SPAGG

Coversheet for Specialist Palliative Audit and Guideline Group Agreed Documentation

This sheet is to accompany all documentation agreed by SPAGG. This will assist maintenance of the guidelines as well as demonstrating the governance process undertaken prior to members seeking local approval in their areas of work.

Document Title	**Use of Subcutaneous Proton Pump Inhibitors**
Document Date	20/4/2023
Document Purpose and Intended Audience	This guidance provides information about the use of subcutaneous proton-pump inhibitors in palliative care patients
Authors	Dr Laura Dewhirst Dr Sophie Jones Dr Alice Martin Dr Jon Tomas
References	See end of document
Consultation Process	Circulated to SPAGG group for comments and approval
Monitoring	This guideline will be audited by members of the SPAGG group at least every 2 years.
Review Date (must be within three years)	5/7/25
Approval Signatures	SPAGG Chair: Dr Jon Tomas SPAGG Secretary: Dr Emma Wooldridge
Date Approved by SPAGG: 5/7/23	
Date submitted to Area Prescribing Committee:	

Use of Subcutaneous Proton Pump Inhibitors

Version History

Version	Date	Summary of change/ process
0.1	April 2023	Guidelines written by Dr Laura Dewhirst, Dr Sophie Jones, Dr Alice Martin and amalgamated into SPAGG format. For circulation to SPAGG.

Contents

1. SCOPE OF GUIDANCE

This guidance has been produced to support patients requiring specialist palliative care input for symptom control management who may need to be considered for administration of subcutaneous (SC) proton pump inhibitors (PPI) when an alternative route is not suitable/desirable.

2. GUIDELINE BACKGROUND

This guidance has been developed to establish a degree of consensus, alongside published case reports, around the use of SC PPI in clinical practice in patients with a palliative diagnosis. Currently there is low quality evidence available.

SC use of PPIs in palliative care patients

Patients with palliative care needs may require treatment to suppress gastric acid secretions, for example in the management of malignant bowel obstruction, gastrointestinal bleeding (treatment and prophylaxis), dyspepsia and reflux symptoms[1]. These patients commonly have swallowing difficulties, therefore necessitating alternate routes to administer medications. Enteral tubes and intravenous cannula can be uncomfortable, invasive and difficult to maintain long term in community settings; consequently, many medications are given subcutaneously.

The use of parenteral ranitidine (a H_2 Receptor Antagonist) had been popular for its use in palliative care patients with malignant bowel obstruction where oral route was not an option. Since 2019, though, the manufacture of ranitidine was stopped due to concerns around the drug's safety profile[1,2]. Famotidine, another H_2 receptor antagonist, can also be administered subcutaneously, but this route is unlicensed and there is a paucity of evidence supporting this use. In contrast, PPIs are more readily available and, although their SC administration is also unlicensed, there are some published case reports and small case series[1] which support their use, particularly esomeprazole, omeprazole and pantoprazole. In addition, PPIs are more potent suppressors of gastric acid than H_2 receptor antagonists[3,4], and are the preferred choice for treating un-investigated dyspepsia.

The choice of PPI will be influenced by numerous factors, including: drug availability, costing, side effect profile, as well as local guidance and formulary classifications.

All medication decisions should be on an individual patient basis and take into account likely risks, potential benefits and patient wishes. Most often, stopping medications is the preferred option to switching route if the patient is unable to swallow.

3. TREATMENT OPTIONS

Mechanism of action

PPIs inhibit gastric acid secretion by irreversibly inhibiting the proton pump (H^+/K^+ - ATPase), thereby blocking gastric acid secretion[5].

Common Indications in Palliative Care

- Dyspeptic symptoms unresolved by other medications/distressing to patient without treatment
- Prevention and treatment of gastro-intestinal (GI) bleeding
- Malignant Bowel Obstruction

Dosing

There is currently insufficient published evidence to recommend one PPI over another. Accordingly, this guidance suggests that any of the following PPIs would be a reasonable option.

Reduce doses in severe hepatic impairment.

Esomeprazole:

- 40mg diluted in 50mls 0.9% sodium chloride, administered by subcutaneous infusion over 20 minutes – 1 hour as a single daily dose [1,9]

- 20mg diluted to a total volume of 33mls (or 40mg to 66mls) using 0.9% sodium chloride and administered by CSCI/24 hours [1,7]

Pantoprazole:

- 40mg, diluted in 10mls 0.9% sodium chloride, administered as a SC bolus over 2 minutes as a single daily dose[1,10]

Omeprazole:

- 40mg diluted in 100mls 0.9% sodium chloride, administered by SC infusion over 3-4 hours as a single daily dose[1,11]

Diluent

0.9% sodium chloride recommended

Compatibility

PPI injections/infusions are alkaline after reconstitution and should therefore not be mixed with other medications[1].

Esomeprazole may appear yellow after mixing[1].

