

Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study

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ABSTRACT

Objective To compare the analgesic efficacy and side effects of the synthetic cannabinoid nabilone with those of the weak opioid dihydrocodeine for chronic neuropathic pain.

Design Randomised, double blind, crossover trial of 14 weeks' duration comparing dihydrocodeine and nabilone.

Setting Outpatient units of three hospitals in the United Kingdom.

Participants 96 patients with chronic neuropathic pain, aged 23-84 years.

Main outcome measures The primary outcome was difference between nabilone and dihydrocodeine in pain, as measured by the mean visual analogue score computed over the last two weeks of each treatment period. Secondary outcomes were changes in mood, quality of life, sleep, and psychometric function. Side effects were measured by a questionnaire.

Intervention Patients received a maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone at the end of each escalating treatment period of 6 weeks. Treatment periods were separated by a 2 week washout period.

Results Mean baseline visual analogue score was 69.6 mm (range 29.4-95.2) on a 0-100 mm scale. 73 patients were included in the available case analysis and 64 patients in the per protocol analysis. The mean score was 6.0 mm longer for nabilone than for dihydrocodeine (95% confidence interval 1.4 to 10.5) in the available case analysis and 5.6 mm (10.3 to 0.8) in the per protocol analysis. Side effects were more frequent with nabilone.

Conclusion Dihydrocodeine provided better pain relief than the synthetic cannabinoid nabilone and had slightly fewer side effects, although no major adverse events occurred for either drug.

Trial registration Current Controlled Trials ISRCTN15330757.

INTRODUCTION

The potential role of cannabinoid agents in the management of neurological disease has attracted considerable interest. Much of the evidence is anecdotal and little clinical research is available. A meta-analysis examining cannabinoids failed to find convincing evidence of analgesic activity beyond that of weak opioids.¹

Nabilone is a synthetic cannabinoid that is licensed in the United Kingdom for the treatment of chemotherapy induced nausea and vomiting. Dihydrocodeine is a weak opioid, which is often prescribed in primary care to treat chronic pain.² Its psychotropic and sedative

side effects make it a good comparative agent for a study with nabilone.³

Neuropathic pain is a common condition associated with various injuries to the central and peripheral nervous systems. It is often refractory to treatment with currently available drugs, and other classes of "adjuvant" drugs may be needed.⁴

Animal work has indicated a potential therapeutic role for cannabinoids in neuropathic pain, and a study of patients with refractory chronic pain conditions showed benefit from treatment with nabilone.⁵ We performed a randomised crossover trial to compare the analgesic efficacy of nabilone with that of dihydrocodeine for neuropathic pain. We also compared the side effects of both drugs.

METHODS

Participants and setting

Our study took place between July 2001 and November 2002 in outpatient facilities of three hospitals in the United Kingdom. All suitable patients with neuropathic pain (such as burning, stabbing, or paraesthesia within the distribution of a peripheral nerve) and a clear clinical history of its cause were referred by the participating pain consultants for screening.

We screened 100 patients aged 24-84 years with chronic neuropathic pain. The patient's mean pain score had to be greater than 40 mm on a 0-100 mm visual analogue scale. Ninety six patients were randomised to one of the two treatment sequences. We allowed participants to keep taking stable analgesics, except for dihydrocodeine.

Procedures

After initial recruitment, patients supplied a daily pain score for one week. Patients underwent an abbreviated neurological examination and a general medical examination. During the screening visit patients filled in a hospital anxiety and depression score (HAD score) and a short form 36 quality of life questionnaire (SF-36).^{6,7}

Our study was a randomised, double blind, controlled, crossover trial of three months' duration. The three trial periods were—treatment period 1 (six weeks), washout period (two weeks), and treatment period 2 (six weeks). Participants made eight specified visits at weeks 0, 2, 4, 6, 8, 10, 12, and 14.

