

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

Subcutaneous Administration of Ondansetron Case

December 2017

PATIENT CASE

CC is a 61 year old female with colon cancer who has no comorbidities and no known drug allergies. She is NPO as the result of a bowel obstruction, has a colostomy, and has a PEG tube in place for nutrition and medication administration.

Current medications:

- Amlodipine 5mg tablet VPT daily PRN for BP > 130/90
- Lorazepam 0.5mg tablet VPT every 4 hours PRN anxiety
- Morphine 20mg/ml; 0.5ml (10mg) VPT every 4 hours PRN pain
- Dexamethasone 4mg tablet; 2 tablets (8mg) VPT every morning and afternoon
- Ondansetron 4mg tablet VPT every 4 hours for nausea/vomiting
- Omeprazole 20mg via suspension VPT daily for dyspepsia

CC's nausea and vomiting has been palliated with ondansetron tablets via the PEG tube until recently when it has become intractable. The hospice interdisciplinary team concluded that a continuous infusion of ondansetron would be the best intervention for CC. CC's prognosis is weeks and she does not have intravenous (IV) access; therefore, the infusion is ordered to be administered subcutaneously following a recommendation from a local infusion pharmacy:

- Discontinue ondansetron tablets
- Administer ondansetron 4mg subcutaneously once as loading dose, then infuse subcutaneously at a continuous rate of 0.5mg/hr with a bolus dose 0.25mg every 30 minutes as needed for nausea/vomiting.

Although the subcutaneous route of administration is off-label for ondansetron¹, there is literature and expert opinion to support using ondansetron subcutaneously.

SUBCUTANEOUS ROUTE BASICS²

- **Placement:** Cannula inserted at a 45-degree angle into subcut. tissue of the upper chest, upper back, abdomen, upper arms or thigh
- **Duration:** Usually used for short term therapy (<7 days)
- **Frequency of catheter change:** Every 72 hours to an alternate site
- **Volume limit:** In general, subcutaneous tissue can absorb up to 2-3ml per intermittent administration (excluding normal saline flush) or 2-3ml/hr of continuous infusion. Some protocols support up to 5mL/hr and per intermittent administration.³

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

- **Maintenance:** Flush with 0.5ml normal saline (sodium chloride 0.9%) after each medication administration. Heparin is not necessary.

ROLE IN HOSPICE

Continuous subcutaneous infusion (CSI, CSCI) and intermittent subcutaneous injection facilitates the administration of pain and symptom control drugs and have been used for many years in the hospice and palliative care settings. The intravenous (IV) route is typically the standard of care when the parenteral route is required, however, this route can be burdensome to patients and families, and the ability to establish and maintain IV access in certain care environments, especially in the home, may be difficult, if not impossible. Therefore, subcutaneous and other non-oral routes of administration should be considered more often in hospice. Other common alternatives to administer medications include topical, transdermal, rectal and transmucosal routes.^{3,4,5}

Indications for use of CSI include:⁵

- Severe dysphagia
- Mouth, throat and esophageal lesions
- Intestinal obstruction
- Profound weakness
- Poor absorption of oral drugs
- Unacceptable number of oral medications or volumes of syrups which make ingestion difficult
- Unconscious patient
- Intractable symptoms that are not well controlled by oral methods
- Rectal route is inappropriate.

BENEFITS

- Less invasive than IV route and less painful than IM route
- Lower risk of infection than IV route⁶
- Appropriate for patients requiring parenteral medications and in whom IV access is no longer feasible
- May be utilized for both intermittent and continuous infusion
- Studies have demonstrated that SQ infusions can produce the same plasma levels of medications as IV infusions^{7,8,9}

LIMITATIONS

- Short duration of use
- Frequency of catheter change
- Volume maximum requiring use of highly concentrated solutions
- Leakage at the infusion site
- Adverse reactions at infusion site
 - Pneumothoraxes (rare) when placing needles in the chest wall area^{5,10}

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

- Skin irritation including itching, burning and pain
- Bleeding
- Infection
- Many parenteral medications are not labeled for subcutaneous use due to irritant properties

LITERATURE SUPPORT FOR OFF-LABEL USE OF COMMON HOSPICE MEDS (NOT ALL-INCLUSIVE):

Via intermittent subcut. injection

- Dexamethasone^{5,11}
- Diphenhydramine¹²
- Fentanyl²
- Haloperidol^{2,5,6}
- Hydromorphone^{2,5,6}
- Midazolam^{2,5,6}
- Morphine^{2,5,6}

Via continuous subcut. infusion

- Dexamethasone^{3,4,5,11}
- Fentanyl^{3,4,7}
- Haloperidol^{3, 4,5}
- Hydromorphone^{3,4,5,7}
- Ketamine^{3,5}
- Lorazepam⁴
- Methadone^{3,7}
- Metoclopramide^{3,4}
- Midazolam^{3,4,5}
- Morphine^{3,4,7}
- Ondansetron^{3,13-15}
- Phenobarbital^{4,16,17}

Due to reports of tissue necrosis when administered subcutaneously, the following medications **should be avoided** via this route: ⁵

- Antibiotics
- Diazepam
- Chlorpromazine
- Prochlorperazine

Pharmacist Assessment:

Ondansetron is not labeled for subcutaneous administration because the medication is formulated as a sterile, aqueous isotonic solution buffered with citrate, which can cause allergic or toxic reactions to the

