Title: Pharmacological Management for Dyspnea in Palliative Cancer Patients: Clinical Review and Guidelines

Date: 10 July 2008

Context and policy issues:

Dyspnea, defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity,¹ is one of the most distressing symptoms experienced by terminally ill cancer patients.² Between 50% and 70% of palliative cancer patients experience dyspnea in the last six weeks of life and the condition is aggravated with the progression of cancer.¹,³,⁴ Not only does the condition cause suffering and severely hamper patient’s quality of life, but also greatly challenges the goal of a good death and deeply bothers family and medical professionals.³ As such, management of dyspnea has become one of the most important issues in palliative care.

Among drug therapies for dyspnea are opioids, nebulized opioids, benzodiazepines, corticosteroids, and bronchodilators. This report will review clinical evidence on the use of these therapies.

Research questions:

1. What is the evidence for optimal pharmacological management of dyspnea in palliative cancer patients?

2. What are the guidelines for optimal pharmacological management of dyspnea in palliative cancer patients?
Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and June 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials and evidence-based guidelines.

Summary of findings:

The literature search identified two systematic reviews,\textsuperscript{1,5} two randomized controlled trials (RCTs),\textsuperscript{6,7} and four guidelines.\textsuperscript{8-11} No health technology assessments were identified.

Systematic reviews and meta-analyses

A systematic review by Ben-Aharon, \textit{et al.}(2008)\textsuperscript{1} evaluated pharmacological and non-pharmacological interventions for the palliation of dyspnea. The review included RCTs assessing the effectiveness of dyspnea interventions compared to no intervention, placebo, or another intervention in terminally ill cancer patients experiencing dyspnea. Excluded in the review were trials involving very few (or no) cancer patients and technical procedures such as intrapleural injection, talcage and bronchoscopic stenting. The primary outcome measures were subjective dyspnea relief measured by visual analog scale (VAS), and dyspnea intensity measured by modified Borg scale.

Eighteen trials were included in the review of which seven assessed morphine, six evaluated oxygen (one of which with helium-enriched air), one examined furosemide, and four assessed non-pharmacological interventions. No RCT comparing the use of steroids with placebo or no intervention was identified. Ben-Aharon established that it was not possible to perform a meta-analysis due to the paucity of studies and heterogeneous outcome measures assessed.

Two trials compared nebulized morphine with placebo and two trials compared subcutaneous morphine with placebo. In all four trials, primary outcome measure was defined as subjective dyspnea relief assessed by VAS. Sample sizes of the trials ranged from 9 to 70 patients. In the two trials assessing subcutaneous morphine, subcutaneous morphine was found to be significantly more effective compared to placebo. No significant benefits of nebulized morphine were observed in the two trials comparing nebulized morphine with placebo. Subcutaneous morphine was compared with nebulized morphine in one trial. No statistically significant difference in intensity of dyspnea was observed between the two groups; however, more patients preferred nebulized morphine at the end of the study. No adverse events were noted throughout the trial.

The role of midazolam as adjunct therapy to morphine in managing severe dyspnea was examined in one trial,\textsuperscript{7} designed as a three-arm trial: morphine with midazolam rescue doses, midazolam with morphine rescue doses, and morphine and midazolam around the clock with morphine rescue doses. Borg scale (measuring the intensity of dyspnea) and the percentage of patients who experienced dyspnea relief were the outcome measures. The results showed that more patients reported a significant improvement in dyspnea in the trial arm involving both...
morphine and midazolam administered around the clock. Also, more episodes of breakthrough dyspnea per patient occurred with morphine compared with the combination of morphine and midazolam.

Two trials showed no significant beneficial effect of oxygen over air, neither during rest nor during mild exertion. One trial found equal beneficial effect of air and oxygen. Helium-enriched air (but not oxygen) achieved a significant reduction in dyspnea VAS score in three trials. No adverse events were reported in any of the trials. One study investigated the use of nebulized furosemide and showed that furosemide tended to worsen dyspnea.

