Pain Management in the Critically Ill Child

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Abstract. Children frequently received no treatment, or inadequate treatment, for pain and for painful procedures. The newborn and critically ill children are especially vulnerable to no treatment or under-treatment. Nerve pathways essential for the transmission and perception of pain are present and functioning by 24 weeks of gestation. The failure to provide analgesia for pain results in rewiring the nerve pathways responsible for pain transmission in the dorsal horn of the spinal cord and results in increased pain perception for future painful results. Many children would withdraw or deny their pain in an attempt to avoid yet another terrifying and painful experiences, such as the intramuscular injections. Societal fears of opioid addiction and lack of advocacy are also causal factors in the under-treatment of pediatric pain. False beliefs about addictions and proper use of acetaminophen and other analgesics resulted in the failure to provide analgesia to children. All children even the newborn and critically ill require analgesia for pain and painful procedures. Unbelieved pain interferes with sleep, leads to fatigue and a sense of helplessness, and may result in increased morbidity or mortality. **[Indian J Pediatr 2001; 68 (8) : 749-769]**

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The treatment and alleviation of pain is a basic human right that exists regardless of age.[1-4] Unfortunately, even when their pain is obvious, children frequently receive no treatment, or inadequate treatment, for pain and for painful procedures.[5] The newborn and critically ill child are especially vulnerable to no treatment or under-treatment.[6-10] The conventional "wisdom" that children neither respond to, nor remember, painful experiences to the same degree that adults do is simply untrue.[11,12] Indeed, all of the nerve pathways essential for the transmission and perception of pain are present and functioning by 24 weeks of gestation.[13] Recent research in newborn animals has revealed that the failure to provide analgesia for pain results in "rewiring" the nerve pathways responsible for pain transmission in the dorsal horn of the spinal cord and results in increased pain perception for *future* painful insults.[12-17] This confirms human newborn research in which the failure to provide anesthesia or analgesia for newborn circumcision resulted not only in short term physiologic perturbations but also in longer term behavioral changes, particularly during immunization.[18]

Vague physician orders contribute to the under-treatment of pain as well. The most common prescription order for potent analgesics, "to give as needed" (*pro re nata*, "PRN"), has come to mean "to give as infrequently as possible". The "PRN" order also means that either the patient must know or remember to ask for pain medication or the nurse must identify when a patient is in pain. Neither of these requirements may be met by children in pain. Children less than 3 years of age or critically ill children may be unable to adequately verbalize when or where they hurt. Alternatively, they may be afraid to report their pain. Many children will withdraw or deny their pain in an attempt to avoid yet another terrifying and painful experience-the intramuscular injection or "shot". Finally, several studies have documented the inability of nurses, physicians, and parents to correctly identify and treat pain even in post-operative pediatric patients.[19-22]

Unfortunately, even when physicians decide to treat children in pain, they rarely prescribe potent analgesics or adequate doses because of their overriding concern that children may be harmed by the use of these drugs. This is not at all surprising because physicians are taught throughout their training that potent analgesics cause respiratory depression, cardiovascular collapse, depressed levels of consciousness, vomiting, and with repeated use, addiction. Rarely, if ever, are the appropriate therapeutic uses of these drugs, or rational dosing regimens, discussed. This reluctance by health-care providers to "overmedicate" often leaves patients

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with periods of inadequate pain control.

Societal fears of opioid addiction and lack of advocacy are also causal factors in the under-treatment of pediatric pain. Unlike adult patients, pain management in children is often dependent on the ability of parents to recognize and assess pain and on their decision to treat or not treat it.[21-25] Parental misconceptions concerning pain assessment and pain management may therefore result in inadequate pain treatment.[24,26] This is particularly true in patients who are too young or too developmentally handicapped to self report their pain. Even in hospitalized patients, most of the pain that children experience is managed by the patient's parents. Parents may fail to report pain either because they are unable to assess it, or are afraid of the consequences of pain therapy. In one study, false beliefs about addiction and the proper use of acetaminophen and other analgesics resulted in the failure to provide analgesia to children.[27] In another, the belief that pain was useful or that repeated doses of analgesics lead to medication not working well resulted in the failure of the parents to provide or ask for prescribed analgesics to treat their children's pain.[22] Parental education is therefore essential if children are to be adequately treated for pain. Unfortunately, the ability to properly educate parents about this issue is often limited by insufficient resources, time, and personnel.

Fortunately, the past ten years have seen an explosion in research and interest in pediatric pain management and over the past 5 years there has been an increase in the development of pediatric pain services, primarily under the direction of pediatric anesthesiologists.[28] The pain service teams provide the pain management for acute, post-operative, terminal, neuropathic and chronic pain. This chapter tries to consolidate in a comprehensive manner some of the recent advances in pain management in an attempt to provide a better understanding of how to manage pain in the critically ill child.

PAIN ASSESSMENT

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[29] Pain is a subjective experience; operationally, it can be defined as "what the patient says hurts" and exists "when the patient says it does". Infants, pre-verbal children, and children between the ages of 2 and 7 (Piaget's "pre-operational thought stage") may be unable to describe their pain or their subjective experiences. This has led many to conclude incorrectly that children don't experience pain in the same way that adults do. Clearly, children do not have to know (or be able to express) the meaning of an experience in order to have the experience.[30,31] On the other hand, because pain is essentially a subjective experience, it is becoming increasingly clear that the child's perspective of pain is an indispensable facet of pediatric pain management and an essential element in the specialized study of childhood pain. Indeed, pain assessment and management are inter-dependent and one is essentially useless without the other. The goal of pain assessment is to provide accurate data about the location and intensity of pain, as well as the effectiveness of measures used to alleviate or abolish it.

Instruments currently exist to measure and assess pain in children of all ages.[32,35] The sensitivity and specificity of these instruments has been widely debated and has resulted in a plethora of studies to validate their reliability and validity. The most commonly used instruments measure the quality and intensity of pain and are "self-report measures" that make use of pictures or word descriptors to describe pain.[36,37] Pain intensity or severity can be measured in children as young as 3 years of age by using either the Oucher scale (developed by Dr. Judy Beyer), a two part scale with a vertical numerical scale (0-100) on one side and six photographs of a young child on the other, or a visual analogue scale, or a 10 cm line with a smiling face on one end and a distraught, crying face on the other.[32,38] In fact, this scale has been validated even by sex and race. In our practice we use the 6 face pain-scale developed by Dr. Donna Wong primarily because of its simplicity (Fig. 1).[33] This scale is attached to the vital sign record and nurses are instructed to use it or a more age-appropriate self-report measure whenever vital signs are taken. Alternatively, color, word-graphic rating scales, and poker chips have been used to assess the intensity of pain in children as well. In infants and newborns, pain has been assessed by measuring physiologic responses to a nociceptive stimulus, such as blood pressure and heart rate changes (Observational Pain Scale or "OPS") or by measuring levels of adrenal stress hormones.[39-42] Alternatively, behavioral approaches have utilized facial expression, body movements, and the intensity and quality of crying as indices of response to nociceptive stimuli.[39,43,44] Finally, it is important to accurately define the location of pain as well. This is readily accomplished by using either dolls or action figures or by using drawings of body outlines, both front and back.

