbuphine administered by PCA for labor analgesia demonstrated no adverse fetal effects suggests that the relatively large (e.g. 5— 20 mg) intravenous and intramuscular bolus doses of nalbuphine commonly used for labor analgesia are more likely to result in adverse fetal effects than is PCA administration.

When comparing the merits of nalbuphine and meperidine labor analgesia, it is worth noting that meperidine also undergoes transplacental transfer and also has various associations with maternal and fetal/neonatal adverse effects (briefly reviewed in.

While the elimination half-life of nalbuphine in neonates is 4.1h, the neonatal elimination half-life of meperidine is 7—32h, and the elimination half-life of neonatally formed normeperidine is 20—36 h. Thus, any fetal effects of transplacentally transferred opioid will be of shorter duration if nalbuphine is used for maternal analgesia, rather than meperidine.

5. Nalbuphine antagonizes side effects of mu-agonist analgesics

The side effects of mu-opioid analgesics are well-known and have been extensively studied and reviewed. The side effects of common clinical concern are pruritis, nausea/emesis, constipation, urinary retention, respiratory depression, excessive sedation, and tolerance, dependence, and withdrawal. The issue of abuse is treated farther below.

5.1. Respiratory depression and sedation

Respiratory depression is one of the most feared

side effects of opioid analgesics and in some cases is a significant limitation on their use. Respiratory depression from most clinically useful opioids is believed due predominantly to mu-receptor-mediated actions, and dense populations of mu-receptors are found in brainstem respiratory areas.

Since respiratory depression in clinical practice seems predominantly mu-receptor-mediated, it would be expected that the mu-antagonistic property of nalbuphine would attenuate it. This is demonstrated by several studies. Whether respiratory depression is due to epidural bolus morphine or intravenous fentanyl, intravenous nalbuphine attenuates it. Additional sedation from the administration of nalbuphine, when it occurs, is minimal, present at the lowest doses of nalbuphine tested, and does not increase with increasing nalbuphine dose.

5.2. Tolerance and dependence

Two well-known aspects of mu-agonist therapy are tolerance (the requirement for gradually increasing doses of medication to achieve the same clinical effect), and dependence (the appearance of the acute physiological symptoms of sudden opioid withdrawal).

Interestingly, co-administration of nalbuphine dose-dependently prevents the development of both tolerance and dependence to repeated administration of morphine in animals, without impairing morphine-induced analgesia. While co-administration of naloxone is also capable of preventing the development of tolerance and dependence to morphine in animals, it also diminishes morphine-induced analgesia. Curiously, the prevention of mu-tolerance by nalbuphine may not be due to its mu-antagonist effect, but rather to its kappa-agonist effect.

The possibility that routine coad-ministration of nalbuphine with mu-agonists might prevent the development of clinical tolerance and dependence has not been addressed in humans.

5.3. Pruritis

There are two mechanisms underlying opioid-induced pruritis. The more widely appreciated mechanism involves release of histamine from mast cells. Morphine in particular is well-known for causing non-opioid receptor-mediated release of histamine from mast cells; the circulating histamine then provokes pruritis. Pruritis caused by this mechanism is effectively treated with standard doses of a histamine H1 antagonist (e.g. diphenhydramine). A second mechanism is mediated by mu-receptors on neurons in the dorsal horn of the spinal cord; this mechanism is naloxone reversible.

In contrast to mu-agonists, nalbuphine does not produce pruritis even at doses sufficient to cover abdominal surgical pain; presumably this is due both to its lack of mu-receptor agonist activity as well as to its lack of histamine release. Further, the mu-antagonist property of nalbuphine can be used to treat mu-receptor-mediated pruritis generated by mu-opioid agonists. Nalbuphine reduces pruritis occurring after intrathecal morphine or epidural morphine, without reducing analgesia after Caesarean section. What makes nalbuphine useful for antagonism of pruritis is that the lower doses of nalbuphine which ameliorate mu-receptor-mediated pruritis do not necessarily antagonize mu-receptor-mediated analgesia.

