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SAFE OPIOID PRESCRIBING

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Despite widespread use of opioids for treating pain, they continue to be the medication class most commonly involved in errors relating to prescribing, administration, and monitoring across Canadian hospitals. The Institute for Safe Medication Practices (ISMP) Canada classifies opioids as "high-alert" medications.

Opioid Risks and Patient Harm

Opioids were implicated in 47% of the 115 medication-related deaths in Canada between 2007 and 2012.[1] Hydromorphone was most frequently implicated, followed by morphine and fentanyl patches. Hydromorphone was also the most common medication associated with harmful outcomes reported to ISMP Canada in the past 13 years.[2] Hydromorphone may be more frequently involved due to increased usage over other opioids, higher potency compared to morphine (~5 times more potent than morphine) and multiple formulations and strengths available.

The most serious risk associated with opioids is respiratory depression leading to coma and/or death. Respiratory depression is always preceded by sedation, as a patient will reach the sedation threshold first.[3,4] Errors in prescribing, administration, and monitoring have been identified as the main reasons for opioid-related incidents. Specifically, excessive starting doses in opioid-naïve patients and inconsistent patient monitoring are of major concern.

Equianalgesic and Pharmacokinetic Comparison of Opioids

Opioids can be divided into three classes: phenanthrenes (morphine, codeine, hydromorphone, oxycodone), phenylpiperidines (fentanyl, meperidine) and diphenylheptanes (methadone). Table 1 outlines the differences in potencies of the different opioids.

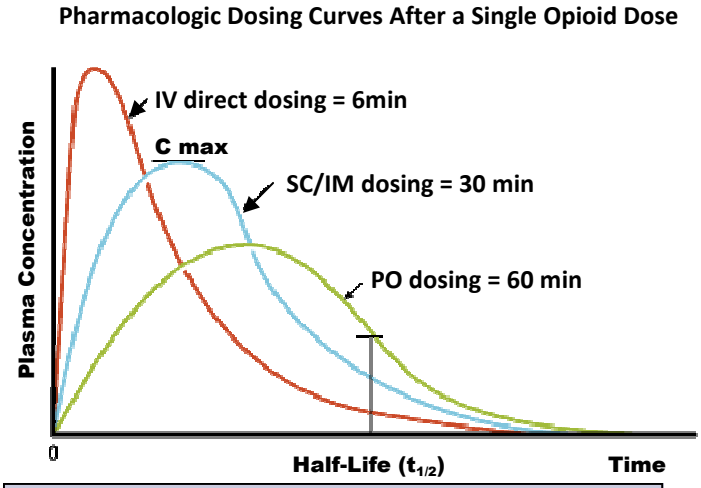
Table 1. Equianalgesic Opioid Doses

Opioid	IV direct (mg)	IM/SC or IV intermittent over 15 minutes (mg)	PO (mg)
Phenanthrene Opioids			
Morphine	1	5	10 to 15
Codeine	-	60	100
Hydromorphone	0.2	1	2
Oxycodone	-	-	7.5 to 10
Phenylpiperidine Opioids			
Fentanyl	0.01 (10 mcg)	0.05 (50 mcg)	-
Fentanyl Transdermal patch	-	25 mcg /hr = 30-66 mg IV/SC morphine/24 hr	25 mcg/hr = 60-134 mg PO morphine/24 hr
Meperidine	10	37.5	150
Diphenylheptane Opioids			
Methadone	-	-	Refer to PDTM

Parenteral routes bypass first-pass metabolism in the liver and thus are at least twice as potent compared to oral administration. As well, there are differences when opioids are administered IV direct versus IV intermittent in a minibag over 15 minutes.

Of most importance, opioid doses given IV direct should be considerably lower than when given IV intermittent. With IV direct administration, there is a quicker onset of action with higher peak levels (Figure 1). IV intermittent administration is more similar in onset and peak effect to subcutaneous (SC) or intramuscular (IM) administration. IV intermittent peak occurs in 20 to 30 minutes versus 30 to 45 minutes for SC/IM.

Figure 1.[3] Time to maximal plasma concentration



Onset and peak effect of opioids:

IV direct > IV intermittent > SC/IM > PO

Initial Opioid Prescribing in Pain Management

Opioid naïve patients are defined as patients who have not had oral morphine 60 mg daily (or equipotent dose of another opioid) for one week or longer.[5] Opioid naïve patients have a lower sedation and adverse reaction threshold and will be more sensitive to the effects and side effects of opioids, including the risk of respiratory depression. A lower initial dose should be prescribed in these patients with a plan to titrate the dose to manage a patient's pain. Gradual dose titration decreases the risk for excessive sedation and respiratory depression. Close monitoring as per current patient care guidelines will allow for safe and appropriate titration.

To help optimize dosing and avoid the use of inadvertent high doses in opioid naïve patients, a table identifying initial dosing for management of ACUTE pain in opioid naïve patients has been created for use at Vancouver Acute (Table 2).