PAIN MANAGEMENT

Physiologic Changes Affecting Pharmacokinetics in the Critically Ill Patient

Unfortunately , very few studies have evaluated the pharmacokinetic and pharmacodynamic properties of drugs in critically ill patients. Most pharmacokinetic studies are performed using healthy adult volunteers, adult patients who are only minimally ill, or adult patients in a stable phase of a chronic disease. These data are then extrapolated to infants, children, adolescents, and to both adult and pediatric critically ill patients. So little pharmacokinetic and pharmacodynamic testing has been performed in children that they are often considered "therapeutic orphans".[45] Indeed, to help remedy this situation, the United States Food and Drug Administration has mandated pediatric pharmacokinetic and dynamic studies in all new drugs that enter the American marketplace.[46-48] Unfortunately, the critically ill will have no such future protection. Unstable patients often present significant hemodynamic alterations and organ dysfunction, which may significantly alter drug absorption, transport, metabolism and excretion of drugs. Studies performed in healthy patients may offer little insight into how these drugs perform in the critically ill.[49-52]

Absorption

Virtually all drugs used in current practice are delivered to their site of action by the blood. Pharmacodynamics describes the relationship between the concentration of drug at the site of action and the physiologic response. How drugs get into the blood and how much gets to the site of action is dependent on pharmacokinetics, that is the study of drug disposition in the body over time. Pharmacokinetics includes the route of administration, absorption, distribution, and elimination of drug molecules from the body over time.

In healthy patients, the enteral (oral and occasionally rectal) route of drug administration is most common and is the most widely studied. Enterally administered drugs must pass through the cells lining the mucosal surface of the gastrointestinal (GI) tract to enter the blood stream. Drainage of intestinal blood flow into the portal system presents the drug to the liver for metabolism before the drug can be distributed throughout the body. This leads to the first-pass effect seen with many oral drugs, that is, much of the absorbed drug is taken directly to the liver via the portal circulation and is rapidly metabolized and "lost" before it ever reaches the systemic circulation. Alteration of venous blood flow such that it bypasses the liver could result in significantly higher serum drug levels after oral absorption and lead to clinical sequelae. Absorption from the GI tract may be reduced in ICU patients for several reasons including altered GI motility and peristalsis (ileus, recent GI surgery), reduced gut function and absorptive surface area (pancreatitis, recent GI surgery), reduced GI blood flow (shock), and physical removal of drug by nasogastric suctioning. Because of this, enteral administration of drugs may not be possible in the critically ill patient. Additionally, oral dosage forms of some drugs may prevent their use in the critically ill patient, even when these other factors are not in play. For example, sustained release tablet preparations of opioids, such as Oxy-contin® and MS-contin® must be swallowed whole and can not be crushed or given via a naso-gastric tube. Obviously, young children and infants and the critically ill will not be able to do this. On the other hand, as a patient's condition improves overall, gut function also improves and the enteral route may be considered as a viable route of drug administration.

Parenteral (intravenous [IV], intramuscular [IM], and subcutaneous [SQ]) drug administration is most common in the critically ill. Intravenous administration deposits drug directly into the bloodstream and is therefore the preferred route of drug administration in the ICU. Intramuscular, transdermal, and SQ injections are rarely used in the critically ill because drug absorption from muscle or through skin or subcutaneous tissue may be decreased because of decreased tissue perfusion and decreased movement of drug through edematous tissue. However, as patients improve, the transdermal route (e.g., fentanyl, clonidine) may become useful, particularly when IV access become a severe problem.

Distribution

Distribution describes the transportation and movement of a drug throughout the body. Several factors associated with critical illness have the potential to affect the distribution of drugs in the body. Poor perfusion is often a factor that limits distribution of a drug to its target tissue. Altered receptor binding as a result of edema, malnutrition, uremic toxins, and down-regulation will also change the amount of drug attached to tissue. Many analgesic drugs are transported through the body attached to the serum proteins albumin and gamma globulin. The extent of protein binding varies considerably among analgesic drugs, from 7% for codeine to 93% for sufentanil.[53] The extent of protein binding may decrease in critical illness, causing elevated free levels of drug and possible toxicity. Additionally, third spacing of fluid may result in additional volume into which the drug can distribute.

Metabolism and Elimination

Metabolism is the physical and chemical alteration of drug molecules for the purposes of detoxifying parent

molecules and rendering fat-soluble chemicals more water-soluble. Drugs or their metabolites are then eliminated by the kidneys. Any disease that affects hepatic or renal function or causes hypoperfusion of the liver or kidneys may diminish metabolism and elimination of the drug, possibly resulting in drug accumulation and toxicity.[49,52,53] It is common for ICU patients to have some degree of either renal or hepatic function impairment. Furthermore, many critically ill children and newborns have diseases in which intra-abdominal pressure is significantly increased (necrotizing enterocolitis, severe ileus, recent GI surgery) which will impair both portal and renal blood flow.[54,55] In critically ill patients with organ dysfunction, the clinician must expect unpredictable metabolism and elimination of drugs and must monitor for therapeutic outcomes and possible adverse effects.

The liver is the major route for drug metabolism and detoxification for a wide variety of analgesic drugs. Analgesic drugs are lipid soluble compounds; this lipid solubility enhances their passage through the blood/brain barrier and also preselects the liver as the organ of elimination (because renal physiology requires drugs to be water soluble to be filtered and excreted). Some degree of hepatic dysfunction is present in many ICU patients and may result in reduced drug clearance because of decreased hepatocellular enzyme activity or reduced hepatic blood and/or bile flow. Most, but not all, drugs are metabolized in a 2 part process, the goal of which is to change fat soluble, active, unexcretable drugs into water soluble, inactive drugs that can be excreted in the bile or by the kidneys (Fig. 1). The first, or phase-I metabolism, commonly involves the P450 (CYP) system, which is a large family of hemoproteins involved in metabolism of drugs and in manufacture of steroids. Phase-I metabolism usually involves oxidation, hydroxylation, hydrolysis or reduction. Phase-I reactions are listed in Table 1.

Table 1. Enzymes Performing Phase-I Reactions

- P450 system
- Alcohol dehydrogenases
- Aldehyde dehydrogenases
- Amine oxidases
- Xanthine oxidases

Table 2. Commonly Used Mu-Agonist Drugs

Agonist	Dose	Duration (hr)	Bioavailability	Comments
Morphine	0.1	3 to 4	20 to 40	• Seizures in newborns; also in all patients at high doses Histamine release, vasodilation avoid in asthmatics and in circulatory compromise MS-contin® 8 to 12 h duration
Meperidine	1.0	3 to 4	40 to 60	• Catastrophic interactions with MAO inhibitors Tachycardia; negative inotrcpe Metabolite produces seizures; not recommended for chronic use
Methadone	0.1	6 to 24	70 to 100	• Can be given IV even though the package insert say SQ or IM
Fentanyl	0.001	0.5 to 1		Bradycardia; minimal hemodynamic alterations Chest wall rigidity (> 5 ug/kg rapid IV bolus), L naloxone or paralyze with succinylcholine or pancuronium Transdermal patch available for chronic pain, contra-indicated in acute pain
Codeine	1.2	3 to 4	40 to 70	• Oral route only Prescribe with acetaminophen
Hydromorphone (Dialaudid)	0.015 to 0.02	3 to 4	40 to 60	• < CNS depression than morphine < Itching, nausea than morphine can be used in IV and epidural PCA
Oxycodone (Component opioid in Tylox)	0.15	3 to 4	50	• A third less than morphine but with better oral bioavailability, it is often used when weaning from IV to oral medication Available as a continuous release preparation

The metabolites of these reactions may be less active or highly reactive and even toxic. The phase-I metabolite is then metabolized further by a phase-II enzyme that conjugates it with either a glucuronide, a sulphide group, an amino acid, or glutathione (Fig. 1). Some drugs are metabolized directly by phase-II enzymes (e.g., morphine). A third metabolic pathway is becoming increasingly important, namely metabolism by blood and tissue esterases. These enzymes are ubiquitous and are found in large supply in the blood and elsewhere. Drugs which are metabolized by esterases such as remifentanil are unlikely to be affected by disease.