5.4. Nausea/emesis

The nausea and emesis which occur after administration of opioid analgesics are thought to be due to stimulation of the chemoreceptor trigger zone in the area postrema of the lower brainstem. Since these effects appear to be mu-receptor-mediated, nalbuphine should not cause nausea or emesis, and it should diminish the occurrence of nausea and emesis provoked by mu-receptor acting analgesics. In post-Caesarean section patients receiving bolus epidural morphine for post-operative pain control, nalbuphine reduced the incidence of nausea and vomiting without compromising morphine-induced analgesia.

In a study of 47 patients following "major gynecological surgery" who received nalbuphine as their sole opioid analgesic, either by intramuscular bolus or PCA, no treatment for nausea or emesis was ever required. In a study of 300 total joint (hip, knee, or hip+knee) patients receiving either nalbuphine, morphine, or meperidine via PCA for post-operative pain control, patients receiving nalbuphine took liquids and solids sooner than either patients receiving either morphine or meperidine, implying less GI upset in the group receiving nalbuphine.

An additional occasional gastrointestinal side effect of mu-opioid analgesics is spasm of the sphincter of Oddi, which can produce symptoms similar to biliary colic.

5.5. Constipation

Morphine decreases gastric emptying and large bowel motility by mu-receptor-mediated

mechanisms, although it is unclear. Nalbuphine, as a mu-antagonist, would not be expected to produce constipation, and in fact might reasonably be expected to reduce the incidence of constipation seen in patients treated with mu-agonists. Nalbuphine is associated with decreased intestinal transit; a maximally analgesic dose of nalbuphine produces only about one-third the decrease in gastrointestinal transit time as a maximally analgesic dose of morphine.

5.6. Urinary retention

Urinary retention is a significant side effect of either peripheral or central opioid administration. In a study of hydromorphone via PCEA for post-Caesarean section analgesia, the addition of low-dose nalbuphine to the PCEA infusate decreased the need for bladder catheterization. Also, there is a case report, including urodynamic measurements, of nalbuphine reversal of urinary retention caused by epidural morphine.

6. Metabolism

Nalbuphine undergoes hepatic metabolism to pharmacologically inactive conjugates. Both unchanged drug and conjugates are secreted into bile. The major route of elimination is fecal, with little renal elimination of either unaltered drug or metabolites. Original studies in adults suggested a plasma elimination half-life of intravenously administered nalbuphine of approximately 2—3h. Subsequent pharmacokinetic studies confirmed these numbers for young (1.9h) and elderly (2.3 h) adults. The plasma elimination half-life in children aged 1.5—8.5 years is significantly less, however, with a mean of 0.9h. All these findings are in contrast to estimates of neonatal plasma elimination half-life after transplacental transfer of intravenous or intramuscular nalbuphine boluses for labor analgesia. In neonates the plasma elimination half-life is estimated at 4.1 h. This longer elimination half-life in neonates is consonant with other findings that drugs requiring hepatic transformation and glucoronidation have relatively prolonged eliminations in newborns.

7. Cautions in using nalbuphine

Because of its demonstrated ability to block mu-opioid receptors, nalbuphine must be used with caution in patients concurrently using mu-receptor analgesics (e.g. morphine, hydromorphone, fentanyl).

There are two reasons for caution. First, nalbuphine in sufficient doses can block the analgesic effects of mu-agonists. This is generally not an obstacle to clinical uses of nalbuphine in combination with mu-agonists because the doses of nalbuphine required for reversal of mu-receptor-mediated analgesia exceed those at which the desirable effects of side-effect reduction are achieved. However, if the intent of starting nalbuphine is to substitute kappa-analgesia for mu-analgesia then a higher dose of nalbuphine is required, and this will likely reverse the mu-analgesia already in place.

