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The Current State of Paramedics' Knowledge of and Attitude towards Morphine as a Pre-Hospital Analgesic in the Ambulance Services of South Australia

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Abstract: ***Prehospital pain management sits at the intersection of clinical urgency and ethical responsibility-particularly when it involves administering opioids like morphine. This article takes a critical look at the evolving role of morphine as a frontline analgesic in emergency settings, especially across Australian ambulance services. It's evident that while morphine remains a cornerstone in managing moderate to severe pain, its use is not without complications. The discussion digs deeper than surface-level administration, exploring how gaps in paramedic education, organizational culture, and protocol familiarity often result in under dosing or misuse-factors that can delay care or even endanger patients. Taking this further, the paper also highlights the necessity of advanced pharmacological training and real-time monitoring, especially in cardiac cases where morphine may mask critical symptoms or cause adverse effects like respiratory depression. What makes this study particularly meaningful is its comprehensive drug profile of morphine, from its molecular structure to receptor interactions and contraindications, offering not just pharmacological detail but also real-world applicability. The inclusion of drug interactions-both OTC and prescription-adds another layer of clinical relevance, underscoring the precision required in emergency pharmacology. Overall, the article argues persuasively for elevating education standards among paramedics to ensure morphine is used as both a powerful tool and a responsibly managed one in prehospital care.***

Keywords: prehospital pain management, morphine use in EMS, paramedic education, opioid analgesics, emergency pharmacology

1. Introduction

Modern pre-hospital emergency medical services (EMS) agencies provide pre-hospital analgesic treatment in the ill or injured setting. Pre-hospital pain management practice is considered a primary function of emergency care and an essential measure of the standard of quality in the pre-hospital emergency care setting. Emergency paramedics have a major responsibility in the pre-hospital environment immediately after life-saving interventions, including for the relief of discomfort (pain) by the provision of adequate opioids in accordance with clinical protocols (Bendall, Simpson, & Middleton, 2011; Lord & Nicholls, 2014; Weber, Maguire, & Dwyer, 2015).

Insufficient knowledge on the part of paramedics of pain management and pre-hospital analgesic interventions result in bad professional practice and may constitute human rights violations, with ethical and legal implications, as well as causing further delays in providing appropriate treatment. Paramedics perform a pivotal role in the assessment and management of complaints in many patients who are suffering pain in a pre-hospital care setting; consequently, they need to be professional in administering effective drugs that reduce pain, improve healthcare outcomes and minimise transport problems. Pre-hospital pharmacological management of moderate to severe pain includes a variety of opioids, for example morphine, methoxyflurane, ketamine and fentanyl (Bendall, Simpson, & Middleton, 2011; Lord & Nicholls, 2014; Weber, Maguire, & Dwyer, 2015). In the pre-hospital setting, morphine is considered the treatment of choice for independent administration by emergency paramedics without the need to ask for the consent of an emergency physician; moreover, morphine has proven efficacy and safety for the treatment of many patients who are suffering moderate to severe pain (Fleischman et al., 2010; Bendall, Simpson, & Middleton, 2011; Lord & Nicholls, 2014; Fabbri et al., 2023).

In the pre-hospital pain management setting, there are various barriers to the effectiveness of morphine administration for pain relief, such as inadequate knowledge on the part of paramedics, poor and inconsistent education of paramedics, pain assessment challenges and legislative controls on the possession of the drug. Furthermore, there has been significant concern about major adverse effects associated with morphine administration, such as respiratory depression, hypotension (especially patients with signs of a right ventricular infraction), nausea and vomiting. Administration of morphine can therefore place many cardiac patients at high risk from unsuspected hypoventilation instead of their myocardial disease. Consequently, the patient's respiratory rate, blood pressure, heart rate and ECG should be carefully monitored during transport to the medical facility and rapid pain relief provided on the way (Weber, Dwyer, & Mummery, 2012; Lord & Nicholls, 2014; Deslandes et al., 2024).

In the 1980s, Australian Ambulance Services approved the use of morphine for prehospital clinical pain management in South Australia, Victoria, and New South Wales. However, due to concerns about patient safety, only highly qualified paramedics were authorized to administer this type of medication. In 2000, most Australian ambulance services used morphine as the strongest parenteral prehospital analgesia for treating patients with moderate to severe pain in prehospital care settings. In addition, the authorization to

administer morphine was extended to all paramedics in South Australia, New South Wales, Western Australia, and Victoria following the establishment of advanced life support training as the base-level qualification for all paramedics (Bendall, Simpson, & Middleton, 2011; Lord & Nicholls, 2014).

Pain management depends on attending paramedics' pharmacological knowledge, protocol familiarity, and the timely initiation of opioid drugs. Inadequate medication and underdosing have been identified as undesired outcomes when health professionals have substandard knowledge or assessment skills. There are a number of possible causes of inadequate knowledge and assessment skills, including organizational culture and a lack of ongoing education for health professionals. In Australian ambulance services, many medical field educators have stated that increasing clinicians' knowledge of pain management through effective, high-quality education and providing continuing education programs will eliminate these barriers (Weber, Maguire, & Dwyer, 2015).

In research on prehospital analgesic agents, advanced pain management practices are a relatively new topic related to understanding pain and methods of managing it. Therefore, significant knowledge of drugs, therapeutic methods, and skills in managing several types of pain are required for emergency paramedics to administer safe and effective prehospital opioid analgesics such as morphine. Historically, prehospital clinical practice has relied on the administration of opioid analgesics, particularly morphine. Consequently, this study focuses primarily on introducing higher explanation of morphine as a major pain analgesic agent in prehospital emergency care. This study aims to improve the pharmacological education levels and attitudes of prehospital clinicians in the management of prehospital pain analgesic medications.

Section 1: Introductory Concepts

1) Begin your drug profile by writing the chemical name, generic name, and the Australia trade names for your chosen drug.

The chemical name for morphine is (5α, 6α)-7, 8-didehydro-4, 5-epoxy-17-methylmorphinan-3,6-diol (Myers 2007).
Chemical formula: C17 H19 NO3 (Myers 2007).
Molecular weight: 285.34 (Myers 2007).
CAS number: 57-27-2 (Myers 2007).

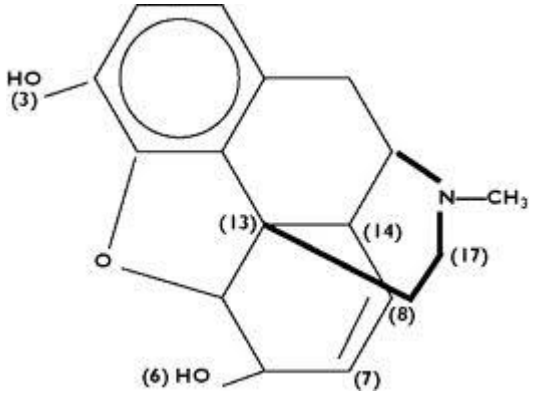

Figure 1: The chemical structure of morphine (Armstrong & Cozza 2003, p. 168).

Generic name: morphine (Sinatra, Jahr & Watkins-Pitchford 2011; Mancano & Gallagher 2012). In Australia, the trade names of morphine include Kapanol®, MS Contin®, Ordine ®, MS Mono®, Anamorph®, MS Contin Suspension® and Sevredol ® (Australian Medicines Handbook; AMH 2008 pp. 52-53).

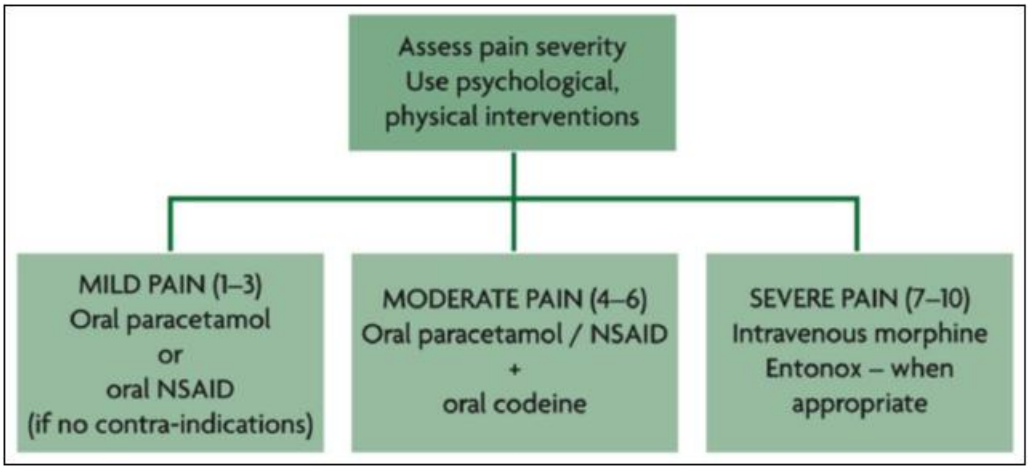

Figure 2: Approach to prehospital pain management. (Smyth et al., 2025).

a) List the approved indications for your drug.

- Relief of moderate to severe pain or chronic pain due to cancer.
- Relief of postoperative pain, pain connected with labour and delivery and also pain which is unresponsive to non-narcotic analgesics.
- Relief of dyspnea connected with acute left ventricular failure and pulmonary oedema.
- Morphine is the only narcotic that can be applied to cure the pain of myocardial infarction (MI).
- Decreased anxiety.
- Sedation.
- Euphoria.
- Cough suppression (antitussive).
- Suppression of bowel motility.
- Facilitation of the induction of anaesthesia or decrease in the amount of anaesthetic required.