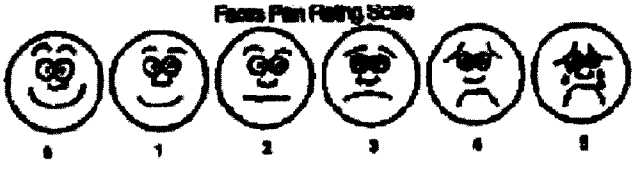

Fig. 1. FACES pain rating scale.[210]

Most pain and sedation medications used in the critically ill are metabolized by phase I or phase II reactions in the liver. In general, the metabolism of opioid analgesics is very effective and is limited more by blood flow to the liver than by the inherent ability of the hepatocyte enzymes. The cytochrome P-450 (CYP) micro-enzyme system is significantly altered in critical illness, decreasing phase I oxidative metabolism.[56-59] One of the P450 enzymes, cytochrome P450 2D6 is subject to genetic polymorphism and does not function in 10% of the population even in normal conditions. This enzyme metabolizes codeine to morphine. In patients who lack a functioning cytochrome P450 2D6, either genetically or because of liver disease, codeine will be a poor or ineffective analgesic.[60,61] In addition to the reduction in the CYP enzyme system, phase-II conjugation pathways such as glucuronidation may also be impaired in ICU patients, particularly if the liver is subjected to low blood flow, hypoxia, and/or stress. Chronic liver disease appears selectively to impair oxidative pathways while leaving glucuronidation intact.

The kidneys are responsible for clearing both the parent drug and metabolites produced by the liver. In renal failure both the parent drug and metabolites may accumulate and result in toxicity. Morphine is metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G does not have

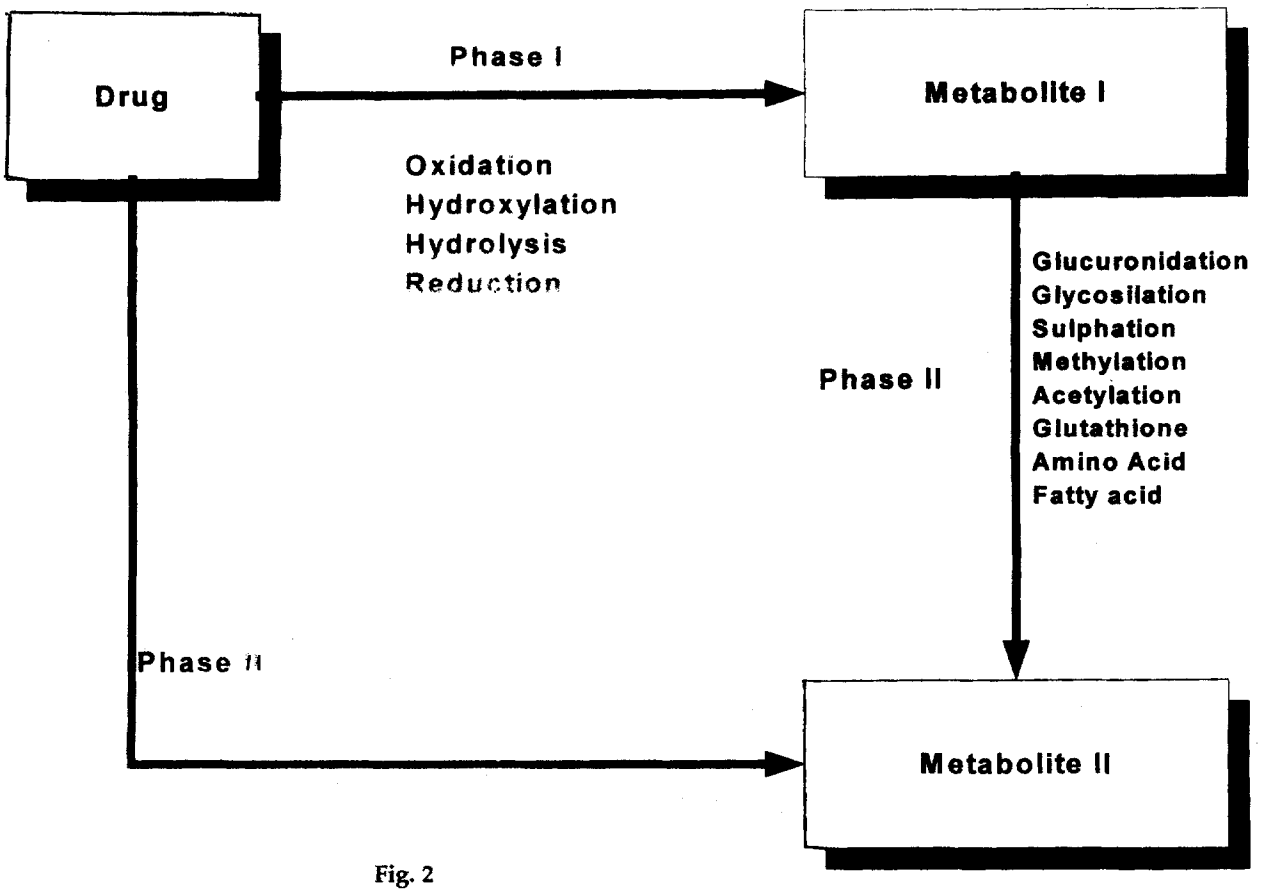

Fig. 2

analgesic activity, while M6G is an active metabolite eliminated by the kidneys. In renal failure M6G may accumulate and has been associated with toxicity.[62,63] Meperidine is also metabolized to a metabolite, normeperidine, which is renally cleared. In renal failure, normeperidine may accumulate and cause central nervous system excitability and possible seizures.

Propofol : Where Theory Collides with Reality

Propofol (Diprivan®), 2,6-diisopropylphenol, is an alkylphenol intravenous sedative general anesthetic widely used in the operating room and in adult ICUs.[64] It is unrelated to other general anesthetics and is formulated as a 1% (10 mg/mL) solution in 10% soybean oil, 2.25% glycerol, and 1.2% egg phosphatide. The lipid component is essentially identical to that used for parenteral nutrition (10% Intralipid®). The drug's rapid onset of action, its dose proportional sedative/anesthetic effects, and its rapid dissipation of clinical effects after discontinuing drug administration are responsible for its widespread acceptance as a general anesthetic, and for its potential use as a sedative to facilitate mechanical ventilation in critically ill patients in the ICU. Propofol, like barbiturates and other general anesthetics, appears to bind to the gamma-aminobutyric acid (GABA) receptor, namely, the A subunit (GABA-A), which potentiates GABA-mediated synaptic inhibition within the central nervous system.

The pharmacokinetics of propofol after bolus doses or following continuous infusions have been studied extensively in healthy children and adults.[64] The drug's disposition profile is best characterized by a three-compartment pharmacokinetic model.[65-67] After intravenous administration, propofol rapidly distributes from the central compartment (blood) into two additional compartments, a larger rapidly equilibrating compartment and an enormous, slowly equilibrating third compartment. Clearance from the central compartment is very rapid, exceeding total hepatic blood flow, and results in rapid recovery of consciousness. It is the rapid clearance from the central compartment rather than metabolism that is responsible for its short duration of effect. Propofol undergoes hepatic metabolism by conjugation and the resultant water soluble compounds are excreted in the kidney. Complete elimination from the body may take many hours or even days despite minimal blood concentrations.[64]

Unlike the operating room, in which propofol is given to relatively healthy patients for periods ranging from minutes to hours, patients in the intensive care unit are by definition critically ill and may receive propofol for days. Because of this, insignificant effects during anesthesia may become very important in the critically ill. Indeed, there have been many reports of unexpected fatal lactic acidosis in critically ill children being sedated with propofol.[68-71] Although this association has been disputed,[72,73] it underscores the importance and need for pharmacokinetic and dynamic studies in critically ill pediatric patients. There are studies which demonstrate uncoupling of oxidative phosphorylation in mitochondria and inhibition of cytochrome P450 in some studies.[74-77] Nevertheless, why propofol would produce lactic acidosis and liver dysfunction following prolonged use and how it can be prevented is unclear. Until these issues are resolved we recommend avoiding prolonged (>6 hour) propofol infusions in critically ill children.