Table 2. Initial Dosing* for Management of Acute Pain in Opioid Naïve Patients

Opioid	IV Direct	IV intermittent over 15 min or IM/SUBCUT	Oral
Hydromorphone	0.1 to 0.4 mg Q10 to 60MIN PRN (max 2 mg/hr)	0.5 to 1 mg Q3 to 4H PRN (**Frail elderly/ sleep apnea:** 0.25 to 0.5mg)	0.5 to 2 mg Q3 to 4H PRN
Morphine	0.5 to 2 mg Q10 to 60MIN PRN (max 10 mg/hr)	2.5 to 5 mg Q3 to 4H PRN (**Frail elderly/ sleep apnea:** 1.25 to 2.5mg)	2.5 to 10 mg Q3 to 4H PRN
Oxycodone	-	-	2.5 to 7.5 mg Q3 to 4H PRN

* doses are not equipotent but reflect initial dosing recommendations for opioid naïve patients

In order to prevent inadvertent overdoses with the IV route, it is recommended the **IV direct route be limited to doses of morphine 2 mg or less and hydromorphone 0.4 mg or less**. The IV intermittent route should be used for doses greater than these, especially in opioid-naïve patients.

Lower initial doses should also be considered for patients with: increased age, decreased weight, impaired renal/hepatic function, interacting drugs/ concurrent CNS depressants, pulmonary disease or conditions that decrease respiratory drive.

Long-acting opioid formulations (i.e. OxyNeo®, Hydromorph Contin®, etc.) and fentanyl patches should not be prescribed as initial therapy in opioid-naïve patients. Fentanyl patches continue to be implicated in harmful outcomes, including death, when prescribed to opioid-naïve patients.[1]

Conclusion

Recommendations to improve opioid safety, especially in opioid naïve patients include:

- Initiate lower doses of opioids in opioid naïve patients (Table 2)

- Initiate even lower doses of opioids in high risk patients, such as frail elderly, those with sleep apnea, renal impairment, or are on concurrent CNS depressants

- Be aware of different opioid potencies (Table 1): : **hydromorphone > oxycodone> morphine**

- Be aware of the differences in routes of administration regarding onset and peak effect: **IV direct > IV intermittent >SC/IM > PO**

- Limit IV administration to IV intermittent over 15 minutes for doses of morphine 2.5 mg or greater and hydromorphone 0.5 mg or greater

- Closely monitor patients receiving opioids as per nursing patient care guidelines.

References

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3. Mount Sinai Hospital. End of life issues and symptom management. Oct 2, 2013. Accessed at: http://geri-em.com/symptom-management/opioid/
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2. SUBLINGUAL FENTANYL AND SUFENTANIL FOR INCIDENT PAIN

Sufentanil and fentanyl are potent opioid analgesics that can be given sublingually (SL) as a short duration analgesic for incident pain (e.g. dressing changes, debridement). Sufentanil is ~ 5 to 10 times more potent than fentanyl and at least 1000 times more potent than morphine. Thus, due to the lower potency of fentanyl, it is recommended over sufentanil for initial treatment of incident pain in opioid-naïve patients.

Fentanyl is slightly less lipid soluble than sufentanil, resulting in longer onset of action and duration of effect (Table 3). Note that ampoules are supplied for both products when the sublingual route is ordered.

Table 3. Fentanyl and Sufentanil Sublingual Comparison

	Fentanyl	Sufentanil
Equivalent Dose	50 to 100 mcg	10 mcg
Dose for Incident Pain	10 to 50 mcg (0.2 to 1 mL) SL pre-procedure. Do not swallow x 5 min after a dose	5 to 25 mcg (0.1 to 0.5 mL) SL pre-procedure (Max 50 mcg). Do not swallow x 2 min after a dose
Onset of Action	5 to 15 min (peak 20 min)	2 to 3 min
When to Administer	10 min prior to procedure	3 to 5 min prior to procedure
Duration	30 to 45 min	10 to 25 min
Monitoring	SS and RR Q5 to 10MIN x 30 min after each dose	SS and RR Q5 to 10MIN x 25 min after each dose

Side Effects

Patients may experience drowsiness, dizziness, nausea, hypotension, or bradycardia. Severe side effects (< 1% incidence) may include tachycardia, chills, pruritus, bronchospasm, or respiratory depression. Respiratory depression is unlikely if lower doses are initiated with appropriate titration.

If respiratory depression occurs (respiratory rate less than 6/minute OR 8-10/minute and patient unable to be roused):
1) call MD STAT;
2) Initiate oxygen at 4 L/minute;
3) give naloxone 0.1 to 0.2 mg IV/SC STAT, then 0.1 to 0.2 mg increments Q10MIN until respirations above 10 /minute.

A drug data sheet can be found in the Pharmacy formulary therapeutic tools section and will be sent with each fentanyl and sufentanil sublingual order. The drug data sheet is located on-line at: http://www.vhpharmsci.com/SAPNF/