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Original Review

A Review of Systemic Opioids Commonly Used for Labor Pain Relief

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Parenteral opioids for pain relief during labor have been the subject of research for many decades. Commonly used systemic opioids provide limited pain relief during labor yet are used extensively for managing labor pain. These opioids share similar pharmacologic profiles but differ in potency, pharmacokinetics, and side effects. This article reviews the pharmacokinetics, pharmacodynamics, and clinical research related to the commonly used systemic labor pain analgesics morphine, meperidine, fentanyl, remifentanil, butorphanol, and nalbuphine.
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INTRODUCTION

Systemic opioids are widely used for providing labor analgesia,[1] yet patterns of intrapartum opioid use are unclear. A 2001 survey[2] of 378 obstetric units in the United States found that 34% to 42% of parturients received parenteral drugs for labor pain. Parenteral opioids commonly used in the United States have been reported to include meperidine (Demerol), morphine, fentanyl (Sublimaze), butorphanol (Stadol), and nalbuphine (Nubain), although no recent surveys have been published to verify this.[1] Recent surveys of intrapartum analgesia in the United Kingdom[3] and Norway[4] reported that pethidine (another generic name for meperidine that is more commonly used in Europe) is still the opioid most commonly used during labor (43% and 77% of obstetric units, respectively), with intramuscular administration being the most common route. In the United Kingdom,[3] 49% of the units surveyed offered patient-controlled analgesia (PCA), with the most common drug being remifentanil (Ultiva), followed by morphine and fentanyl. Similarly, in Belgian labor and delivery units, 36% of those surveyed used opioid PCA administration, with remifentanil being the most common (77%) patient-controlled drug used.[5]

This article reviews the pharmacokinetics, pharmacodynamics, and clinical research related to commonly used systemic labor pain analgesics. Morphine, meperidine, fentanyl, remifentanil, butorphanol, and nalbuphine are addressed.

BACKGROUND

The fundamental principles underlying management of opioid use for labor pain are individualization of care and the balancing of pain relief with maternal, fetal, and neonatal safety. The optimal labor opioid has a rapid onset and offset of action; rapid metabolism and elimination; and minimal undesired maternal, fetal, and neonatal side effects. The analgesic should not affect the woman's ability to participate in labor and birth.

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When women choose opioids for labor pain relief, counseling regarding medication options includes maternal, fetal, and neonatal risks and benefits; unknown short-term and long-term risks; type of opioids available in a particular setting; optimal timing of dosing; realistic expectations of analgesia results and their limitations; and review of alternatives. Understanding each woman's plan for pain relief measures includes knowing whether she prefers to initiate a request for analgesia rather than being offered opioids, because offering analgesia may inadvertently undermine a woman's plan for a labor without analgesia.

Strategies used for the selection of a safe systemic labor pain analgesic center around an opioid's efficacy for pain relief; side effect profile; and maternal, fetal, and neonatal safety. When managing opioid dosing, it is important to keep in mind that women vary highly in their physiologic responses to opioids. They also vary in their perceptions of the degree to which pain must be reduced to be meaningful. Continuation of a supportive presence and nonpharmacologic methods of pain relief should accompany the provision of opioids.

To minimize neonatal effects, opioid analgesics are used primarily in the active phase of labor. Following opioid administration, close supervision of the woman and newborn for unwanted side effects and having oxygen and naloxone (Narcan) available are important safety considerations. Additional lactation support for establishing breastfeeding may be helpful for women who have received opioids during labor.

OVERVIEW OF OPIOIDS

The pharmacologic differences and characterization of opioids are the result of their interactions with opioid receptors. Opioid receptors located throughout the central nervous system and peripheral tissues are part of an endogenous pain-relieving system that includes the production of naturally occurring opioid peptides (eg, enkephalins, endorphins, dynorphins) or *ligands*. These naturally occurring morphine-like ligands as well as exogenous opioid ligands (eg, morphine, fentanyl) bind specifically and reversibly to opioid receptors and activate a response. There are 3 different types of opioid receptors: mu, kappa, and/or delta.[6]

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The Agonist Versus Antagonist Response

The subsequent biologic response and pharmacologic difference of the opioid ligand-receptor complex depends on which opioid receptor the drug binds to and whether the opioid ligand functions as agonist, antagonist, or mixed agonist-antagonist. An agonist is a molecule that combines with 1 or more receptors to trigger a physiologic reaction. An antagonist is a molecule that binds to a cell receptor without eliciting a biologic response and blocks binding by agonists. Agonist-antagonists initiate mixed reactions because of an agonist effect at 1 receptor type and an antagonist effect at a different receptor type. The response of the ligand-receptor complex also is differentiated by the strength of interaction between a ligand and its receptor (affinity) and the strength of the effect of the response (efficacy).[6]

Most clinically relevant opioids are mu agonists and have their primary activity at mu receptors. Mu receptors mediate analgesia, sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, decreased gastrointestinal motility, and urinary retention. Kappa receptors are responsible for sedation, dyspnea, dysphoria, spinal analgesia, and dependence. The effects of delta receptors are not well studied but may be related to psychomimetic and dysphoric effects.[6] Morphine and fentanyl have a high affinity for mu receptors and are potent analgesics. Meperidine, in contrast, is a relatively weak mu and delta agonist. Butorphanol is an example of an agonist-antagonist and acts as a kappa receptor agonist and a mu receptor antagonist. Naloxone, an opioid antagonist, binds to each of the 3 receptors and has its highest affinity for the mu opioid receptor.[7]

Opioids commonly used for treating labor pain share similar pharmacologic profiles but differ in receptor relationships, potency, pharmacokinetics (eg, elimination half-life, metabolism), analgesic effect, and side effects. In addition, an individual's opioid sensitivity varies and is determined by genetic variation in the mu opioid receptor and differences in metabolism related to age, sex, genetic make-up, renal function, and concurrent use of medications.[6]

The Effect of Pharmacogenomics

The rapidly progressing field of pharmacogenomics, the study of an individual's genetic make-up and response to a drug, offers insight into why individuals have different clinical responses to the same dose of an opioid. Genetic variations, or polymorphisms, within genes encoding mu opioid receptors, metabolic enzymes, and transport proteins affect an individual's response to opioid medications. The most commonly identified polymorphism (G118) in the gene encoding the mu opioid receptor (OPRM1) has been linked to the variability of the analgesic effect of morphine. Individuals with G118 polymorphism have a reduced or variable response to morphine and increased opioid dose requirements during opioid therapy.[8]

Polymorphisms within genes encoding metabolic enzymes may contribute to either diminished, absent, or excessive metabolism of an opioid, leading to differences in drug effectiveness and altered risk for adverse drug effects. Codeine, for example, is metabolized to the active metabolite, morphine, by the enzyme CYP2D6. This metabolite formation must take place to obtain an analgesic effect. Individuals with deletions or inactive variants of the CYP2D6 gene will not metabolize codeine to morphine and therefore will not get pain relief. These individuals are classified as poor metabolizers. On the other end of the spectrum, those with gene variants resulting in extra copies of CYP2D6 may metabolize codeine to morphine more rapidly and completely than others. These ultrarapid metabolizers are more likely to have higher than normal levels of morphine following codeine ingestion.[9] Life-threatening adverse effects following codeine ingestion have been reported in individuals who are ultrarapid metabolizers. In 2007, the US Food and Drug Administration issued a public health advisory for breastfeeding mothers taking codeine following the death of a breastfed newborn from morphine toxicity. The breastfeeding mother, an ultrarapid metabolizer, was taking codeine for pain relief; produced excessive amounts of codeine's metabolite, morphine; and unknowingly passed excessive amounts on to her newborn through her breast milk.[10] Individuals also can be classified as intermediate metabolizers or extensive (normal) metabolizers. Among different ethnic groups, the frequency of polymorphisms varies considerably.[9]

Polymorphisms in genes encoding opioid transport proteins also have been associated with pain relief variability. Genetic variants in transport proteins influence bioavailability of some opioids and may reduce transport of opioids across the blood-brain barrier. These variations also have been linked to the variable responses of morphine, fentanyl, and methadone.[8]

Efficacy of Opioids for Labor Analgesia

Studies addressing the effect of opioids as labor analgesia report absent-to-modest reductions in pain scores and are challenging to interpret as a whole.[11,12] Varying conclusions about the efficacy of intrapartum opioids can in part be explained by differences in study design, lack of sufficiently powered studies, individual variation in response to opioids, and the escalating and intermittent nature of labor pain. In addition, the sedation that accompanies opioids may mask a weak analgesic effect by producing a generalized quieting effect with an apathetic or suppressed affective response to labor pain.[13] Whether the main effect of opioids is analgesic or sedative is unclear. Attempts to improve the analgesic effect with increasing doses results in increased sedation, increased side effects, and more newborns requiring naloxone therapy, but doses higher than those commonly used have not been shown to produce better labor analgesia. Pharmacokinetics, usual doses, and drug-drug interactions associated with opioids commonly used for labor analgesia are summarized in Tables 1 and 2.