Opioid Analgesics

Historically, opium and its derivatives (e.g. paregoric, morphine) were used for the treatment of diarrhea (dysentery) and pain. Indeed, the beneficial psychological and physiological effects of opium, as well as its toxicity and potential for abuse have been well known to physicians and the public for centuries.[78,79] On the other hand, many physicians through the ages have under-utilized opium when treating patients in pain because of their fear that their patients would be harmed by its use. In the present era, addiction is particularly feared. Opium's easy availability, despite every effort by the government to control it, has resulted in a scourge of addiction that has devastated large segments of our population. Until and unless we can separate opium's dark consequences (*yin*) from its benefits (*yang*), innumerable numbers of patients will suffer unnecessarily.

Opioid Receptors

Over the past twenty years multiple opioid receptors and subtypes have been identified and classified.[79-85] An understanding of the complex nature and organization of these multiple opioid receptors is essential for an adequate understanding of the response to, and control of, pain.[86] In the central nervous system there are four primary opioid receptor types, designated mu (μ) (for morphine), kappa (κ), delta (δ) and sigma (σ). Recently, the σ, κ, and * receptors have been cloned and have yielded invaluable information of receptor structure and function.[87-90]

The differentiation of agonists and antagonists is fundamental to pharmacology. A neurotransmitter is defined as having agonist activity, while a drug that

blocks the action of a neurotransmitter is an antagonist.[91-95] By definition, receptor recognition of an agonist is "translated" into other cellular alterations (that is, the agonist initiates a pharmacologic effect), whereas an antagonist occupies the receptor without initiating the transduction step (that is, it has no intrinsic activity or efficacy).[96] The intrinsic activity of a drug defines the ability of the drug-receptor complex to initiate a pharmacologic effect. Drugs that produce less than a maximal response have a lowered intrinsic activity and are called partial agonists. Partial agonists also have antagonistic properties, because by binding the receptor site, they block access of full agonists to the receptor site. Morphine and related opiates are μ agonists and drugs that block the effects of opiates at the μ receptor, such as naloxone, are designated antagonists.

The μ, *, and κ are distinct receptors but produce analgesia primarily by inhibiting synaptic transmission in the central nervous system and in the myenteric plexus. They are usually found on the presynaptic nerve terminal and decrease the release of excitatory neurotransmitters from terminals carrying nociceptive stimuli. As a result, neurons are hyperpolarized, which suppresses spontaneous discharge and evoked responses. These receptors are coupled to guanine nucleotide (GTP) binding regulatory proteins (G proteins) and regulate trans membrane signaling by regulating adenylate cyclase (cyclic AMP), various ion (K, Ca, Na) channels and transport proteins, and phospholipases C and A2 (diacylglycerol and inositol triphosphate activation of protein kinase C).[82-98]

Drug Selection

The opioids most commonly used in the management of pain are μ agonists. These include morphine, meperidine, methadone, codeine, oxycodone, and the fentanyls. Mixed agonist-antagonist drugs act as agonists or partial agonists at one receptor and antagonists at another receptor. Mixed (opioid) agonist-antagonist drugs include pentazocine (Talwin®), butorphanol (Stadol®), nalorphine, dezocine (Dalgan®) and nalbuphine (Nubain®). Most of these drugs are agonists or partial agonists at the 6 and μ receptors and antagonists or partial agonists at the μ receptor. Thus, these drugs will produce antinociception alone and will dose-dependently antagonize the effects of morphine.

Buprenorphine (Buprenex®) is considered a partial agonist at the *mu* and *kappa* receptors and may have a role in the prevention or treatment of patients who will or have become dependent on opioids.[99,100]

Opioid narcotic analgesics such as morphine, fentanyl, meperidine, and hydromorphone are extensively used in the intensive care unit for providing both analgesia and sedation. The partial agonists and mixed agonist-antagonist opioids such as pentazocine, butorphanol and buprenorphine are associated with a ceiling effect for analgesia, have a high incidence of psychotomimetic effects, and may induce acute opioid withdrawal in opioid-dependent patients. Therefore, they are not usually useful agents in the ICU setting. Butorphanol, however, does have a transnasal formulation which may be of benefit in patients with limited IV access; its onset of activity is comparable to the parenteral formulation.

Pharmacodynamic effects of all the pure opioid agonists are similar and include analgesia, respiratory depression, stimulation of the chemoreceptor trigger zone, tolerance, and physical dependence. While the opioids may cause some sedation, they are usually not amnestic agents, and they require the addition of other anxiolytic medications such as benzodiazepines or propofol in most patients.

Pain relief with opioids occurs when a minimum effective analgesic concentration (MEAC) in the serum is achieved. Serum concentrations are used as a surrogate for central nervous system (CNS) concentrations. Clinicians attempt to maintain analgesic drug concentrations above the MEAC without considerably exceeding it, utilizing various administration techniques and with an understanding of pharmacokinetic and pharmacodynamic principles. The MEAC differs among patients and also varies from day to day in the same patient. With both altered pharmacokinetic parameters and a changing MEAC in critically ill pediatric patients, achieving adequate analgesia requires close monitoring and careful patient assessment. Use of incremental doses and infusions carefully titrated to patient response is critical for achieving adequate analgesia in the ICU. Physical dependence, sometimes referred to as "neuroadaptation", is caused by repeated administration of an opioid which necessitates the continued administration of the drug to prevent the appearance of a withdrawal or abstinence syndrome that is characteristic for that particular drug. It usually occurs after 2-3 weeks of morphine administration, but may occur after only just a few days of therapy. Very young infants treated with very high dose fentanyl infusions following surgical repair of congenital heart disease and/or who required extra-corporeal membrane oxygenation (ECMO) have been identified to be at particular risk.[101-104] Several studies have suggested that the intrinsic efficacy of an opioid analgesic can determine, in part, the degree of tolerance to that agent. Specifically, animal and human studies have demonstrated that the tolerance that

develops to equi-effective doses of opioid analgesics with high intrinsic efficacy is less than the tolerance that develops to lower-intrinsic-efficacy compounds.[105,106] Additionally, these effects occur more rapidly after continuous infusion compared to intermittent dosing.[107]

The pharmacological effects of the opioid drugs are generally similar among drugs. The major differences are in their pharmacokinetic, pharmacodynamic, and physiochemical properties, all of which may affect the latency, potency, and duration of analgesic action. In many classes of drugs, drug selection is based on pharmacokinetic parameters such as half-life. With the opioids, the terminal or beta phase half-life alone is not an appropriate measure for drug selection, because the onset and duration of effect with a single dose may have more to do with distribution and redistribution of the drug into and out of the brain than with elimination half-life. Opioid distribution into the brain is based partially on the lipid solubility of the drug. The more lipid-soluble the drug, the faster its penetration into the brain and the quicker the response. Fentanyl, for example, a very lipid-soluble drug, has a rapid onset and short duration of action following a single bolus dose because of the rapid redistribution of drug out of the brain, not because of a short elimination half-life. Continuous long-term opioid administration may be associated with the accumulation of the drug in fat tissue. As a result, duration of action may be affected more by the redistribution of drug out of fat tissue than by the elimination half-life. An understanding of the pharmacokinetic, pharmacodynamic, and physiochemical properties of each opioid is important, as each drug has unique characteristics.