Non-pharmacological interventions were assessed in four trials. In three out of the four studies, interventions involved nursing-led programs based on breathlessness rehabilitation technique and focused on emotional experience of symptoms as well. Dyspnea scores were evaluated after 8 to 12 weeks of intervention. All three trials showed a positive effect in terms of reduction in VAS dyspnea scores. In one trial, acupuncture was evaluated; no therapeutic benefit was observed. Though Ben-Aharon, et al. stated the inclusion of 18 trials in total, only 17 trials were reported.

Ben-Aharon, et al. concluded that opioids are effective in the management of dyspnea in cancer patients and stated the following:

There is evidence that subcutaneous morphine is effective in treating dyspnea in advanced cancer patients. The role of nebulized morphine remains less certain because it has been found to be equally effective to subcutaneous morphine, yet was not significantly superior when compared with placebo. (p2402)

A systematic review by Viola et al. (2008) examined the effectiveness of four drug classes (opioids, phenothiazines, benzodiazepines, and systemic corticosteroids) for relieving dyspnea experienced by advanced cancer patients. The authors identified 3 systematic reviews, 2 practice guidelines, 23 fully published RCTs, 2 abstracts of RCTs, and 3 non-randomized trials. Most of the trials examined the effects of opioids, generally morphine, on dyspnea. No relevant trials of systemic corticosteroids in cancer patients were identified. Meta-analysis was not performed due to significant heterogeneity observed among opioid trials and limited number of benzodiazepine and phenothiazine trials.

Two of three systematic reviews identified by Viola et al. evaluated the effectiveness of nebulized opioids on dyspnea. Viola et al. did not provide the details on characteristics and results of the two reviews but reported that the reviews found no evidence in support of the use of nebulized opioids. The third systematic review identified found a significant benefit for dyspnea with systemic opioids.

Of the 23 RCTs and 3 non-randomized studies, six trials included only cancer patients and three involved some cancer patients. Only five trials reported using a washout period and five trials reported sample size. The common outcome measures were VAS, a 100-mm scale from zero (no breathlessness) to 100 (worst possible breathlessness), and the Borg scale, a categorical scale from zero (no breathlessness) to 10 (maximal breathlessness). The quality of the studies varied from very low quality to high quality. Many of the studies were randomized crossover studies with small sample sizes ranging from 5 to 101 patients.

Seven systemic opioid studies found a statistically beneficial effect of opioids on patient-reported breathlessness. Of the seven studies, three evaluated morphine and the rest studied dihydrocodeine. Also, of the seven systemic opioid studies, three (non-randomized) did not
include a placebo comparison. Three randomized studies reported benefits with opioids on exercise duration. Five placebo-controlled studies reported negative results of systemic opioids; four of these evaluated morphine and one studied diamorphine. Compared to placebo, nebulized morphine was found not beneficial in relieving dyspnea or improving exercise tolerance in eight studies. One study found no therapeutic difference in relieving dyspnea between the same dose of morphine administered subcutaneously or administered by nebulizer. Four controlled benzodiazepines trials involving non-cancer patients did not show any benefit for managing dyspnea.

Viola, R. et al. found that main systemic opioid adverse effects were constipation, drowsiness, nausea, and vomiting. There was no significant effect on oxygen saturation with systemic opioids, and the differences in respiratory rate and carbon dioxide levels were clinically small in the three studies reporting significant effects. Overall, this study established that evidence from RCTs and non-randomized studies is contradictory, but a beneficial effect of some systemic opioids on dyspnea and exercise tolerance was found. The authors noted that only three systemic opioids (morphine, dihydrocodeine, and diamorphine) have been studied in controlled trials, and two (oral or parenteral morphine and dihydrocodeine) have been shown beneficial. Studies consistently show that nebulized morphine is not effective in relieving dyspnea.