Side Effects and Adverse Effects of Opioids

There are several undesirable side effects that may follow intrapartum opioid administration. Higher doses increase the likelihood of maternal, fetal, and neonatal adverse effects and neonatal naloxone use. The most serious adverse effect is respiratory depression. Other side effects include sedation,

Table 1. Significant Drug-Drug Interactions of Systemic Opioids Used for Labor Analgesia

Opioid	Drug	Effect
All[a]	Alcohol	Increased CNS depressant effect of alcohol
All	Amphetamines	Increased analgesic effect of opioid
All	Phenothiazines	Increased hypotensive effect of opioid; some increase in respiratory-depressant effects, sedation, and/or analgesic effect
All	Antihistamines	Potentiates sedation and respiratory depression
All	CNS depressants (eg, barbiturates)	Potentiates sedation and respiratory depression
All	Cimetidine (Tagamet)	Inhibits opioid metabolism; increased CNS toxicity
All	Erythromycin	Increased opioid effects
All	SSRIs	Increased serotonergic effect of SSRI; may cause serotonin syndrome
All	Antihypertensives	Increased orthostatic hypotension
Meperidine, fentanyl	MAOIs	Increased respiratory depression, hyperpyrexia, CNS excitation, delirium, seizures; enhances serotonergic effect of meperidine
Fentanyl	Ketoconazole (Nizoral), Itraconazole (Sporanox)	CYP34A inhibitor; increases fentanyl blood levels
Fentanyl	Selected HIV retrovirals[b]	CYP34A inhibitor; increases fentanyl blood levels
Remifentanil, fentanyl	Beta blockers	Increased bradycardic and hypotensive effect
Remifentanil, fentanyl	Calcium channel blockers	Increased bradycardic and hypotensive effect
All	Herbs: valerian, St. John's wort, kava kava, gotu kola	May increase CNS depression

Abbreviations: CNS, central nervous system; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Morphine, meperidine (Demerol), fentanyl (Sublimaze), remifentanil (Ultiva), butorphanol (Stadol), nalbuphine (Nubain).
[b]Drug-drug interactions of retrovirals are beyond the scope of this article. Prescribers should consult comprehensive pharmacology references for information about specific retrovirals.

nausea and vomiting, dizziness, altered mental status, euphoria, decreased gastric mobility, decreased gastric emptying, and urinary retention. Sedation may result in less maternal mobility and time in upright positions. This in turn can affect a parturient's pain perception. An altered mental status may also affect a parturient's ability to engage in decision making.

Fetal effects include a temporary decrease in fetal heart rate variability or a pseudosinusoidal fetal heart rate pattern. This may result in additional interventions such as continuous electronic fetal heart rate monitoring. In the neonate, opioids may cause respiratory depression and subtle neurobehavioral changes.

The effects of opioids on breastfeeding behaviors have not been adequately studied. Riordan et al[14] has postulated:

When present at concentrations below that needed to induce respiratory depression, opioids may exert other, more subtle, effects on the central nervous system, including neurobehavioral effects. Without optimal muscle tone and reflexes, the neonate is unlikely to suckle correctly, causing trauma, soreness, and pain, which will deter all but the most determined women.

Epidemiologic studies have found an association between intrapartum fetal exposure to opiates and opiate addiction later in life.[15–17] In a 2000 case-control study[17] of individuals who were followed from the prenatal period through 18 to 27 years of age, investigators compared labor pain analgesia and other obstetric variables in 69 drug-abusing men and women with 33 non-abusing siblings. They observed that 3 or more doses of meperidine, phenobarbital (Luminal), and/or secobarbital (Seconal) given within 10 hours before birth was associated with a 4.7 times greater odds ratio for drug addiction later in life (95% confidence interval [CI], 1.0-44.1).

MORPHINE

Morphine was first isolated in 1806 and named *morphium* for the god of sleep. It was introduced as a labor pain medication in the late 1800s but was soon abandoned because of concerns related to neonatal depression. Its intrapartum use reappeared in the early 1900s as a component of twilight sleep, a combination of morphine and scopolamine. Combining scopolamine with morphine allowed for reduced amounts of morphine to be used; however, this drug combination produced confusion, amnesia, little analgesic effect, and neonatal respiratory depression.[18] After the 1920s, providers gradually increased the amounts of morphine and began to combine twilight sleep with other forms of anesthesia.[19] Despite its undesirable effects, use of twilight sleep continued for many years. After meperidine was introduced as an intrapartum analgesic in the 1940s, and subsequent studies indicated that morphine was associated with a higher risk

Table 2. Pharmacokinetic Profiles of Selected Opioids

Drug (Brand name)	Usual Dose	Onset (Minutes)	Peak Effects (Minutes)	Duration of Action	Elimination Half-life	Comments
Morphine Active metabolite of morphine: M6G	IV: 2-5 mg/ 4 h[a] IM: 10 mg/ 4 h[a]	IV: 5[a] IM: 10-20[b]	IV: 20 IM: 0.5-1[b] 45[d]	IV: 1-3 h IM: 3-5 h[b]	Adults: 2 h[b] Maternal: 43 min[c] Neonates: 6.5 ± 2.8 h[d] Adults: 2-4 h Neonates: 13.9 h[d]	Faster absorption when administered in deltoid muscle compared with gluteal muscle Use lower doses with patients with impaired ventilation or asthma Metabolite produces greater analgesic effect than morphine; can accumulate with repeated doses
Meperidine or pethidine (Demerol) Active metabolite of meperidine: normeperidine	IV: 25-50 mg/ 1-2 h[a] IM: 50-100 mg/ 2-4 h[a]	IV: 5[a] IM: 10-20[b]	IV: 5 IM: 30-60[b]	IM, IV: 2-4 h IM: 2-5[b]	Maternal: 3-7 h Neonates: 18-23 h Maternal: 21 h Neonates: 63 h	Fetal exposure highest 1-4 h after maternal administration, with associated neonatal respiratory depression; highest 2-3 h after administration May temporarily decrease FHR variability Normeperidine accumulates in maternal plasma after multiple doses and affects newborn neuroadaptive scores and breastfeeding behaviors
Fentanyl (Sublimaze)	IV: 50-100 mcg/ h[a] IM: 50-100 mcg/ h[a]	IV: 1[a] IM: 7-15[b]	IV: 5[b] IM: 10-20[b]	IV: 30-60 min IM: 1-2 h[b]	Adults: 3-4 h[a] Neonates: 75-440 min	When administered as an infusion, context sensitive decrement time (the time to a 50% reduction in blood concentration after cessation of a steady infusion) increases; With higher doses or prolonged infusions, fentanyl becomes longer acting[e] Transient decreased FHR variability Maximum cumulative labor dose is usually 500-600 mcg

Continued

Table 2. Pharmacokinetic Profiles of Selected Opioids

Drug (Brand name)	Usual Dose	Onset (Minutes)	Peak Effects (Minutes)	Duration of Action	Elimination Half-life	Comments
Remifentanil (Ultiva)	PCA administration with varying dosing	0.5–1[f]	2[f]	20 min[f]	Adults: 9 min[f]	Potent maternal respiratory depressant Dose at beginning of uterine contraction
Butorphanol (Stadol)	IV: 1-2 mg q 3-4 h[a] IM: 1-2 mg q 3-4 h[a]	IV: 2-3 IM: 10-20[b]	IV: 5-10 IM: 30-60[b]	IV or IM: 4-6 h[b]	Adults: 2.5-3.5 h[b]	Maternal ceiling effect on respiratory depression and analgesia Fetal transient pseudosinusoidal FHR pattern May precipitate acute withdrawal syndrome in an opiate-dependent mother and neonate
Nalbuphine (Nubain)	IV or IM: 10 mg/3 h[a]	IV: 2-3[a] IM: <15[b]	IV: 30 IM: 30-60[b]	IV: 2-4 h IM: 4-6 h[b]	Adults: 2-5 h[b]	Maternal ceiling effect on respiratory depression and analgesia at 30 mg May precipitate acute withdrawal syndrome in an opiate-dependent mother and neonate

Abbreviations: FHR, fetal heart rate; IM, intramuscular; IV, intravenous; M6G, morphine-6-glucuronide; PCA, patient-controlled analgesia.
[a] ACOG[75]
[b] Baumann[76]
[c] Gerdin et al[23]
[d] Kart et al[25]
[e] Gustein et al[69]
[f] Hinova et al[64]

of newborn respiratory depression than was meperidine,[20,21] morphine declined in popularity. Since that time, few scientific studies have evaluated the analgesic effect and side effects of morphine. A 1986 study comparing the pain relief efficacy and side effects of meperidine and morphine found no difference between the 2 drugs.[22] In contrast to earlier beliefs, some authors have proposed that morphine is preferred over meperidine because it has a shorter half-life and more rapid plasma clearance in pregnant women.[4,23]

Morphine is a relatively long-acting opiate mu agonist. The principal metabolites of morphine are morphine-6-glucuronide and morphine-3-glucuronide. Morphine-6-glucuronide, an active opioid agonist, binds to mu receptors and produces respiratory depression and a greater analgesic effect than morphine. Morphine-3-glucuronide is the predominate metabolite of morphine and does not have opioid activity but in high doses may have a neuroexcitatory effect.[24,25]

Efficacy and Side Effects of Morphine

Side effects and adverse effects of morphine include euphoria, altered mental status, respiratory depression, nausea and vomiting, decreased intestinal motility and constipation, urinary retention, flushing of skin, urticaria, orthostatic hypotension, and decreased fetal heart rate variability. Morphine and its metabolite morphine-3-glucuronide accumulate in colostrum and breast milk and are excreted in breast milk in small amounts.[26]

In recent years, a small (N = 20), prospective, randomized, double-blind study[27] comparing intravenous morphine (mean 12.4 mg, range 3.8-14.4 mg) to intravenous pethidine (mean 108 mg, range 90-132 mg) as labor analgesia found no significant analgesic effect following administration of either medication. Women in both groups equally reported sedation after dosing, and sedative scores increased with each repeated dose. There was no change in strength of uterine contractions as measured with intrauterine pressure catheters. The rate of nausea was significantly higher in the pethidine group (6/10 vs 1/10, $P < .03$), although differences in rates of emesis were not statistically significant. There was no correlation between dose and Apgar scores and no neonatal respiratory depression necessitating treatment. The median time between the end of opioid administration and birth was 6.3 hours (range 1.0-15.5 hours). The authors concluded that labor pain is not sensitive to intravenous morphine or pethidine and that the primary effect of intrapartum use of these drugs is heavy sedation.

Effect of Morphine on Labor

There have been no published, randomized clinical trials addressing the effect of morphine on labor.