Morphine

Morphine (from Morpheus, the Greek God of Sleep) is the gold standard for analgesia against which all other opioids are compared. When small doses, 0.1 mg.kg-1 (iv, im), are administered to otherwise unmedicated patients in pain, analgesia usually occurs without loss of consciousness. The relief of tension, anxiety and pain usually results in drowsiness and sleep as well. Older patients suffering from discomfort and pain usually develop a sense of well being and/or euphoria following morphine administration. Interestingly, when morphine is given to pain-free adults they may show the opposite effect, namely, dysphoria and increased fear and anxiety. Mental clouding, drowsiness, lethargy, an inability to concentrate and sleep may occur following morphine administration even in the absence of pain. Less advantageous central nervous system effects of morphine include nausea and vomiting, pruritus, especially around the nose, miosis, and at high doses, seizures.[108] Seizures are a particular problem in the newborn because they may occur at commonly prescribed doses (0.1 mg/kg)[109-112]

Although morphine produces peripheral vasodilation and venous pooling it has minimal hemodynamic effects (e.g., cardiac output, left ventricular stroke work index, pulmonary artery pressure, etc.) in normal, euvolemic, supine patients. The vasodilation associated with morphine is primarily due to its histamine releasing effects. The magnitude of morphine induced histamine release can be minimized by limiting the rate of morphine infusion to 0.025-0.05 mg/kg/min, by keeping the patient in a supine to a slightly head down (Trendelenburg) position, and by optimizing intravascular volume. Significant hypotension may occur if sedatives such as diazepam are concurrently administered with morphine or if a patient suddenly changes from a supine to a standing position. Otherwise, it produces virtually no cardiovascular effects when used alone. It will cause significant hypotension in hypovolemic patients and its use in trauma patients is therefore limited.

Morphine (and all other narcotics at equipotent doses) produces a dose dependent depression of ventilation primarily by reducing the sensitivity of the brainstem respiratory centers to hypercarbia and hypoxia. Opioid agonists also interfere with pontine and medullary ventilatory centers that regulate the rhythm of breathing. This results in to prolonged pauses between breaths and to periodic breathing patterns. This explains the classic clinical picture of opioid induced respiratory depression. Initially respiratory rate is affected more than tidal volume, but as the dose of morphine is increased tidal volume becomes affected as well. Increasing the dose further results in apnea. Morphine also depresses the cough reflex by a direct effect on the cough center in the medulla and is not related to its effects on ventilation. It also depresses the sense of air hunger that occurs when arterial carbon dioxide levels rise. This explains morphine's use as a sedative in terminally ill patients and in critically ill patients who are "fighting the ventilator".

Morphine (and all other narcotics at equipotent doses) inhibits intestinal smooth muscle motility. This decrease in peristalsis of the small and large intestine and increase in tone of the pyloric sphincter, ileocecal valve, and anal sphincter explains the historic use of opioids in the treatment of diarrhea as well as its "side-effect" when treating chronic pain, namely, constipation. Indeed, the use of opium to treat dysentery (diarrhea) preceded its use in western

medicine for analgesia. The gastrointestinal tract is very sensitive to opioids even at low doses. In the rat, 4 times more morphine is needed to produce analgesia than is needed to slow GI motility.[113] Opioids affect the bowel centrally and by direct action on gut mu and delta opioid receptor sites. In fact, loperamide, an opioid receptor agonist with limited ability to cross the blood brain barrier is used clinically to treat diarrhea suggesting that direct, local gut action is present in the opioid-constipating effect in diarrhea. Tolerance to the constipating effects of morphine is minimal. Because of this, we routinely prescribe laxatives or stool softeners for patients expected to be treated with morphine (and all other opioids) for more than two or three days. Alternatively, naloxone a non-selective opioid antagonist can prevent or treat opioid induced constipation. Unfortunately it also antagonizes opioid induced analgesia. Yuan *et al* in a series of experiments have demonstrated that methylnaltrexone, a quaternary derivative of naltrexone, can selectively block the peripheral effects of opioids (constipation) without affecting analgesia.[114] This drug which is in the early stages of development may be useful for other opioid induced side effects such as pruritus.[115]

Morphine will potentiate biliary colic by causing spasm of the sphincter of Odi and should be used with caution in patients with, or at risk for, cholelithiasis (e.g. sickle cell disease). This effect is antagonized by naloxone and glucagon (2 mg IV in adult patients). Biliary colic can be avoided by using mixed agonist-antagonist opioids such as pentazocine. Whether other pure μ agonists such as meperidine or fentanyl produce less biliary spasm than morphine is disputed in the literature. Some studies show that meperidine produces less biliary spasm than morphine and others show that at equi-analgesic doses they produce virtually identical increases in common bile duct pressure.

The nausea and vomiting that are seen with morphine administration is due to stimulation of the chemo-receptor trigger zone in the brainstem.[116] This may reflect the role of opioids as partial dopamine agonists at dopamine receptors in the chemoreceptor trigger zone and the use of dopamine antagonists such droperidol, a butyrophenone, or chlorpromazine, a phenothiazine, in the treatment of opioid induced nausea and vomiting. Morphine increases tone and contractions in the ureters, bladder, and in the detrusor muscles of the bladder which may make urination difficult. This may also explain the increased occurrence of bladder spasm and pain that occur when morphine is used to treat post-operative bladder surgery patients.

Regardless of its route of administration, morphine (and fentanyl) commonly produce pruritus that can at times be maddening and impossible to treat. Indeed, some patients refuse opioid analgesics because they would rather hurt than itch. Opioid-induced itching is caused either by the release of histamine and histamine's effects on the peripheral nociceptors or via central mu receptor activity.[117,118] Traditional antihistamines such as diphenhydramine and hydroxyzine are commonly used to treat this side effect. Additionally, there is an increasing use of low dose mu antagonists (naloxone and nalmefene) and mixed agonist antagonists (butorphanol) in the treatment of opioid induced pruritus.[119,120-12] Interestingly, these latter agents may also be effective for non-opioid induced pruritus such as the itching that accompanies end stage liver and kidney disease.[122]

There is now a considerable body of literature which demonstrates a modulatory function of the immune system by opioids. This modulation takes the form of an alteration in the biochemical and proliferative properties of the various cellular components of the immune system.[123] Vertebrates and invertebrates have been shown to possess a peptide which is a proenkephalin and has a strong antibacterial action. This peptide is called enkelytin (proenkephalin-A) and there is a strong sequence homology between invertebrate and mammalian enkelytin.[124-125] It has been suggested that immune or neural signaling leads to enhanced proenkephalin proteolytic cleaving thereby causing the release of both opioid peptides and enkelytin simultaneously. This scenario would allow a two-pronged attack. Opioid peptides would modulate neutrophil chemotaxis, phagocytic activity and the secretion of cytokines, while the simultaneously liberated enkelytin would exert an antibacterial action.

Moreover, inflammatory mediators have been shown to modify the release of opioid peptides from immune system cells and also from cells of the peripheral and central nervous system. The potential effects of exogenously administered opioids on the immune system cannot be ignored. Opioids released from cells of the immune system may modulate release of cytokines from the same and other cells of the immune system.[126] Additionally, it has been suggested that T lymphocytes may act as a vector to deliver b-endorphin to inflamed tissues. The significance of this hypothesis is that it would allow the potential for highly specific opioid control of peripheral analgesia by targeted delivery of b-endorphin directly to sites of inflammation. This would maximize the potential analgesic and anti-inflammatory effects of endogenous opioids acting at peripheral receptors and also by inhibiting the release of the inflammatory peptide substance P from primary afferent neurones.[127,128] On

the other hand, chronic morphine treatment is a mechanism used in laboratory experiments to render mice immunocompromised and parenteral drug abuse is a significant risk factor for contracting human immunodeficiency virus type I (HIV-1).[129,130] Furthermore, gamma interferon-stimulated natural killer cell cytotoxicity is significantly suppressed after short-term exposure to morphine in humans.[131]

Morphine can be administered in the critically ill patient using the IV, oral, IM, epidural, intrathecal, and rectal routes, for both analgesia and sedation. It is a moderately potent opioid, and is commonly administered intravenously in doses of 0.1 mg/kg. Obviously, this dose must be modified based on patient age and disease state. Indeed, in order to minimize the complications associated with intravenous morphine (or any opioid) administration, we always recommend titration of the dose at the bedside until the desired level of analgesia is achieved. When administered by the oral route, morphine has an oral dose ratio of approximately 1 : 3 (0.1 mg/kg IV morphine = 0.3 mg/kg PO morphine). This ratio reflects the high first-pass effect rather than the extent of absorption which is nearly 100%. In healthy children the terminal elimination half life (t ½) is 2 to 3 hours. Peak effect occurs within 20 minutes with a duration of action of 2 to 7 hours following IV administration. Compared to fentanyl, morphine is less lipid soluble, so it has a slower onset of action and a longer duration. Due to its lower lipid solubility, it also has a smaller volume of distribution than fentanyl. In adults, morphine has a serum MEAC of approximately 10 to 50 mug/L.