In their review, Viola R. et al. identified two guidelines for management of dyspnea. The first guideline recommended both corticosteroids and opioids as options for managing dyspnea while acknowledging that the strength of the evidence was weak. The second guideline recommended opioids, steroids, and benzodiazepines for the treatment of dyspnea. The authors noted that in this guideline the evidence was only cited for the opioid recommendations, which were based on a systematic review. In conclusion Viola R. et al. stated that:

systemic opioids, administered orally or parenterally, can be used to manage dyspnea in cancer patients. Oral promethazine may also be used, as a second line agent if systemic opioids cannot be used or in addition to systemic opioids. Nebulized morphine, prochlorperazine, and benzodiazepines are not recommended for the treatment of dyspnea, and promethazine must not be used parenterally. (p329)

Randomized controlled trials

Two RCTs (Navigante et al. and Bruera et al.) were identified. Both are included in the above discussed systematic reviews.

Navigante et al. (2006) conducted a trial in Argentina examining the effect of the benzodiazepine midazolam given in addition to morphine in 101 terminally ill cancer patients experiencing severe dyspnea in the last week of life. Primary outcomes were dyspnea intensity measured by modified Borg scale and dyspnea relief (yes or no) after the intervention. Secondary outcomes were number of subjects requiring rescue medication, and frequency and severity of adverse events. All patients were given subcutaneous morphine and midazolam and were randomized to one of three groups: 2.5 mg morphine every 4 hours around the clock with midazolam rescue for breakthrough dyspnea (group MO); midazolam every 4 hours around the clock with morphine rescue for breakthrough dyspnea (group MI); or a combination of morphine and midazolam every 4 hours around the clock with morphine rescue for breakthrough dyspnea (group MM).

At 24 hours, 92% of patients reported dyspnea relief in the MM group, which was statistically significant compared to 69% (p =0.003) in the MO group and 46% (p = 0.0004) in the MI group. The authors observed no significant decrease in dyspnea intensity among the groups. In 24 hours non-statistical significant breakthrough dyspnea was observed in 34.3% of patients in the
MO group, 36.4% in MI group, and 21.2% in MM group. Navigante et al. concluded that adding midazolam to morphine improved dyspnea control. The study is limited by the fact that it was single blinded and the physician’s knowledge of patient’s therapy regimens may have influenced the need for giving rescue medication for breakthrough dyspnea.

Bruera et al. (2005) compared nebulized and subcutaneous morphine in a double-blinded RCT. Patients were eligible for the study if they had advanced cancer related dyspnea with an intensity of at least 3 on a 0 to 10 scale (0 = no breathlessness 10 = worst breathlessness) and were on oral or parenteral opioids with no dose change for 72 hours. On day 1, patients received either subcutaneous morphine plus nebulized placebo or nebulized morphine plus subcutaneous placebo. On day 2, a crossover was made, and patients received the alternate treatment.

Total of 11 patients completed the study. Dyspnea decreased from a median of 5 (range 3-8) to 3 (range, 0-7) after subcutaneous morphine ($p = 0.025$) and from 4 (range, 3-9) to 2 (range, 0-9) after nebulized morphine ($p = 0.007$). There was no significant difference in dyspnea intensity between nebulized and subcutaneous morphine at one hour. The authors noted that due to limited sample size, there was insufficient power to rule out a significant difference between both routes of administration. They concluded that nebulized morphine is as effective as subcutaneous morphine.

**Guidelines**

Based on the systematic review by Viola R. et al., a Cancer Care Ontario program published clinical practice guidelines for the management of dyspnea in cancer patients. No information was provided about the level of evidence and the following recommendations were made:

**Opioids**
- Systemic opioids, by the oral or parenteral routes, can be used to manage dyspnea in advanced cancer patients.
- Nebulized morphine should not be used to treat dyspnea.