Clinical Considerations

Although systemic morphine is sometimes used for labor analgesia,[4] morphine is most often administered in the subarachnoid space as a part of regional anesthesia or in the epidural space for postoperative pain relief. Additionally, it is used for therapeutic rest in the treatment of prolonged latent phase of labor.[28] Morphine doses for therapeutic rest recommended by Friedman[29] are 15 mg subcutaneously or intramuscularly. An additional 10 mg may be considered 20 minutes later if contractions continue and there is no respiratory depression. After morphine administration, 85% of women will benefit from 6 to 10 hours of rest and awake in active labor, 10% will stop having contractions, and 5% will continue with the same contraction pattern. Hydroxyzine (Vistaril) 25 mg to 50 mg intramuscularly can be administered along with morphine to potentiate its analgesic effect and prevent nausea. Hydroxyzine additionally has an anxiolytic effect. Promethazine (Phenergan) 25 mg to 50 mg may be administered with morphine to prevent emesis; it also has a sedative effect.

Further studies are needed to evaluate the effectiveness and adverse effects of morphine as labor analgesia and to further understand the effect of its active metabolite on the newborn.

MEPERIDINE/PETHIDINE

In the 1940s, meperidine began to replace morphine for labor pain analgesia and has since become the most widely used systemic labor medication. This popularity may in part be related to familiarity, low cost, and studies that were performed more than 30 years ago that concluded that meperidine was associated with a lower risk of respiratory depression than morphine.[20,21,30] Its use in obstetrics has become increasingly controversial because of its undesirable effects on the woman and neonate.

Meperidine is a relatively weak synthetic mu agonist that binds to both mu and kappa opioid receptors. It is estimated to have 10% of the effectiveness of morphine.[6] Promethazine 25 mg to 50 mg may be used in combination with meperidine to reduce nausea and provide a sedative effect.

Efficacy and Side Effects of Meperidine

Investigations of meperidine's intrapartum analgesic efficacy have varied in their conclusions. Some authors have found meperidine to provide little[31] to no labor pain relief.[27] In contrast, when compared with a placebo, investigators[32] found a modest but significant ($P = .01$) reduction in visual analogue pain scores with 100 mg of intramuscular meperidine. Common maternal side effects include sedation[27,32–34] and nausea and vomiting.[27,32,34–36] A temporary decrease in fetal heart rate variability also is associated with meperidine use during labor.[33,34]

The woman, fetus, and newborn metabolize meperidine in the liver to the active metabolite normeperidine, which can produce analgesia and central nervous system stimulation in adults or depression and neurobehavioral changes in neonates. Meperidine and normeperidine cross the placenta and have long half-lives in women and neonates (Table 2). The birth of a newborn between 1 and 4 hours following meperidine administration is associated with neonatal respiratory depression, with maximal respiratory depression occurring between 2 and 3 hours after administration.[37,38] Additionally, with multiple doses of meperidine, both meperidine and normeperidine accumulate in maternal plasma and in fetal tissues; therefore, a newborn whose mother received multiple injections of meperidine may have high normeperidine levels at birth. Further, because of the lengthy elimination half-life of normeperidine, long drug-to-delivery intervals may result in high levels of maternal and fetal normeperidine, which may put neonates at risk for neurobehavioral depression.[38,39] Most importantly, these metabolite-related adverse effects cannot be reversed with naloxone.[26]

Two trials have compared the effect of a single dose of 100 mg of meperidine with placebo on newborn outcomes. With a mean drug-to-delivery interval of 2 hours, investigators found that meperidine was associated with a 4-fold increase in the number of 1-minute Apgar scores of less than 7 (RR, 4.11; 9% CI, 1.72-9.8) and significantly more 5-minute Apgar scores of less than 7 (RR, 11.82; CI, 0.66-210.25).[40] Other investigators demonstrated that with a mean drug-to-delivery interval of 5.3 hours, there was no significant difference between the meperidine and placebo group in the number of 1-minute and 5-minute Apgar scores of less than 7, umbilical artery pH, and admissions to neonatal intensive care units.[32]

Effect of Meperidine on Labor

Most studies have found no effect of meperidine on labor outcomes. In a randomized controlled trial, Sosa et al[40] investigated the effect of meperidine on the length of labor in parturients with a diagnosis of dystocia during the active phase of labor. Four hundred and seven parturients were randomized to receive 100 mg of intravenous meperidine or a placebo. There were no significant differences between groups in duration of labor or route of birth. There were, however, significantly more women in the meperidine group who required oxytocin augmentation (RR 2.24; 95% CI, 1.13-4.43). When meperidine was compared with other opioids, no difference in duration of labor,[1,33,41,42] oxytocin use,[33] cesarean birth,[27,33] or route of birth[1,42] was demonstrated.

Effect of Meperidine on Breastfeeding

Meperidine and its metabolites accumulate in colostrum and breast milk and may be associated with newborn neurobehavioral alterations and unfavorable effects on developing breastfeeding behaviors. Wittels et al[43] conducted a prospective, randomized study of breastfeeding women who underwent cesarean births and compared intravenous PCA administration of meperidine to intravenous PCA administration of morphine. Meperidine was associated with significantly more neurobehavioral depression in breastfeeding newborns on the third and fourth days of life when compared with the

behavior of the newborns in the morphine cohort ($P < .05$), despite similar overall doses of morphine and meperidine.[26,43]

Nissen et al[44] demonstrated that newborns of parturients who received 100 mg of intramuscular pethidine administered between 1.1 and 5.3 hours before birth had depressed newborn sucking behavior ($P < .05$) and delayed initiation of lip and mouth movement (22 minutes vs 11 minutes; $P = .01$) when compared with newborns who were exposed to meperidine 8.1 to 9.9 hours before birth.

Clinical Considerations

Because neonatal adverse effects are related to dose-delivery interval, timing of meperidine administration becomes important. Ideally, to reduce the risk of neonatal respiratory depression, meperidine is not given when birth is anticipated within 1 to 4 hours after administration. Because multiple dose regimens may result in maximum fetal accumulation of both meperidine and normeperidine, with associated newborn depression, single doses of meperidine during labor are preferable to multiple doses.[38]

In summary, meperidine's well-documented adverse effects in the neonate, effect on breastfeeding behaviors, active metabolite, and slow clearance do not support any advantage to its use during labor. Other short-acting opioids with rapid onset and offset and no active metabolites may be preferred.

FENTANYL

Fentanyl citrate, a synthetic opioid derivative of meperidine, was first synthesized in the 1950s and was initially used as an intravenous anesthetic. Studies of intravenous fentanyl use during labor first appeared in the literature in 1989.[45] It is now used in many labor and delivery units for labor pain relief.

A potent opioid agonist, fentanyl interacts primarily with mu receptors. It has a greater analgesic potency than morphine, with 100 mcg of fentanyl equivalent in analgesic effect to 10 mg of morphine. Fentanyl is metabolized in the liver by CYP34A to the inactive and nontoxic metabolites hydroxy fentanyl, norfentanyl, and despropionyl fentanyl.[46] Fentanyl is eliminated in urine and stool and by the lungs.[47]

Efficacy and Side Effects of Fentanyl

Rapidly crossing the blood-brain barrier, fentanyl produces analgesia, sedation, and may cause respiratory depression, nausea, and vomiting. Because it is highly lipophilic, fentanyl rapidly crosses the placenta. In animal studies (sheep) it is present in the fetal blood within 1 minute and its level peaks at 5 minutes after maternal intravenous administration.[48] Fetal exposure to fentanyl is associated with temporary depressant effects such as fewer body movements between contractions, less overall time moving, and temporary abolishment of breathing movements at 10 minutes after dosing.[49] Short-term fetal heart rate variability between uterine contractions is reduced for approximately 30 minutes following administration.[45,49,50]

Although fentanyl may be administered by other routes, published studies regarding use for intrapartum parenteral analgesia have assessed only intermittent intravenous bolus administration and PCA administration (Table 3).

Rayburn et al[45] compared parturients who received intravenous fentanyl for labor pain to women who did not receive analgesia or anesthesia during labor and determined that at low doses of intravenous fentanyl, laboring women experienced temporary analgesia and sedation with no immediate risks to them and their newborns.

When intravenous fentanyl was compared with intravenous meperidine for labor pain relief in a randomized, nonblinded trial (N = 105 women with uncomplicated pregnancies at term in active labor), both fentanyl and meperidine produced similar reduction in pain scores; however, fentanyl was associated with less sedation, nausea, and vomiting and fewer newborns requiring naloxone therapy (1/49 vs 7/56, respectively; $P < .05$). There was no difference in rates of decreased fetal heart rate variability, Apgar scores, and neonatal neurologic and adaptive capacity scores. Because fentanyl had fewer maternal and newborn side effects, the investigators suggested that fentanyl might be preferable to meperidine for labor analgesia.[33]

When fentanyl and butorphanol were compared, butorphanol was found to provide better pain relief in the early stages of active phase labor ($P < .05$), yet both drugs reduced pain scores only slightly during the latter part of first-stage labor (cervical dilation 7-9 cm). Rates of maternal sedation, nausea, and vomiting were found to be similar as well as frequency of decreased fetal heart rate variability persisting beyond 30 minutes, Apgar scores, neonatal neurologic and adaptive capacity scores, naloxone therapy, and umbilical cord gas values. The authors concluded that although rates of maternal and neonatal side effects were comparable, butorphanol might be preferable to fentanyl for pain relief in early active labor.[50]

Effect of Fentanyl on Labor

Studies of the effect of intermittent intravenous bolus administration of fentanyl on labor outcomes have had inconsistent findings. When compared with women who did not receive analgesia or anesthesia during labor, women who received intravenous fentanyl were more likely to have oxytocin augmentation and a longer active phase of labor.[45] In contrast, the clinical trials that compared intravenous fentanyl to intravenous meperidine, butorphanol, or PCA fentanyl demonstrated no difference in contraction frequency or duration,[50] oxytocin augmentation,[33,50] length of labor,[33] or route of birth.[33,50]

Patient-controlled Administration of Fentanyl

Low doses of intravenous bolus fentanyl (cumulative dose 161.6 mcg ± 109.2 mcg) also have been compared with equivalent doses of PCA fentanyl and were found to have no clinical advantage over intravenous bolus administration.[51]

High doses of PCA fentanyl have been compared with epidural anesthesia and have demonstrated varying results. Nikkola et al[52] found that although epidural anesthesia was more effective for pain relief than PCA fentanyl (cumulative dose range 190 mcg-885 mcg) during active labor, overall satisfaction with analgesia did not differ between groups.

