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A randomized, double-blind, double-dummy comparison of short- and long-acting dihydrocodeine in chronic non-malignant pain

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ABSTRACT

Guidelines for opioid treatment of chronic non-malignant pain recommend long-acting over short-acting opioid formulations. The evidence for this recommendation is weak. This study is a randomized, double-blind, double-dummy, 8-week comparison of long-acting dihydrocodeine tablets (DHC-Continus) with short-acting dihydrocodeine tablets in 60 patients with chronic non-malignant pain who were referred to a multidisciplinary pain clinic. All patients used codeine-paracetamol tablets before the trial, and paracetamol was added in both groups during the trial. The primary outcome was stability in pain intensity, measured as the difference between the highest and least pain intensity reported on an 11-point numerical rating scale in a 7-day diary. The secondary outcomes were differences in quality of life, quality of sleep, depression, and episodes of breakthrough pain between the 2 formulations. Spontaneously reported adverse events were recorded. In all, 38 patients completed the trial, and 22 withdrew before the end. The reasons for withdrawal were adverse events, lack of efficacy, or both, and were similar between the groups. There were no significant differences in stability of pain intensity between groups. There were no significant differences between groups in quality of sleep, depression, health-related quality of life, or adverse events. Breakthrough pain was experienced in both groups during the trial. Long-acting dihydrocodeine was not observed to be superior for any of the outcomes in this trial. The results of this study do not support current guidelines recommending long-acting opioids.

1. Introduction

International and national guidelines recommend chronic opioid therapy in selected patients with chronic non-malignant pain. However, the level of evidence for both patient selection and therapy strategies is low [10,29]. One of the questions that results from such limited evidence is whether short- or long-acting opioid formulations are a better choice in any respect. Many guidelines recommend the use of long-acting instead of short-acting opioids for chronic non-malignant pain [19,32,34], although 1 influential guideline states that there is no evidence to recommend long-acting opioids over short-acting ones [11].

Short-acting, rapid-onset opioids taken when needed are thought to increase the risk of addiction through reward-dependent mechanisms, compared with long-acting opioids taken at regular intervals [6]. Most long-acting opioids lead to a slower increase in effect-site concentration and a more stable concentration for a longer time; and some, but not all, have a less steep decline in concentration compared with short-acting opioids [23]. It is hypothesized that long-acting opioids taken at set times also provide better and more stable pain relief with fewer episodes of end-of-dose failure, and that they have fewer side effects because of lower peaks in the drug plasma concentration [29]. Long-acting opioid formulations might also provide pain relief through a longer dosing interval and thus provide the patient with an undisturbed night of sleep. However, important outcomes such as depression, quality of life, and episodes of breakthrough pain have not been compared in randomized controlled trials of short- and long-acting opioids. Previous trials have been of varying quality, all sponsored

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by industry, and they did not investigate stability in pain intensity [1,9,14,16,27,31]. These trials found no difference in sleep between long- and short-acting opioids [1,9,27], but the assessment of sleep problems in most of these studies was not optimally performed [1,9].

Dihydrocodeine is a so-called "weak" opioid that can be used if non-opioid analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) provide insufficient pain control [22]. It is available both as a short-acting tablet, with dosing every 4 to 6 hours, and a long-acting tablet developed for dosing every 12 hours. This drug is widely used in several countries, but not in Norway, where short-acting codeine is by far the most commonly used opioid. Thus, it was possible to include patients who initially used codeine and to compare a short-acting and long-acting formulation of an opioid closely related to codeine but unknown to the patients.

The main aim in this randomized, double-blind, and double-dummy trial was to examine whether switching patients from codeine as needed to slow-onset, long-acting dihydrocodeine by the clock would provide more stable pain intensity than a switch to rapid-onset, short-acting dihydrocodeine by the clock. The primary outcome was stability of pain intensity, measured as the difference between worst and least pain intensity on an 11-point numeric rating scale (NRS) during the last week of participation. The research hypothesis was that the group randomized to long-acting dihydrocodeine would achieve at least 2 units more of stable pain intensity than the short-acting dihydrocodeine group.