- Commonly used when preparing for surgery and can also be administered during the operation to suppress nociceptive stimuli.
- Prevention of visceral and somatic pain (Mckay et al. 2010, p. 256; Lehne 2010, p. 262-263; Aschenbrenner & Venable 2009, p. 380-381).

b) Determine whether your drug is approved for paramedic use in South Australia, and if it is, identify the approved paramedic indications for your drug in South Australia.

Morphine is one of the analgesics approved for paramedic use is in South Australia. Morphine is used by paramedics alongside fentanyl to treat patients who have acute or severe chest pain related to myocardial infarction (AMI), unstable angina (UA) and angina which is not relieved by GTN. Morphine is also used by paramedics in South Australia to cure patients who have severe pain caused by musculoskeletal injuries, burns and amputations. Morphine can be used by paramedics to treat patients who have severe pain associated with myocardial infarction or dyspnoea and acute or severe pain related with left ventricular failure and pulmonary oedema (PE) (South Australian Ambulance Service, SAAS 2010; South Australian Ambulance Service, SAAS 2011).

Section 4: Over-The-Counter & Complementary and Alternative Medicines

2) Add to your drug profile:

a) A list of conventional over-the-counter (OTC) medicines, complementary alternative medicines (CAMs) and prescription medicines that are known or suspected to undergo clinically relevant interactions with your profile drug in humans.

b) List the source(s) of information you have used and indicate the strength of the evidence (e.g. anecdotal report, clinical case, clinical trial, etc) for each of the interactions that you have identified.

- St John's wort (*Hypericum perforatum*): St John's wort (*Hypericum perforatum*) is a common OTC antidepressant and can be applied for the treatment of depression (Twycross 2002, p.88). Thus, St John's wort (*Hypericum perforatum*) in combination with morphine enhances sedation (Kee, Hayes & McCuistion 2010, p. 330).
- Paracetamol: There is increasing evidence, supported by clinical studies/observations and a variety of scientific research, that morphine reduces the rate of absorption of paracetamol (Tiziani 2006, p. 573; Aschenbrenner & Venable 2009, p. 406).
- Droperidol: Clinical studies have shown that administration of droperidol potentiates respiratory depression of morphine (Tiziani 2006, p. 573 and p. 338).
- CNS Depressants: Use of morphine together with all CNS depressant drugs such as benzodiazepines and barbiturates induce an increase in respiratory depression and sedation which occurs via morphine and other opioid drugs (Lehne 2010, p. 266).
- Anticholinergic Drugs: Use of antihistamines, tricyclics antidepressants and atropine in combination with morphine may intensify morphine-induced urinary retention and constipation (Lehne 2010, p. 266).
- Hypotensive Drugs: Use of antihypertensive drugs, as well as other drugs which reduce blood pressure, in combination with morphine may intensify morphine induced hypotension (Lehne 2010, p. 266).
- Monoamine Oxidase Inhibitors: Use of morphine in combination with a monoamine oxidase (MAO) inhibitor leads to a syndrome characterized by severe respiratory depression, hyperpyrexia, delirium and convulsions (Lehne 2010, pp. 266-267).
- Amphetamine, Clonidine and Dextromethorphan: Use of Amphetamine, clonidine and dextromethorphan in combination with morphine may increase morphine-induced analgesia, while amphetamine can equalize sedation (Lehne 2010, p. 267).

Drug Profile activities for Module 2

Section 3: Signal Transduction Mechanisms for Receptors

3) For your drug:

a) Discuss in detail the mechanism of action. Your answer should:

- Identify how the interaction of the drug with its molecular target(s) accounts for the major therapeutic effect (i.e. the effect you want the drug to cause in clinical practice; e.g. for paracetamol - pain relief)
- Include a description of how the drug alters function at the cellular level.
- Include a description of how the altered cellular function manifests as a change in body system function, and the eventual major therapeutic response

Morphine is an agonist analgesic and causes analgesia via binding to particular G protein-coupled receptors which are found in the areas of the brain and spinal cord included in the transmission and modulation of pain. Some impacts may also be mediated via opioid receptors on peripheral sensory nerve endings (Katzung et al. 2009, p. 534).

In addition, opioid receptors are located in the presynaptic membranes of neurons in the principal pain pathways of the CNS and in the peripheral nervous system. They can be classified into three main receptors (mu (μ), kappa (κ) and delta (δ)) that mediate different effects (Waller et al. 2005).

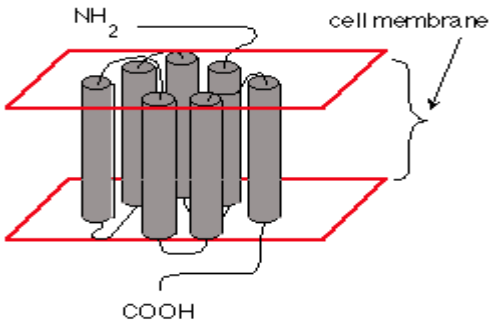

Figure 3: Diagram of the human mu opioid receptor (Chahl 1996 p. 64).

All opioid receptors are bonded to inhibitory G-proteins and receptor stimulation suppresses adenylate cyclase that breaks down adenosine triphosphate (ATP) and the intracellular generation of cyclic adenosine monophosphate (cAMP). All three types of opioid receptors couple to adenylate cyclase in this way. Suppression of adenylate cyclase can induce

suppression of neurotransmitter release (Waller et al. 2005; Chahl 1996, p. 66).

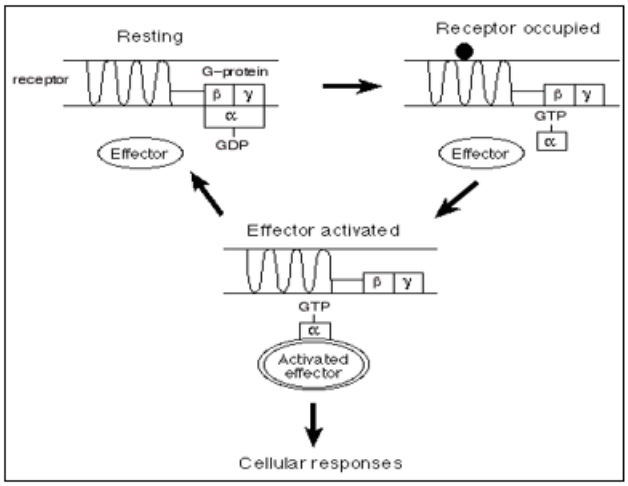

Figure 4: The function of G-proteins under the action of morphine (Chahl 1996, p. 65).

The principle action of morphine is to relieve moderate to acutely severe pain by mimicking the action of endogenous opioid peptides, such as enkephalins, dynorphins and endorphins, primarily at mu (μ) receptors but also at kappa (κ) receptors (Lehne 2010; Aschenbrenner & Venable 2009; Trescot, Datta, Lee & Hansen 2008).

Morphine stimulates the mu (μ) receptor, which is responsible for supra-spinal analgesia, respiratory and physical depression, miosis, euphoria and decreased gastrointestinal activity (GI). Morphine also stimulates the kappa (*k*) receptor, which is related to spinal analgesia, miosis and sedation. However, the analgesic effects of morphine are mainly mediated by the mu (μ) receptors. Therefore, its action is associated with the distribution of opioid receptors (Aschenbrenner & Venable 2009, p. 381; Trescot, Datta, Lee & Hansen 2008, p. 135).

In addition, mu (μ) opioid receptors exist at the periphery, at presynaptic and postsynaptic locations in the brainstem, in the dorsal horn of the spinal cord, and the medial thalamus, hypothalamus and cortex that form the ascending pain transmission system (Aschenbrenner & Venable 2009, p. 381; Inturrisi 2002, p. 4). Mu (μ) opioid receptors are also found in the midbrain periaqueductal grey, the nucleus raphe magnus and the rostral ventral medulla, where they constitute a descending inhibitory system that transfers spinal cord pain transmission (Inturrisi 2002, p. 4).

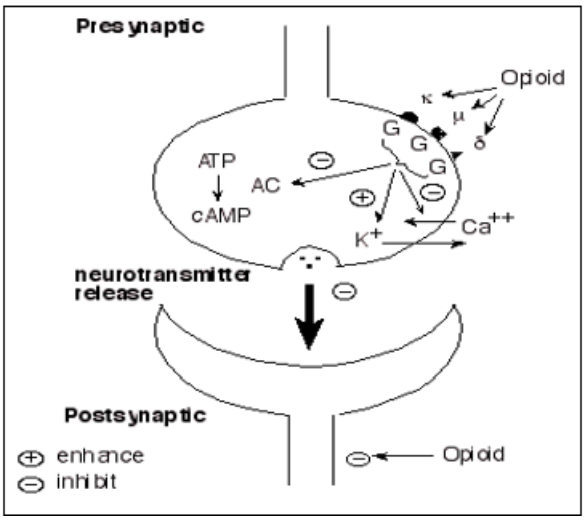

Figure 5: How morphine inhibits the release of neurotransmitters (Chahl 1996, p 66).

At the cellular level, opioid receptors constitute a family of proteins which physically couple to G proteins and throughout this interaction act to modulate intracellular Ca2+ disposition, ion channel gating and protein phosphorylation states (Katzung et al. 2009, p. 534; Waller et al. 2005, p. 256-257; Inturrisi 2002, p. 4). Morphine produces an effect at two sites in the neurons: the presynaptic nerve terminal and the postsynaptic neuron. The action of morphine on the postsynaptic neuron is normally inhibitory while the action on the presynaptic nerve terminal is to prevent the release of neurotransmitters (Chahl 1996, p. 66).