Table 3. Summary of Comparative Investigations of Fentanyl (Sublimaze) for Labor Pain Relief

Authors of Study	Study Design Participants	Interventions	Outcomes
Rayburn et al[45]	Prospective nonrandomized controlled trial 137 parturients in active labor	*Experimental*: IV bolus of fentanyl 50-100 mcg/h. Mean (SD) cumulative fentanyl dose 140 mcg/h (42 mcg) ranging 50-600 mcg. Two-thirds of group received ≤ 100 mcg total dose, and 90% received < 300 mcg. *Control:* No analgesia or anesthesia	*Maternal:* Fentanyl group with temporary analgesia, mild sedation, mood modification, temporary relief of fears, relaxation, drowsiness. *Fetal:* 30 min of decreased variability. *Labor:* Fentanyl group had higher rate of oxytocin augmentation ($P < .0001$) and longer active phase labors ($P < .001$). No difference in route of birth. *Newborn*: No differences in frequencies of newborn depressed respirations, low Apgar scores, or neurologic and adaptive capacity scoring at 2-4 h and 24 h following birth.
Rayburn et al[33]	Prospective randomized controlled trial 105 parturients in active labor	*Experimental:* IV bolus of fentanyl 50-100 mcg/h *Control:* IV bolus of meperidine (Demerol) 25-50 mg/h	*Maternal:* VAS pain scores were not significantly different between groups. Pain scores improved only slightly between 8-10 cm and more so at 4-7 cm cervical dilation. Nausea, vomiting, and prolonged sedation less common in the women in the fentanyl group ($P < .05$). *Fetal:* FHR variability not statistically different between groups. *Labor:* No significant differences in duration of labor, oxytocin use, cesarean birth. *Newborn:* Significantly fewer neonates required naloxone in the fentanyl group (2% vs 13%; $P < .05$). No difference in Apgar scores, umbilical artery pH, or neurologic and adaptive capacity scoring at 2-4 h and 24 h postnatally.
Atkinson et al[50]	Prospective randomized double-blind, controlled trial 100 parturients in active labor	*Experimental:* IV bolus of fentanyl 50-100 mcg/h, limit 5 doses. *Control:* IV bolus of butorphanol (Stadol) 1-2 mg every 1-2 h, limit 5 doses	*Maternal*: Significantly greater reduction in VAS pain scores at 15 and 60 min following initial dose of butorphanol ($P < 0.05$) compared with fentanyl. At 7-9 cm cervical dilation, pain scores increased and both drugs reduced pain scores only slightly at 15 min after dosing. Mothers in fentanyl group requested more doses ($P < .05$) and had more requests for epidural ($P < .05$). Rates of nausea, vomiting, prolonged sedation, and decreased respiratory rate were similar.

Continued

Table 3. Summary of Comparative Investigations of Fentanyl (Sublimaze) for Labor Pain Relief

Authors of Study	Study Design Participants	Interventions	Outcomes
			Fetal: No difference in temporary decrease in FHR variability and pseudosinusoidal pattern. *Labor:* No difference in contraction frequency or duration, oxytocin augmentation, or cesarean birth. *Newborn*: No difference in Apgar scores, cord gas values, naloxone use, or neuroadaptive scoring.
Rayburn et al[52]	Prospective randomized controlled trial 80 parturients in active labor	*Experimental:* PCA fentanyl 50 mcg loading dose, 10 mcg/h baseline, 10 mcg demand dose; lockout interval 12 min Maximum hourly dose 60 mcg Cumulative dose used: 149.0 mcg (62.2 mcg), range 70-305 mcg *Control:* IV bolus of fentanyl 50 mcg loading dose, then 50-100 mcg/h Cumulative dose used: 161.6 mcg (109.2 mcg), range 50-500 mcg	*Maternal*: No difference in pain scores, sedation scores. *Fetal:* No difference in persistent decreased FHR variability. *Labor:* No difference in duration of labor. *Newborn*: No difference in Apgar score, naloxone therapy, or neurologic and adaptive capacity scoring at 24 h.
Nikkola et al[52]	Randomized controlled trial 20 parturients in active labor	*Experimental:* IV PCA fentanyl Loading dose 50 mcg fentanyl, 20 mcg demand dose; lockout interval 5 min; maximum dose 240 mcg/h Cumulative dose range 190 and 885 mcg, mean 447 (202 mcg) *Control:* epidural (bupivacaine 0.5%)	*Maternal*: Epidural provided significantly better pain relief ($P = .01$) per VAS pain score. Six of 10 mothers rated effectiveness of fentanyl as good to excellent; 8 of 10 rated epidural effectiveness as good to excellent. Satisfaction with analgesia did not differ significantly between groups. Mothers in fentanyl group had significantly more tiredness and dizziness ($P = .001$). No difference in rates of nausea and vomiting. *Fetal:* No difference in FHR variability 1 h after medication. *Labor:* No difference in labor duration. *Newborn:* No difference in Apgar scores, umbilical pH, or neurologic and adaptive capacity scoring at 1 and 13 h. During the first 12 h of life, minimum and maximum SpO_2 values were significantly lower in the infants in the fentanyl group. $SpO_2 < 90\%$ was more common with fentanyl group ($P = <$ .001); no infants required O_2. Episodes of desaturation $< 80\%$ did not differ between groups. No neonates required naloxone.

Continued

Table 3. Summary of Comparative Investigations of Fentanyl (Sublimaze) for Labor Pain Relief

Authors of Study	Study Design Participants	Interventions	Outcomes
Halpern et al[53]	Prospective randomized controlled trial 242 parturients in active labor and second stage labor	*Experimental:* Patient controlled epidural (0.08% bupivacaine and fentanyl 1.6 mcg/mL) Mean cumulative epidural fentanyl dose 200 mcg (range 132-244 mcg) *Control:* IV PCA fentanyl. Loading dose 100 mcg, then 50 mcg as needed until adequate pain relief. Followed by 25-50 mcg PCA demand dose; lockout interval 10 min. Lockout and demand dose could be increased or decreased by anesthesiologist. Total dose used: mean cumulative dose of 940 mcg (range 350-1625 mcg)	*Maternal:* Epidural group with significantly greater reductions in VAS pain scores ($P < .001$) and higher satisfaction scores ($P = .02$). Also, less antiemetic therapy ($P = .01$) and lower sedation scores ($P < .001$). *Fetal:* Not evaluated. *Labor:* Epidural was associated with significantly longer second stage labor ($P = .02$). No difference in incidence of maternal fever, spontaneous vaginal births, assisted vaginal births, or cesarean births. *Newborn:* No difference in 5-min Apgar scores, umbilical artery gas values, or neonatal fever. More neonates in fentanyl group required active resuscitation ($P = .001$), naloxone (17% vs 3%; $P = .001$), and had lower 1-min Apgar scores.

Abbreviations: FHR, fetal heart rate; IV, intravenous; PCA, patient-controlled analgesia; SpO_2, oxygen saturation with pulse oximetry; VAS, visual analogue scale.

Women who received PCA fentanyl were more likely to have dizziness and tiredness. There was no difference between groups in nausea, vomiting, labor duration, Apgar scores, and neonatal neurologic and adaptive capacity scores. No newborns received naloxone. During the first 12 hours of life, minimum and maximum oxygen saturation values were significantly lower in the newborns in the fentanyl group. An oxygen saturation with pulse oximetry (SpO_2) of less than 90% also was more common with newborns in the fentanyl group, although none of the newborns required oxygen supplementation. Because newborn desaturation events occurred during the first 12 hours of life, the authors recommended monitoring SpO_2 for several hours after birth in newborns whose mothers receive the reported doses of PCA fentanyl. Conversely, Halpern et al[53] found that pain relief and satisfaction with analgesia scores were better in the women receiving epidural anesthesia (bupivacaine plus fentanyl) when compared with parturients receiving PCA fentanyl (cumulative dose 350 mcg-1625 mcg). There was no difference between groups in route of birth, umbilical cord gas values, or 5-minute Apgar scores, although a longer second stage of labor was associated with epidural use. Women in the intravenous fentanyl group experienced more sedation and lower 1-minute Apgar scores. Active resuscitation was required in 52% of the neonates of women who received the studied doses of PCA fentanyl, compared with 31% in the epidural group. At the high doses studied, a large number of neonates required naloxone therapy (17% of the neonates in the PCA fentanyl group, 3% in the epidural group).

Effect of Fentanyl on Breastfeeding

A small amount of fentanyl transfers into human milk following analgesic dosing. Women who received 50 mcg to 400 mcg of fentanyl intravenously during labor were found to have a very small amount of fentanyl in their breast milk.[54] In another study,[46] fentanyl was detected in colostrum in very small amounts following intravenous fentanyl analgesic dosing (126 mcg-189 mcg) during cesarean birth or postpartum tubal ligation. Highest concentrations in colostrum were at 45 minutes after intravenous administration, and fentanyl was undetectable at 10 hours after administration. Because of the small amount of fentanyl in colostrum, the small amount of colostrum initially consumed, the low bioavailability of fentanyl, and rapid decline in colostrum with time, the amount of fentanyl transferred to the neonate via colostrum is very low.