**Phenothiazines, Benzodiazepines, and Systemic Corticosteroids**
- Oral promethazine may be used to manage dyspnea, as a second-line agent if systemic opioids cannot be used or in addition to systemic opioids. Promethazine must not be used parenterally.
- Prochlorperazine is not recommended as a therapy for managing dyspnea.
- No comparative trials are available to support or refute the use of other phenothiazines, such as chlorpromazine and methotrimeprazine, for managing dyspnea.
- Benzodiazepines are not recommended for managing dyspnea.
- No comparative trials are available to support or refute the use of systemic corticosteroids for managing dyspnea in advanced cancer patients. (p1-2)

In 2007, The American College of Physicians published clinical practice guidelines for improving palliative care of pain, dyspnea, and depression at the end of life. The guidelines make the following recommendation with regards to managing dyspnea (see Appendix 1 for grading system per American College of Physicians):

In patients with serious illness at the end of life, clinicians should use therapies of proven effectiveness to manage dyspnea, which include opioids in patients with unrelieved dyspnea and oxygen for short-term relief of hypoxemia (Grade: strong recommendation, moderate quality of evidence). (p144)
Finnish Medical Society Duodecim also published guidelines in palliative treatment of cancer in 2007. The guidelines make the following recommendations with regards to pharmacological management of dyspnea (see Appendix 2 for grading system per Finnish Medical Society Duodecim):

- If pulmonary dyspnoea is moderate, starting with a combination of morphine, corticosteroid, and benzodiazepine works usually best.
- If obstruction is associated (see the Finnish Medical Society Duodecim guideline Long term Management of Asthma):
  - Bronchodilator (inhaled salbutamol; theophylline)
  - Theophylline mixture may bring subjective relief.
- Prednisone 20 to 80 mg x 1 or dexamethasone 3 to 10 mg x 1 to 3 with dose tapering according to response
- Opioids are effective in the treatment of dyspnoea (Jennings et al., 2001) [A].
  - Starting dose with a morphine solution 12 to 20 mg x 1 to 6
  - Starting dose with a long-acting morphine 10 to 30 mg x 2
  - Dose is increased by 20 to 30% (up to 50%)
- Benzodiazepines
  - Lorazepam 0.5 to 2 mg x 1 to 3 orally (p.o.), intramuscular (i.m.), intravenously (i.v.), or 2 to 4 mg/day subcutaneous (s.c.)/i.v. infusion
  - Diazepam (5-10 to 20 mg at night, 5 to 10 mg x 1 to 3 p.o/per rectum (p.r.); 5 to 20 mg/day i.v. infusion
- If necessary, start antidepressive medication.
- Give the patient (written) instructions on medication for acute attacks of dyspnoea: the patient should always have 1 to 2 doses of morphine solution and 1 to 2 doses of benzodiazepine available (e.g., in the pocket, in the purse, or on the bedside table).
- If effective sedation is required
  - Continue the symptomatic medication.
  - Titrate effective morphine medication.
  - Add a benzodiazepine (e.g., diazepam [2.5]-5 to 10 mg [p.o., p.r.] i.v. once every hour until the patient is calm); plan continuous medication on the basis of the dose needed to calm the patient.
  - Haloperidol often enhances sedation (e.g., haloperidol 2.5 to 5 mg i.m./i.v. once every hour until the patient is calm); plan continuous medication on the basis of the dose needed to calm the patient.
- Agree upon emergency medication if a catastrophe, e.g., tracheal bleeding/compression, is to be expected:
  - The patient must not be left alone; stay calm.
  - For example, diazepam 5 to 20 mg i.v. or 10 to 20 mg p.r. +/- morphine 10 to 20 mg i.v./i.m. (the dose is determined by the patient's earlier medication)
  - If necessary, repeat the dose until the patient gets better. In very severe cases, the medication must be repeated, until the patient becomes unconscious. (p4-5)

Except for the recommendation on the use of opioids, no other recommendations above were assigned a grade showing the strength level of evidence.