Morphine acts to stimulate opioid receptors and, as a result, suppresses neuronal voltage-gated Ca2+ channels on presynaptic nerve terminals. Thus, it decreases the release of pain neurotransmitters in the presynaptic space. These pain neurotransmitters include glutamate and substance P, which modulates pain perception (substance P discharges from primary afferent neurons in the dorsal horn of the spinal cord). The presynaptic action (depressed transmitter release) releases a greater number of neurotransmitting substances such as P, glutamate, the principle excitatory amino acids discharged from nociceptive nerve terminals, acetylcholine, serotonin and norepinephrine (Katzung et al. 2009, p. 534; Waller et al. 2005, p. 256-257; Inturrisi 2002, p. 4). Furthermore, the G-proteins are immediately bonded to K+ channels and morphine raises K+ conductance. Morphine hyperpolarises the target cells and makes them less responsive to depolarising impulses, thus increasing potassium ion efflux, leading to the hyper-polarization of postsynaptic dorsal horn neurons, and reducing synaptic transmission by opening K+ channels (Katzung et al. 2009, p. 534; Waller et al. 2005, p. 256-257; Inturrisi 2002, p. 4).

Additionally, in the nucleus raphe magnus of the brain, mu (μ) receptor motivation reduces the action of inhibitory gamma-aminobutyric acid (GABA) neurons which project to serotonergic neurons in the brainstem. This increases the rate of firing of these reducing inhibitory serotonergic neurons, which associate presynaptically with afferent nociceptive fibres in the dorsal horn of the spinal cord. Thus, analgesia is generated via suppression of the discharge of the pain pathway mediators including glutamate, substance P and nitric oxide from the afferent nociceptive neurons (Katzung

et al. 2009, p. 534; Waller et al. 2005, p. 256-257; Inturrisi 2002, p. 4).

However, although morphine can cause nausea and vomiting because it directly stimulates the chemoreceptor trigger zone (CTZ), an antiemetic, such as prochlorperazine, can be given to decrease these symptoms (Aschenbrenner & Venable 2009; Trescot, Datta, Lee & Hansen 2008).

Morphine's major therapeutic function is in treating chronic pain, whether it is caused by cancer, other diseases or injury. This agonist analgesic can also be applied for dyspnea related to pulmonary oedema or severe acute pain due to left ventricular failure and myocardial infarction (MI). Morphine can also be used to sedate patients and to relieve anxiety (Aschenbrenner & Venable 2009; Trescot, Datta, Lee & Hansen 2008).

b) Using 4 journal articles, critically review the evidence for the clinical effectiveness of your drug in humans. Your answer should identify and critique the:

- **Type of study**
- **Comparator agent (e.g. placebo, current gold standard therapy, etc)**
- **Sample size**
- **Measures of effectiveness**

The findings of study a done by Wiffen & McQuay (2010) highlight the fact that oral morphine is a more effective analgesic for patients who experience pain associated with cancer. Morphine is said to be the gold standard for stopping pain that is characterised as moderate to severe. In addition, the authors indicated that the purpose of this review was to evaluate the effectiveness of oral morphine in stopping cancer pain and to evaluate the occurrence and severity of unfavourable side effects. In this review, adults and children (3749 participants) who suffered cancer pain and required treatment with opioid analgesics were included. The review asserted that oral morphine is an effective analgesic compared with a placebo, other opioids or morphine via different administrations routes. The study group participants in this review demonstrated that morphine provides good relief for cancer pain but it produces unfavourable effects such as vomiting, nausea and constipation.

In contrast, a review that had carried out by Mercadante (2010) indicted that intravenous morphine is an advisable route to control pain in patients with chronic cancer pain. This review asserts that IV morphine can be beneficial for patients with poor peripheral circulation, generalised oedema, coagulative disorders and erythema. However, the major benefit of IV morphine for most patients, specifically patients with chronic cancer pain, included pharmacokinetic effects, the short time required for administration into the circulation, its fast and predictable effects and lack of problems with absorption (see panel).

The findings of this review indicated that IV morphine, given for the management of 945 patients with breakthrough pain, was safe, effective and had rapid onset without life-threatening undesirable effects. This review emphasized that IV morphine provided rapid and effectual plasma concentrations compared with other administration routes such as oral or transdermal methods. The analgesic impacts of IV morphine onset rapidly therefore, this route of administration can be recommended to manage pain for the most patients, specifically patients with chronic cancer pain. The reviews done by Trescot et al (2008a) & Trescot et al (2008b) evaluated the effectiveness of oral morphine in the treatment of patients with chronic non-cancer pain in the long–term (for 6 months or more). Both reviews included 680 participants with chronic low back pain and 121 patients with chronic non-cancer pain who ingested either oral sustained morphine or another opioid analgesic. Both reviews assessed pain relief, quality of life, disease progression and adverse effects involving bowel function. The findings of both reviews demonstrated that morphine is safe and effective in the treatment of patients with chronic non-cancer pain when compared with other opioid analgesics in the long-term (for 6 months or more). In addition, both reviews asserted that patients who received morphine in the long-term demonstrated greatly reduced pain intensity, greater contentment with the pain control, development in physical status and increased quality of life.

Drug Profile activities for Module 3

Section 1: Renal Excretion of Drugs and their Metabolites

4) Determine whether your drug is:

- **Primarily excreted unchanged (as the parent drug) in the urine (renally cleared)**
- **Excreted in the urine principally as metabolites (metabolised; hepatically cleared).**

Morphine is converted in the liver via conjugation (phase II) and glucuronidation predominantly to glucuronide conjugates M3G (45-55%) and M6G (10-15%) while around 5% of the drug is demethylated into normorphine. This functions to raise the water solubility of morphine and to expedite excretion (Trescot et al 2008, p. 142; Lugo & Kern 2002, p. 12; Glare & Walsh 1991, p.15). Excretion of morphine is primarily renal as an unchanged substance in the urine via glomerular filtration of water-soluble conjugates. The principally renal excretion of morphine glucuronides can be compared with the biliary excretion of bilirubin glucuronide; a different transport mechanism of morphine may exist at the cellular level (Trescot et al. 2008, p. 142; Lugo & Kern 2002, p. 12; Glare & Walsh 1991, p. 15; Lotsch et al. 1999, p. 1031).

Section 2: Drug Metabolism

5) For your drug:

a) Using a diagram (if possible) as an aid discuss its metabolism noting the types of reactions, that is either functionalisation or conjugation reactions, and identify the involvement of any CYP, UGT or other drug metabolising enzymes.

Metabolism of opioid analgesic is carried out extensively by a first-pass metabolism in the liver, before it enters the systemic circulation. This first-pass metabolism acts decrease the bioavailability of the opioid (Smith 2009, p. 614). Moreover, opioid metabolism takes place predominantly in the liver, which generates enzymes for this reason. These enzymes are also able to produce two forms of metabolism:

phase I metabolism (functionalisation reactions) and phase II metabolism (conjugation reactions) (Smith 2009, p. 614). In phase I metabolism, the drug undergoes oxidation or hydrolysis. Cytochrome P450 (CYP) enzymes are also involved in reactions such as *N*-, *O*-, and *S*- dealkylation, aromatic, aliphatic or *N*- hydroxylation, *N*- oxidation, sulfoxidation, deamination and dehalogenation. Here, opioids are metabolized by the CYP pathways and this primarily involves CYP3A4 and CYP2D6 enzymes. In addition, the CYP3A4 enzyme acts to metabolize more than 50% of the drugs. As a result, opioids have a high risk of drug-drug interaction when they have been metabolised via the CYP3A4 enzyme. On the other hand, the CYP2D6 enzyme acts to metabolize a smaller proportion of drugs and, therefore, is connected with an intermediate risk of drug-drug interactions (Smith 2009, p. 614).

In contrast, Phase II metabolism conjugates the drug to hydrophilic substances such as sulphates, glucuronic acid, glycine or glutathione (Smith 2009, p. 614). Thus, the most significant phase II metabolism (conjugation reaction) is glucuronidation, via the enzyme uridine diphosphate glucuronosyltransferase (UGT). Glucuronidation generates molecules which are highly hydrophilic; hence they are easily eliminated (Smith 2009, p. 614). Opioids can also undergo phase II metabolism by conjugation. As a result, when opioids undergo phase II metabolism (conjugation reaction) they have only slight or no involvement with the CYP system and there is only a very small chance of interactions occurring (Smith 2009, p. 614).

