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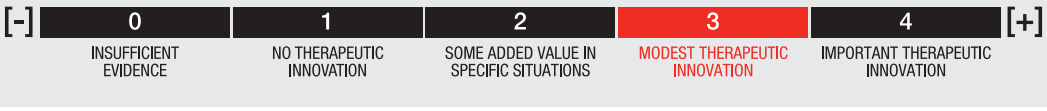
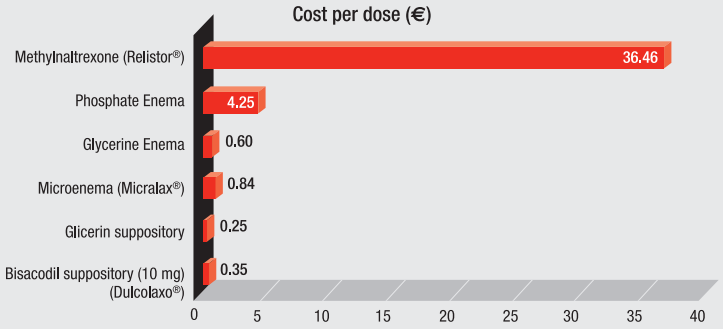
METHYLNALTREXONE▲ FOR OPIOID-INDUCED CONSTIPATION (RELISTOR®)

Subcutaneous route instead of suppository or enema in terminal patients





- The use of methylnaltrexone should be limited to palliative care patients treated with opioids and with no response to common laxatives.
- Its main advantage is the avoidance of suppositories or enemas.
- There is no data regarding use for more than 4 months, and therefore prolonged use is not advised.
- Its cost is considerably higher than common treatments.
- Its benefit-risk relation is only acceptable in patients with a life expectancy of one to six months.

Therapeutic indications[1]

Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient

Mechanism of action and pharmacokinetics[1]

This agent is a selective antagonist of peripheral opioid mu-receptors in the gastrointestinal tract. Methylnaltrexone does not cause any alteration in the analgesic effect of opioids in the central nervous system as it does not cross the blood-brain barrier.

It is rapidly absorbed and peak concentrations are reached in 0.5 hours. It is eliminated primarily in its unaltered active form. Approximately 50% is found in urine and somewhat less in faeces. Its half-life is about 8 hours.

Opioid-induced constipation should initially be treated with usual laxatives

Posology and mode of administration[1]

According to weight:
Between 38 and 61 kg, 8 mg (0.4 ml).
Between 62 and 114 kg, 12 mg (0.6 ml)
Rest, 0.15 mg/kg

It is added to usual laxatives as a rescue agent to induce prompt bowel movements when the common laxatives employed are unsuccessful.

A single dose is administered every other day, although it may be given with longer intervals according to the clinical situation.

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

A consecutive dose may be given after a 24 hour interval in the case where no bowel movement is achieved after administering a dose the previous day.

The agent is administered subcutaneously. The most recommended areas are thighs, abdomen, and the upper arms.

Clinical efficacy[2-4]

The efficacy of methylnaltrexone has been evaluated in two double blind, placebo controlled, randomized multicenter trials. The patients were under stable opioid therapy and laxatives (median: two laxatives) and did not present any bowel movements in the last 24 hours or not more than three bowel movements in the last week. The primary endpoints were percentage of patients with bowel movements without rescue laxatives (enema or suppository) after 4 hours of administering methylnaltrexone and the percentage of patients with bowel movements in the 4 hours following the second, third and fourth doses.

In the first trial[3], methylnaltrexone 0.15 mg/kg (n=62) was compared to placebo (n=71) with administration every 48 hours for a period of two weeks. During the second week the dose could be increased to 0.3 mg/kg if on the eighth day there were less than three bowel movements. Compared to placebo, methylnaltrexone significantly improved the percentage of patients with bowel movements 4 hours after the first dose [methylnaltrexone = 48%, placebo = 15%; NNT = 3 (95%CI, 2 - 6)]. The percentage of patients with bowel movements 4 hours after the second, third and fourth dose was also significantly higher with methylnaltrexone (52%) vs placebo (8%). The study carried on for 3 months with an open phase in which methylnaltrexone was employed on demand with an interval between doses of at least 24 hours. During this phase, between 45 and 58% of the patients achieved effective bowel movements.

