TITLE: Sufentanil for Palliative Pain Relief: A Review of the Clinical Effectiveness, Cost-Effectiveness and Guidelines

DATE: 18 November 2015

CONTEXT AND POLICY ISSUES

Palliative care is defined by the World Health Organization (WHO) as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of identification and impeccable assessment and treatment of pain and other physical, psychosocial and spiritual problems”.[1] Pain is a frequent component in the constellation of health burdens that occur during end of life treatment and is an important target of palliative care. The Canadian National Palliative Care survey of cancer patients referred for palliative care or admitted to palliative care units across Canada reported that 70% of patients had daily pain, which was considered moderate or worse in 48% of cases.[2] The presence of pain during end of life care is common in patients with cancer, HIV infection and AIDS, multiple sclerosis, cardiovascular disease, and dementia.[3] In addition to substantial detriment to quality of life, pain may hinder an individual’s ability to complete important tasks like putting affairs in order at end of life.[4]

The WHO has stated that all patients have a right to receive treatment for their pain at end of life.[5] Palliative care patients differ from non-palliative patients in that the focus of treatment shifts to symptom management and maintenance of quality of life. Therefore, some of the concerns surrounding pain medication such as risk of addiction may be reduced. Accordingly, criteria for provision of medications differ. For instance, the Ontario Drug Benefit enables exceptional access to certain treatments including opioids for palliative care patients.[6] In 2013, the WHO recommended ibuprofen and morphine in various formulations as essential medicines in palliative care due to demonstrated efficacy of morphine for severe pain and insufficient evidence to support one NSAID over another.[7] Cancer Care Ontario suggests the provision of opioids (morphine, hydromorphone, or oxycodone) for cancer patients with moderate to severe pain.[8] Opioids are one of the most frequently used drug classes in palliative pain management though there is uncertainty regarding the optimal drug and dose.[8]

Sufentanil is a highly lipophilic opioid fentanyl analogue typically used for surgical analgesia with a proposed therapeutic role in cancer pain and opioid tolerance.[9] It is a rapid-onset opioid, a

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group of drugs designed for breakthrough pain that can be absorbed via trans-mucosal route. It has approximately 10 times the potency of fentanyl, and, like fentanyl, does not have active metabolites. Sufentanil is likely safe for use in patients with renal failure and doesn’t decrease bowel transit time or induce nausea and vomiting to the same extent as alternative opioids. Yet, like other opioids there is a risk of skin irritation, bradycardia and other cardiovascular concerns, somnolence and CNS depression, chest wall rigidity, and blurred vision.

Sufentanil is currently indicated for surgical procedures as an intravenous or epidural anesthetic agent so use in pain management outside of this context is off-label. Off-label use of sublingual sufentanil for breakthrough cancer pain has been noted in Canada. There is evidence for the efficacy of sufentanil in pain management, but evidence specific to the context of palliative care is limited. Sufentanil has been observed in small non-randomized studies and case studies to improve breakthrough pain in patients (primarily with cancer) receiving palliative care.

Despite the off-label indication and lack of evidence, sufentanil for palliative pain relief has been mentioned in the Canadian context. Both the British Columbia Ministry of Health and Fraser Health — a provincial health authority in Metro Vancouver — mention sufentanil within clinical practice guidelines for palliative care. These guidelines do not recommend giving sufentanil to opioid naïve patients unless by a palliative care specialist, provide guidance for dosing, and caution against using sufentanil for incident pain when other immediate release or long acting opioids are being used.

Sufentanil is considerably more expensive than short-acting opioids like oral morphine and hydromorphone. The cost of palliative care per patient in Canada was estimated to be approximately $26,000 CAD in urban areas and $31,000 in rural areas, with families assuming approximately 20% of the cost. This highlights the importance of identifying the most cost-effective approaches to elements of palliative care such as pain management.

An evaluation of the evidence behind the use of sufentanil in palliative pain relief is warranted given the proposed and observed off-label use in palliative care, and the mention of sufentanil within palliative care guidelines. Further, the relatively high cost of sufentanil necessitates an evaluation of resource implications. This report will review the evidence on clinical effectiveness and cost-effectiveness, as well as evidence-based guidelines regarding sufentanil for pain relief specifically in the context of palliative care.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of sufentanil for relief of palliative pain?
2. What is the cost-effectiveness of sufentanil for relief of palliative pain?
3. What are the evidence-based guidelines regarding the palliative use of sufentanil?

KEY FINDINGS

One systematic review was identified regarding the clinical effectiveness of sufentanil for the relief of palliative pain. It identified one poor quality study suggesting that there is insufficient evidence to draw conclusions regarding the clinical effectiveness of sufentanil use in the context of palliative care. In addition, no cost-effectiveness analyses or current evidence-based guidelines were identified on this topic.
METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and October 22, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td>Population</td>
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<td>Intervention</td>
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<td>Comparator</td>
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<td>Outcomes</td>
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<td>Study Designs</td>
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Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Health technology assessment reports, systematic reviews (SR), meta-analyses, and evidence-based guidelines were excluded if there was incomplete reporting of methodology or if they were superseded by a more recent, rigorous, or updated review or guideline. Randomized controlled trials and non-randomized studies were excluded if they were included within a selected SR.