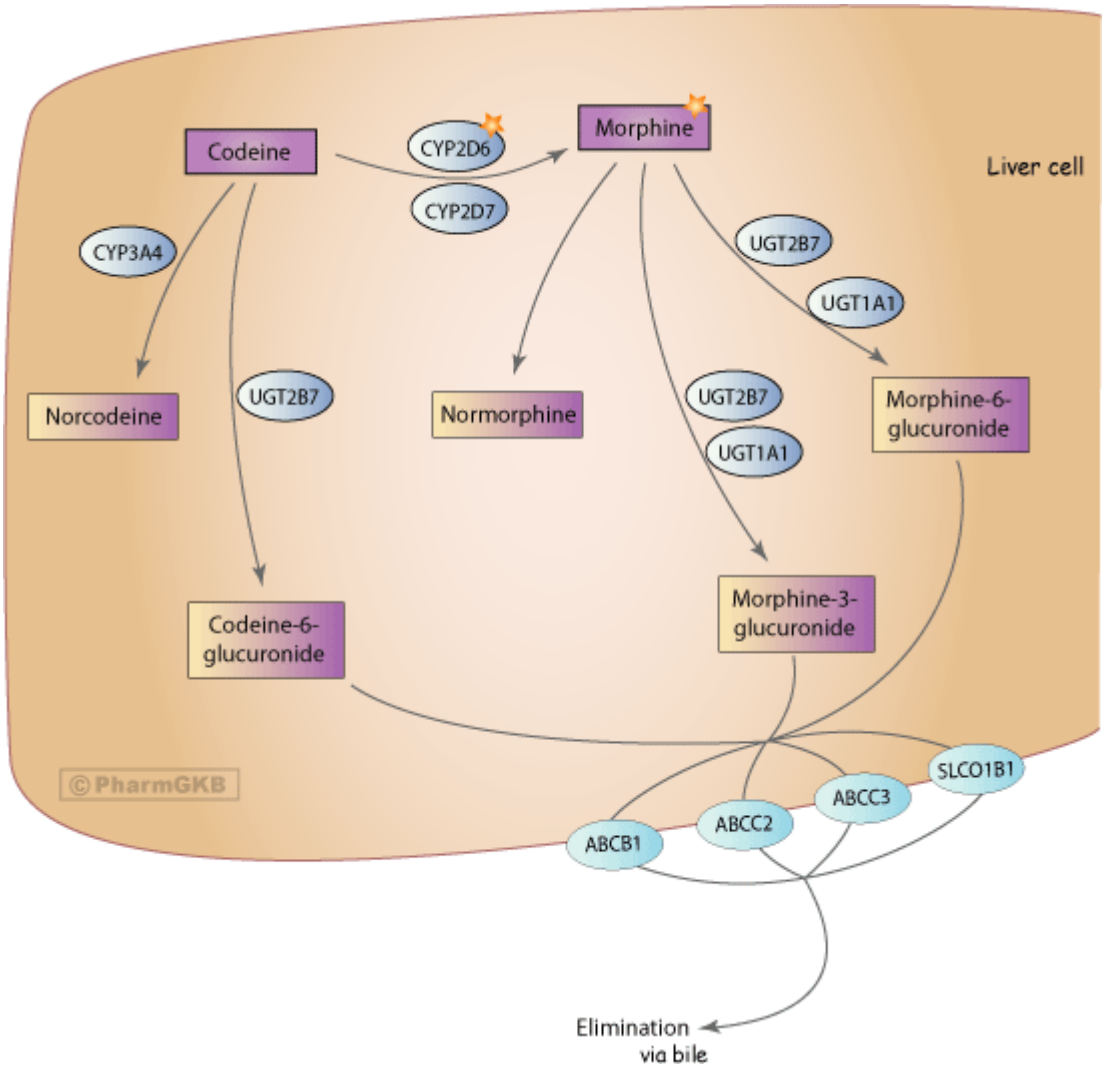

Figure 6: The metabolism of codeine and morphine (Thorn et al 2009 p 556).

Although the major pathway for metabolism of morphine happens in the liver by phase II metabolism (conjugation reaction), other *in vitro* studies have shown that UDPGT activity occurs in the kidney, gut and brain (Andersen et al. 2003, p. 76). Morphine is predominantly metabolized in the liver by uridine-5-diphosphate (UDP) glucuronosyltransferase which has a particular affinity for the UGT2B7 isozyme. The UGT2B7 isozyme is considered responsible for the metabolism of morphine glucuronidation (morphine 3-glucuronide and morphine 6- glucuronide) (Andersen et al. 2003, p. 76; Wittwer & Kern 2006, p. 384).

Despite, the findings of *in vitro* studies indicating the significant role of UGT1A1 in the generation of morphine 3-glucuronide, *in vivo* UGT2B7 isozyme is the principal morphine metabolism site. Additionally, the difference in production of these two metabolites is possibly due to physicochemical and steric problems which impede the linking of morphine to the phase II enzyme. (Wittwer & Kern

2006, p. 384). Furthermore, UGT2B7 is thought to be the major enzyme for metabolism of morphine and plays an important role in the metabolism of numerous endogenous and exogenous compounds. Principally among them are the steroid hormones and bilirubin in newborn and infants, which are substrates for UGT2B7, and can be metabolized via several different liver enzymes (Andersen et al. 2003, p. 76; Wittwer & Kern 2006, p. 384). However, UGT2B7-mediated opioid metabolism can be affected by interactions with other drugs which are either inhibitors of this enzyme or substrates (Smith 2009, p. 616).

b) Identify the main metabolites (note those on your figure), and state the percent of the parent compound metabolised to the specific metabolite.

The liver is the main site for biotransformation of morphine. 45-55% of morphine is glucuronidated to morphine-3-glucuronide, whereas 10-15% is converted to morphine-6-glucuronide. This metabolic reaction is primarily motivated via UGT2B7 in the liver. Moreover, UGT1A1 can play a minor role in the production of morphine-3-glucuronide and UGT1A1 and UGT1A8 are able to catalyse the production of morphine-6-glucuronide *in vitro,* thus, contributing to this pathway (Trescot et al. 2008, p. 142; Thorn et al. 2009, p. 556; Lugo & Kern 2002, p.12).

Morphine is metabolized by glucuronidation and demethylation. Glucuronidation is the major route of morphine metabolism and produces the main metabolites, morphine-6-glucuronide and morphine-3-glucuronide in a ratio of 6:1. About 5% of the morphine is demethylated into normorphine (Bryant & Knights 2011, p. 295; Trescot et al. 2008, p. 142; Andersen et al. 2003, p. 76). In addition, morphine can be metabolised by *N*-demethylation to normorphine or normorphine 6-glucuronide, diglucuronidation to morphine-3, 6-diglucuronide and formation of morphine ethereal sulphate (Smith 2009, p. 617). Morphine-6-glucuronide (M6G) is an active metabolite of morphine and is able to produce further analgesic effects through its action on several receptor subtypes (Inturrisi 2002, p. 5; McQuay 1999, p. 2230). Morphine-6-glucuronide connects to opioid receptors and is able to produce deep analgesic effects. Like morphine, morphine-6-glucuronide (M6G) has an affinity to mu-1 receptors, although its affinity to mu-2 receptors is 4 to 5 times lower than that of morphine (Andersen et al. 2003).

In contrast, morphine-3-glucuronide (M3G) is an inactive metabolite of morphine and has little affinity to the opioid receptors (Trescot et al. 2008, p. 142; Andersen et al. 2003, p. 79; Paice 2007, p. 4). However, the findings of previous studies confirm that morphine-3-glucuronide (M3G) does not have any analgesic properties but potentially results in hyperalgesia when it is in a sufficiently high concentration. It can also contribute to adverse effects, for example hyperalgesia (extreme sensitivity to pain), myoclonus (unexpected involuntary jerking of a muscle or muscle group) and allodynia (pain from non-painful stimuli) (Trescot et al. 2008, p. 142; Andersen et al. 2003, p. 79; Paice 2007, p. 4).

Section 3. Sources of variability in drug metabolism

6) In relation to the metabolism of your drug discuss the influence of host (e.g. disease states) and environmental factors in terms of enzyme induction and/or inhibition on the metabolism of your drug.

The medical condition (state of disease) of the patient will affect the metabolism of morphine. Patients with cirrhosis and decompensated chronic hepatic disease have reduced plasma clearance and a prolonged elimination of morphine's half-life compared with patients who do not have liver disease (Lugo & Kern 2002, p. 13; Hasselstrom et al. 1990, pp. 295-296).

In addition, the cirrhotic liver demonstrates several pathologic characteristics that reduce enzyme content or reduce intrinsic clearance and intra and extrahepatic shunting of blood, which should be considered significant for morphine elimination (Lugo & Kern 2002, p. 13; Hasselstrom et al 1990, pp. 295-296). Furthermore, the findings of recent studies show that extrahepatic clearance occurs via glucuronidation for numerous drugs and approximately 30% of the total clearance of morphine can be accounted to extrahepatic glucuronidation in cirrhotic patients compared with 10% in controls with normal hepatic function. Thus, it is important to reduce the dosage of morphine in cirrhotic patients to prevent toxicity (Lugo & Kern 2002, p. 13; Hasselstrom et al. 1990, pp. 295-296).

Patients with renal dysfunction have lower clearance and longer elimination of morphine's half-life. Therefore morphine-3-glucuronide and morphine-6-glucuronide accumulation can contribute to toxic reaction in patients with renal impairment and this accumulation of morphine glucuronides in patients with renal failure is connected with undesirable side effects such as excessive sedation, respiratory depression and myoclonic spasms (Smith 2009, p. 621; Andersen et al. 2003, p. 78). The enzymes responsible for the metabolism of morphine may also be subject to several factors. Various studies have shown that UGT2B7-mediated morphine metabolism is affected by interactions with other drugs. These drugs may be either inducers or inhibitors of the enzyme (Bryant & Knights 2011, p. 142; Trescot et al. 2008, p. 142).

