Methylnaltrexone for Opioid-induced Constipation in Cancer Treatment

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

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Institution	Norwegian Knowledge Centre for the Health Services (Nasjonalt kunnskapssenter for helsetjenesten) John-Arne Røttingen, *Director*
Authors	Movik, Espen, *Project leader, Researcher* Ringerike, Tove, *Researcher* Linnestad, Kristin Kamilla, *Researcher* Hofmann, Bjørn, *Ethicist* Harboe, Ingrid, *Research librarian* Klemp, Marianne, *Research manager*

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Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Norwegian Directorate for Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, October 2009

Key messages

Methylnaltrexone for Opioid-induced Constipation in Cancer Treatment

Background

Constipation is a condition with slow and incomplete bowel evacuation and a pathological increase in the digestive tract transit time. Constipation has a negative influence on the quality of life of cancer patients. The use of opioids is a frequent cause of non-obstructive constipation. The Norwegian Knowledge Centre for the Health Services was asked by The Norwegian Directorate of Health to evaluate efficacy, safety, cost effectiveness and ethical aspects regarding use of methylnaltrexone as adjuvant treatment in patients with cancer in palliative care.

Methods

We searched for studies in several databases. Included studies were critically reviewed. The evidence base was evaluated using GRADE. A simple health economic model was developed using TreeAge software.

Results

- We identified two relevant randomised controlled trials which compared methylnaltrexone to placebo, with a total of 287 patients. Methylnaltrexone was significantly more effective in terms of response within 4 hours, both following the initial dose as well as repeated doses. In the double blind period abdominal pain was the most common adverse effect.
- We found a cost per quality adjusted life year of NOK 718 000. The sensitivity analyses showed that the results were particularly sensitive to the assumptions on quality of life, and the clinical evidence.
- Ethically methylnaltrexone makes it possible to treat vulnerable patients. The treatment can also ease the care for these patients. Low efficiency calls for prioritization.

Conclusions

Our review suggests that methylnaltrexone was more effective than placebo in terms of time to laxation. From an ethical point of view methylnaltrexone may contribute to help a vulnerable patient group and professionals in everyday care. Our health economic model nevertheless does not provide us with the grounds to conclude that the drug is cost-effective.

Executive summary

Methylnaltrexone for Opioid-induced Constipation in Cancer Treatment

BACKGROUND

Constipation is a condition with slow and incomplete bowel evacuation and a pathological increase in the digestive tract transit time. It is followed by symptoms such as a bloated stomach, pain, discomfort and pressure feeling. Constipation has a negative influence on the quality of life of cancer patients. The use of opioids is a frequent cause of non-obstructive constipation. According to the guidelines for palliative cancer care, constipation occurs in 50-60% of patients with advanced cancer. It is nevertheless not easy to estimate – in absolute terms – the number of patients suffering from opioid-induced constipation in Norway at any given time. If oral laxatives alone fail to provide relief, additional treatment with enemas or suppositories may be given. Should this not succeed, one may try methylnaltrexone (Relistor™), a peripheral opioid receptor antagonist derived from naltrexone. The introduction of the methyl group results in increased polarity and lower lipid solubility and thereby limits its passage across the blood-brain barrier. It may thus selectively inhibit the opioid effects on the gastroenteral system without reducing the pain-relieving effect.

METHODS

This report comprises a review of the literature on clinical efficacy and safety as well as a simple health economic model and a chapter on ethical aspects. We searched for studies in the following databases: The Cochrane Library, CRD, Ovid Medline and Embase. Two employees at the Norwegian Knowledge Centre for the Health Services evaluated all titles, abstracts and later potentially relevant studies in full text, against the predetermined inclusion and exclusion criteria. Subsequently included studies were critically reviewed with the aid of a risk of bias checklist. In addition, the evidence base with regard to specific outcomes has been assessed using GRADE.

A simple health economic model was developed using TreeAge software based on clinical trials, literature on quality of life and resource use as well as information provided by clinical experts.