All patients were asked to fill in a diary recording the average daily pain score, the number of hours slept, and the amount of study drug taken. During the washout

Secondary outcomes for patients with neuropathic pain treated with nabilone or dihydrocodeine

Outcome measured	Number of patients analysed	Treatment effect (95% confidence interval)	P value
Available case analysis			
Sleep	71	0.2 (-0.1 to 0.5)	0.20
Anxiety	70	-0.6 (-1.4 to 0.3)	0.19
Depression	70	-0.2 (-1.2 to 0.9)	0.72
Change in health	70	0.0 (-0.2 to 0.2)	0.88
Physical functioning	71	-1.2 (-4.5 to 2.1)	0.48
Social functioning	71	3.4 (-4.1 to 10.8)	0.37
Role, physical	69	8.9 (1.1 to 16.7)	0.03
Role, emotional	69	-1.2 (-11.8 to 9.5)	0.83
Mental health	71	2.5 (-2.7 to 7.6)	0.35
Vitality	71	-2.0 (-7.2 to 3.3)	0.46
Bodily pain	71	-5.2 (-10.1 to -0.4)	0.03
General health	70	0.8 (-3.1 to 4.6)	0.70
Per protocol analysis			
Sleep	63	0.2 (-0.1 to 0.5)	0.28
Anxiety	62	-0.6 (-1.6 to 0.3)	0.18
Depression	62	-0.2 (-1.2 to 0.9)	0.78
Change in health	62	0.0 (-0.3 to 0.2)	0.76
Physical functioning	63	-1.4 (-5.1 to 2.4)	0.47
Social functioning	63	2.3 (-5.3 to 9.9)	0.54
Role, physical	62	10.8 (2.3 to 19.2)	0.01
Role, emotional	62	-0.6 (-11.4 to 10.2)	0.92
Mental health	63	2.0 (-3.2 to 7.1)	0.45
Vitality	63	-2.3 (-7.6 to 3.0)	0.39
Bodily pain	63	-5.7 (-10.9 to -0.5)	0.03
General health	63	0.5 (-3.7 to 4.7)	0.81

Positive values indicate higher scores with nabilone. Negative values indicate higher scores with dihydrocodeine.

phase the patients recorded the number of rescue tablets taken.

At each visit the patients filled in a side effects assessment form. During the fourth and eighth visits they also filled in a HAD score and SF-36 form and worked through the six psychometric tests.

Outcome measurements

The pain score was the primary outcome variable. Secondary outcomes were anxiety and depression, each of the eight domains and the “change in health” measured by the SF-36,⁸ and the weekly average number of hours slept each night. We calculated the scores for the psychometric tests.

We used an eight item questionnaire that asked about the most common side effects of dihydrocodeine and nabilone.

Study drugs

The trial drugs were given in an escalating manner. If the patient developed side effects, the dosage was reduced to the previous value for the remainder of the trial period. Patients did not take any trial drug for the last six days of the washout period but were allowed up to eight tablets of rescue drugs a day.

Statistical considerations

We randomised patients to receive nabilone first then dihydrocodeine or vice versa. We used a model with fixed patient effect, period effect, and treatment effect but no term for the carryover effect of treatment to analyse the data.⁹

We collected data at the end of each six week period for all variables except the pain score; this score was recorded daily and weekly means were analysed. We based the analysis on data from the last two weeks of each treatment period.

Two analyses are presented. The available case analysis used the fullest dataset—all patients randomised who provided data in each treatment period. The per protocol analysis excluded patients who did not comply with the trial drugs, as assessed by their pain diary.

RESULTS

We allocated 48 patients to receive dihydrocodeine and 48 to receive nabilone as first treatment. The available case analysis included 73 patients, and 64 were retained for the per protocol analysis. We found no differences between centres or treatment sequences.

The mean baseline visual analogue score was 69.6 mm (range 29.4-95.2) on a 0-100 mm scale. The mean (SD) visual analogue score was 59.93 (24.42) for patients taking nabilone and 58.58 (24.08) for those taking dihydrocodeine. The mean (SD) for nabilone minus dihydrocodeine was 1.59 (9.19) for patients who took nabilone first then dihydrocodeine and -4.39 (10.32) for patients who took dihydrocodeine first then nabilone.