Enzyme induction

Research into the induction of many UGT enzymes tends to depend on *in vitro* experiments conducted with primary cultures of human hepatocytes or cultured human cell lines (Kiang et al. 2005, pp. 105-106). Inducible human UGT enzymes include UGT1A1, UGT1A3, UGT1A6, UGT1A9 and UGT2B7. In addition, several inducers of UGT enzymes may raise the expression level of different drug-metabolising enzymes, for example cytochrome P450. Enzymes such as carbamazepine, phenobarbital, rifampicin and phenytoin also enhance UGT-mediated glucuronidation reactions; however, they tend to be inducers of different cytochrome p 450 enzymes (Kiang et al. 2005, pp. 105-106). The findings of current studies indicate that the same set of transcription factors perform to regulate the expression of several drug-metabolising enzymes, including UGT1A1 (Kiang et al. 2005, pp. 105-106**).**

Enzyme inhibition

Many drugs have been recognized *in vitro* as inhibitors of UGT-mediated glucuronidation reactions. Furthermore, immunosuppressants have been shown to be particularly potent UGT inhibitors, as demonstrated by the inhibition of mycophenolic acid glucuronidation in human kidney microsomes via tacrolimus and cyclosporine (Kiang et al. 2005, pp. 105-106). Other *in vitro* UGT inhibitors include benzodiazepines, tricyclic antidepressants and nonsteroidal anti-inflammatory drugs. Diclofenac is also a comparatively strong UGT inhibitor, although its influence is not enzyme-selective (Kiang et al. 2005, pp. 105-106).

Additionally, probenecid and valproic acid are usually applied as *in vivo* inhibitors of UGT; however, the particular UGT enzymes suppressed by these drugs *in vivo* are not identified. Furthermore, at concentrations comparable with those *in vivo*, probenecid suppresses many UGT1 enzymes *in vitro* and UGT1A7 is the most responsive. Valproic acid suppresses UGT2B7-catalysed zidovudine (AZT)-glucuronidation *in vitro* with a *K*i of 1600 μM; however, it has little or no influence on UGT1A1, UGT1A6, UGT1A9 or UGT2B15 (Kiang et al. 2005, pp. 105-106).

Section 4. Drug-Drug Interactions

7) For your drug:

a) List all known drug-drug interactions involving the metabolism of your drug.

Drug-drug interactions with morphine are uncommon. Tresco et al. (2008, p. 142) show that drugs which perform to inhibit the UGT2B7 pathways can change the amount of M3G and M6G available. Drugs that are considered the most potent inhibitors of this pathways are benzodiazepines, ranitidine, rifampin, diclofenac, ketamine, naloxone, amitriptyline, nortriptyline and clomipramine, chloramphenicol, tricyclic and heterocyclic antidepressants, carbamazepine, fluconazole, tamoxifen and valspodar (Tresco et al. 2008, p. 142; Armstrong & Cozza 2003, p. 169; Bryant & Knights 2011, p. 187). However, the findings of other studies indicate that ranitidine and rifampin have a strong ability to change morphine metabolism (Tresco et al. 2008, p. 142).

b) Explain the mechanism of each of the interactions (i.e. Drug A inhibits the metabolism of Drug B by Enzyme X).
c) Note the clinical consequences of each of the interactions (e.g. increases the plasma concentration of Drug B leading to an enhanced pharmacological effect and toxicity).

Benzodiazepines

All the benzodiazepines (diazepam, lorazepam, nitrazepam, clonazepam, flunitrazepam, oxazepam and N-desmethyldiazepam) inhibit UGT enzymes and reduce the formation of M3G and M6G. Thus, benzodiazepines decrease the glucuronidation of morphine between 42% and 86% and can alter morphine's metabolism. Clonazepam is the strongest inhibitor, while nitrazepam is the least powerful inhibitor among the benzodiazepines. Morphine in combination with a benzodiazepine can generate over sedation, as well as the occurrence of respiratory depression (Armstrong & Cozza 2003, p. 169; Borchardt 1999, p. 70; Pacifici et al. 1988, p. 1).

Ranitidine

Ranitidine acts to reduce the ratio of either ratio of M3G of M6G produced by morphine metabolism. On the other hand, the AUC of morphine M3G and M6G and the urinary ratio of M3G to M6G are not impacted. Ranitidine does not prevent the creation of M6G and M3G. M6G is also more efficient in producing analgesia and adverse effects than morphine, while M3G may suppress the action of morphine. Thus, a change in the proportion of M3G to M6G can have an influence on the pharmacological and toxicological effects of morphine, and the combination of morphine and ranitidine can cause clinically important adverse effects (Kiang et al. 2005, p. 106; Lugo & Kern 2002, p. 14). However, Armstrong & Cozza (2003, p. 169) indicate that ranitidine acts to reduce the serum M3G and M6G ratio and raises the AUC of morphine, making it probable that ranitidine inhibits UGT2B7 and 1A3.

Rifampin

Rifampin induces an absolute lack of analgesia because of the decrease in morphine-6-glucuronide (M6G) concentration in the plasma. It acts to reduce the AUC of morphine and reduces M3G and M6G so that pain thresholds are the same as if a placebo were administered. Although, rifampin does not reduce effectiveness of morphine, the reduction in AUC of UGT metabolites M3G and M6G has been suggested as a probable mechanism, rather than the induction of UGT enzymes (Armstrong & Cozza 2003, p. 169; Lugo & Kern 2002, p. 14).

Diclofenac

Diclofenac binds irreversibly to the UGT enzyme responsible for metabolism of morphine, forming an inactive complex. It acts to reduce morphine consumption by 20% while levels of M6G are not changed. The mechanism has not been identified but it possibly occurs through suppression of renal clearance of M6G, instead of UGT inhibition. This increases the plasma concentration of morphine (Armstrong & Cozza 2003, p. 169).

Ketamine

UGT2B7 is the main human UGT that encourages the production of morphine glucuronide. Recombinant human UGT1A1 and 1A8 are able to form M3G but their activities are small compared with UGT2B7. Furthermore, UGT1A8 is not expressed in the liver. Ketamine is metabolised principally by *N*-demethylation to norketamine via cytochrome P450 (Xiaoxin Qi et al. 2010, pp. 729-731).

Ketamine can occupy locations on the UGT(s) which result in a decrease in the creation of M3G. Therefore, ketamine decreases the clearance of morphine by 54% ($P<0.05$) because of suppression of the hepatic UGT(s) which stimulates M3G and M6G formation (Xiaoxin Qi et al. 2010, pp. 729-731).

Naloxone

Naloxone is a competitive antagonist and is categorized as a pure antagonist of the natural opioid receptors. Naloxone has a strong affinity for all of the three classical opioid receptors (delta (δ) kappa (κ) and mu (μ)) but its strongest affinity is for the mu (μ) receptors (Bullock & Manias 2011; Bryant & Knights 2011). Thus, Naloxone acts to block morphine action by competing for morphine receptor sites and reverses most

effects of morphine such as respiratory depression and coma (Aschenbrenner & Venable 2009, p. 391; Lehne 2010, p. 278).

Amitriptyline, nortriptyline and Clomipramine

These drugs are able to inhibit UGT enzymes and reduce the metabolism of morphine, thus decreasing the production of M3G and M6G. Consequently, they contribute to the accumulation/toxicity of morphine in the body and reduce the efficacy of morphine (Armstrong & Cozza 2003 p169).

Chloramphenicol

Chloramphenicol increases the inhibition of UGTs leading to the inhibition of morphine's glucuronidation (Armstrong & Cozza 2003, p. 169).

Drug Profile activities for Module 4

Section 1. Drug absorption

8) For your drug:

a) Determine and state the oral bioavailability

Bioavailability can be defined as the percentage of the administered dosage which gets to the systemic circulation as whole drug (Bryant & Knights 2011, p. 135). The amount of drug getting the systemic circulation is determined by two factors:

- The proportion of the drug that is absorbed from the gastrointestinal area, which differs extensively for orally administered drugs (Bryant & Knights 2011, p. 135).
- The proportion of the drug escaping extraction via the liver (hepatic first pass metabolism) (Bryant & Knights 2011, p. 135). The oral bioavailability of morphine is usually 20% (Mckay et al. 2010, p. 256). However, Bryant & Knights (2011, p. 295) indicate that morphine can have a poor bioavailability of around 40% if given orally.

b) Discuss whether the bioavailability is influenced by gastrointestinal absorption, first pass hepatic extraction or both?

The gastrointestinal tract is the main location of drug absorption. For morphine (the basic drug), the small intestine is the better site for absorption because it has a large surface area, which allows greater and faster absorption (Bullock & Manias 2011, pp. 139-140). In addition, oral morphine is quickly absorbed in the upper bowel and undergoes extensive metabolism on its first pass through the liver (Bullock & Manias 2011, pp. 139-140). Morphine is not well absorbed if it is administered orally and has low and variable bioavailability because of the extensive first-pass metabolism in the liver (Bryant & Knights 2007, p. 264; Bullock & Elizabeth 2011, p. 139). Therefore, because of the high hepatic extraction ratio, the oral bioavailability of morphine is highly impacted by the first pass extraction within the liver, such that 30mg oral morphine is equal to 10mg morphine administered IV, IM and SC (Bryant & Knights 2011, p. 135).

Additionally, Hoskin et al. (1989, p. 499) indicated that the absolute bioavailability of morphine is 23.9% in an oral aqueous solution, 22.4% in a controlled release oral tablet (MST-Continus) and 18.6% in a controlled release buccal tablet (Hoskin et al 1989, p. 499). However, some studies indicate that the bioavailability of oral morphine can be enhanced significantly by taking with a high-fat meal (Aschenbrenner & Venable 2009, p. 382; Bryant & Knights 2007, p. 295; Lehne 2010, p. 267). Oral absorption of immediate- release (IR) morphine, such as tablets and solutions, is nearly achievable and peak plasma concentrations are 5 to 10 times less than those acquired following parenteral administration and happen between 30 and 90 minutes. After oral administration, quick and extensive first pass metabolism occurs and the average bioavailability is 30% to 40%, though this can vary between 19% and 47% (Lugo and Ken 2002, pp. 9-10).

