Neuraxial Opiates – The Positive and the Negative.

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INTRODUCTION

It is 117 years since August Bier's first spinal anesthetic with the cocaine in 1898. There are presently more than 5000 published articles on spinal anesthesia, and 1000 referring to intrathecal morphine. This presentation will focus exclusively on the use of intrathecal opiates in particular the longer acting ones.

Spinal anesthesia or intrathecal anesthesia is not a generic procedure and studies can produce different results simply by varying the smallest details. Superficially similar studies may differ on the vertebral level of injection, rate of injection, amount of barbotage used, patient position at time of injection, patient position after injection, aim of the pencil point needle side orifice, timing of patient position changes and numerous other technical factors. Studies can also produce different results when one drug injected is in hyperbaric solution and another drug injected is in a hypobaric solution, and then whether the two drugs are injected together as in mixture or as two separate injections. The hyperbaric drug can drag the second drug with it if they are mixed together. Where the second drug comes to pool dominantly in the subarachnoid space can affects its effects in the central nervous system.

These above factors contribute to very widely varying spinal anesthesia practices and techniques, and great difficulty extracting pure scientific conclusion from available published comparative research data.

INTRATHECAL FENTANYL

The lipid soluble opiates are popular additives to the intrathecal local anesthetic as they have been well shown to accelerate the onset of the block and improve the density of the block. This has been shown for fentanyl, sufentanil, and alfentanil[1]. **Best results are found using 25 to 50 µg of fentanyl**. Remifentanil cannot be used for neuraxial blocks due to the fact its solution contains glycine, a neurotransmitter, in damaging amounts.

The late Dr. Bernards in his annual ASA and other lectures and writings stated the mechanism whereby fentanyl accelerated block onset was likely via slightly alkalinizing of the local anesthetic solution. Research showed fentanyl cannot diffuse deep onto the thick spinal cord due to its rapid absorption into capillary and its removal from tissues. This is because fentanyl is very lipid soluble. This means any fentanyl effect of dorsal horn π opioid receptors after intrathecal injection follows fentanyl absorption into the blood and then dilation by the whole blood volume and redistribution back to the dorsal horn via the capillaries, rather than from direct diffusion onto the dorsal horn form the intrathecal space. This also explains why equal analgesia from one dose of fentanyl infusion rate is produced regardless of whether the drug is infused epidural or intravenous.

This author however fully supports use of intrathecal fentanyl for its very favorable effects improving the surgical local anesthetic block. Intrathecal fentanyl also increases postoperative opiate needs 63% due to inducing acute opiate tolerance. The use of fentanyl is however well justified, despite it later pain worsening effect due to it causing very substantial acceleration of onset, and improvement in the surgical grade block of the spinal local anesthetic.

INTRATHECAL MORPHINE (ITM)

The pioneering use of intrathecal morphine (ITM) revealed ***some*** patients remained pain free for 24 hours from smaller doses than what could be achieved via intravenous or intramuscular injection of morphine. That aroused great interest in ITM.

The classic Bailey volunteer study showed that all intrathecal morphine doses from 200µg to 600µg caused pruritus, urinary retention, and ventilatory depression. Higher doses gave the worst ventilatory depression[2]. Another classic study combining intrathecal morphine with local anesthetic drug showed no low dose ITM patient achieved 24 hours analgesia. Only when doses reached 300µg did then 5% of patients achieved 24 hours analgesia[3]. Clearly the mythical 24 hour analgesia effect of ITM is not a standard effect. All groups down to 100µg doses experienced significant incidences of protracted nausea. Significant respiratory

depression only occurred in the 300µg group on 5% of the patients. This study and many others have shown there is no low dose capable of achieving any analgesia that is exempt from opiates side effects. Patients receiving doses under 100µg morphine mostly experienced no analgesia. Patients needed doses exceeding 200µg morphine are required to achieve consistent longer analgesia of 6 hours or more duration, but the morphine side effects then becoming overwhelming. It is suggested that doses higher or lower than 200µg morphine are respectively too dangerous or too ineffective.