The second reason for caution is that administration of sufficient nalbuphine to mu-agonist tolerant patients does not merely negate opioid analgesia, but can in fact induce frank opioid withdrawal, just as if a reversal dose of naloxone had been administered. In general, the adverse physiological effects of withdrawal induced by nalbuphine (e.g. hypertension, elevated plasma catecholamines) are of less severe magnitude than those induced by naloxone. There is a reported case, however, of pulmonary edema after nalbuphine reversal of overnarcotization in the immediate post-operative setting, similar to what has been reported for the pure antagonist naloxone. Thus, complete reversal of mu-opioid effects by nalbuphine is something to be avoided and a reason for caution if transitioning frommu-based to kappa-based analgesia.

10. Conclusions

The use of the opioid mixed agonist—antagonist nalbuphine as an analgesic agent provides a number of advantages. Used as the sole opioid analgesic, it can satisfactorily cover mild to moderate pain with a low incidence of side effects. The ceiling effect of nalbuphine, which prevents it from supplying sufficient analgesia to cover the most severe discomfort, also prevents increasing sedation and respiratory depression as the dose is increased, potentially providing an increased safety margin in comparison to mu-agonists.

When nalbuphine is used concurrently with mu-agonists (e.g. morphine, hydromorphone, fentanyl), the benefits of both mu- and kappa-analgesia can be obtained, with simultaneously decreased incidence and severity of the common mu-agonist side effects (pruritis, nausea/emesis, constipation, urinary retention, respiratory depression and undesirable sedation). Data from animal studies also suggest that combined nalbuphine and mu-agonist

administration may decrease the development of opioid tolerance and dependence.

Nalbuphine is associated with a withdrawal syndrome that is milder than the mu-agonists after abrupt cessation of therapy, and is associated with minimal residual drug craving even after prolonged use. It has a lower abuse potential than the mu-agonists, both for patients and for staff.

In practical terms, then, nalbuphine may be considered for use as the primary analgesic when intravenous/PCA, intramuscular, or subcutaneous dosing is possible (since there is no oral form, and epidural/intrathecal dosing is not FDA approved). The patient will not have been on prolonged mu-agonist therapy, and therefore not be opioid tolerant. The pain to be treated will be of mild to moderate intensity. If the patient has a history of mu-agonist-induced pruritis, nausea/emesis, or other mu-side effects, or a preexisting respiratory impairment, then nalbuphine might be particularly considered. Nalbuphine is probably suitable for any age group, although neonates may not have the benefit of a ceiling effect on respiratory depression that adults enjoy. Nalbuphine is at least an acceptable alternative for labor analgesia, if the practitioner is comfortable with the possible increased complexity of analysis of fetal heart rate tracings. If nalbuphine is used as a labor analgesic, it is probably best administered by PCA.

The disadvantages associated with nalbuphine use are fewer, but require careful consideration. The ceiling effect of nalbuphine means that increasing the dose for increasing discomfort will not necessarily provide increasing analgesia. If more pain is encountered than nalbuphine and adjuncts (e.g. non-steroidal antiinflammatories, acetaminophen) can alleviate, the next step would often be to transition to mu-agonist based analgesia. The mu-antagonist property of nalbuphine means, though, that transition to a mu-agonist based regime with a nalbuphine load already in place would require careful planning and execution. Similarly, adding nalbuphine to a patient already on a mu-agonist regime must be done with care, since an excessive nalbuphine dose could negate some of the existing mu-analgesia, or, in the case of a higher nalbuphine dose, induce a frank opioid withdrawal syndrome. A final disadvantage of nalbuphine is its relative unfamiliarity; while all practitioners have considerable experience with the classic mu-agonists, few have much exposure to the use of the mixed agonists—antagonists.

While the future of opioid based analgesia may include receptor-specific ligands that can avoid or suppress some of the troublesome side effects seen with currently available agents, those days are not yet here. Until then we must make the best use of the materials at hand. Existing clinical and laboratory data suggest that nalbuphine can be a valuable addition to the practitioners opioid armamentarium.

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