Moreover, absorption of morphine can be associated with the timing of administration as there are circadian rhythms that alter the absorption in the upper areas of the gastrointestinal tract. Because of morphine's short half-life, immediate release dosage forms should be administered every 4 hours. Furthermore, if administered orally as a single dose, morphine is a poor analgesic and the oral to parenteral ratio is 1:6 to 1:8. However, if given in repeated doses, morphine will be more efficient in curing pain, mainly because of the creation of large amounts of active metabolite M6G through the first pass by the liver leading to the increase of M6G in the central nervous system with repeated doses (Lugo and Ken 2002, pp. 9-10).

In addition, in the treatment of patients with chronic cancer pain, the oral to parenteral potency ratio is 1:2 to 1:3 after repeated doses. Therefore, a patient who is getting 10 mg intravenous morphine every 4 hours by may have their dose changed to 30mg immediate release morphine every 4 hours or 90mg controlled release morphine every 12 hours (Lugo and Ken 2002, pp. 9-10). Demand to increase the dosing interval is increasing due to the improvement of the controlled release (CR) formulation and the complete bioavailability after administration of CR morphine is similar to that of an oral solution. Thus, no dosage adaptation of CR morphine is needed if switching between IR and CR formulation and peak plasma concentrations happen 2 to 3 times later than with IR morphine. As a result, a patient who is treated with CR morphine should be cured of breakthrough pain using IR morphine. The elimination half-life of CR morphine is similar to that of the IR formulation (Lugo and Ken 2002, pp. 9-10).

On the other hand, parenteral administration of morphine helps to avoid hepatic biotransformation (the first pass effect) and the glucuronide concentrations are low compared with oral administration. Thus, parenteral administration of morphine is a quicker and more effective pain control than oral preparations (slower route) and is better for patients for whom oral administration is precluded or for patients with poor gastrointestinal absorption (Mahajan et al 2011, p. 89; Mercadante 2010, p. 484). The parenteral route is therefore a quick method of drug administration and a high concentration of drug is transferred rapidly into the systemic circulation. Absorption of the drug from intramuscular injection and subcutaneous locations is quicker than by the oral route but is less acceptable when local blood flow diffusion throughout tissues impedes absorption (Trescot et al. 2008; Bryant & Knights 2007, p. 295; Lehne 2010, p. 267).

c) If your drug is only available as a parenteral formulation discuss whether that is principally due to problems with gastrointestinal absorption or excessive first pass metabolism.

Morphine can be administered by oral route for example as a solution, as tablets (5-30mg) and as sustained-released preparations (10-200mg) (Bryant & Knights 2011, p. 293).

Section 2. Drug formulation and routes of administration

9) For your drug:

a) List all of the dose forms and strengths available in Australia. (Identify brand names only if they are important for distinguishing between dose forms or they describe combination products)

Sevredol ® 10 mg tablets scored blue; 20 mg tablets scored pink (Australian Medicines Handbook; AMH 2008, p. 52-53).

Anamorph ® 30 mg tablets scored white (Australian Medicines Handbook; AMH 2008, pp. 52-53).

Ms Contin® 5mg tablets (controlled release, white); 10mg tablets (controlled release, tan); 15mg tablets (controlled release, light green); 30mg tablets (controlled release, purple); 60mg tablets (controlled release, orange), 100mg tablets (controlled release, grey); 200mg tablets (controlled release, turquoise) (Australian Medicines Handbook; AMH 2008, pp. 52-53).

Kapanol® 10mg capsules (controlled release, clear); 20mg capsules (controlled release, clear); 50mg capsules (controlled release, clear); 100mg capsules (controlled release, clear) (Australian Medicines Handbook; AMH 2008, pp. 52-53).

MS Mono® 30 mg capsules (controlled release, light blue); 60mg capsules (controlled release, brown); 90mg capsules (controlled release, pink); 120mg capsules (controlled release, green) (Australian Medicines Handbook; AMH 2008, pp. 52-53).

Ordine® oral liquid, 1mg/Ml, 200mL; oral liquid, 2mg/mL, 200mL; oral liquid, 5mg/mL, 200mL; oral liquid, 10mg/mL, 200mL (Australian Medicines Handbook; AMH 2008, pp. 52-53).

MS Contin Suspension® oral liquid, 20mg (controlled release, granules); oral liquid, 30mg (controlled release, granules); oral liquid, 60mg (controlled release, granules); oral liquid, 100mg (controlled release, granules); oral liquid, 200mg (controlled release, granules) (Australian Medicines Handbook; AMH 2008, pp. 52-53).

Morphine sulphate

Injection, 5mg/mL, 1mL, 5, Morphine sulphate (MX); injection, 10mg/mL, 1mL, 5, Morphine sulphate (MX), PBS; injection, 15mg/mL, 1mL, 5, Morphine sulphate (MX), PBS; injection, 30mg/mL, 1mL, 5 & 50, Morphine sulphate injection (MX) PBS (Australian Medicines Handbook; AMH 2008, pp. 52-53).

Morphine tartrate

Injection, 80mg/mL, 1.5mL, 5, Morphine tartrate (MX), PBS; injection, 80mg/mL, 5mL, 5, Morphine tartrate (MX) (Australian Medicines Handbook; AMH 2008, pp. 52-53).

b) Discuss any administration issues that are followed for safe efficacious use.

Morphine can be administered orally, IV, IM and SC or rectally. In the case of controlled release tablets (MS Contin®), they should be swallowed whole and not chewed, broken or crushed (Australian Medicines Handbook; AMH 2008, pp. 52-53). Alternatively, when swallowing is hard, controlled release capsules such as Kapanol® or MS Mono® can be split open and the pellets can be scattered on soft food such as jam, apple sauce or yoghurt to help aid administration. Kapanol® can ingested in 30 minutes while MS Mono® can be ingested over 60 minutes or can be mixed with 30 mL liquid (Australian Medicines Handbook; AMH 2008, pp. 52-53; Tiziani 2006, p. 579; AusDI 1999, pp. 1420-1421). However, pellets should not be crushed or chewed and the mouth must be washed to make sure every part of the pellets have been swallowed. For a controlled release suspension (MS Contin®), the contents of the sachet can be mixed with the recommended quantity of water and ingested directly (Australian Medicines Handbook; AMH 2008, pp. 52-53; Tiziani 2006, pp. 579; AusDI 1999, pp. 1420-1421). Also, one should make sure that the accurate strength of syrup is chosen as it can be available in different strengths.

Oral solution reacts to light and should be discarded 6 months after opening. Alcohol should be avoided when taking Kapanol® capsules because it can impact the release of morphine from the capsules and enhances the probability of adverse effects (Australian Medicines Handbook; AMH 2008, pp. 52-53; Tiziani 2006, p. 579; AusDI 1999, pp. 1420-1421). The risk of microbial contamination can be avoided if a morphine sulphate injection is administered within 24 hours of opening (Australian Medicines Handbook; AMH 2008, pp. 52-53; Tiziani 2006, p. 579; AusDI 1999, pp. 1420-1421). Moreover, adverse effects are common with morphine and can be avoided or minimized by checking the dose and patient status carefully, regularly monitoring vital signs, particularly the respiratory rate, and considering the use of an antidote such as naloxone in an emergency (Aschenbrenner & Venable 2009, p. 389). The use of morphine should be avoided in cases of CNS depression, respiratory depression, increased intracranial pressure, cerebrospinal pressure, hypersensitivity, cardiac arrhythmias, head injury, upper airway obstruction and acute or severe bronchial asthma (Aschenbrenner & Venable 2009, p. 389). The use of morphine should be avoided in premature infants and throughout labour if delivery of a premature infant is expected (Aschenbrenner & Venable 2009, p. 389).

Section 3. Drug distribution

10) For your drug determine from the primary literature whether it is bound to plasma proteins

a) State the percent bound

Morphine does not bind strongly to plasma protein (35%), instead binding generally to albumin. It is relatively hydrophilic and as a result, morphine crosses slowly into the

central nervous system. Consequently, oral morphine doses need to be 2-6 times higher than parenteral administrations (Bryant & Knights 2007, pp. 119-265; Trescot et al 2008, p. 142; Lehne 2010, p. 267).

b) Calculate the unbound fraction

The unbound fraction of morphine is: (100-35) / 100 = 65% or 0.65 (Bryant & Knights 2011, p. 137).

11) For your drug, determine from the primary literature its volume of distribution (VD) in either litres per kilogram (L/kg) or litres (L):

a) Is your drug's V_D small or large relative to blood volume?
b) What does the volume of distribution tell you about the way your drug is distributed throughout the body? (Discuss in terms of plasma protein and tissue binding, distribution into adipose tissue, etc).

Morphine distributes quickly into a wide range of tissues such as the heart, liver, lungs, kidneys, spleen and, to a small extent, the brain. Though morphine has poor lipid solubility, it is distributed throughout the body and it has a distribution volume of approximately from 2.1 to 4.0 L/kg (Lugo & Kern 2002, p. 11). Furthermore, because morphine has poor lipid solubility, penetration of the blood-brain barrier (BBB) is postponed and the peak impact does not happen until 20 minutes after intravenous (IV) administration (Lugo & Kern 2002, p. 11). Protein binding, in particular to albumin and gamma-globulin, at therapeutic doses is only 20% to 40%. As a result, disturbances of protein concentration do not lead to significant effects on the pharmacologically active concentration of drug in patients (Lugo & Kern 2002, p. 11). Following oral administration, only around 40% to 50% of the administered dose gets the central nervous system in 30 minutes for the immediate release morphine and 90 minutes for the extended released form. The reason for this poor penetration is poor lipid solubility, protein binding, quick conjugation with glucuronic acid and ionization of the drug at a physiological pH (Lugo & Kern 2002, p. 11; Trescot et al. 2008; Bryant & Knights 2011, p. 295). Morphine concentrations in skeletal muscle can be much lower; however, this tissue acts as a major reservoir for the drug due to its larger bulk. Although blood flow to fatty tissue is less than that to highly perfused tissues, build up may be significant, specifically after repeated high dose administration or constant infusion of morphine (Katzung et al. 2009).