The liver is the major site of biotransformation for most opioids. The major metabolic pathway for most opioids is oxidation. The exceptions are morphine and buprenorphine, which primarily undergo glucuronidation, and remifentanil, which is cleared by ester hydrolysis.[132-134] Many of these reactions are catalyzed in the liver by microsomal mixed-function oxidases that require the cytochrome P450 system, NADPH, and oxygen. The cytochrome P450 system is very immature at birth and does not reach adult levels until the first month or two of life.[135,136] This immaturity of this hepatic enzyme system may explain the prolonged clearance or elimination of some opioids in the first few days to weeks of life. On the other hand, the P450 system can be induced by various drugs (phenobarbital) and substrates and matures regardless of gestational age. Thus, it may be the age from birth, and not the duration of gestation, that determines how premature and full term infants metabolize drugs. Indeed, Greeley *et al* have demonstrated that sufentanil is more rapidly metabolized and eliminated in 2-3 week old infants than newborns less than a week of age.[137]

Morphine is primarily glucuronidated into 2 forms, an inactive form, morphine-3-glucuronide and an active form, morphine-6-glucuronide. Both glucuronides are excreted by the kidney. In patients with renal failure or with reduced glomerular filtration rates (e.g., neonates), the morphine 6-glucuronide can accumulate and cause toxic side-effects including respiratory depression. This is important to consider not only when prescribing morphine but when administering other opioids that are metabolized into morphine such as methadone and codeine.

The pharmacokinetics of opioids in patients with liver disease and in critically ill patients requires special attention. Many disease states common in ICU patients may alter the metabolism and elimination of morphine. Severe cirrhosis, septic shock, and renal failure decrease the clearance of morphine and its metabolites, resulting in prolonged duration and possible toxicity. Oxidation of opioids is reduced in patients with hepatic cirrhosis, resulting in decreased drug clearance (meperidine, dextropropoxyphene, pentazocine, tramadol and alfentanil) and/or increased oral bioavailability caused by a reduced first-pass metabolism (meperidine, pentazocine and dihydrocodeine). Although glucuronidation is thought to be less affected in liver cirrhosis, the clearance of morphine is decreased and oral bioavailability increased. The consequence of reduced drug metabolism is the risk of accumulation in the body, especially with repeated administration. Lower doses or longer administration intervals should be used to minimize this risk. Meperidine poses a special concern because it is metabolized into normeperidine, a toxic metabolite which causes seizures and accumulates in liver disease.[138,139] On the other hand, drugs which are inactive but are metabolized in the liver into active forms such as codeine may be ineffective in patients with liver disease. Finally, the disposition of a few opioids, such as fentanyl, sufentanil and remifentanil, appears to be unaffected in liver disease and are the drugs we use preferentially in managing pain in patients with liver disease.[140]

The pharmacokinetics of morphine have been extensively studied in adults, older children, and in the premature and full term newborn.[110-144] Following an intravenous bolus, 30% of morphine is protein bound in the adult versus only 20% in the newborn. This increase in unbound ("free") morphine allows a greater proportion of active drug to penetrate the brain. This may explain, in part, the observation of Way *et al* of increased brain levels of morphine in the newborn and its more profound respiratory depressant

effects.[145,146] The elimination half life of morphine in adults and older children is 3-4 hours and is consistent with its duration of analgesic action. The t½∃ is more than twice as long in newborns less than a week of age than older children and adults and is even longer in premature infants and children requiring pressor support.[104-148] Clearance is similarly decreased in the newborn compared to the older child and adult. Thus, infants less than one month of age will attain higher serum levels that will decline more slowly than older children and adults. This may also account for the increased respiratory depression associated with morphine in this age group.[149]

Interestingly, the half life of elimination and clearance of morphine in children older than one to two months of age is similar to adult values. Thus the hesitancy in prescribing and administering morphine in children less than 1 year of age may not be warranted. On the other hand, the use of any opioid in children less than 2 months of age, particularly those born prematurely must be limited to a monitored, intensive care unit setting not only because of pharmacokinetic and dynamic reasons but because of immature ventilatory responses to hypoxemia, hypercarbia, and airway obstruction in the neonate.[150-153]

Morphine Dosing

As stated previously, the "unit" dose of intravenously administered morphine is 0.1 mg/kg. However this is an average dose and is modified based on patient age and disease state. Indeed, in order to minimize the complications associated with intravenous morphine (or any opioid) administration, we always recommend titration of the dose at the bedside until the desired level of analgesia is achieved. Based on its relatively short half life (3-4 h), one would expect older children and adults to require morphine supplementation every two to three hours when being treated for pain, particularly if the morphine is administered intravenously.[154,155] This has led to the recent use of continuous infusion regimens of morphine (0.02-0.03 mg/kg/hr) and patient controlled analgesia (see below) which maximize pain-free periods.[156-161] Alternatively longer acting agonists such as methadone (see below) may be used.[162-166]

FENTANYL(S)

Because of its rapid onset (usually less than 1 minute) and brief duration of action (30-45 minutes), fentanyl has become a favored analgesic for short procedures, such as, bone marrow aspirations, fracture reductions, suturing lacerations, endoscopy and dental procedures. Fentanyl is approximately 100 (50-100) times more potent than morphine (the equi-analgesic dose is 0.001 mg.kg-1) and is largely devoid of hypnotic or sedative activity. Sufentanil is a potent fentanyl derivative and is approximately 10 times more potent than fentanyl. It is most commonly used as the principle component of cardiac anesthesia and is administered in doses of 15-30 μg/kg. Alfentanil is approximately 5-10 less potent than fentanyl and has an extremely short duration of action, usually less than 15-20 minutes. Remifentanil (Ultiva®) is a new μ-opioid receptor agonist with unique pharmacokinetic properties. It is approximately 10 times more potent than fentanyl and must be given by continuous intravenous infusion because it has an extremely short half life.[167,168]

Fentanyl is considered to demonstrate superior hemodynamic stability compared to other opioids. It has become the opioid of choice for intensive care unit patients. Nevertheless, the principles of careful monitoring and titration to effect also apply to fentanyl, particularly in the hypovolemic patient. Furthermore, in addition to its ability to block the systemic and pulmonary hemodynamic responses to pain, fentanyl also prevents the biochemical and endocrine stress (catabolic) response to painful stimuli that may be so detrimental in the seriously ill patient. Fentanyl does have some serious side effects, namely, the development of glottic and chest wall rigidity following rapid infusions of 0.005 mg.kg-1 or greater and the development of bradycardia. The etiology of the glottic and chest wall rigidity is unclear, but its implications are not, namely, it may make ventilation difficult or impossible. Chest wall rigidity can be treated with either muscle relaxants, such as succinylcholine or pancuronium, or with naloxone.