There are innumerable studies showing analgesia effects from spinal morphine studies but rarely showing meaningful benefit over administering morphine via conventional routes sufficient to justify the risks and side effects of intrathecal morphine.

Rebel in 2011 evaluated a technique of using high dose intrathecal morphine of about 1000 µg, versus PCA morphine[4]. The intrathecal morphine group received a simultaneous naloxone infusion. The intrathecal morphine and naloxone infusion group achieved better analgesia and earlier ambulation. The technique is however severely limited in that any incidental problem with the naloxone infusion rate will call catastrophic morphine over dose (too little naloxone) or alternatively severe pain (too much naloxone).

Intrathecal morphine's benefits and side effects have had three recent reviews and meta-analyses[5,6]. The studies consistently found that all high and low doses of intrathecal morphine cause nausea, vomiting and pruritus. Spinal morphine also caused respiratory depression, in dose related fashion, with the worst cases seen at doses of 300 µg intrathecal morphine and upwards. With an intrathecal dose of 200µg morphine only 42% of the patients still needed supplementary opiates in the first 12 hours, and 8 patients developed critical respiratory depression. Eleven percent of the patients disliked the pulse oximeter and the false alarms disturbing their sleep.

The Meylan meta-analysis specifically reviewed intrathecal morphine used alone (no local anesthetic)[7]. Intrathecal morphine compared to no intrathecal morphine given to patients, did reduce the need for supplementary morphine, as well as pain scores. The magnitude of group average pain improvement was small being 1 cm for rest pain and 2 cm for movement induced pain on a 10 cm Visual Analogue Scale (VAS) for pain. **One key observation was the complete lack of correlation between patients who achieved benefit and the doses administered**. There was great variability and unpredictability in analgesia responses between individual patients. There was a pattern that more cephalad surgery patients (cardiothoracic) derived less analgesia benefit than more distal surgery (lower abdomen) patients. The very serious side effect of respiratory depression was highly increased by use of solo drug intrathecal morphine. One in 85 intrathecal morphine patients had critical respiratory events. The control group who got no ITM had zero incidence of critical respiratory events. Meylen emphasized that there is no good way to monitor for or predict serious respiratory depression. A pulse oximeters do not predict hypercarbia. Sedation, pupil size and respiratory rate do not correlate well with oxygenation saturation either. Meylan's final conclusion is that there is, all considered in terms of benefits and risks, the practice of solo-drug spinal morphine should be abandoned

Delayed severe respiratory depression is the most feared side effect of intrathecal morphine. Rawal determined the risk of respiratory depression (particularly late depression) to be 1/275 in spinal morphine patients[8].

A 2006 study showed 40% of patients with spinal morphine will have retention of urine for over 24 hours[9]. Strong consideration must be given to catheterizing all patients for 24 hours who have received intrathecal morphine.

It must be emphasized that as the rate of breathing and the tidal volumes both become suppressed by high morphine doses the arterial PCO2 increases early and in linear fashion. There is unfortunately no way to measure that arterial PCO2 continuously and non-invasively. Sampling of exhaled patient gasses is a poor measure as the end-tidal CO2 to arterial PCO2 increases with diminishing respiratory tidal volume and the hypercarbia is concealed. PaO2 is however well reflected by the pulse oximeter, but the limitation is that PaO2 falls in a non-linear fashion as ventilation becomes suppressed. A normal range of PaO2 is maintained until the respiration suppression has long reached critical levels and the patient is critically acidotic and at a point that the oxygen saturation is falling very steeply and critically. In summary there is no good non-invasive monitoring of patient physiology to assess opiate induced suppression of respiration.

MICRODOSE INTRATHECAL MORPHINE;

Some researchers investigated intrathecal doses down to 15µg morphine[10,11,12]. No low dose could be found that was free of side effects. Analgesia was very inconsistent with less 50% of patients achieved 24 hours analgesia in the highest study dose group of 50 µg. The lower dose groups achieved exceptionally analgesia. This inconsistency of intrathecal morphine analgesia is standard observation of all studies.