12) For your drug (*Answer 13a OR 13b*):

a) If given as a loading dose, indicate the usual loading dose.

Morphine administration as a loading dose is possible because morphine has a poorer onset of action than more than lipid soluble opioids used for analgesia; therefore, a loading dose can be needed to have an effect (Aubrun et al 2007, p. 124). This dose would normally be between 2.5 to 15 mg given slowly via intravenous injection over a period of four to five minutes diluted to at least 4 to 5 ml with sodium chloride 0.9% or 0.5 to2 mg/hour via continuous intravenous infusion depending on the diagnosis and condition of the patient (Tiziani 2006, p. 579; AusDI 1999, p. 1421; Aschenbrenner & Venable 2009, p. 380). Newborn babies (neonates) can be administered a loading dose of intravenous morphine in 5% dextrose (100mcg/kg/h) over two hours, followed by a continued infusion of 25mcg/kg/hour whereas, the dose for children is 0.05 to 0.1 mg/kg (Lehne 2010, p. 268; Sabatino et al. 1997, p. 266).

Intravenous administration of morphine is usually required for severe pain relief in the immediate postoperative period. Thus; the use of morphine in small intravenous boluses in the post-anaesthesia care unit (PACU) enables quick titration of the dosage required for sufficient pain relief (Aubrun et al 2007, p. 126). Moreover, Aubrun et al. (2007, p. 127) indicate that intraoperative morphine loading (0.15mg kg) moderately reduced the postoperative pain scales while not significantly decreasing the time required to effect complete pain relief in the PACU or affecting morphine consumption 24 hours postoperatively. However, intraoperative morphine loading dose induces a rise in the occurrence of morphine-related adverse effects (Aubrun et al. 2007, p. 127).

Section 4. Clearance Concepts

13) For your drug (*Answer 14a OR 14b*):

a) If primarily metabolised by the liver (i.e. if fe is < 0.5):

- Determine systemic (total) clearance.
- Does it have low, intermediate or high hepatic clearance?
- Would you predict that your drug has low, intermediate of high first pass extraction?
- What effect would hepatic enzyme induction or inhibition have on the hepatic clearance of your drug?

Total Clearance = V_d x ($0.693/t_{1/2}$)

where: 0.693 = ln2; $t_{1/2}$ = drug elimination half-life; V_d for morphine = 4; $t_{1/2}$ for morphine = 2 hrs.

Total hepatic CL therefore = (4 x 1000) × (0.693/120) = 23.1 mL/min/kg.

Morphine has a high hepatic clearance with a high first-pass metabolism in the liver prior to entering the systemic circulation. Therefore, the first-pass metabolism decreases the bioavailability of morphine. Morphine has a high hepatic clearance as (CLH > 60 L/h) and high hepatic extraction (EH > 0.67) (Smith 2009, p. 614; Bryant & Knights 2011, pp. 160-295).

Though the systemic clearance of morphine (high hepatic clearance) is not greatly impacted by alterations in drug-metabolising enzyme activity, alterations in enzyme activity will influence the bioavailability of morphine (high hepatic clearance). However, alterations in hepatic extraction (EH) significantly alter hepatic clearance in low hepatic clearance drugs but have an insignificant influence on bioavailability. Clinically, the effect of enzyme induction or enzyme inhibition will depend on the drug and the metabolising enzymes (Bryant & Knights 2011, p. 161).

Section 5. Half-life

14) For your chosen drug:

a) State the half-life.

Morphine has half-life of 1.5 to 2 hours (approximately 120 minutes) (Bryant & Knights 2011, p. 297; Trescot et al. 2008, p. 142).

b) How long will it take (in hours) to reach steady-state after commencing oral administration?

Oral administration of morphine is common for chronic pain and peak plasma concentration activity often happens in the first hour after oral administration. The duration of action is 5 to 7 hours. Although the mean elimination half-life is 2 to 3 hours, this is enhanced with slow release preparations such as capsules, tablets, oral suspensions and granules. As such, a steady state is affected within 4 to 8 hours after oral dosing and therapeutic impacts can last from 16 to 24 hours (Bryant & Knights 2011, p. 295; Abrams et al. 2007, p. 85). The difference in the duration of analgesia compared to the plasma half-life is due to the fact that morphine has a low solubility and so crosses slowly into the central nervous system (Mahajan et al. 2011, p. 89).

c) If the systemic clearance of your drug decreased by 40% calculate the new half-life and time to steady state.

To calculate the new half-life and time to steady state if the systemic clearance of morphine decreased by 40%:
The $t_{1/2}$ = (0.693 x Vd) / clearance (Bryant & Knights 2011, p. 164).

If the clearance is decreased by 40%, this means the new systematic clearance will be 60% of 23.1 mL/min/kg = 13.86 mL/min/kg

The new half-life therefore = (4 x 1000 x 0.693) / 13.86 = 200 mins.

The half-life is useful in estimating the time needed for a drug to reach steady state. One needs approximately four half-lives to attain about 96% of a new steady state. Therefore, the time to reach steady state from the above new half-life = (200 x 4) = 800 mins.

Section 6. Therapeutic Drug Monitoring

15) How is the response to your drug monitored pharmacodynamically when administered in the hospital setting?

The drug response is monitored pharmacodynamically in the body when administered in the hospital setting.

- Before treatment, professional health workers (physicians or nurses) should conduct a physical examination to institute a baseline in order to monitor the drug's influences and assess effects on orientation, affect, respiratory rate, adventitious sounds and the character of bowel sounds. In addition, when the patient has a previous history of liver dysfunction, nurses should conduct liver function tests, as morphine is primarily metabolised in the liver (Aschenbrenner & Venable 2009, p. 383).
- Professional health workers (physicians or nurses) should evaluate the category, site and duration of pain before administering morphine (Aschenbrenner & Venable 2009, p. 383).
- Professional health workers (physicians or nurses) should evaluate the patient for the existence and severity of pain and their present health status may show whether pain can be expected (Aschenbrenner & Venable 2009, p. 383).
- Morphine should be administered before pain reaches its peak to increase the effectiveness of the drug (Aschenbrenner & Venable 2009, p. 389).
- In the hospital setting, a record of pain management with morphine must include the following: 1- the pain scale applied to the patient; 2- the rating stated by the patient; 3- the amount of morphine, route and the time every dose is given; 4- the grade of pain relief gained from morphine treatment; 5- the efficiency of adjunct drug therapy and non-pharmacologic interventions applied; 6- any morphine induced side effects (Aschenbrenner & Venable 2009, p. 389).
- The major issue in morphine treatment is sufficient control of pain balanced against the significant side effects of respiration depression and excessive sedation. Thus, the purpose of treatment is to maintain efficient breathing >10 per minute in spite of respiratory depression (Aschenbrenner & Venable 2009, p. 385).
- Documentation of the occurrence of undesirable adverse effects such as vomiting, nausea, dizziness, bradycardia, flushing and anorexia (Aschenbrenner & Venable 2009, p. 389).
- Naloxone (Narcan) can be given as an antidote to inhibit respiratory depression when morphine overdose occurs (Kee et al 2009, pp. 380-381; Aschenbrenner & Venable 2009, p. 389).

If your drug is used in the pre-hospital setting does the monitoring differ from the hospital setting?

- In the pre-hospital setting, paramedics should assess both the existence and severity of pain and pain should be evaluated using the reliable tools (Alonso-Serra & Wesley 2003, p. 485; Lvovschi et al. 2008, p. 677).
- Paramedics should document the patient's clinical status before and after morphine administration is recommenced (Alonso-Serra & Wesley 2003, p. 485; Lvovschi et al 2008, p. 677).
- Clinical monitoring should include the heart rate, blood pressure, respiratory rate measurements and pulse oximetry (Spo2). Morphine should not be administered when the patient's respiratory rate is less than 12 breaths per minute or Spo2 is less than 95% or if the patient has suffered a serious adverse incident associated with morphine administration, such as bradycardia, hypotension, severe pruritus, vomiting and nausea (Alonso-Serra & Wesley 2003, p. 485; Lvovschi et al. 2008, p. 677).
- Serial measurements using a pain scale must be applied to decide what dose of morphine is sufficient and cardiac monitoring should also be used (Alonso-Serra & Wesley 2003, p. 485).
- Naloxone should be given in case of severe respiratory depression (respiratory rate < 10 breaths per minute) until the respiratory rate is > 12 breaths per minute (Alonso-

Serra & Wesley 2003, p. 485; Lvovschi et al. 2008, p. 677).
- Any significant alteration in clinical status, any corrective action taken and vital signs should be recorded directly based on transport time and patient situation (Alonso-Serra & Wesley 2003, p. 485; Lvovschi et al. 2008, p. 677).

Drug Profile activities for Module 5

Section 1: Life stages as a factor in variability

16) For your drug:

a) Ascertain if dosage is adjusted for age and indicate the change in dosage (e.g. higher or lower in young or elderly etc)

Elderly patients are more sensitive to morphine and current studies have shown that elderly patients (over 60 years of age) have a decreased distribution volume that induces elevated peak plasma concentrations and a decreased clearance of morphine (Lugo & Kern 2002, p. 13).