In adults, the serum MEAC of fentanyl is approximately 0.5 to 2.5 mug/L. Fentanyl like morphine is primarily glucuronidated into inactive forms that are excreted by the kidney. It is highly lipid soluble and is rapidly distributed to tissues that are well perfused, such as the brain and the heart. Normally, the effect of a single dose of fentanyl is terminated by rapid redistribution to inactive tissue sites such as fat, skeletal muscles, and lung, rather than by elimination. This rapid redistribution produces a dramatic decline in the plasma concentration of the drug. In this manner its very short duration of action is very much akin to other drugs whose action is terminated by redistribution such as thiopental. However, following multiple or large doses of fentanyl (*e.g.*, when it is used as a primary anesthetic agent or when used in high dose or lengthy continuous infusions), prolongation of effect will occur, because elimination and not distribution will determine the

duration of effect. Indeed, it is now clear that the duration of drug action for many drugs is not solely the function of clearance or terminal elimination half life but rather reflects the complex interaction of drug elimination, drug absorption and rate constants for drug transfer to and from sites of action ("effect sites"). The term "context sensitive half time" refers to the time for drug concentration at idealized effect sites to decrease in half.[169] The context sensitive half time for fentanyl increases dramatically when it is administered by continuous infusion.[169,170] In newborns receiving fentanyl infusions for more than 36 hours, the context sensitive half life was greater than 9 hours following cessation of the infusion.[171] Even single doses of fentanyl may have prolonged effects in the newborn, particularly those neonates with abnormal or decreased liver blood flow following acute illness or abdominal surgery.[172-174,175] Additionally, certain conditions that may raise intra-abdominal pressure may further decrease liver blood flow by shunting blood away from the liver via the still patent *ductus venosus*.[54,55,175,176]

Fentanyl and its structurally related relatives, sufentanil, alfentanil, and remifentanil are highly lipophilic drugs that rapidly penetrate all membranes including the blood brain barrier. Following an intravenous bolus, fentanyl is rapidly eliminated from plasma as the result of its extensive uptake by body tissues. The fentanyls are highly bound to alpha-1 acid glycoproteins in the plasma, which are reduced in the newborn.[177,178] The fraction of free unbound sufentanil is significantly increased in neonates and children less than a year of age (19.5±2.7 and 11.5±3.2 percent respectively) compared to older children and adults (8.1±1.4 and 7.8±1.5 percent respectively) and this correlates to levels of alpha-1 acid glycoproteins in the blood.

Fentanyl pharmacokinetics differ among newborn infants, children and adults. The total body clearance of fentanyl is greater in infants 3-12 months of age than in children older than 1 year of age or adults (18.1±1.4, 11.5±4.2, and 10.0±1.7 ml.kg-1.min-1, respectively) and the half life of elimination is longer (233±137, 244±79, and 129±42 min, respectively).[179] The prolonged elimination half life of fentanyl from plasma has important clinical implications. Repeated doses of fentanyl for maintenance of analgesic effects will lead to accumulation of fentanyl and its ventilatory depressant effects.[179-182] Very large doses (0.05-0.10 mg/kg^{-1}, as used in anesthesia) may be expected to induce long-lasting effects because plasma fentanyl levels will not fall below the threshold level at which spontaneous ventilation occurs during the distribution phases. On the other hand, the greater clearance of fentanyl in infants greater than 3 months of age produces lower plasma concentrations of the drug and may allow these children to tolerate more drug without respiratory depression.[173,179] In adult studies, the mean plasma concentration of fentanyl needed to produce analgesia varies between 0.5-1.5 ng/mL.[183,184]

Alfentanil has a shorter half life of elimination and redistribution than fentanyl an may cause less postoperative respiratory depression than either morphine or fentanyl and is often given by infusion. Following a bolus dose of Gronert *et al* observed very little respiratory depression when alfentanil was used intraoperatively even in very young infants.[185] The pharmacokinetics of alfentanil differ in the neonate compared to older children. Compared with older children, premature infants demonstrated a significantly larger apparent volume of distribution (1.0 +/- 0.39 vs. 0.48 +/- 0.19 l/kg), a smaller clearance (2.2 +/- 2.4 vs. 5.6 +/- 2.4 ml/kg/min) and a markedly prolonged elimination half-life (525 +/- 305 vs. 60 +/- 11 min).[186]

The pharmacokinetics of remifentanil are characterized by small volumes, rapid clearances, and low variability compared to other intravenous anesthetic drugs.[167-134] The drug has a rapid onset of action (half-time for equilibration between blood and the effect compartment = 1.3 min) and a short context-sensitive half life (3-5 min). The latter property is attributable to hydrolytic metabolism of the compound by non-specific tissue and plasma esterases. Virtually all (99.8%) of an administered remifentanil dose is eliminated during the " half-life (0.9 minutes) and ∃ half-life (6.3 minutes). The pharmacokinetics of remifentanil suggest that within 10 minutes of starting an infusion, remifentanil will nearly reach steady state. Thus, changing the infusion rate of remifentanil will produce rapid changes in drug effect. The rapid metabolism of remifentanil and its small volume of distribution mean that remifentanil will not accumulate. Discontinuing the drug rapidly terminates its effects regardless of how long it was being administered.[169,170] Finally, the primary metabolite has little biologic activity making it safe even in patients with renal disease. Fentanyl is metabolized by the liver to inactive metabolites which are eliminated by the kidney. Due to its rapid penetration into the brain, it has an onset of effect within 30 seconds and a peak effect occurring in 5 to 15 minutes following IV administration. It has a relatively short duration of action, 30 to 60 minutes, due to redistribution out of the brain as a result of its high lipid solubility . Compared to morphine, fentanyl has a larger volume of distribution, slower clearance, and a longer terminal half-life of approximately 8 hours. While renal failure

does not significantly alter the pharmacokinetics and pharmacodynamics of fentanyl in most patients, a few studies have demonstrated increases in the volume of distribution and elimination half life in critically ill patients with renal failure receiving continuous fentanyl infusions. A study in renal-failure patients who received kidney transplants found a decrease in fentanyl clearance associated with prolonged ventilatory depression.

Metabolism of fentanyl is determined primarily by liver perfusion. Diseases associated with decreased liver blood flow, such as cardiac failure, may decrease the clearance of fentanyl. Long-term continuous infusions of fentanyl may result in a prolonged elimination t½ and duration of action as a result of drug accumulation in peripheral tissues. Administering fentanyl by continuous infusion requires frequent titration, as the terminal t½ may be as long as 16 hours in this setting. Unlike morphine, fentanyl is not associated with mast cell histamine release and may be preferred in patients susceptible to the cardiovascular effects of morphine.

PATIENT (PARENT AND NURSE) CONTROLLED ANALGESIA

Because of the enormous individual variations in pain perception and opioid metabolism, fixed doses and time intervals make little sense. Based on the pharmacokinetics of the opioids, it should be clear that intravenous boluses of morphine may need to be given at intervals of 1-2 hours in order to avoid marked fluctuations in plasma drug levels. Continuous intravenous infusions can provide steady analgesic levels and are preferable to intramuscular injections. Continuous infusions have been used with great safety and effectiveness in children.[111,148,188] However, they are not a panacea, because the perception and intensity of pain is not constant. For example, a post-operative patient may be very comfortable resting in bed and may require little adjustment in pain management. This same patient may experience excruciating pain when coughing, or voiding, or getting out of bed. Thus, rational pain management requires some form of titration to effect, whenever any opioid is administered. In order to give patients, and in some cases parents and nurses, some measure of control over their, or their children's, pain therapy, demand analgesia or patient controlled analgesia (PCA) devices have been developed.[156,160,189,190] These are micro-processor driven pumps with a button that the patient presses to self administer a small dose of opioid.

