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[Intervention Review]

Low dose naltrexone for induction of remission in Crohn's disease

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ABSTRACT

Background

Crohn's disease is a transmural, relapsing inflammatory condition afflicting the digestive tract. Opioid signalling, long known to affect secretion and motility in the gut, has been implicated in the inflammatory cascade of Crohn's disease. Low dose naltrexone, an opioid antagonist, has garnered interest as a potential therapy.

Objectives

The primary objective was to evaluate the efficacy and safety of low dose naltrexone for induction of remission in Crohn's disease.

Search methods

A systematic search of MEDLINE, Embase, PubMed, CENTRAL, and the Cochrane IBD Group Specialized Register was performed from inception to 15 January 2018 to identify relevant studies. Abstracts from major gastroenterology conferences including Digestive Disease Week and United European Gastroenterology Week and reference lists from retrieved articles were also screened.

Selection criteria

Randomized controlled trials of low dose naltrexone (LDN) for treatment of active Crohn's disease were included.

Data collection and analysis

Data were analyzed on an intention-to-treat basis using Review Manager (RevMan 5.3.5). The primary outcome was induction of clinical remission defined by a Crohn's disease activity index (CDAI) of $\leq$ 150 or a pediatric Crohn's disease activity index (PCDAI) of $\leq$ 10. Secondary outcomes included clinical response (70- or 100-point decrease in CDAI from baseline), endoscopic remission or response, quality of life, and adverse events as defined by the included studies. Risk ratios (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. The methodological quality of included studies was evaluated using the Cochrane risk of bias tool. The overall quality of the evidence supporting the primary outcome and selected secondary outcomes was assessed using the GRADE criteria.

Main results

Two studies were identified (46 participants). One study assessed the efficacy and safety of 12 weeks of LDN (4.5 mg/day) treatment compared to placebo in adult patients (N = 34). The other study assessed eight weeks of LDN (0.1 mg/kg, maximum 4.5 mg/day) treatment compared to placebo in pediatric patients (N = 12). The primary purpose of the pediatric study was to assess safety and tolerability. Both studies were rated as having a low risk of bias. The study in adult patients reported that 30% (5/18) of LDN treated patients achieved clinical remission at 12 weeks compared to 18% (3/16) of placebo patients, a difference that was not statistically significant (RR 1.48, 95% CI 0.42 to 5.24). The study in children reported that 25% of LDN treated patients achieved clinical remission (PCDAI $\leq$ 10) compared to none of the patients in the placebo group, although it was unclear if this result was for the randomized placebo-controlled trial or for the open label extension study. In the adult study 70-point clinical response rates were significantly higher in those treated with LDN than placebo. Eighty-three per cent (15/18) of LDN patients had a 70-point clinical response at week 12 compared to 38% (6/16) of placebo patients (RR 2.22, 95% CI 1.14 to 4.32). The effect of LDN on the proportion of adult patients who achieved a 100-point clinical response was uncertain. Sixty-one per cent (11/18) of LDN patients achieved a 100-point clinical response compared to 31% (5/16) of placebo patients (RR 1.96, 95% CI 0.87 to 4.42). The proportion of patients who achieved endoscopic response (CDEIS decline $\geq$ 5 from baseline) was significantly higher in the LDN group compared to placebo. Seventy-two per cent (13/18) of LDN patients achieved an endoscopic response compared to 25% (4/16) of placebo patients (RR 2.89; 95% CI 1.18 to 7.08). However, there was no statistically significant difference in the proportion of patients who achieved endoscopic remission. Endoscopic remission (CDEIS < 3) was achieved in 22% (4/18) of the LDN group compared to 0% (0/16) of the placebo group (RR 8.05; 95% CI 0.47 to 138.87). Pooled data from both studies show no statistically significant differences in withdrawals due to adverse events or specific adverse events including sleep disturbance, unusual dreams, headache, decreased appetite, nausea and fatigue. No serious adverse events were reported in either study. GRADE analyses rated the overall quality of the evidence for the primary and secondary outcomes (i.e. clinical remission, clinical response, endoscopic response, and adverse events) as low due to serious imprecision (sparse data).

Authors' conclusions

Currently, there is insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN used to treat patients with active Crohn's disease. Data from one small study suggests that LDN may provide a benefit in terms of clinical and endoscopic response in adult patients with active Crohn's disease. Data from two small studies suggest that LDN does not increase the rate of specific adverse events relative to placebo. However, these results need to be interpreted with caution as they are based on very small numbers of patients and the overall quality of the evidence was rated as low due to serious imprecision. Further randomized controlled trials are required to assess the efficacy and safety of LDN therapy in active Crohn's disease in both adults and children.

PLAIN LANGUAGE SUMMARY

Low dose naltrexone for treatment of active Crohn's disease

What is Crohn's disease?

Crohn's disease is a chronic inflammatory condition of the gut, which can affect people anywhere from the mouth to anus. Common symptoms include abdominal pain, diarrhea and weight loss. People with Crohn's disease who are experiencing symptoms have 'active' disease. When the symptoms stop, it is called 'remission'.

What is naltrexone?

Naltrexone is a long-acting opioid antagonist. It is a drug that counteracts the effects of opoid drugs. This drug is commonly used for the treatment of alcohol and opioid abuse and is taken by mouth. Specific hormones (proteins that transmit instructions in the body) that are known to be involved in pain response may be involved in the inflammation that underlies Crohn's disease. Perhaps by giving people a low dose of naltrexone Crohn's disease can be improved.

What did the researchers investigate?

The researchers studied the effectiveness and safety (i.e. side effects) of low dose naltrexone therapy for inducing remission in people with active Crohn's disease.

What did the researchers find?

This review identified two small randomized controlled trials that included a total of 46 participants. One study compared 12 weeks of treatment with low dose naltrexone (4.5 mg/day) to a placebo (i.e. a fake drug such as a sugar pill) in 34 adult patients with active Crohn's disease. The other study compared eight weeks of treatment with low dose naltrexone (0.1 mg/kg up to a maximum 4.5 mg/day) to a placebo in 12 children with active Crohn's disease. The results from both studies were imprecise with regard to the proportion of patients who achieved clinical remission. The results of the study in adult patients suggest that low dose naltrexone may provide a benefit in terms of clinical response (i.e. an improvement in disease symptoms) and endoscopic response (i.e. a reduction in inflammation of the gut as shown by examining the gut with a scope). We could not tell whether low dose naltrexone led to specific side effects including sleep disturbance, unusual dreams, headache, decreased appetite, nausea and fatigue due to the low number of people who experienced these problems in the studies. The results of this review need to be interpreted with caution as they are based on small numbers of patients and the overall quality of the evidence was rated as low due to lack of precision of the results. Thus no firm conclusions can be made regarding the effectiveness and side effect profile of low dose naltrexone treatment for patients with active Crohn's disease. Further randomized controlled trials are required to assess the effectiveness and side effects of low dose naltrexone therapy in active Crohn's disease in both adults and children.