SOME specific studies.

Hein A. *Low dose intrathecal morphine effects on post-hysterectomy pain: a randomized placebo-controlled study*[13]. One hundred and forty-four woman underwent hysterectomy under spinal anesthesia with 12 mg hyperbaric bupivacaine. They were randomized into four groups receiving either additional intrathecal morphine of 100, 200 or 300 microgram morphine, or added saline (placebo) with their spinal blocks.

The conclusion is that intrathecal morphine saved the costs of 1.3 to 1.9 ampules morphine (13 to 19 mg) over the placebo group use during the first 6 hours after surgery only.

Sakowska M. *A change in practice from epidural to intrathecal morphine analgesia for hepato-pancreato-bilary surgery*[14]. This retrospective study done as an audit, did not reveal the epidural techniques used. They did report they had previously had higher than acceptable analgesia failure with epidural and PCA analgesia due to their limited staff expertise, and insufficient nursing cover after working hours. Their audit found intrathecal morphine to be the better analgesia method to use than THEIR poorly managed epidural block or PCA service. A healthcare system with adequate resources would have different results.

It is thus an argument that the best place for spinal morphine is when there are no alternate ways to administer opiates or regional anesthesia are not available. Some third world hospitals administer no opiates at night due to a lack of trained nurses being on duty.

METABOLISM OF MORPHINE

Morphine is metabolized mainly in two locations, namely the liver and within the central nervous system. A small insignificant amount of metabolism also occurs in the kidneys. Eighty-seven percent of a single morphine dose is eliminated by 24 hours after administration via metabolites excreted in the urine. The enzyme involved at both metabolic sites is UDP – glucuronosyl transferase-2B7 (UGT2B7).

The metabolites are 60% morphine-3-glucuronide (M3G), 10% morphine-6-glucuronide, and 30% of a group of other metabolites including normorphine, codeine, and hydromorphone. The elimination half-life of morphine is 120 minutes, but with wide individual variation. Metabolism rate is affected by age, gender, diet, disease, and genetic factors. All of the main substances, morphine, M3G, and M6G are highly water soluble and thus cross the blood brain barrier very poorly to only achieve low CNS concentrations where the primary analgesia affects occur. Morphine-6-glucuronide (M6G) is an active metabolite. A 2002 human clinical study by Cann showed that when both drugs were administered intravenously, morphine and M6G in equal milligram doses they were equi-analgesic[15]. The study drugs were only injected once. The M6G group of study subjects were however dramatically less prone to nausea, and sleepiness compared to the morphine group over the first 24 hours after surgery.

The M3G metabolite has no analgesia effects and conversely induces hyperalgesia.

Systemic morphine achieves it analgesia via small amounts of morphine that is absorbed across the blood brain barrier into the Central nervous system (CNS) and very small amounts of systemic manufactured M6G. Of the small amount of morphine that absorbs into the CNS further M6G is manufactured. It is likely that CNS M6G is the final primary agent of analgesia after systemic morphine rather than unaltered morphine in the CNS. M3G formed peripherally will only minimally reach the CNS due to its high water solubility minimizing it's absorption across the blood brain barrier into the CNS. M3G enhances pain in and hyperalgesia via toll-like receptor 4 (TLR4)[16].

Morphine-6-glucuronide (M6G) has been studied as an analgesic agent on its own. Interest in M6G is due to its very significantly lower side effect profile than morphine in its own. One study administered the drug 60 minutes before the end of surgery, and was compared to morphine similarly administered[17]. The study affirmed the significantly better side effect profile of M6G versus morphine, but showed that the onset of analgesia from M6G is very long. M6G will need to be administered well more than an hour before awakening after surgery to have immediate benefit analgesia effects upon awakening of the patient.