Clinical Considerations

To date, 1 study has investigated the effect of mu opioid polymorphisms on the effect of labor analgesia. Landau et al[55] demonstrated that parturients with the mu opioid receptor 304G variant required lower doses ($P < .001$) of intrathecal fentanyl to achieve labor pain relief. Although the effect of the 304G variant on a parturient's response to intravenous fentanyl during labor has not been studied, other trials have found that intravenous morphine analgesia in nonpregnant patients with this variant increased, rather than decreased, morphine requirements. It is suggested that individual differences in analgesic response to route of

administration in persons with this polymorphism may be related to a difference in spinal and systemic opioid pharmacokinetics.[54] Currently, genotyping is not part of standard care; therefore, practitioners do not know whether parturients have variants that could affect analgesia sensitivity. Starting with low doses of opioids and titrating to a safe dose allows for individual variation in response.

Fentanyl's rapid onset, short half-life, and lack of active metabolite make it a suitable choice for labor analgesia. Most commonly administered by intravenous bolus or PCA devices, lower doses of fentanyl provide modest amounts of pain relief with minimal adverse effects. Higher doses are associated with limited pain relief but with more maternal sedation and newborn respiratory depression. Even high doses lack effectiveness in the latter part of active labor.

REMIFENTANIL

Remifentanil use during labor was first reported in the late 1990s as an adjunct to general anesthesia for cesarean births.[56] Since that time, various labor analgesia dosing regimens and their effect on laboring women and neonates have been studied.[42,56–59] Remifentanil, like fentanyl, is in the anilidopiperidine class of synthetic opioids. It is an ultra short–acting synthetic mu opioid receptor agonist characterized by rapid onset of action and rapid offset.[59] Because of its rapid offset, remifentanil is administered via intravenous PCA at the beginning of a uterine contraction and is likely to provide its peak effect with the next contraction. Remifentanil has a half-life of 4 minutes, metabolizes to the inactive metabolite remifentanil acid, and is virtually gone within 3 half-lives or 9 to 10 minutes after initial administration.

Efficacy and Side Effects of Remifentanil

Remifentanil results in temporary reduction in labor pain scores; pain reduction is dose related.[58,60,61] Undesirable side effects include sedation, respiratory depression, and nausea and vomiting (range 0%-60%). Many studies of this opioid have reported periods of maternal desaturation during labor that have required oxygen supplementation.[58–60,62]

Remifentanil rapidly crosses the placenta and is quickly metabolized and redistributed in the fetus.[56] The fetal side effects may include temporary decreased fetal heart rate variability.[63] There have been no reports of associated low Apgar scores or need for naloxone therapy.

Several randomized controlled trials have addressed unique dosing regimens and have demonstrated varying effects on pain scores and side effects (Table 4). When a fixed dose of PCA remifentanil was compared with PCA pethidine, Blair et al[41] found no significant difference in reduction of pain relief scores during a 2-hour observation period but found satisfaction scores to be higher in the remifentanil group. Sedation scores increased over time in both groups. There was no significant difference in fetal heart rate baseline, Apgar scores, umbilical cord arterial pH values, naloxone use, or neonatal neurologic and adaptive capacity scores at 2 hours after birth. Neonatal neurologic and adaptive capacity scores were higher with remifentanil at 30 minutes after birth. The authors concluded that the doses of remifentanil studied resulted in no better pain scores than pethidine and that differing dose regimens may provide better pain relief.

In contrast, Thurlow et al[60] found that PCA remifentanil provided better pain relief compared with intramuscular meperidine during the same-length observation period. Satisfaction scores were higher with remifentanil. Both groups experienced comparable rates of nausea and vomiting or minimum PO_2 saturation rates and comparable Apgar scores. The authors concluded that remifentanil is an acceptable alternative to meperidine, but because of its potential for respiratory depression, it must be administered with adequate supervision of the parturient. The authors also emphasized the importance of timing the remifentanil bolus dose at the start of contractions rather than when the contraction becomes painful to receive maximum pain relief and minimize side effects.

Evron et al[63] compared increasing weight-based doses of PCA remifentanil to intramuscular meperidine and found better pain relief scores in the remifentanil group 2 hours after administration and better satisfaction scores 24 hours after birth. Remifentanil was associated with less sedation, less nausea and vomiting, and fewer desaturation events. Decreased fetal heart rate variability occurred less frequently with remifentanil. There were no differences in Apgar scores or umbilical cord arterial pH values. Rates of breastfeeding difficulties were not significantly different between groups (remifentanil 6.3%, meperidine 12.8%). The authors concluded that the intermittent incremental regimen of remifentanil studied provided better pain relief and had fewer side effects than meperidine.

Finally, when PCA remifentanil was compared with PCA meperidine or fentanyl, all pain scores initially improved, but remifentanil produced greater improvement than meperidine and fentanyl at 1 hour after administration. Three hours after opioid exposure, pain scores were not significantly different from the baseline in all groups. Sedation increased in all groups and was greatest with remifentanil. Desaturation events were more common with remifentanil and fentanyl compared with meperidine. Overall satisfaction scores were highest with remifentanil. There was no difference in neonatal outcomes. The authors concluded that, at the doses studied, remifentanil provided more pain relief than meperidine and fentanyl for a short time only and was associated with more sedation and respiratory depression.[42]

Effect of Remifentanil on Labor

Studies of the effect of remifentanil on labor outcomes have had inconsistent findings. Women who received remifentanil had no difference in rates of oxytocin use[42,63] or length of labor.[41,42,63] One study[60] found more operative vaginal births associated with remifentanil when compared with meperidine; another[63] found no difference. When remifentanil was compared with fentanyl, remifentanil was associated with more operative births.[42]

Effect of Remifentanil on Breastfeeding

The effect of remifentanil on breastfeeding has not been adequately studied. Only 1 study[63] has addressed breastfeeding

Table 4. Randomized Controlled Trials Comparing Remifentanil (Ultiva) to Other Opioids

Author	Participants Study Design	Interventions	Outcomes
Blair et al[41]	Double-blind, randomized controlled trial 39 parturients during first and second stage labor	*Experimental*: PCA remifentanil 40 mcg/dose, 2 min lockout interval Total doses not reported. *Control:* PCA meperidine (Demerol) 15 mg/dose, 10 min lockout interval Total doses not available Nitrous oxide option available to both groups	*Maternal:* No difference between groups in reduction of VAS pain scores during 2 h observation. Overall maternal satisfaction higher ($P = .001$) with remifentanil. No difference between groups in nausea, anxiety, or maternal desaturation less than 94% or 90%. Sedation increased over time and was similar between groups. *Fetal:* No change in FHR baseline with both groups. *Labor:* No difference between groups in labor duration. *Newborn:* Neurologic and adaptive capacity scores higher ($P = .003$) with remifentanil at 30 min but similar at 2 h after birth. No difference in Apgar scores or cord pH. Naloxone was not used in either group.
Evron et al[63]	Double-blind, randomized controlled trial 88 parturients, labor stage not reported	*Experimental:* Increasing doses of PCA remifentanil, 0.27-0.93 mcg/kg/bolus, maximum 1500 mcg/h. Mean total dose/h 270 mcg/kg *Control:* Intravenous infusion meperidine 75 mg over 30 min. With insufficient analgesia, another 75 mg administered. Additional 50 mg as needed. Maximum dose 200 mg (range 75-200 mg). Mean total dose 150 mg	*Maternal*: Remifentanil associated with lower ($P < .001$) VAS pain scores at 1 h after initiation of medication and end of first stage labor and higher ($P < .001$) patient satisfaction scores 24 h after birth. Remifentanil also associated with less ($P < .001$) sedative effect, fewer ($P < .007$) desaturation events <95%, and less nausea and vomiting ($P < .001$) *Fetal*: Less frequent ($P < .001$ for both) decreased FHR variability and variable decelerations with remifentanil. *Labor*: No difference in oxytocin use, route of birth, or length of active and second stage labor. *Newborn*: No difference in Apgar scores and cord blood pH. Neurologic and adaptive capacity scoring and naloxone administration not addressed. Feeding difficulties were similar between groups.
Thurlow et al[60]	Randomized controlled trial 36 parturients, labor stage not reported	*Experimental:* PCA remifentanil 20 mcg bolus over 20 s, 3 min lockout interval, no background infusion Total doses not reported *Control:* IM meperidine 100 mg, plus promethazine (Phenergan) 25 mg or prochlorperazine (Compazine) 12.5 mg as antiemetic Nitrous oxide option available to both groups.	*Maternal:* VAS pain scores 60 min and maximum pain scores during first 2 h after analgesia significantly lower ($P = .0004$ and 0.009, respectively) in the remifentanil group. Overall effectiveness of analgesia within 2 h of birth, rated by mothers and midwives, was higher ($P = .002$) in remifentanil group. No significant difference between groups in nausea and vomiting. No significant difference in minimum saturation between groups, but authors concluded that the overall saturation may have been lower for women receiving remifentanil. *Fetal:* No outcomes evaluated.