In the second study[4], a single dose of metylnaltrexone 0.15 mg/kg (n=47) or methylnaltrexone 0.30 mg/kg (n=55) was compared to placebo (n= 52). The proportion of patients with bowel movements within a four hour period after administration of metylnaltrexone was significantly higher than placebo (61.7%, 58.2% and 13.5%, respectively); NTT = 2 (2 to -3) at the 0.15 mg/kg dose. The trial had an open phase for 4 weeks (n=136) in which, the results were similar to those obtained with the single dose, and posteriorly an extended phase of three more months (only 21 patients).

Studies with methylnaltrexone are limited to a few patients and for a two-week period during the blind phase and up to 3 months in the open phase. The trials did not include any evaluation of the degree of patient satisfaction with this treatment. Long-term efficacy of metylnaltrexone or effects on analgesia or unknown side effects remain unknown.

Safety and precautions[2]

Information on the safety of methylnaltrexone is limited given the short duration of the clinical trials and the scarce number of patients recluted for them.

In the trials, the most frequent adverse effects affected the gastrointestinal and nervous system. When compared to placebo, the incidence of abdominal pain was (28.5% vs 9.8%), flatulence (13.3% vs 5.7%), nausea (11.5% vs 4.9%), dizziness (7.3% vs 2.4%) and diarrhoea (5.5% vs 2.4%).

The incidence of side effects was similar in both groups in active treatment (methylnaltrexone 0.15 mg/kg and 0.30 mg/kg) except for abdominal pain which appeared in 38.2% of the patients administered with the 0.30 mg/kg dose with respect to 23.6% in patients with 0.15 mg/kg.

No safety data is available beyond the three month period. Given the possible safety problems, the indications and approved conditions for use should be strictly adhered to: patients with advanced disease in palliative care and with an inadequate response to common laxatives may be given rescue doses or a dose every other day. In the trials advanced illness was defined as palliative care.

Warnings and precautions[1]

This agent can only be employed in patients under palliative care with opioid-induced constipation.

Methylnaltrexone should be administered as associated therapy with usual laxatives.

Clinical trials have not studied the effects of methylnaltrexone for more than 4 months, and therefore its use should be limited to short periods.

No studies have been carried out on patients with colostomies, peritoneal catheters, active diverticular disease or with fecal impaction. Cases of gastrointestinal perforation in patients with digestive tract disorders such as cancer, peptic ulcer or pseudo obstruction have been reported. Therefore precaution is necessary in these patients.

Special situations[1]

Severe renal failure (creatinine clearance lower than 30 ml/min): the dose should be reduced to 8 mg or to 0.075 mg/kg. There is no data with regard to patients with terminal renal failure in dialysis, and therefore this agent is not recommended in such patients.

Severe liver dysfunction (Child Pugh Class C): in the absence of data on these patients, this product is not recommended.

Place in therapy

Constipation is the most frequent side effect associated with opioid use. It produces discomfort, limits dose requirements and pain management. Common laxatives are necessary in palliative care patients under opioid therapy.

Guidelines recommend anticipating the onset of constipation and combining stimulant laxatives such as senosids with osmotic agents like lactulose[5]. The next step would be to add an emollient laxative like paraffin. If these measures do not produce any satisfactory result then a rescue laxative should be administered (glycerin suppository, bisacodil, enemas) or even, in some cases manual extraction.

Methylnaltrexone could be an alternative option in rescue treatment for those palliative care patients in which constipation is caused mainly by opioid use.

The lack of response could be due to constipation provoked by other drugs administered or to progression of the disease and these factors should be taken into account. The use of methylnaltrexone has not been studied beyond a three month period. It still remains unknown whether long-term use could affect analgesia

Presentations

Relistor® vial 12 mg/0.6 ml, solution for injection (Wyeth Europe Ltd).
Package of 1 vial for injection, 1 syringe and 2 swabs: 44.49 €
Package of 7 vials for injection, 7 syringes and 14 swabs: 255.23 €
Prescription only medicine.

References

All references can be consulted in the complete report on methylnaltrexone, available at: http://www.dtb.navarra.es

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