PCA devices allow patients to administer small amounts of an analgesic whenever they feel a need for more pain relief. The opioid, usually morphine, is administered either intravenously or subcutaneously.[156,160,189] The dosage of opioid, number of boluses per hour, and the time interval between boluses (the "lock-out period") are programmed into the equipment by the pain service physician to allow maximum patient flexibility and sense of control with minimal risk of overdosage. Generally, because older patients know that if they have severe pain they can obtain relief immediately, many prefer dosing regimens that result in mild to moderate pain in exchange for fewer side effects such as nausea or pruritus. The most commonly prescribed opioids for IV PCA are morphine, hydromorphone and fentanyl. Typically, we initially prescribe morphine, 20 μg/kg per bolus, at a rate of 5 boluses/hour, with a 6-8 minute lock-out interval between each bolus . (156;160;189) Variations include larger boluses (30-50 μg/kg), shorter time intervals (5 min), etc. Hydromorphone may have fewer side effects than morphine and is often used when pruritus and nausea complicate morphine PCA therapy. Because it is 5-7 times more potent than morphine, the size of the bolus dose is reduced to 3-4 μg/kg.[157] The fentanyl equivalent is less clear. Although fentanyl is considered 50-100 times more potent than morphine when given as a single bolus, Monitto *et al* used a conversion of 40 :1 in a study in which parents and nurses controlled the PCA pump.[161] In this study, fentanyl 0.5 mcg/kg was administered by continuous infusion, and bolus doses were 0.5 mcg/kg.

The PCA pump computer stores within its memory how many boluses the patient has received as well as how many attempts the patient has made at receiving boluses. This allows the physician to evaluate how well the patient understands the use of the pump and provides information to program the pump more efficiently. Many PCA units allow low "background" continuous infusions (morphine, 20-30 μg/kg/hour, hydromorphone 3-4 μg/kg/hour, fentanyl 0.5 μg/kg/hour) in addition to self administered boluses. This is sometimes called "PCA-Plus". A continuous background infusion is particularly useful at night and often provides more restful sleep by preventing the patient from awakening in pain. It also increases the potential for overdosage.[156,161,191] Although the adult literature on pain does not support the use of continuous background infusions, it has been our experience that continuous infusions are essential for both the patient and us (fewer phone calls, problems, etc.).[192] Indeed, in our practice, we almost always use continuous background infusions when we prescribe IV (or epidural) PCA.

PCA requires a patient with enough intelligence and manual dexterity and strength to operate the pump.

Thus, it was initially limited to adolescents and teenagers, but the lower age limit in whom this treatment modality can be used continues to fall. In fact, it has been our experience that any child able to play Nintendo® can operate a PCA pump (age 5-6). Allowing parents or nurses to initiate a PCA bolus is controversial. In our practice, we empower nurses and parents to initiate PCA boluses and use this technology in children less than even a year of age. In our experience, the incidence of common opioid-induced side effects is similar to that observed in older patients.[161] Interestingly, respiratory depression is very rare, but does occur, reinforcing the need for close monitoring and established nursing protocols. Difficulties with PCA include its increased costs, patient age limitations, and the bureaucratic (physician, nursing, and pharmacy) obstacles (protocols, education, storage arrangements) that must be overcome prior to its implementation. Contraindications include inability to push the bolus button (weakness, arm restraints), inability to understand how to use the machine, and a patient's desire not to assume responsibility for his/her own care.

Opioid Dependence and Prevention of Withdrawal

Tolerance and *physical dependence* with repeated opioid administration is a characteristic common to all μ agonist opioids.[193-199] *Tolerance* is the development of a need to increase the dose of an opioid or benzodiazepine agonist to achieve the same analgesic or sedative effect previously achieved with a lower dose.[200,201] Tolerance usually develops following 10-21 days of morphine administration, although the constipating and miotic actions of morphine may persist. Additionally, cross-tolerance develops between all of the μ opioid agonists. *Physical dependence*, sometimes referred to as "neuroadaptation", is caused by repeated administration of an opioid which necessitates the continued administration of the drug to prevent the appearance of a withdrawal or abstinence syndrome that is characteristic for that particular drug.[193] It usually occurs after 2-3 weeks of morphine administration, but may occur after only just a few days of therapy. Recently very young infants treated with very high dose fentanyl infusions following surgical repair of congenital heart disease and/or who required extra-corporeal membrane oxygenation (ECMO) have been identified to be at particular risk.[101,202-204]

Physical dependence must be differentiated from *addiction*.[193] *Addiction* is a term used to connote a severe degree of drug abuse and dependence that is an extreme of behavior, in which drug use pervades the total life activity of the user and of the range of circumstances in which drug use controls the user's behavior. Patients who are addicted to opioids often spend large amounts of time acquiring or using the drug, abandon social or occupational activities because of drug use, and continue to use the drug despite adverse psychological or physical effects. In a sense addiction is a subset of physical dependence. Anyone who is addicted to an opioid is physically dependent, however, not everyone who is physically dependent is addicted. Patients appropriately treated with morphine and other opioid agonists for pain can become tolerant and physically dependent. They rarely, if ever, become psychologically dependent or addicted.[205]

When physical dependence has been established, sudden discontinuation of an opioid or benzodiazepine agonist produces a *withdrawal* syndrome within 24 hours of drug cessation. Symptoms reach their peak within 72 hours and include abdominal cramps, vomiting, diarrhea, tachycardia, hypertension, diaphoresis, restlessness, insomnia, movement disorders, reversible neurologic abnormalities, and seizures.[193,194,206-209]

Clinical and experimental data suggest that the duration of receptor occupancy is an important factor in the development of tolerance and dependence. Thus, continuous infusions may produce tolerance more rapidly than intermittent therapy.[208,209] This is particularly true for fentanyl. Fentanyl is a potent, rapidly acting, lipophilic opioid that is frequently used for procedure-related pain (e.g., dressing changes, laceration repair) and for pain management in critically ill children. Tolerance and dependence *predictably* develops following only 5-10 days (2.5 mg/kg total fentanyl dose) of continuous fentanyl infusions.[101,202,208,208] Nevertheless prolonged therapy (> 10 days) even by intermittent bolus administration should be *expected* to produce opioid dependence.

It is our practice to wean patients from their opioids rather than abruptly stopping therapy.[2,197] We believe that this is a more appropriate clinical strategy than one designed to treat the symptoms of withdrawal and is akin to the therapeutic strategy used in weaning patients from other drugs (e.g., steroids) where abrupt cessation can be catastrophic. To simplify the weaning process, we make every effort to convert the patient from intravenous to oral therapy and from continuous infusions to intermittent bolus therapy.[2,197] This makes the care of the patient significantly easier and allows for the final tapering and weaning to be accomplished in an out-patient setting. In most cases the same opioid can be used in weaning that was used therapeutically. For practical reasons though, it may be necessary to

change from one opioid to another because of ease of administration, duration of action, and ability to taper the dose.

On changing from one opioid to another, equianalgesic dosing is mandatory (Table 2). Additionally, in order to avoid over- or under-dosing when converting from one drug to another, we recommend being conservative and titrating the dosage upward to achieve the desired clinical effect. Furthermore, the calculated conversion should be given for 24-48 hours before any attempt at weaning is made. Once this is accomplished, we administer the drugs on a 6 hour (morphine) or 12 hour (methadone) around the clock basis and weaning is begun. The patient's drug regimen is decreased by 10-20% of the original total opioid dose a day. When the lowest doses are reached, usually in 5-7 days, the interval of drug dosing is increased from every 6 hours to every 8 or 12 hours, to once a day. Therapy is then stopped completely. We believe that this schedule should be strictly adhered to. If symptoms of withdrawal develop, we treat these symptoms with clonidine 2-4 μg/kg every 4-6 hours on an as needed basis.

CONCLUSION

We have attempted to consolidate in a comprehensive manner much of the available information on pain management in critically ill children. All children, even the newborn and critically ill require analgesia for pain and for painful procedures. Unrelieved pain interferes with sleep, leads to fatigue and a sense of helplessness, and may result in increased morbidity and/or mortality. It also lessens a part of our fundamental humanity and role as healers and physicians.

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