Fraser Health, British Columbia and the Fraser Valley Cancer Center published symptom guidelines in 2006. The following recommendations were made with regards to pharmacotherapy management of dyspnea:
Opioids

- Opioids are the drug of first choice in the palliation of dyspnea in advanced disease of any cause.
- When dyspnea occurs with most/any activity or for dyspnea at rest, initiate opioids while continuing with non-pharmacological strategies.
- Dose is individualized and titrated until patient states they are comfortable or until restlessness, agitation or apparent breathlessness are controlled in non-verbal/confused patients. Continued titration may be necessary as tolerance develops.
- Nebulized opioids have NOT been shown to be superior to oral opioids and are therefore not recommended.
- Relief occurs in the absence of significant changes in blood gases or oxygen saturation.\(^1\)\(^3\)
- Respiratory depression from opioids is rare and they do not hasten death if appropriately titrated.
- Provide access to prophylactic anti-emetic and introduce palliative care bowel protocol to avoid iatrogenic symptoms when initiating opioids.
- If using parenteral route remember S.C. and I.V. = ½ PO dose (for example 10 mg I.V. or S.C. = 20 mg PO).

**Opioid naïve protocol.**

- Morphine 2.5 to 5 mg PO q4h. Use lower dose in the elderly.
- Hydromorphone 0.5 to 1 mg PO q4h. Use lower dose in the elderly.
- Oxycodone 5mg PO. Titrate dose q4h.
- Consider hydromorphone in the elderly and if there is decreased renal function.
- Breakthrough ½ of q4h dose ordered q1h p.r.n.
  - Opioid tolerant – increase current dose by 25% to 50%.

Corticosteroids

- Corticosteroids are particularly indicated in the presence of bronchial obstruction, SVC or lymphangitic carcinomatosis. They may also be useful in pulmonary fibrosis for brief periods. Taper and avoid long-term use if possible (increased risk of proximal myopathy which can be very debilitating).
- Initiate dexamethasone at 8 to 24 mg PO or S.C. or I.V. daily depending on severity of dyspnea.

Neuroleptics

- Neuroleptics can be a useful adjuvant in chronic dyspnea.
- Methotrimeprazine: starting dose 2.5 to 5 mg q8h and titrate to effect. Start low to test tolerance as wide variation in patient response; may require much higher doses to 25 mg q4h.

Benzodiazepines

- Prescribe on a p.r.n. rather than regular dosing schedule, for severe anxiety and respiratory “panic attacks”.
- Lorazepam 0.5 to 2 mg SL q2-4h p.r.n.

Oxygen

- There are multiple triggers contributing to the sensation of dyspnea. Hypoxemia is only one. Measure oxygen saturation to determine if hypoxemia is a factor in the patient’s experience of dyspnea.
- Careful selection is necessary to identify those people who will benefit from oxygen therapy. Individualized care is paramount.
Hypoxic patients:
• There is low-grade scientific evidence that both oxygen and airflow improve dyspnea in hypoxic patients with advanced disease at rest.
• Provide supplemental oxygen therapy for hypoxic patients according to the Home Oxygen Program guidelines (see Appendix A).

Non-hypoxic patients:
• A systematic review showed that there is insufficient evidence that supplemental oxygen is beneficial for non-hypoxic patients.
• Use other interventions as first line to manage dyspnea with non-hypoxic patients.
• The Home Oxygen Program guidelines will not fund supplemental oxygen at home for non-hypoxic patients.
• If dyspnea is not managed with maximum treatment and medications, refer for hospice palliative care consultations. (p5-6)\(^8\)

These guidelines were based on literature review. The guidelines provide no grade showing the strength level of recommendations. Definitions for the abbreviations used in this guideline are found in Appendix 3.