Dihydrocodeine was a significantly better analgesic than nabilone. The available case analysis produced a treatment effect (in the direction nabilone minus dihydrocodeine) of 6.0 mm (95% confidence interval 1.4 to 10.5, $P=0.01$). The equivalent figures for the per protocol analysis were 5.6 mm (0.8 to 10.3, $P=0.023$).

Three of the 64 patients in the per protocol dataset had a clinically relevant response (a drop in the visual analogue score of more than 10 mm) on nabilone compared with 12 patients on dihydrocodeine. No patient responded to both of the drugs. Forty nine patients had no clinically relevant drop in their pain score on either treatment.

The table gives details of the secondary outcomes. In the available case analysis, the treatment effect for the SF-36 domain “role physical” was 8.9 (1.1 to 16.9, $P=0.03$); these figures were 10.8 (2.3 to 19.2, $P=0.01$) for the per protocol analysis. In this domain, higher scores indicate a better outcome, so these results show that nabilone was significantly superior to dihydrocodeine on this measure. In the available case analysis, the treatment effect for the SF-36 domain bodily pain was -5.2 (-10.1 to -0.4, $P=0.03$); these figures were -5.7 (-10.9 to -0.5, $P=0.03$) for the per protocol analysis. Higher scores in the bodily pain domain indicate a better outcome, so these results show that dihydrocodeine was statistically superior to nabilone. These

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cannabinoids have been used as analgesics for centuries but the evidence base for their use is poor

Psychotropic side effects limit therapeutic dosing in patients with chronic pain

Neuropathic pain is a common and difficult to treat condition that has limited treatment options

WHAT THIS STUDY ADDS

Nabilone, a synthetic oral cannabinoid, is not more effective for treating neuropathic pain than the oral opioid dihydrocodeine

results agree with those of the primary outcome analysis.

Analysis of the psychometric testing found no significant differences between the two drugs. Nabilone was associated with more sickness than dihydrocodeine. Dihydrocodeine was associated with more tiredness and nightmares than nabilone. No major adverse events occurred when patients were taking either drug and both drugs were equally well tolerated.

DISCUSSION

The weak opioid, dihydrocodeine, was a statistically better treatment for chronic neuropathic pain than nabilone. More patients had clinically significant pain relief from dihydrocodeine, although a small number of patients responded well to nabilone. The side effects of both treatments were generally mild and in the expected range.

Strengths and weaknesses

Our study had intrinsic sensitivity as it showed a difference between the two treatments. Weaker points of the study were that 33 patients failed to complete the trial and the population studied had a variety of neuropathic pain syndromes. The high dropout rate can be explained partially by the crossover design—this type of trial exposes patients to two rather than one treatment.

Implications

The analgesic effects of opioids and cannabinoids are mediated by separate mechanisms—the analgesic effects of nabilone are not mediated by opioid receptors.¹⁰ A recent study found that the cannabinoid delta-9-tetrahydrocannabinol was not an effective analgesic when used alone but had a synergistic effect when used with an opioid.¹¹ We found that the weak opioid, dihydrocodeine, provided better pain relief than the cannabinoid, nabilone, in the treatment of chronic neuropathic pain. However, the clinical significance of this difference is small, and neither drug was particularly effective.

No data are available for the therapeutic dosing of nabilone, and the dose of 2 mg was arrived at as a compromise between safety and the effective dose seen in our clinical practice.¹² The observed side effect profile argues against giving higher doses of nabilone.

Dihydrocodeine is a low potency opioid but was more effective than the potent cannabinoid, nabilone, which argues against using this cannabinoid in clinical practice.¹³

Recent studies investigated an oromucosal spray of delta-9-tetrahydrocannabinol as a way to deliver it to the central nervous system rapidly.¹⁴ However, the rapid administration of psychotropics has different effects from those seen after slower administration. Smoking, “snorting,” or injecting certain drugs has a greater effect on the system than oral ingestion. For this reason, the results of studies using rapid administration must be interpreted with caution. Oral ingestion avoids high peak concentrations, and considerations relating to bioavailability are less relevant when drugs are used to treat chronic pain, where fixed regular dosing is the norm.

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