In order to handle ethical issues associated with methylnaltrexone treatment, or the lack thereof, we have employed a method which involves the discussion of a selected

number of moral questions (from a total of 32) which tend to be closely associated with health interventions. No specific literature pertaining to ethics and methylnaltrexone was found.

RESULTS

We identified two relevant randomised controlled trials on the efficacy and safety of methylnaltrexone compared to placebo, with a total of 287 patients. The proportion of patients responding following the initial dose, defined as defecation within four hours, was higher in the methylnaltrexone group compared to placebo, RR 3,65 (2,30 – 5,80). The proportion of patients responding to subsequent doses (after two or more of the first four and after four or more of the total seven doses) was higher in the methylnaltrexone group compared to placebo group (p<0,001). Both studies investigated the time from dose administration to defecation. All comparisons showed that time elapsed was shorter in the methylnaltrexone group compared to the placebo group (p<0,002).

The safety of methylnaltrexone in opioid-induced constipation was investigated through assessment of adverse events and serious adverse events. In the double-blind phase of the studies, abdominal pain was the most prevalent adverse event in the methylnaltrexone group. Flatulence, nausea and dizziness were also apparently associated with the use of methylnaltrexone, but for a lower proportion of patients. Serious adverse events related to methylnaltrexone were in one of the studies' open-label extensions found to be muscular spasms (one patient) as well as abdominal pain reduction in the pain relieving opioid effect (one patient).

We considered the most important outcome measures to be those associated with whether methylnaltrexone produced a higher proportion of patients with defecation within four hours than placebo after the initial dose and whether this effect was maintained following repeated doses. Even though the clinical efficacy associated with methylnatlrexone seemed large, it was based on few patients and events. The evidence base was therefore deemed to be of medium quality. This entails that there is a possibility that future research will affect our confidence in these results significantly, and that future estimates may be different.

HEALTH ECONOMIC ANALYSIS

We made a cost-utility model where methylnaltrexone, administered in addition to traditional laxatives, was compared to a regime of traditional laxatives alone. The models efficacy data were taken from the double-blind phase of the two included studies, extrapolated to 4 months and forming the basis for the calculation of symptom-free time and quality-adjusted life years. Only costs directly associated with methylanltrexone and rescue medication were included. Methylnaltrexone costs NOK 17 369 for 120 days (4 months' treatment) whereas the placebo alternative costs NOK 5163, implying an incremental cost of NOK 12 206. Methylnaltrexone also

provides an additional 0,017 quality-adjusted life years (QALYs). This represents an incremental cost-effectiveness ratio (ICER) of NOK 718 000 per QALY. If one were to prefer a cost-effectiveness threshold of NOK 500 000 per QALY gained, one could not claim that a regime of methylnaltrexone, administered every alternate day, would be cost-effective as an additional treatment for patients with advanced illness and opioid-induced constipation in palliative care. The results should nevertheless be interpreted with caution, given that it rests on the assumptions made. The sensitivity analyses showed that the results were particularly sensitive with regard to the assumptions on quality of life with and without constipation. More studies on efficacy and safety of methylnaltrexone might also have affected the results.

ETHICS

A comprehensive ethical review suggests that methylnaltrexone has the potential to relieve opioid-induced constipation in patients who belong to a particularly vulnerable group. The treatment may also help to alleviate the work burden on staff. Nevertheless, it may draw resources away from other patient groups.

CONCLUSION

Our review suggests that methylnaltrexone is significantly more effective than placebo in terms of the outcome measure response within 4 hours, both following the inital dose as well as repeated doses. The drugs is also significantly better than placebo with regard to the time to defecation, approximately half the responders experienced defecation within half an hour after dose administration. From an ethical point of view methylnaltrexone may contribute to improving the day by day quality of life in a vulnerable group. Our health economic model nevertheless does not provide us with the grounds to conclude that the drug is cost-effective.

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Norwegian Knowledge Centre for the Health Services
PB 7004 St. Olavs plass
N-0130 Oslo, Norway
Telephone: +47 23 25 50 00
E-mail: post@kunnskapssenteret.no
Full report (pdf): www.kunnskapssenteret.no