Continued

Table 4. Randomized Controlled Trials Comparing Remifentanil (Ultiva) to Other Opioids

Author	Participants Study Design	Interventions	Outcomes
			Labor: Remifentanil associated with more ($P = .04$) nonvaginal routes of births; 6 of 7 women had also received epidural. *Newborn:* No difference in Apgar scores between groups.
Douma et al[42]	Double-blind, randomized controlled trial 159 parturients in active phase labor	*Experimental:* PCA remifentanil 40 mcg loading dose, 40 mcg/bolus, 2 min lockout interval, maximum dose limit 1200 mcg/h *Control:* PCA meperidine 49.5 mg loading dose, 5 mg bolus, 10 min lockout interval, total dose limit 200 mg *Odds Ratio:* PCA fentanyl (Sublimaze) 50 mcg loading dose, 20 mcg bolus, 5 min lockout interval, maximum dose limit 240 mcg/h	*Maternal:* VAS pain scores decreased in all groups. Greatest decrease in pain scores with remifentanil at 1 h after administration (remifentanil vs meperidine, $P < .05$; remifentanil vs fentanyl, $P < .01$; meperidine vs fentanyl, $P =$ NS). At 2 h after initiation of treatment, pain scores with meperidine were no different from baseline, and at 3 h, pain scores were not significantly different from baseline in all groups. Sedation increased in all groups; at 1 h and 2 h sedation was greater with remifentanil compared with meperidine and fentanyl (remifentanil vs meperidine, $P < .05$; remifentanil vs fentanyl $P < .01$). At 3 h, sedation scores with remifentanil were greater ($P < .05$) than with fentanyl only. Itching more common with remifentanil ($P < .05$). More crossover to epidural in meperidine group ($P < .05$). No difference in rates of nausea and vomiting. Overall satisfaction after birth greater in remifentanil group when compared with meperidine ($P < .05$). No difference in satisfaction between remifentanil and fentanyl or meperidine and fentanyl. Remifentanil and fentanyl associated with 1 or more periods of desaturation < 95% compared with meperidine (remifentanil vs meperidine, $P < .0001$; remifentanil vs fentanyl, $P =$ NS; meperidine vs fentanyl, $P < .05$). *Fetal:* No difference in reactive/nonreactive FHR patterns. *Labor:* No difference in duration of labor, oxytocin use. Fentanyl associated with more spontaneous deliveries ($P < .05$). *Newborn:* No difference in Apgar scores, neurologic and adaptive capacity scores at 15 and 120 min, cord blood pH and base excess.

Abbreviations: FHR, fetal heart rate; IM, intramuscular; NS, not significant; PCA, patient-controlled analgesia; VAS, visual analogue scale.

issues, and it found that 6.3% of newborns exposed to intrapartum remifentanil had breastfeeding difficulties.

Clinical Considerations

Depending on dosing regimen, remifentanil may produce modest pain relief for time-limited periods, with associated sedation and periods of maternal oxygen desaturation that may be corrected by oxygen supplementation or a dose reduction. Because remifentanil is a potent respiratory depressant, its intrapartum use requires continuous monitoring of parturients. Recommended guidelines for safe practice include 1-to-1 nursing supervision, continuous pulse oximetry, evaluation of sedation scores every 30 minutes, no other

opioid use during the 4 previous hours, and clear indications for contacting the anesthesia provider (eg, excessive sedation, not responsive to voice, respiratory rate less than 8 breaths per minute, or SpO_2 of less than 90% while breathing room air). Women should be informed of potential side effects, including a 10% chance of requiring supplemental oxygen.[64] Although no studies have reported low Apgar scores or a need for neonatal naloxone, naloxone and resuscitation support should be available for the newborn at the time of birth. Newborns exposed to remifentanil during the intrapartum period may need additional breastfeeding support while establishing breastfeeding.

Current studies are limited by short observation periods, small samples, differing routes of administration, and concomitant nitrous oxide use. More extensive controlled studies are needed to evaluate dosing regimens and safety for laboring women and newborns, including implications for breastfeeding behaviors.

BUTORPHANOL TARTRATE

Butorphanol tartrate is a synthetic opioid agonist-antagonist with antagonist activity at mu opioid receptors and agonist activity at kappa opioid receptors.[50] Metabolism takes place in the liver, where butorphanol's primary and inactive metabolite, hydroxybutorphanol, is produced.[6] Butorphanol has an analgesic and respiratory ceiling effect such that higher doses do not provide any additional pain relief or respiratory depression but will increase the likelihood of other side effects.

Efficacy and Side Effects of Butorphanol

Maternal side effects may include somnolence, sedation, nausea, vomiting, and respiratory depression. A transient pseudosinusoidal fetal heart rate pattern has been associated with butorphanol.[65] Neonatal neurologic and adaptive capacity scores have results similar to those of meperidine.

Four double-blind randomized controlled trials[34,36,66,67] have compared butorphanol with meperidine for labor pain analgesia and found no significant difference in most outcomes. Three of the trials[36,66,67] compared 1 to 2 mg of intramuscular butorphanol to 40 to 80 mg of intramuscular meperidine and found no differences in pain relief, nausea and vomiting, fetal heart rate patterns, Apgar scores, umbilical cord gas values, or neonatal resuscitation requirements.[66] With intravenous comparisons, 1 study demonstrated better analgesia with butorphanol (95% CI, −1.02 to −0.18),[67] and the other found no difference.[36] Less nausea and vomiting (95% CI, 0.00-0.67) was associated with butorphanol in 1 intravenous comparison,[36] and no difference was found in another.[67] There were no differences between groups in sedation, Apgar scores, or neonatal neurologic and adaptive capacity scores. In a fourth study,[34] a combination of 25 mg intravenous meperidine plus 0.5 mg butorphanol was compared with 50 mg intravenous meperidine or 1 mg intravenous butorphanol. All 3 groups had similar reductions in pain intensity following treatment. Sedation increased to a similar degree in all 3 groups, and there was no difference in decreased fetal heart rate variability, nausea, or Apgar scores. A transient sinusoidal fetal heart rate pattern was identified in 1 woman in the meperidine group and 1 in the combination group.

Intravenous butorphanol for labor analgesia also has been compared with intravenous fentanyl. In a double-blind randomized controlled trial,[26] investigators demonstrated that women receiving butorphanol (1-2 mg every 1-2 hours) had greater reductions in pain scores ($P < .05$) during the first hour after dosing compared with women in the fentanyl (50-100 mcg every 1-2 hour) group. As labor pain increased, both groups had only marginal improvements in pain scores, although fewer doses of butorphanol were requested ($P < .01$). Side effects occurred in both groups, but there was no statistically significant difference in a need for antiemetics (butorphanol 12%, fentanyl 24%), prolonged sedation (butorphanol 8%, fentanyl 4%), or respiratory rate less than 10 breaths per minute (butorphanol 4%, fentanyl 12%). Nor were there differences in rates of decreased fetal heart rate variability (butorphanol 32%, fentanyl 24%), pseudosinusoidal fetal heart rate pattern (butorphanol 20%, fentanyl 10%), or rates of neonatal naloxone use (butorphanol 16%, fentanyl 28%) between groups.

Effect of Butorphanol on Labor

Butorphanol has not been associated with a change in uterine contraction patterns for 1 hour after dosing, change in duration of first and second stages of labor, or rate of cesarean birth.[50]

Effect of Butorphanol on Breastfeeding

Butorphanol transports into human milk and has been associated with impaired sucking behaviors during the first 14 hours of life but is not associated with duration of breastfeeding within the first 6 weeks postpartum.[68]

Clinical Considerations

Butorphanol is a high-potency labor analgesic with a ceiling effect for both analgesia and respiratory depression. Two milligrams of intravenous butorphanol produces respiratory depression similar to that of 10 mg of intravenous morphine or 70 mg of intravenous meperidine. However, 4 mg of butorphanol will produce less respiratory depression than 20 mg of morphine or 140 mg of meperidine.[69]

Although the pseudosinusoidal fetal heart rate pattern associated with butorphanol is thought to be benign, its presence may complicate the interpretation of some fetal heart rate tracings.

Butorphanol is contraindicated for women who are opioid dependent, because the antagonist effects stimulated by this agent may precipitate withdrawal symptoms.

NALBUPHINE HYDROCHLORIDE

Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist chemically related to oxymorphone (Opana) and naloxone. Although it binds to mu, kappa, and delta receptors, it is primarily a kappa agonist and partial mu antagonist analgesic. The analgesic potency of nalbuphine is equivalent

to morphine on a milligram-to-milligram basis. Nalbuphine is metabolized to an inactive metabolite. Nalbuphine has a respiratory depression ceiling effect, with a maximum respiratory depression occurring at a dose of 30 mg per 70 kg.[70] An analgesic ceiling effect also occurs at these levels.[69]

Efficacy and Side Effects of Nalbuphine

The most common maternal side effect of nalbuphine when used for labor analgesia is sedation and less frequently nausea, vomiting, drowsiness, and dizziness.[71] Respiratory depression can occur and can be reversed with naloxone.[70] Undesired fetal effects are temporary decreased fetal heart rate variability[71] and decreased number of fetal heart rate accelerations.[70] One case report identified a sinusoidal fetal heart rate associated with nalbuphine.[72]

Studies comparing the effect of nalbuphine with meperidine on labor pain have found conflicting results. Two double-blind, randomized trials found no significant difference in reduction of pain scores with either 10 mg intravenous nalbuphine versus 50 mg intravenous pethidine[73] or 20 mg intramuscular nalbuphine versus 100 mg intramuscular pethidine.[35] In contrast, another double-blind, randomized trial[74] demonstrated that PCA nalbuphine (3-mg increments, maximum 18 mg/hour) when compared with PCA meperidine (15-mg increments, maximum 90 mg/hour) was associated with lower pain scores ($P < .01$). There were no differences between nalbuphine and meperidine in rates of nausea,[35] vomiting,[35,71] dizziness,[35] sedation,[35,71] or respiratory rate.[71] Apgar scores were no different in 2 trials[35,71]; more neonates had lower 1-minute Apgar scores in another.[73] In 1 trial, nalbuphine was associated with lower neonatal neurologic and adaptive capacity scores ($P < .001$) at 2 to 4 hours after birth, but there was no difference at 24 hours.[35] Another trial found no difference in neonatal neurologic and adaptive capacity scores at 6 to 10 hours.[74]

Giannina et al[70] randomized 28 parturients to receive either 10 mg intravenous nalbuphine or 50 mg intravenous meperidine and examined the effect on intrapartum fetal heart rate patterns 1 hour after administration. Nalbuphine significantly ($P = .001$) decreased the frequency of accelerations and was associated with more decreased variability (long-term $P = .002$; short-term $P = .03$). There were no differences in Apgar scores or umbilical artery pH at birth.