PHARMACOLOGY of M6G[19]. All comments refer to comparison to morphine. When used as a drug M6G is highly polar and 12 times more water soluble (or conversely *less* fat soluble) than morphine. This results in a ten times smaller volume of distribution for M6G than morphine. The combination of restricted tissue distribution and low lipid solubility results in a very restricted

passage of M6G across the blood brain barrier. Higher dose of M6G are thus needed to achieve analgesia, and the onset of analgesia is much slower.

M6G is exclusively excreted via the kidneys. That creates risk for drug accumulation if M6g were to be administered via an infusion or redosed repeatedly in patients in renal failure. A small amount of M6G is excreted in bile. When the M6G reaches the gut it gets hydrolyzed into morphine which gets absorbed and metabolized back into M6G and small amount of M3G. M3G blood levels become measureable when M6G has been continuously administered by infusion.

A recent review in July 2014 analyzed the extent of analgesia following morphine administration that is attributable to the metabolite M6G[18]. It states that peripheral morphine is converted 57% to M3G, and 10% to M6G. It then concludes after analyzing the available research data 85%-96% of the analgesia effect of morphine is due to M6G. This in fact makes morphine a pro-drug. A well-established fact is that individual persons vary greatly in their analgesia experienced from a set dose of morphine. This analgesic effect variability has many interpatient factors, one of which is certainly the genetic polymorphism of the UGT2B7 enzyme that degrades morphine.

The poorly predictable patient response variability for analgesia effect from morphine may be managed by titrating morphine either by a discretion decision by a healthcare provider to administer the next fixed dose at an earlier or later time, or to vary the dose administered at fixed times, or even by varying both dose size and dosing interval. In some circumstances the patient may control their own morphine administration via electronic device and the onset of opioid induced patient sleepiness and analgesia becomes the event stopping the patient repeating morphine administration. Modern medicine has moved away from administering morphine in pre-decided fixed large dose intramuscular and fixed intervals regardless for set duration of time. There is however one exception to that newer practice. Many practitioners still administer intrathecal morphine in the hope that it achieves long duration of analgesia for "small dose". In truth it is a large dose of morphine that bypasses the blood brain barrier, is un-titratable after administration and produces sustained pruritus and nausea in the majority of patients. Long duration analgesia is then only found in a minority of patients. This will be discussed again later.

INTRAVENOUS M6G. Van Dorp a M6G researcher reviewed the drug as an intravenous administered drug compared to morphine[19]. Morphine-6-Glucoronide (M6G) if an effective analgesic drug to morphine, provided it is used in dose exceeding 5mg per 70 kg patient weight. It shows zero analgesia at lower doses than that. Exact equivalent doses for M6G compared to morphine are not yet confidently determined, but will range from 1mg::1mg to 3mg::1mg (M6G::morphine).

Early evidence shows M6G has a $t_{½}k_{eo}$ of 6-8 hours versus a $t_{½}k_{eo}$ of 1.5-4 hours for that of morphine. When M6G was administered 1h before the end of surgery it had very little immediate analgesia for the patient upon awakening due to this slow onset of analgesia. M6G however much longer duration of analgesia after a single dose compared to morphine. Morphine produces 2-4 hours of analgesia versus the 12 to 24 hours of analgesia resulting from M6G.

Regarding side effects M6G compared to morphine in equi-analgesic systemic doses produced dramatically 50% less nausea than morphine. M6G produces less sedation. M6G produced slightly less respiratory suppression of the patients in one study.

