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Article of the Month

Cannabinoids in cancer pain

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Abstract

This article of the month presents results of a clinical study conducted in the UK and Romania, which evaluated the efficacy of a THC:CBD cannabis extract (Sativex®) and a THC cannabis extract in the treatment of 177 patients with cancer pain, who experienced inadequate pain reduction despite intake of opioids [Johnson et al. J Pain Symptom Manage, 2010, in press]. Sativex resulted in a significant improvement of mean pain scores on a primary outcome measure, a Numerical Rating Scale (NRS) from 0 to 10 compared to placebo (improvement of -1.37 versus -0.69), while the THC extract caused a non-significant improvement (-1.01). Conversely, there was a significant improvement in total pain according to the Brief Pain Inventory-Short Form in the THC-group compared to placebo but a non-significant improvement following Sativex.
Keywords: cannabis, THC, cannabidiol, chronic pain, cancer, clinical trial.

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Background Information

Less than 10 years ago there were only very limited clinical data available on the possible benefits of cannabinoids in chronic pain [1]. Several studies evaluated their analgesic potential in acute pain states, where they often even increased pain. In sum, clinical data did not allow any conclusions on the role of cannabis and cannabinoids in chronic pain conditions at that time and suggested only a limited potential of cannabinoids in the treatment of pain, contradicting personal experiences of patients, who successfully self-medicated with cannabis.

This picture changed within recent years with a number of clinical studies with different cannabinoid preparations (dronabinol, nabilone, cannabis extracts, inhaled cannabis) demonstrating analgesic effects in different chronic pain conditions [5]. There is evidence that endocannabinoids produced in the spinal cord can enhance pain by dampening the activity of inhibitory neurons [2]. This pain-promoting action of endocannabinoids wanes during the development of chronic inflammatory or neuropathic pain. This may explain the differences of cannabinoid effects in acute and chronic pain.

Experiences of pain patients were usually made with cannabis preparations high in THC (dronabinol) concentration and very low in other cannabinoids since cannabis strains available on the illegal market bred for high dronabinol mostly contain only negligible amounts of other cannabinoids [3]. Thus, cannabidiol (CBD) was introduced into therapy only in recent years by pharmaceutical companies and scientific institutes, albeit some patients may have unwittingly experienced the effects of CBD mainly when using cannabis resin (hashish), which more often may contain high CBD concentrations than cannabis herb (marijuana).

Currently two whole-plant cannabis extracts (Cannador® and Sativex®) are under investigation or in clinical use. Cannador (Institute for Clinical Research, Germany) contains dronabinol and other cannabinoids (mostly CBD) in a ratio of about 2:1 and is administered as a capsule (oral use). Sativex (GW Pharmaceuticals, UK) contains dronabinol and cannabidiol in a ratio of about 1:1 and is administered as a spray into the mouth (oromucosal use). The pharmacokinetic profile of THC in Sativex is similar to THC after oral use, suggesting that most of the extract is swallowed and absorbed by the gastrointestinal tract [4].

Summary of the original article

Johnson et al. (2010) compared the efficacy of Sativex and a THC cannabis plant extract with placebo in re-

lieving pain in patients with advanced cancer. Eligible patients recorded a pain severity score of 4 or above on a 0-10 Numerical Rating Scale (NRS) on both days of a two-day baseline period before study start, despite using strong opioids for at least one week. Patients maintained this opioid medication for the duration of the study.

In total, 177 patients with cancer pain entered the two-week, double-blind, placebo-controlled, parallel-group trial. Patients were recruited in 28 European centres, mainly in the UK and Romania. Patients were randomly assigned to receive either Sativex (n = 60), THC extract (n = 58), or placebo (n = 59). They self-titrated to their optimal dose during the first week

The co-primary endpoints of the study were the change from baseline in NRS pain score and the use of additional (breakthrough) pain medication. The NRS question "indicate your level of pain" was answered by patients three times daily using the anchors 0 = no pain and 10 = very bad pain. The secondary endpoints included among others sleep quality, appetite and total pain according to the Brief Pain Inventory-Short Form (BPI-SF). This pain score is the sum of pain scores of four questions answered on a scale from 0 = no pain to 10 = pain as bad as you can imagine, that ask to describe "your pain at its worst in the last 24 hours", "your pain at its least in the last 24 hours", "your pain on average", and the "pain you have right now."

The change from baseline in mean pain NRS score was statistically significant (p = 0.014) in favour of Sativex compared with placebo (improvement of -1.37 versus -0.69), whereas the THC group showed a non-significant improvement (-1.01 versus -0.69). Twice as many patients taking Sativex showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (43% versus 21%), whereas the number of THC group responders was similar to placebo (23% versus 21%). There was no change from baseline in median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups. There was a significant improvement (p = 0.048) in total pain according to the BPI-SF in the THC group compared to placebo (treatment difference: -4.07) whereas the Sativex group showed a non-significant improvement (treatment difference: -1.04). Most drug-related adverse events were mild or moderate in severity. Adverse effects that led to permanent cessation of study medication were observed in 17%, 12%, and 3% for Sativex, THC extract and placebo.

Comment

Sativex showed a significant reduction in the NRS pain score, while the THC extract did not. Conversely, the THC extract showed a significant reduction in the BPI-SF pain score, while Sativex did not. While the first result led the authors to conclude "that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain," the latter result is not mentioned in the abstract and in the results part of the article. It is listed only in a table and mentioned in one sentence of the discussion, which can easily be overlooked. While this kind of handling may be partly justified by the fact that the NRS pain score was a primary and the BPI-SF pain score a secondary endpoint, I would have liked a more independent presentation of the results from the interests of the sponsor.

Sativex and THC seemed to influence different aspects of pain. CBD shows promising therapeutic effects of its own including anti-cancer, anxiolytic and anti-inflammatory effects by different mechanisms of action. It has also been reported to reduce "the potential unwanted effects of THC by means of antagonism at CB1 receptors" [6]. However, it is unlikely that only selected effects of THC are antagonised at the CB1 receptor and not others, for example analgesia and muscle relaxation. The role of CBD in cannabis preparations is still unclear with mixed results in comparison with THC alone and cannabis rich in THC concerning both therapeutic and adverse effects. A high CBD concentration may be advantageous in some indications while it may be different in other medical conditions.

Conflict of interests

The author is working for pharmaceutical companies, mainly THC Pharm, Germany, and Bionorica Ethics, Germany.

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