Effect of Nalbuphine on Labor

Studies have found no difference between nalbuphine and meperidine in effects on frequency of uterine contractions,[70,74] length of the second stage of labor,[74] or mode of birth.[70]

Effect of Nalbuphine on Breastfeeding

Nalbuphine rapidly transfers to the fetus and is found in small amounts in human milk. This opioid has been associated with impaired sucking behaviors in the first 14 hours of the postpartum period but is not associated with duration of breastfeeding during the first 6 weeks postpartum.[14]

Clinical Considerations

Although nalbuphine's respiratory ceiling effects may be of benefit, comparative studies of nalbuphine's analgesic effect and side effects are inconclusive. Nalbuphine, like butorphanol, is contraindicated for women who are opioid dependent because it may precipitate withdrawal symptoms.

CONCLUSION

Systemic opioids provide little to modest labor pain relief. Pain relief is incomplete, temporary, accompanied by sedation, and more effective in the early part of active labor. Opioids may lack effectiveness after 7 cm of dilation. Despite their limitations, the temporary easing of labor pain following opioid administration may be a helpful and satisfactory pain management strategy for many parturients. For others seeking greater pain relief, the effect of systemically administered opioids may not be satisfactory.

Comparisons of morphine, meperidine, fentanyl, remifentanil, butorphanol, and nalbuphine for labor analgesia demonstrate no significant differences between these opioids for most outcomes. Comparisons of intramuscular administration of meperidine to morphine,[22] butorphanol,[66] or nalbuphine[73] found no significant differences in labor pain relief or maternal and neonatal side effects. Only 1 study[35] reported that nalbuphine was associated with lower newborn neuroadaptive scores at 2 to 4 hours of life but no difference at 24 hours.

Comparisons of intravenous opioids for pain relief efficacy are inconclusive. In some studies, butorphanol (1[67] of 3 studies), nalbuphine (1[74] of 2 studies), and remifentanil (2[42,63] of 3 studies) were associated with better labor pain relief than meperidine. Other comparisons of the same drugs found no difference in analgesia effect.[27,33,34,36,41,73] Butorphanol[50] and remifentanil (1[42] of 2 studies) were associated with better pain relief than fentanyl. When PCA remifentanil and intramuscular meperidine were compared, remifentanil was associated with better pain relief scores.[60]

Most comparisons of the adverse effects of intravenous opioids were inconclusive.[34,41,50,59,66,73,74] When other opioids were compared with meperidine, several studies found more significant adverse effects associated with meperidine. Compared to meperidine, butorphanol was associated with less dizziness, nausea, and vomiting (1[36] of 3 studies); fentanyl was associated with less sedation, nausea, vomiting, and naloxone use[33]; and morphine appears to cause nausea less often than does meperidine.[27] Conversely, desaturation events and sedation were more common with PCA remifentanil and PCA fentanyl than with PCA meperidine[42] (1 study). Patient-controlled analgesia remifentanil was associated with less sedation, nausea and vomiting, and desaturation than intravenous meperidine.[63]

Although it is not clear from comparison studies which opioid is best for labor analgesia, some practical recommendations may be considered based on pharmacokinetic and pharmacodynamic profiles. Opioids with rapid onset and offset of action; rapid metabolism and elimination; minimal undesired maternal, fetal, and neonatal side effects; and lack of active metabolites may be optimal. Although intramuscular opioids have the advantage of simplicity, intravenous

administration may be preferable because it results in rapid onset of pain relief and allows for titration of medication. Intramuscular administration has variable absorption and a delay in onset. Intravenous PCA with fentanyl, morphine, nalbuphine, or remifentanil may provide a more consistent analgesic effect and allow a parturient to control and adjust an opioid to her individual need.

Selecting opioids that have a rapid offset and lack active metabolites may be advantageous to women and newborns. Both meperidine and morphine produce active metabolites, with meperidine's metabolite having the longest half-life and, therefore, more effects on the neonate and breastfeeding behaviors. Other opioids such as fentanyl, remifentanil, butorphanol, and nalbuphine do not have active metabolites. Remifentanil's ultrarapid offset and lack of an active metabolite may be a promising newer alternative; however, more scientific studies are necessary to evaluate maternal and neonatal safety, the effect of dosing on the balancing of pain relief with sedation, and its effect on breastfeeding behaviors.

Scientific investigations of systemic opioids with sufficiently powered studies are still needed so that we may further understand the effect of opioids on pain relief, maternal and neonatal safety, breastfeeding behaviors, and long-term safety. Most studies conducted to date have compared 1 opioid to another or to epidural anesthesia. It may be informative to include in future investigations a comparison group of women and newborns who have not received any analgesics during labor.

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CONFLICT OF INTEREST

The author has no conflicts of interest to disclose.

REFERENCES

1. Evron S, Ezri T. Options for systemic labor analgesia. *Curr Opin Anaesthesiol*. 2007;20(3):181-185.
2. Bucklin BA, Hawkins JL, Anderson JR, Ullrich FA. Obstetric anesthesia workforce survey: twenty-year update. *Anesthesiology*. 2005;103(3):645-653.
3. Saravanakumar K, Garstang JS, Hasan K. Intravenous patient-controlled analgesia for labour: a survey of UK practice. *Int J Obstet Anesth*. 2007;16(3):221-225.
4. Tveit TO, Halvorsen A, Rosland JH. Analgesia for labour: a survey of Norwegian practice—with a focus on parenteral opioids. *Acta Anaesthesiol Scand*. 2009;53(6):794-799.
5. Lavand'homme P, Roelants F. Patient-controlled intravenous analgesia as an alternative to epidural analgesia during labor: questioning the use of the short-acting opioid remifentanil. Survey in the French part of Belgium (Wallonia and Brussels). *Acta Anaesthesiol Belg*. 2009;60(2):75-82.
6. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. *Pain Physician*. 2008;11(suppl 2):S133-S153.
7. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain*. 2002;18(suppl 4):S3-S13.
8. Argoff, CE. Clinical implications of opioid pharmacogenetics. *Clin J Pain*. 2010;26(suppl 10)S16-S120.
9. Zhou S. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet*. 2009;48(11):689-723.
10. US Food and Drug Administration. Public Health Advisory: Use of codeine by some breastfeeding mothers may lead to life-threatening side effects in nursing babies http://www.fda.gov/cder/drug/advisory/codeine.htm(17August 2007). Accessed September 30, 2010.
11. Bricker L, Lavender T. Parenteral opioids for labor pain relief: a systematic review. *Am J Obstet Gynecol*. 2002;186(suppl 5 Nature):S94-S109.
12. Ullman R, Smith LA, Burns E, Mori R, Dowswell T. Parenteral opioids for maternal pain relief in labour. *Cochrane Database Syst Rev*. 2010;(9):CD007396.
13. McCool WF, Packman J, Zwerling A. Obstetric anesthesia: changes and choices. *J Midwifery Womens Health*. 2004;49(6):505-513.
14. Riordan J, Gross A, Angeron J, Krumwiede B, Melin J. The effect of labor pain relief medication on neonatal suckling and breastfeeding duration. *J Hum Lact*. 2000;16(1):7-12.
15. Jacobson B, Nyberg K, Gronbladh L, Eklund G, Bygdeman M, Rydberg U. Opiate addiction in adult offspring through possible imprinting after obstetric treatment. *BMJ*. 1990;301(6760):1067-1070.
16. Nyberg K, Allebeck P, Eklund G, Jacobson B. Socio-economic versus obstetric risk factors for drug addiction in offspring. *Br J Addict*. 1992;87(12):1669-1676.
17. Nyberg K, Buka SL, Lipsitt LP. Perinatal medication as a potential risk factor for adult drug abuse in a North American cohort. *Epidemiology*. 2000;11(6):715-716.
18. Bricker L, Lavender T. Parenteral opioids for labor pain relief: a systematic review. *Am J Obstet Gynecol*. 2002;186(suppl Nature):S94-S109.
19. Caton D. "In the present state of our knowledge". Early use of opioids in obstetrics. *Anesthesiology*. 1995;82(3):779-784.
20. Way WL, Costley EC, Leongway E. Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clin Pharmacol Ther*. 1965;6:454-461.
21. Little DM, Tovell RM. The role of analgesia and anesthesia in the production of asphyxia neonatorum. *J Indiana State Medical Assoc*. 1949;42(3):201-210.
22. Prasertsawat P, Herabutya Y, Chaturachinda K. Obstetric analgesia: comparison between tramadol, morphine, and pethidine. *Curr Ther Res*. 1986;40(6):1022-1028.
23. Gerdin E, Salmonson T, Lindberg B, Rane A. Maternal kinetics of morphine during labour. *J Perinat Med*. 1990;18(6):479-487.
24. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. *J Pain Palliat Care Pharmacother*. 2002;16(4):5-18.
25. Kart T, Christrup L, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1-pharmacokinetics. *Paediatr Anaesth*. 1997;7(1):5-11.
26. Wittels B, Scott DT, Sinatra RS. Exogenous opioids in human breast milk and acute neonatal neurobehavior: a preliminary study. *Anesthesiology*. 1990;73(5):864-869.
27. Olofsson C, Ekblom A, Ekman-Ordeberg G, Granstrom L, Irestedt L. Lack of analgesic effect of systemically administered morphine or pethidine on labour pain. *Br J Obstet Gynaecol*. 1996;103(10):968-972.
28. Greulich B, Tarrant B. The latent phase of labor: diagnosis and management. *J Midwifery Womens Health*. 2007;52(3):190-198.
29. Friedman EA. *Labor: Clinical evaluation and management*. 2nd ed. New York: Appleton-Century-Crofts; 1978.
30. Aly EE, Shilling RS. Are we willing to change? *Anaesthesia*. 2000;55(5):419-420.
31. Soontrapa S, Somboonporn W, Komwilaisak R, Sookpanya S. Effectiveness of intravenous meperidine for pain relief in the first stage of labour. *J Med Assoc Thailand*. 2002;85(11):1169-1175.
32. Tsui MH, Ngan Kee WD, Ng F, Lau TK. A double blinded randomised placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. *BJOG*. 2004;111(7):648-655.