INTRATHECAL MORPHINE-6-GLUCURURONIDE (M6G) The drug M6G is not commercially available. It has however been available for research from about 1988. Its "promise" is that it is better than morphine in producing less nausea, depression of respiration, itchiness, and less induction of chronic pain syndromes in patients. Its one major drawback is its slowness to reach the brain and the resulting slow onset of analgesia. This makes the intrathecal use of M6G an attractive analgesia technique. Intrathecal injection is injection to within side of the blood brain barrier. M6G's one major drawback has been shown to be its very slow onset of analgesia benefit when administered systemically[15,20]. Grace did the first human study on intrathecal M6G[21]. The M6G doses studied were 100µg and 125 µg, versus morphine 500 µg. Morphine at that very large dose only produced equal analgesia for the first 6 hours after which both M6G doses produced significantly better group analgesia. The M6G groups both trended towards having less nausea and vomiting and the lack of significance is possibly a type 2 statistical error in this early trial. More research is needed. Pilot studies performed in the planning for this reported study suggested M6G

intrathecal doses under 75 µg were sub-therapeutic and that doses exceeding 175 µg produced excessive sedation.

M6G IN SUMMARY: This above information on a drug not yet commercially available is discussed primarily to emphasize and understand the problems of intrathecal morphine. It was hoped that administered M6G would be vastly superior to administered morphine with respect to duration of analgesia and absence of side effects, would be very large and also fully attributable to the absence of M3G, the "bad metabolite".

INTRATHECAL OPIATES - LONG TERM CONSEQUENCES.

The addition of 25 micrograms fentanyl to 10 mg Bupivacaine in Caesarean Section spinal anesthesia improve local anesthetic effects, but increases postoperative morphine consumption was increased 63%[22]. The spinal fentanyl causes acute opiate tolerance and hyperalgesia.

Animal research shows spinal morphine induces two days of hyperalgesia after the initial analgesia wears off[23]. The spinal morphine has mu receptor analgesia effects. The morphine M3G and M6G metabolites formed in the CNS have a lot of other relevant effects. The morphine-3-glucoronide metabolite (M3G) formed in the brain releases of pro-inflammatory interleukin-1, nitric oxide, and cholecystokinin (CCK) from brain glial cells worsening the hyperalgesia and allodynia[24,25,26,27,28].

Studies by Dennis showed that a patient's positive analgesic response to the intrathecal morphine depended correlates with how high the CSF M6G level is to the M3G CSF levels[29]. Most of the CNS M6G is produced in the CNS as peripheral M6G crosses with blood barrier with extreme difficulty. The same applies to the "bad" M3G, but only more so. M6G if injected alone into the CSF, it produces good analgesia and relatively few side effects[30.31,32]. The sustained analgesia observed with intrathecal morphine injection is due to the M6G metabolite in the brain. M3G however induces hyperalgesia, allodynia, opiate tolerance and convulsions[33]. M3G is also more persistent in the CNS than M6G due to the greater imperviousness it experiences at the blood brain barrier.

In summary very limited morphine reaches the brain by diffusion due it being hydrophilic and due to that its only access to the brain is rate limited transport system. The major analgesia effects from morphine are from its metabolite M6G which is much more potent than morphine, and also is strongly hydrophilic and also only reaches the brain through a rate limited transport system, however the brain gets a second source of M6G which is locally produced M6G from the little morphine that reaches the brain. The main M3G in the brain is from metabolism of morphine within the CNS.

SPINAL CORD NEUROPLASTICITY AFTER OPIOID EXPOSURE.

Neuroplasticity is the brain's ability to reorganize itself by forming new neural connections throughout life. Neuroplasticity occurs when neurons in the CNS compensate for injury and disease or adjust their activities in response to new situations or to changes in their environment. It is observed as histological changes in the cells and by the appearance of "axonal sprouting" when undamaged axons grow new nerve endings to reconnect neurons whose links were injured or severed. New neural pathways are formed and CNS Function is altered.

Spinal opiates up-regulated NMDA receptor activity. This induces cascades of up-regulating effects on Protein Kinase C (PKC) and an enzyme called PARS which causes some neurons to change appearance into Dark Neurons[34]. These spinal NMDA receptors regulate all abnormal pain phenomena and not central NMDA receptors. The abnormal pain states are hyperalgesia, opiate tolerance, allodynia, persistent post-surgical pain and spontaneous pain.