Side effects noted in the literature

- Local site irritation[6,7,8]

Cautions [1,5]

- Maximum daily dose should be reduced in severe hepatic impairment
- Rebound acid hypersecretion and dyspepsia can occur after stopping long term PPIs
- May increase risk of gastro-intestinal infections e.g. clostridium difficile
- May reduce absorption of vitamin B12
- May increase risk fractures when used at high doses for >1 year (less likely in our cohort)

- Severe hypomagnesaemia if used long term
- Increased risk of pneumonia
- Hyponatraemia (risk Syndrome inappropriate ADH with PPI use)

Interactions

Esomeprazole and omeprazole are weak-moderate inhibitors of CYP2C19. Important interactions include:

- Inhibition of the metabolism of **citalopram** and **escitalopram**, increasing the risk of QT interval prolongation (see SSRIs and QT prolongation); the maximum daily dose should be reduced (see SPC) [10]
- A reduction in the antithrombotic effect of **clopidogrel** (a pro-drug activated by CYP2C19); avoid concurrent use with any PPI, use an H_2 antagonist instead [11]
- Inhibition of the metabolism of **diazepam**
- Inhibition of the metabolism of **warfarin**; isolated reports of raised INR with all PPIs. [9]

4. ROLE OF OTHER AGENTS

H_2 Receptor Antagonists

Although SC Ranitidine is no longer in production, famotidine is widely available and, although unlicensed for SC administration, there are reports of safe use via this route though evidence is lacking. Famotidine injection is not available in the UK but can be imported as a special product – liaise with your pharmacy teams for further advice and costings.

Suggested administration guidance as per PCF8:

Famotidine 20mg can be given IV b.d. diluted to 5mL with sodium chloride 0.9% and given over 2min

- Famotidine 20mg SC b.d. as a SC infusion or neat bolus (case series poster, n=35) [11] *or*
- Famotidine 40mg/24h CSCI, using WFI or sodium chloride 0.9% as diluent. [12]

Reduce doses in renal impairment

5. PRESCRIBING INFORMATION

Refer to local formulary/guidance – may be specialist use only. Some items are classed as hospital only and therefore will affect community availability.

Omeprazole 40mg powder for solution for infusion vials (pack of 5)
Esomeprazole 40mg powder for solution for injection vials (pack of 5)
Pantoprazole 40mg powder for solution for injection vial (pack of 1 or 5)

Famotidine 20mg/2ml injection vial – (requires fridge storage) – **not available in UK unless special order/import**

6. REFERENCES

[1] Wilcock A, Howard P, Charlesworth S. *Palliative Care Formulary*. 8th ed. Pharmaceutical Press; 2023

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[3]Zhang C, Kwong JS, Yuan RX, et al. Effectiveness and tolerability of different recommended doses of PPIs and H 2 RAs in GERD: network meta-analysis and GRADE system. Sci Rep. 2017;7(1):1-27

[4]Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: a comprehensive review. *Gut Liv*. 2017;11(1):27–37

[5] Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on April 20th 2023]

[6] Thomas B. Malignant bowel obstruction symptoms: subcutaneous bolus esomeprazole-retrospective case series. BMJ Support Palliat Care. 2022 Jan 12:bmjspcare-2021-003510. doi: 10.1136/bmjspcare-2021-003510. Epub ahead of print. PMID: 35022187

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[11] Agar M, Webster R, Lacey J, Donovan B, Walker A. The use of subcutaneous omeprazole in the treatment of dyspepsia in palliative care patients. J Pain Symptom Manage. 2004 Dec;28(6):529-31. doi:10.1016/j.jpainsymman.2004.10.005. PMID: 15589074

Audit Form

Monitoring of the guideline
The use of this guideline will be monitored via regional data collection/audit by SPAGG.
Please use the following audit form to collect data:

Setting of use (please circle)	IPU Hospital Community Other (please state): ………………………………………………………………………
Age	
Sex	
Diagnosis	
Reason for SC PPI	
Switch from oral PPI? (please circle)	Yes No
SC PPI chosen (please circle)	Esomeprazole Omeprazole Pantoprazole
Dose of SC PPI (mg)	
Reason for choice of SC PPI (e.g. availability, familiarity, ease of administration)	
SC PPI administration method chosen (please circle)	CSCI SC infusion SC bolus

Diluent used (please circle)	0.9% sodium chloride Water for injection
Duration of administration (minutes/hours)	
Length of time on SC PPI (days)	
Reason for stopping SC PPI (e.g. no symptomatic benefit, clinical deterioration, death etc.)	
Renal function if known (numerical/NA)	
Evidence of symptomatic benefit (e.g. reduced pain, reduced nausea etc.)	
Adverse events (please circle)	None Site irritation – mild Site irritation – moderate Site irritation – severe Clinically significant renal impairment Clostridium difficile infection Hypomagnesaemia Hyponatraemia Other (please state): …………………………………………………………………..
Comments (please add any additional comments below)	