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

skin due to its acidic pH. However, in 1996 Macario and colleagues published a case report of a patient who tolerated this route and achieved symptom relief. It was postulated that the slower rate of infusion lent itself to this positive outcome.¹³

In 2012 Reichmann and Kirkbride studied continuous subcut. administration of metoclopramide and ondansetron to treat nausea and vomiting during pregnancy. The result was that continuous subcut. metoclopramide was significantly less-tolerated than continuous subcut. ondansetron (31.8% vs. 4.4%; P<0.001), indicating the superior tolerance of ondansetron treatment over metoclopramide.¹⁴

A 2014 published study examined the tolerability and pharmacokinetic properties of ondansetron administered subcutaneously with recombinant human hyaluronidase PH20 (rHuPH20) in healthy volunteers and mini-pigs. They compared the effect of this therapy to IM, IV, and PO administration of ondansetron monotherapy. The result was that systemic exposure of ondansetron after subcutaneous administration was similar to IM and IV administration and significantly greater than PO administration. Subcutaneous ondansetron and rHuPH20 combination therapy was also generally well-tolerated.¹⁵

Order for patient CC reads, *“ondansetron 4mg subcutaneously once as loading dose, then infuse subcutaneously at a continuous rate of 0.5mg/hr with a bolus dose 0.25mg every 30 minutes as needed for nausea/vomiting.”*

- Ondansetron solution for injection is available in 2mg/mL vials and 32mg/50mL premixed bags with dextrose 5%
- The bolus dose (4mg) would yield a volume of 2mL
- Using the commercial premixed bag, the continuous infusion will yield an hourly rate of approximately 0.8mL/hr
- Intermittent “as needed” doses, will yield 0.25mg each, yielding 0.5mg each hour and equal to approximately 0.8mL each hour
- **Volume of initial bolus at 2mL is appropriate for subcutaneous absorption**
- **Potential maximum infused each hour (continuous infusion plus “as needed” doses) will be 1.6mL and deemed appropriate for this route**

Recommendations

- Continue with ondansetron CSI therapy as ordered
- Place subcut. catheter in the tissue of the upper chest, upper back, abdomen, upper arms or thigh
- Change catheter every 72 hours to an alternate location site to prevent skin irritation and other complications
- Maintain site by flushing with 0.5ml normal saline (sodium chloride 0.9%) after each medication administration and/or bag change. Heparin is not necessary.

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

For additional information on this topic, please review these references:

1. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2017. Accessed 2017 Nov. [Site link](#)
2. Subcutaneous medications and palliative care: A guide for caregivers. Caring Safely at Home: Palliative care education for caregivers. 3rd ed. 2016 April. [Site link](#)
3. Owens D. Interdisciplinary team consult: Continuous subcutaneous infusions. *J Hospice Palliat Nurs*. 2005 Nov/Dec;7(6):310.
4. Herndon CM, Fike DS. Continuous subcutaneous infusion practices of United States hospices. *J Pain Symptom Manage*. 2001;22:1027–1034.
5. NHS Lanarkshire guidelines for the use of subcutaneous medications in palliative care. 2011. [PDF link](#)
6. Bartz L, et al. Subcutaneous administration of drugs in palliative care: Results of a systematic observational study. *J Pain Symptom Manage*. 2014 Oct;48(4): 540-547.
7. Weissman DE. Fast Facts and Concepts #28: Subcutaneous Opioid Infusions. 2015 May. [Site link](#)
8. Nelson KA, et al. A prospective, within-patient, crossover study of continuous intravenous and subcutaneous morphine for chronic pain. *J Pain Symptom Manage*. 1997;13(5):262-267.
9. Dickman A, et al. The Syringe Driver Continuous Subcutaneous Infusions in Palliative Care. Oxford, England: Oxford University Press; 2005.
10. Hutton N, et al. The hospice and palliative medicine approach to caring for pediatric patients In: Hospice and palliative care training for physicians: A self-study program. 3rd edition. Storey CP, ed, et al. 2008; Glenview, American Academy of Hospice and Palliative Medicine.
11. Use of dexamethasone formulations in palliative care: A palliativedrugs.com response to recent changes. Palliativedrugs.com. 2014 Dec.
12. Chen A, et al. Safe use of subcutaneous diphenhydramine in the inpatient hospice unit. *Amer J Hospice Palliat Med*. 2016. DOI: 10.1177/1049909116668160
13. Macario A, et al. Improved outcome with chronic subcutaneous infusion of ondansetron for intractable nausea and vomiting. *Anesthesia & Analgesia*. 1996 Jul;83(1):194-195. [Abstract link](#)
14. Reichmann JP, Kirkbride MS. Reviewing the evidence for using continuous subcutaneous metoclopramide and ondansetron to treat nausea & vomiting during pregnancy. *Manag Care*. 2012 May;21(5):44-7. [Article link](#)
15. Dychter SS, et al. Tolerability and pharmacokinetic properties of ondansetron administered subcutaneously with recombinant human hyaluronidase in mini-pigs and healthy volunteers. *Clin Ther*. 2014 Feb 1;36(2):211-24. [Abstract link](#)
16. Hosgood JR, et al. Evaluation of subcutaneous phenobarbital administration in hospice patients. *Am J Hosp Palliat Care*. 2016 Apr;33(3):209-13. [Abstract link](#)
17. Phenobarbital In: Scottish Palliative Care Guidelines. 2014; Accessed 2017 Nov. [Site link](#)