Limitations
Evidence from three systematic reviews, amid mixed results among individual trials, suggests that oral or parenteral systemic opioids can be used to manage dyspnea. Poor quality of trials included in systematic reviews weakens the strength of the findings. Quality levels of individual trials in systematic review by Viola et al.\(^5\) ranged from very low to high and sample sizes ranged from 5 to 101 patients, whereas in Ben-Aharon et al.,\(^1\) study sample sizes of the trials ranged from 9 to 70 patients. Also, the two systematic reviews report significant heterogeneity among trials, hence restricting meta-analyses.

Comparative evidence on systemic corticosteroids is lacking, hence constituting a major shortcoming of the research literature on dyspnea management in cancer patients. Similarly, high-quality RCTs involving cancer palliative cancer patients examining the effectiveness of systemic opioids other than morphine are lacking. Also, while the existing evidence does not support the use of nebulized morphine, no comparative trials assessing other nebulized opioids have been published.

The above limitations of evidence on pharmacotherapy of dyspnea are directly reflected in the available clinical practice guidelines. The guidelines show significant uncertainty with regards to strength levels of recommendations. In many cases such levels have not been reported. Also, there is inconsistency in the guidelines. For example, benzodiazepines are recommended in the Finnish guidelines but not in the guidelines by Cancer Care Ontario. Currently, it appears that guideline recommendations are drawn from clinical judgment, rather than from scientific evidence.

Conclusions and implications for decision or policy making:
The available evidence from controlled trials supports the use of systemic opioids for managing dyspnea in palliative cancer patients. The use of nebulized morphine is not supported at the present. There is no evidence to support the effectiveness of benzodiazepines on dyspnea. No clinical trials on systemic corticosteroids and bronchodilators were identified. With few exceptions, many studies are not RCTs that involve sufficient numbers of patients to demonstrate statistical significance with adequate power to show therapeutic effects. The
characteristics and results of clinical trials included in systematic reviews raise many clinical questions that perhaps require further research to substantiate conclusions. All guidelines that were identified recommended the use of opioids for treatment of dyspnea. Overall, it appears that opioids may be effective in the treatment of dyspnea, however, additional research regarding this treatment as well as other treatments for dyspnea should be conducted.

Prepared by:
Stephen K Membe, BA (Hon), MDE, Health Economist
Kelly Farrah, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
References:


Appendix 1: The American College of Physician’s Guideline Grading System

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benefits outweigh risks and burden or risk and burden clearly outweigh benefits</td>
<td>Benefits finely balanced with risks and burden</td>
</tr>
<tr>
<td>High</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>Moderate</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>Low</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>Insufficient evidence to determine net benefits or risks</td>
<td></td>
<td>I - recommendation</td>
</tr>
</tbody>
</table>

Source: adopted from The American College of Physician’s guidelines.

Appendix 2: Grading System as Applied by Finnish Medical Society Duodecim

<table>
<thead>
<tr>
<th>Level</th>
<th>Quality of evidence</th>
<th>Basis of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Further research is very unlikely to change confidence in the estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Several high-quality studies with consistent results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In special cases: one large high quality multi-centre trial</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>Further research is very likely to have an important impact on confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One high quality study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Several studies with some limitations</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One or more studies with severe limitations</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Expert opinion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No direct research evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One or more studies with very severe limitations</td>
</tr>
</tbody>
</table>

Source: adopted from Finnish Medical Society Duodecim guidelines in palliative treatment of cancer.

Appendix 3: Abbreviations Used in the Fraser Health Guidelines

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>prn</td>
<td>as needed</td>
</tr>
<tr>
<td>PO</td>
<td>orally</td>
</tr>
<tr>
<td>q1h</td>
<td>every one hour</td>
</tr>
<tr>
<td>q4h</td>
<td>every 4 hours</td>
</tr>
<tr>
<td>q8h</td>
<td>every 8 hours</td>
</tr>
<tr>
<td>q2-4h</td>
<td>every 2 to 4 hours</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SL</td>
<td>sublingual</td>
</tr>
</tbody>
</table>