Critical Appraisal of Individual Studies

The included SRs were critically appraised using AMSTAR criteria. The methods used when conducting the literature search, study selection, data extraction, quality assessment, and for
summarizing the data were assessed. Summary scores were not calculated; rather, the strengths and limitations of each included study are described narratively.

**SUMMARY OF EVIDENCE**

**Quantity of Research Available**

A total of 390 citations were identified in the literature search. Following screening of titles and abstracts, 388 citations were excluded and two potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these three potentially relevant articles, one publication was excluded because of publication type (non-systematic review article), and one evidence-based guideline was excluded as it did not mention sufentanil.25 One publication26 met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

**Summary of Study Characteristics**

Detailed study characteristics are summarized in Appendix 2.

**Study Design**

One SR26 was identified regarding the clinical effectiveness of sufentanil for the relief of palliative. It searched evidence from database inception to July 2009 and identified prospective and retrospective non-randomized studies. Of the 15 studies included, one retrospective study (published as a letter to the editor in 2008) investigated the clinical effectiveness of sufentanil.12 The other studies assessed other opioids. Results were described narratively and no meta-analysis of studies was conducted.

**Country of Origin**

The SR26 and the single sufentanil-related study12 included in the review were both conducted by authors located in the UK.

**Patient Population**

Studies on patients with cancer-related pain and renal impairment were included in the systematic review.26 While palliative status was not explicitly stated, the study was published in a palliative care journal and the single study12 referring to sufentanil as the intervention specified inclusion of palliative care patients.

**Interventions and Comparators**

The clinical effectiveness of a range of opioids, including sufentanil was assessed.26 The single relevant sufentanil study did not include any comparators. Sufentanil was administered as a continuous subcutaneous infusion starting with a median dose of 95 mcg per hour (range = 15 to 600 mcg per hour) which was adjusted to a median dose of 130 mcg/hour (range = 15 to 700 mcg per hour).
Outcomes

While many different outcomes related to pain, function, safety and quality of life were considered by the studies included in the SR, the one included sufentanil study did not consider formal outcome measures and only discussed the quality of pain control descriptively. No formal methods of measuring pain were reported.

Summary of Critical Appraisal

A summary of study strengths and limitations is presented in Appendix 3.

The SR was well conducted. A non-published a priori protocol was referenced. Duplicate study selection and extraction was not explicitly stated, but reference was made to three authors being involved in the process. A comprehensive literature search was conducted on multiple databases as well as a comprehensive grey literature search. A list of included studies and study characteristics was provided, but a list of excluded studies was not. All studies were assessed for quality using GRADE criteria. Results were presented narratively as there was insufficient evidence to perform a meta-analysis. A high likelihood of publication bias was stated, but the method of assessment was unclear. Both funding sources and conflict of interest (none) were disclosed. The single study assessing sufentanil was difficult to interpret as it was published within a letter to the editor and had several reporting deficiencies. Further, this study did not report any clear efficacy outcomes or adverse events.

Summary of Findings

Detailed study findings are presented in Appendix 4.

What is the clinical effectiveness of sufentanil for relief of palliative pain?

This single study concerning sufentanil within the SR reported that provision of a continuous subcutaneous infusion of sufentanil to cancer patients receiving palliative care and who had previously received other opioids resulted in “generally favorable” responses for pain control.

What is the cost-effectiveness of sufentanil for relief of palliative pain?

No evidence was identified regarding the cost-effectiveness of sufentanil for relief of palliative pain; therefore, no summary can be provided.

What are the evidence-based guidelines regarding the palliative use of sufentanil?

No evidence-based guidelines were identified regarding the palliative use of sufentanil; therefore, no summary can be provided.

Limitations

Reporting

The sufentanil study within the SR was published within a letter to the editor, and consequently, reporting was abbreviated and incomplete. There was very limited information provided regarding study design, patient characteristics, and outcome measures.
Outcome Measures

The outcome measure of ‘effect on pain control’ was reported descriptively. It is unclear how this outcome was measured; therefore, the reliability and validity of this outcome and the findings, in general, could not be verified.

Generalizability

The evidence presented for this study only pertains to sufentanil used as a continuous subcutaneous infusion, not the transdermal sublingual route most commonly proposed for palliative care patients. As such, the generalizability of these findings for other routes of administration may be limited. Similarly, this study concerned cancer patients so it is unclear how this evidence might apply to non-cancer patients receiving palliative care. Patients were not opioid naïve so the study does not describe the appropriateness of sufentanil for patients who had not previously been treated with opioids.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is insufficient evidence to draw conclusions on the clinical effectiveness or cost-effectiveness of sufentanil in the context of palliative pain relief. Further, there are no recent evidence-based guidelines providing recommendations regarding the use of sufentanil in palliative care.

The included SR\textsuperscript{26} was conducted to support a guideline development process aimed at making recommendations for the use of opioid analgesics in the treatment of cancer pain. The published guideline could not include any recommendations specific to sufentanil due to insufficient evidence.\textsuperscript{26} The single study\textsuperscript{12} identified regarding the use of sufentanil in a palliative care setting suggested a benefit to patients in terms of pain control, but reporting deficiencies and the lack of formal outcome measures suggest that these results are unreliable.