33.Rayburn WF, Smith CV, Parriott JE, Woods RE. Randomized comparison of meperidine and fentanyl during labor. *Obstet Gynecol*. 1989;74(4):604-606.
34.Nelson KE, Eisenach JC. Intravenous butorphanol, meperidine, and their combination relieve pain and distress in women in labor. *Anesthesiology*. 2005;102(5):1008-1013.
35.Wilson CM, McClean E, Moore J, Dundee JW. A double-blind comparison of intramuscular pethidine and nalbuphine in labour. *Anaesthesia.* 1986;41(12):1207-1213.
36.Hodgkinson R, Huff RW, Hayashi RH, Husain FJ. Double-blind comparison of maternal analgesia and neonatal neurobehaviour following intravenous butorphanol and meperidine. *J Int Med Res*. 1979;7(3):224-230.
37.Belfrage P, Borus LO, Hartvig P, Irestedt L, Raabe N. Neonatal depression after obstetrical analgesia with pethidine: the role of the injection-delivery time interval and of the plasma concentrations of pethidine and norpethidine. *Acta Obstet Gynecol Scand*. 1981;60(1):43-49.
38.Kuhnert BR, Kuhnert PM, Philipson EH, Syracuse CD. Disposition of meperidine and normeperidine following multiple doses during labor. II. Fetus and neonate. *Am J Obstet Gynecol*. 1985;151(3):410-415.
39.Kuhnert BR, Philipson EH, Kuhnert PM, Syracuse CD. Disposition of meperidine and normeperidine following multiple doses during labor. I. Mother. *Am J Obstet Gynecol.* 1985;151(3):406-409.
40.Sosa CG, Balaguer E, Alonso JG, Panizza R, Laborde A, Berrondo C. Meperidine for dystocia during the first stage of labor: a randomized controlled trial. *Am J Obstet Gynecol*. 2004;191(4):1212-1218.
41.Blair JM, Dobson GT, Hill DA, McCracken GR, Fee JP. Patient controlled analgesia for labour: a comparison of remifentanil with pethidine. *Anaesthesia.* 2005;60(1):22-27.
42.Douma MR, Verwey RA, Kam-Endtz CE, Van Der Linden PD, Stienstra R. Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour. *Br J Anaesth.* 2010;104(2):209-215.
43.Wittels B, Glosten B, Faure EA, et al. Postcesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia: neurobehavioral outcomes among nursing neonates. *Anesth Analg*. 1997;85(3):600-606.
44.Nissen E, Widstrm AM, Lilja G, et al. Effects of routinely given pethidine during labour on infants' developing breastfeeding behaviour: effects of dose-delivery time interval and various concentrations of pethidine/norpethidine in cord plasma. *Acta Pædiatrica.* 1997;86(2):201-208.
45.Rayburn W, Rathke A, Leuschen MP, Chleborad J, Weidner W. Fentanyl citrate analgesia during labor. *Am J Obstet Gynecol*. 1989;161(1):202-206.
46.Steer PL, Biddle CJ, Marley WS, Lantz RK, Sulik PL. Concentration of fentanyl in colostrum after an analgesic dose. *Can J Anesth*. 1992;39(3):231-235.
47.Wang H, Li EY, Xu GW, Wang CS, Gong YL, Li P. Intravenous fentanyl is exhaled and the concentration fluctuates with time. *J Int Med Res*. 2009;37(4):1158-1166.
48.Craft JB, Coaldrake LA, Bolan JC, et al. Placental passage and uterine effects of fentanyl. *Anesth Analg*. 1983;62(10):894-898.
49.Smith CV, Rayburn WF, Allen, KV Bane TM, Livezey GT. Influence of intravenous fentanyl on fetal biophysical parameters during labor. *J Matern Fetal Med*. 1996;5(2):89-92.
50.Atkinson BD, Truitt LJ, Rayburn WF, Turnbull GL, Christensen HD, Wlodaver A. Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *Am J Obstet Gynecol.* 1994;171(4):993-998.
51.Rayburn WF, Smith CV, Leuschen MP, Hoffman KA, Flores CS. Comparison of patient-controlled and nurse-administered analgesia using intravenous fentanyl during labor. *Anesthesiol Rev*. 1991;18(1):31-36.
52.Nikkola EM, Ekblad U, Kero PO, Alihanka JJ, Salonen MA. Intravenous fentanyl PCA during labour. *Can J Anesth*. 1997;44(12):1248-1255.
53.Halpern SH, Muir H, Breen TW, et al. A multicenter randomized controlled trial comparing patient-controlled epidural with intravenous analgesia for pain relief in labor. *Anesth Analg*. 2004;99(5):1532-1538.
54.Leuschen MP, Wolf LJ, Rayburn WF. Fentanyl excretion in breast milk. *Clin Pharm*. 1990;9(5):336-337.
55.Landau R, Kern C, Columb MO, Smiley RM, Blouin JL. Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain*. 2008;139(1):5-14.
56.Kan RE, Hughes SC, Rosen MA, et al. Intravenous remifentanil: placental transfer, maternal and neonatal effects. *Anesthesiology*. 1998;88(6):1467-1474.
57.Volmanen P, Sarvela J, Akural EI, Raudaskoski T, Korttila K, Alahuhta S. Intravenous remifentanil vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. *Acta Anaesthesiol Scand*. 2008;52(2):249-255.
58.Volikas I, Butwick A, Wilkinson C, Pleming A, Nicholson G. Maternal and neonatal side-effects of remifentanil patient-controlled analgesia in labour. *Br J Anaesth*. 2005;95(4):504-509.
59.Volmanen P, Akural EI, Raudaskoski T, Alahuhta S. Remifentanil in obstetric analgesia: a dose-finding study. *Anesth Analg*. 2002;94(4):913-917.
60.Thurlow JA, Laxton CH, Dick A, Waterhouse P, Sherman L, Goodman NW. Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour. *Br J Anaesth*. 2002;88(3):374-378.
61.Volmanen P, Akural E, Raudaskoski T, Ohtonen P, Alahuhta S. Comparison of remifentanil and nitrous oxide in labour analgesia. *Acta Anaesthesiol Scand*. 2005;49(4):453-458.
62.Balki M, Kasodekar S, Dhumne S, Bernstein P, Carvalho JC. Remifentanil patient-controlled analgesia for labour: optimizing drug delivery regimens. *Can J Anesth*. 2007;54(8):626-633.
63.Evron S, Glezerman M, Sadan O, Boaz M, Ezri T. Remifentanil: a novel systemic analgesic for labor pain. *Anesth Analg*. 2005;100(1):233-238.
64.Hinova A, Fernando R. Systemic remifentanil for labor analgesia. *Anesth Analg*. 2009;109(6):1925-1929.
65.Hatjis C, Meis P. Sinusoidal fetal heart rate pattern associated with butorphanol administration. *Obstet Gynecol*. 1986;67:377-380.
66.Maduska AL, Hajghassemali M. A double-blind comparison of butorphanol and meperidine in labour: maternal pain relief and effect on the newborn. *Can Anaesth Soc J.* 1978;25(5):398-404.
67.Quilligan EJ, Keegan KA, Donahue MJ. Double-blind comparison of intravenously injected butorphanol and meperidine in parturients. *Int J Gynecol Obstet*. 1980;18(5):363-367.
68.Riordan J, Gross A, Angeron J, Krumwiede B, Melin J. The effect of labor pain relief medications on neonatal suckling and breastfeeding duration. *J Hum Lact*. 2000;16(1):7-12.
69.Gutstein H, Akil, H. Opioid analgesics. In: Brunton L, Lazo J, Parker K, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. McGraw-Hill; 2006:547-590.
70.Giannina G, Guzman ER, Lai YL, Lake MF, Cernadas M, Vintzileos AM. Comparison of the effects of meperidine and nalbuphine on intrapartum fetal heart rate tracings. *Obstet Gynecol*. 1995;86(3):441-445.
71.Nicolle E, Devillier P, Delanoy B, Durand C, Bessard. Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. *Eur J Clin Pharmacol*. 1996;49(6):485-489.
72.Feinstein SJ, Lodeiro JG, Vintzileos AM, Campbell WA, Montgomery JT, Nochimson DJ . Sinusoidal fetal heart rate pattern after administration of nalbuphine hydrochloride: a case report. *Am J Obstet Gynecol.* 1986;154(1):159-160.

73.Dan U, Rabinovici Y, Barkai G, Modan M, Etchin A, Mashiach S. Intravenous pethidine and nalbuphine during labor: a prospective double-blind comparative study. *Gynecol Obstet Invest*. 1991;32(1):39-43.
74.Frank M, McAteer EJ, Cattermole R, Loughnan B, Stafford LB, Hitchcock AM. Nalbuphine for obstetric analgesia: a comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA). *Anaesthesia*. 1987;42(7):697-703.
75.American College of Obstetricians and Gynecologists. Obstetric analgesia and anesthesia. ACOG practice bulletin. Number 36. *Obstet Gynecol*. 2002;100:177-191.
76.Baumann T. Pain management. In: DiPiro J, Talbert R, Yee G, et al. eds. *Pharmacotherapy: A Pathophysiologic Approach*, 6th ed. New York: McGraw-Hill; 2005:1089-1104.

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