Infants have decreased ability to carry out glucuronidation; hence, they have a lower clearance, especially in the first few weeks of life. For a neonate more than two months old, morphine's half-life is 6.5±2.8 hours. Morphine clearance increases linearly with postnatal age in the first year of life (Lugo & Kern 2002, p. 13). Consequently, changes in morphine pharmacokinetics, especially in very old or young patients, can lead to a greater risk of undesirable side effects if the appropriate dose of morphine is not adjusted (Lugo & Kern 2002, p. 13).

b) If the dosage is adjusted for age is the change due to altered pharmacokinetic or pharmacodynamic factors? (only answer part b if the dosage is adjusted for age)

In the elderly and in infants less than 1 year, dosages are required to be decreased due to the increased central nervous system sensitivity and reduced clearance (pharmacokinetic factors) (Bryant & Knights 2011, p. 292). In addition, infants do not have a well-developed blood-brain barrier, thus they generally need smaller dosages than older children and adults. The elderly and infants are usually more prone to morphine-induced respiratory depression so the use of morphine with these patients must be carefully monitored (Lehne 2010, p. 262).

Age-related diminution in the glomerular filtration rate influences the clearance of morphine. Thus, accumulation of morphine metabolites that are primarily eliminated by the kidneys may increase the half-life of morphine and increase the risk of toxicity and the significance of drug-related adverse effects (Pergolizzi et al. 2008, p. 291; Lugo & Kern 2002, p. 13; Mangoni et al. 2009, p. 3).

In elderly patients, morphine's active metabolites (M6G) can accumulate due to age-related diminution in renal function or due to relative dehydration. This is particularly clear when morphine is administrated on regular basis. Thus, the accumulation of active morphine metabolites (M6G) contributes to the prolonged half-life and can result in respiratory depression and delirium in these patients (Bryant & Knights 2011, p. 292; Pergolizzi et al. 2008, p. 293; Australian Medicines Handbook; AMH 2008, p. 51).

In the elderly or young patients with renal impairment, morphine glucuronides accumulate, which is connected with side effects such as excessive sedation, respiratory depression, nausea, vomiting and myoclonic spasms (Smith 2009, p. 621; Andersen et al. 2003, p. 78). The elimination of morphine metabolites is decreased in these patients; hence, the accumulation of morphine glucuronides induces elevated plasma concentrations of M6G which can lead to toxic reactions. In addition, the clearance of M3G and M6G has been demonstrated to be closely associated with creatinine clearance (Pergolizzi et al. 2008, p. 300; Andersen et al. 2003, p. 78; Glare & Walsh 1991, p. 16; Lugo & Kern 2002, p. 13). In the elderly or young patients with renal impairment, M6G has a lower plasma clearance and prolonged half-life of elimination (more than week) after a dose of morphine has been given. This is due to the fact that M6G is pharmacologically active and the half-life of M3G is raised from 4 to 41 hours. Pharmacologically M3G is inactive but M3G levels could induce intoxication so the dose of morphine should be decreased in elderly or young patients with renal impairment. This change in dosage is primarily due to pharmacokinetic factors (Andersen et al. 2003, p. 78; Glare & Walsh 1991, p. 16; Pergolizzi et al. 2008, p. 291; Lugo & Kern 2002, p. 13).

Section 2: Impact of disease states

17) For your drug:

a) Ascertain if dosage adjustment is required in individuals with hepatic disease

Patients with hepatic disease can accumulate an active form of morphine M6G so they become more sensitive to the depressant effects of morphine (Bryant & Knights 2011, p. 292). As a result, oral or intravenous morphine dosage should be adjusted carefully in patients with cirrhosis and decompensated chronic liver disease because morphine clearance and volume of distribution are decreased (Bryant & Knights 2011, p. 292; Lugo & Kern 2002, p. 13).

As the liver is the main location for the glucuronidation of morphine, it can be expected that hepatic dysfunction could contribute to changes in morphine metabolism (Andersen et al. 2003, p. 77; Smith 2009, p. 621). This impairment of morphine metabolism is due to a decrease in the intrinsic hepatic clearance. The glucuronidation pathway can be impaired in patients with severe liver disease but this metabolic pathway may be maintained in patients with milder liver disease. Thus, extrahepatic metabolism of morphine can perform a significant role in individuals with limited liver function (Andersen et al 2003 p77).

A previous study in 1990 found that the elimination half-life and peak plasma concentration of morphine were significantly raised in seven patients who have severe cirrhosis. The oral bioavailability of morphine was also higher (65-147%) in these patients than in healthy patients (47%). Moreover, M3G is an inactive metabolite but it is found at higher concentrations in cirrhotic patients than in controls (Smith 2009, p. 621; Hasselstrom et al. 1990, p. 292).

Furthermore, morphine hepatic extraction is 25% lower in patients with cirrhosis and this decrease is conferred by decreased enzyme ability instead of impairment to blood flow (Smith 2009, p. 621). Non-malignant chronic liver disease patients also have lower metabolic production, lower morphine clearance and longer terminal half-life of morphine after morphine administration (Andersen et al. 2003, p. 77).

Consequently, one should administer a lower dosage of morphine to individuals with hepatic disease. This is because patients with liver diseases have a decreased plasma clearance of morphine and protracted elimination half-life of morphine, while increased oral bioavailability of morphine results from a decreased presystemic metabolism in these patients compared with normal liver function. These data clearly demonstrate that patients with cirrhosis and decompensated chronic liver disease should be administered a lower dosage of morphine to avoid toxicity (Lugo & Kern 2002, p. 13; Andersen et al. 2003, p. 77; Hasselstrom et al. 1990, p. 296).

Section 3: Drug dependence, misuse and abuse

18) For your drug;

a) Describe the potential for overdose (intentional or accidental) associated with your drug, the clinical signs and symptoms expected and the patient treatment plan.

The major problem with morphine treatment is balncing sufficient management of pain with the significant side effects. As such, morphine-induced respiratory depression is considered to be one of the major clinical issues in the treatment of acute to severe pain and, consequently, morphine should be stopped when the patient has a respiratory rate lower than 12 breaths per minute. Morphine is also subject to abuse due to its capability to produce pleasurable experiences such as sedation, euphoria and a sensation in the lower abdomen resembling orgasm (Lehne 2010, p. 266; Lvovschi et al. 2008, p. 677; Aschenbrenner & Venable 2009, p. 389).
The clinical signs and symptoms of morphine overdose are:

1) Respiratory Depression
2) Excessive Sedation
3) Constipation
4) Urinary Retention
5) Neurotoxicity
6) Euphoria/Dysphoria
7) Emesis
8) Miosis
9) Elevation of Intracranial Pressure
10) Orthostatic Hypotension (Lehne 2010).

Naloxone is a competitive antagonist and is categorized as a pure antagonist of the natural opioid receptors. It therefore inhibits the action of morphine. Naloxone has a stronger affinity for all three classical opioid receptors (delta (δ) kappa (κ) and mu (μ)) than most agonists, but its highest affinity is for the mu (μ) receptors (Bullock & Manias 2011; Bryant & Knights 2011). Naloxone is used mainly to reverse the undesirable side effects or symptoms of overdose of opioid agonists, such as heroin, morphine and fentanyl. Naloxone acts rapidly and is commonly used to reverse the respiratory depression, papillary miosis (constriction), sedation and euphoria related to high doses of opioid analgesics (Bryant & Knights 2011; Brunton, Chabner, Knollmann 2011).

Newborn babies with respiratory depression can be treated with naloxone when opioid analgesics are used for pain relief during labour. Naloxone is a synthetic derivative of oxymorphone that is given parentally and has a short half-life of around 0.5 to 1 hour. This is much less than opioid agonists such as morphine, which has a long half-life of about 1.5 to 2 hours. Thus, frequent doses of naloxone may be required to ensure that the signs of overdose do not come back (Bryant & Knights 2011; Bullock & Manias 2011; Golan et al 2008). Also, observation of patients who are given naloxone is required for two to three hours after treatment to make sure that they do not relapse. This concern is especially significant in cases of methadone overdose, where the impacts of narcosis may extend for more than 24 hours (Bryant & Knights 2011; Bullock & Manias 2011; Golan et al 2008). Naloxone can be administered via IM, SC or IV routes. The quickest onset is accomplished via IV administration (2 minutes), and this method is recommended in emergency situations (Aschenbrenner & Venable 2009). However, respiratory depression occurring via non-opioids, such as barbiturates, CNS depression or respiratory disease will not commonly respond to opioid antagonist drug therapy (Bryant & Knights 2011).

2. Conclusion

The aim of this study is to present the crucial clinical effects of pharmacological prehospital analgesic therapy. As a result, prehospital pain relief has become a primary task in emergency medical services (EMS) systems and is a fundamental aspect of prehospital analgesic quality in the prehospital emergency care setting. Morphine is commonly used to relieve pain or to manage moderate to severe pain for many patients in prehospital emergency care settings. Morphine has been approved as an effective pain management option by the largest sector of the Australian prehospital emergency care system and has demonstrated a high quality of therapeutic care in the prehospital care setting.

Morphine is initially dependent on the paramedics' pharmacological knowledge and adherence to prehospital pain care clinical guidelines or clinical protocols for increasing the effectiveness of paramedic pain management practice in a prehospital care setting. Furthermore, advanced paramedics are fully educated and highly trained in advanced levels of qualifications—including basic life support skills, advanced life support skills, and resuscitation skills—in relation to opiate-based analgesia. This study demonstrates the efficacy and safety of morphine administration in prehospital emergency care settings and discusses morphine as a pain analgesic agent from the perspective of paramedicine pharmacology studies to improve the quality of the paramedicine curriculum.

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