Research also shows the peripheral pain events that cause chronic pain spinal changes are additive to the spinal neural effects of spinal opiates. This is clinically interesting as opiates are frequent used as therapy for chronic pain states. The spinal neuroplastic changes underlie the phenomena of opiate tolerance and opiate induced hyperalgesia.

The question of whether single dose intrathecal morphine can increase the incidence of chronic pain after specific major surgery, such as arthroplasty has never been examined, but the expected answer is yes. Other studies show early post-surgical pain treated with exclusively or dominantly with systemic opiates correspond to higher incidences of chronic pain than that seen similar groups of patients who received less opiates in the postoperative period due to use of regional anesthesia.

SPINAL MEPERIDINE (PETHIDINE) ANESTHESIA

Spinal meperidine (pethidine) can be used in neuraxial anesthesia[35]. Meperidine has sodium channel blocking effects and thus also has some local anesthetic effects[36]. Respiratory depression from meperidine spinal anesthesia only occurs associated with co-administered sedative drugs and the patients are easily aroused[37].

Colleagues with extensive intrathecal pethidine (meperidine) experience (Xavier LeDoux, Saint Martin, personal communication) use 66mg meperidine in dextrose (volume 2 ml) mg intrathecal meperidine. It produces anesthesia within 5 minutes. A weak motor block is seen at around 30 minutes later. That dose provides about 120 minutes surgical grade anesthesia and about 24 hours analgesia after surgery. There is mild hypotension appearing around 40 minutes after injection.

Meperidine has been utilized as sole spinal drug with caesarean sections[38.] Although providing surgical grade block it caused occasional hypotension, and occasional nausea. In addition general anesthesia became needed if the surgery took longer than expected. Another study showed meperidine in a dose of 1mg/kg intrathecal provides 40 to 90 minutes surgical anesthesia but doses over that up to 1.8 mg/kg did not increase the dermatomal height of sensory block, nor the duration of operating grade anesthesia[39]. Only side effects of fatigue, pruritus, nausea respiratory depression, and hypotension increased with doses exceeding 1mg/kg.

Spinal doses of meperidine as sole anesthetic of 0.5 mg and 0.75mg per kilogram patient weight were studied versus plain bupivacaine 13.5 mg in urological surgery patients[40.] Surgical conditions were good in all three groups. Sensory level T5-6 blocks were achieved in all three groups. The motor block lasted 300 minutes for bupivacaine, 80 minutes for meperidine 0.5 mg/kg, and 105 minutes for 0.75 mg/kg meperidine groups. Only meperidine patients had pruritus, and only bupivacaine patients vomited. Significantly fastest block onset was in the 0.75mh/kg meperidine group.

This author's own experience with spinal meperidine used 25mg for perianal surgery. All patients had enough analgesia for the surgery without supplementary sedation or analgesia. They also still had enough preservation of motor function at surgery conclusion to transfer themselves from lithotomy position and onto the transport cart without assistance.

CONCLUSION

The benefit of injecting morphine intrathecal over other routes of administration is very small and relates to trivial cost savings. Intrathecal morphine increases opiates side-effects compared to morphine injected via other routes. The risk of late or additive respiratory depression when supplementary opiates are injected to a patient already having received intrathecal morphine mandate the patient be nursed in a high area with special monitoring. Intrathecal morphine also increases the pain of the patient from 6 to 49 hours after surgery and likely also the incidence of late post-surgical pain syndromes.

The best indication for intrathecal morphine, is when it is the only opiate the patient will ever receive. Never exceed a dose of 200 µg intrathecal morphine. In all other circumstances morphine is more safely administered in an individualized dose via PCA, or nurse titration via IV or IM routes.

Finally all current principles of perioperative pain management regional anesthesia and multimodal analgesia, is focused on opiate minimization. Intrathecal morphine is in effect a massive dose of opiate injected direct into central nervous system beyond the blood brain barrier.

<u>Additional references,</u> used but not referenced in the above text;

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