Current use of sufentanil to control breakthrough pain is off-label and informed by clinical expertise and patterns of practice rather than direct evidence. Further research on the use of sufentanil in palliative care patients is required to inform appropriate use in this context. Some relevant issues to consider include the ability of palliative care patients with cognitive conditions (e.g., dementia) to hold sublingual preparations in their mouth for the instructed 1 to 2 minutes,\textsuperscript{19} uncertainty regarding appropriate doses, lack of consensus on dose equivalency of sufentanil versus other opioids,\textsuperscript{27} potential adverse effects such as exacerbation or onset of respiratory depression, and risks of concurrent use of other opioids or CYP3A4 inhibitors.\textsuperscript{19} With the recent development of a sufentanil sublingual tablet system (Zalviso; currently not approved by the FDA or Health Canada) as an alternative to intravenous patient-controlled analgesia, the comparative efficacy of different routes of administration also warrants investigation.

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REFERENCES


APPENDIX 1: Selection of Included Studies

390 citations identified from electronic literature search and screened

→

388 citations excluded

2 potentially relevant articles retrieved for scrutiny (full text, if available)

→

1 potentially relevant report retrieved from other sources (grey literature, hand search)

→

3 potentially relevant reports

→

2 reports excluded:
- other (review articles, editorials)(1)
- Incorrect intervention (no mention of sufentanil)(1)

→

1 report included in review
APPENDIX 2: Characteristics of Included Publications

| Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| First Author, Publication Year, Country          | Types and numbers of primary studies included | Population Characteristics | Intervention | Comparator(s) | Clinical Outcomes, Length of Follow-Up |
| King, 2011, UK                                  | N = 15 studies (n = 8 prospective, n = 8 retrospective non-randomized studies) | Patients with cancer pain and renal impairment* | Provision of various opioids † to patients with impaired renal function | Provision of various opioids to patients without impaired renal function; Alternate route of administration; No comparator | Adverse events, pain control, requirement for opioid rotation, toxicity, cognitive function, quality of life |

**Sufentanil Studies Included in King et al.**

| White, 2008, UK                                 | Retrospective chart review; | Terminal cancer patients with advanced malignant disease in the hospital palliative care setting who were previous users of fentanyl, morphine and other opioids, n = 48 | Sufentanil (starting dose 15 to 600 µg/24 hours, median final dose 130 µg/24 hours) | No comparator | Described effect on pain control (no formal efficacy outcomes or harms reported) |

*Noted that patient groups were relevant to palliative cancer care
†Of the 15 included studies, one investigated sufentanil as the intervention. Other studies focused on alternative opioids including alfentanil, pethidine, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine (meperidine), tramadol, oxycodone, buprenorphine, fentanyl, alfentanil, methadone, remifentanil, and naloxone
‡Sufentanil study indicates that patients receiving palliative care were included
UK = United Kingdom
**APPENDIX 3: Critical Appraisal of Included Publications**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>AMSTAR Items</strong></td>
<td><strong>AMSTAR Items</strong></td>
</tr>
<tr>
<td>- Reference made to ‘pre-defined, unregistered protocol’ suggesting a priori design</td>
<td>- List of excluded studies not provided</td>
</tr>
<tr>
<td>- Duplicate study selection and extraction not clearly stated but reference to discussion among three authors suggestive of involvement of at least two authors</td>
<td>- Insufficient evidence to conduct meta-analysis – only narrative summaries presented</td>
</tr>
<tr>
<td>- Comprehensive literature search performed on multiple databases as well as a thorough grey literature search</td>
<td>- High chance of publication bias stated but method of assessment not disclosed</td>
</tr>
<tr>
<td>- List of included studies and study characteristics provided</td>
<td>- Single relevant included study published as a letter to the editor; therefore, there were many reporting deficiencies</td>
</tr>
<tr>
<td>- All studies assessed for quality using GRADE</td>
<td>- Study did not report formal efficacy outcomes or harms just generally described pain relief</td>
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<tr>
<td>- Quality considered in formulation of conclusions</td>
<td></td>
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<tr>
<td>- Funding sources and conflict of interest (none) disclosed</td>
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AMSTAR = Assessing the Methodological Quality of Systematic Reviews; GRADE = Grading of Recommendations Assessment, Development and Evaluation
APPENDIX 4: Main Study Findings and Author’s Conclusions

**Table A5: Summary of Findings of Included Systematic Reviews**

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
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<tr>
<td>King, 2011**</td>
<td>• Very limited low-quality evidence that sufentanil may be beneficial for pain relief in palliative cancer patients that was insufficient to formulate recommendations</td>
</tr>
<tr>
<td>• Sufentanil produced a ‘generally favorable result’ for cancer-related breakthrough pain as a continuous subcutaneous infusion in patients with difficulties using other opioids</td>
<td>• Insufficient evidence or experience to make conclusions about the safety of sufentanil in this patient population – insufficient evidence to make a recommendation for chronic use</td>
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