2. Methods

2.1. Patients and setting

Patients between 18 and 75 years of age who were referred to the multidisciplinary pain center at St. Olav's University Hospital in Trondheim, Norway, were eligible for the study. The inclusion criteria were chronic non-malignant pain and a previous daily codeine intake between 150 and 300 mg. In Norway, codeine is used in a combination tablet of 30 mg codeine and 400 or 500 mg of paracetamol (Paralgin Forte and Pinex Forte), which means that patients consumed between 5 and 10 codeine–paracetamol tablets 1 day before inclusion. Exclusion criteria were severe mental disorders, known substance abuse, liver failure, and active cancer. The trial was performed at the multidisciplinary pain centre at St. Olav's University Hospital in Trondheim, Norway. Data were collected from October 2007 to May 2012.

2.2. Recruitment of patients

Patients referred to the multidisciplinary pain clinic who met the inclusion criteria were asked about their medication. If they used between 5 and 10 codeine–paracetamol tablets per day, they were invited to an evaluation and possible enrolment in the clinical trial at the pain centre. They received written information before and oral information during the evaluation. The patients were also given the opportunity to ask questions. The flow of patients during the trial is depicted in Fig. 1.

2.3. Study design

This study was a randomized, controlled, double-blind, and double-dummy trial with duration of eight weeks. Patients were randomized to 2 groups. One group of patients was treated with active long-acting dihydrocodeine every 8 to 12 hours and received a placebo 4 times daily, whereas the other group of patients was treated with short-acting dihydrocodeine 4 to 6 times daily and received a long-acting dihydrocodeine–placebo every 12 hours (Table 1). Paracetamol was added at set times for both groups 4 to 6 times per day, similar to the dose and timing before the trial (Table 1). The paracetamol tablets were taken together with the short-acting dihydrocodeine/placebo. The use of extra paracetamol, opioids, or NSAIDs as needed was not allowed. There was no period of washout of the codeine tablets before switching to the trial drugs.

2.4. Randomization and blinding

Randomization was performed using a Web-based randomization system developed and administered by the Unit of Applied Clinical Research, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway [28]. Patients were randomized in blocks of varying size, and the hospital pharmacy was notified by the Unit of Applied Clinical Research as to which active medications/placebo should be provided to each patient. The randomization was stratified into 3 groups, depending on the previous intake of codeine, as shown in Table 1. Tablets were concealed in colored capsules to achieve blinding. The tablets were packed in the capsules by 1 of the investigators. For the first 32 patients, all tablets were hidden in capsules. Because of a change in tablet design, the short-acting dihydrocodeine tablets did not fit into capsules for the remaining patients. Because this second batch was more similar to the placebo tablets (not totally identical, but the same color, size, and shape), the short-acting/placebos for the last 28 patients were not concealed in capsules. The long-acting/placebo tablets for all patients were concealed in blue and white capsules. The local hospital pharmacy delivered the pre-packed boxes of medications to the patients to ensure that all investigators were kept blinded.

2.5. Study medication

Dihydrocodeine is a semisynthetic "weak" opioid, metabolized by CYP2D6 to dihydromorphine [22]. Dihydrocodeine is not commercially available in Norway, and it was thus assumed that all patients would be naive to this opioid. None of the patients who were approached for inclusion had received dihydrocodeine previously. The 60-mg tablets of long-acting dihydrocodeine (DHC Continus) were imported from NAPP Pharmaceuticals (Cambridge, UK), whereas the short-acting tablets (dihydrocodeine 30 mg) were imported from CP Pharmaceuticals (Wrexham, UK). The placebo tablets were purchased from Kragerø pharmacy (Kragerø, Norway), and colored capsules were purchased from Capsugel (Bornem, Belgium). The capsules were made of hard gelatin of the DBcaps type, designed for double-blind clinical trials. These capsules typically disintegrate within 3 minutes in the stomach and are documented not to influence pharmacokinetic variables such as bioavailability and T_{max} [13]. No rescue medication was allowed during trial. Pre-trial medications taken at set times at stable daily dosages, including NSAIDs, antiepileptics, and antidepressants, were allowed to continue at unchanged dosages during the trial.

2.6. Outcome measures

The primary outcome was stability in pain intensity at the end of the study, when effect site concentrations were assumed to have been in steady state for at least 6 to 7 weeks. Pain intensity was measured with questions 4 to 6 from the Brief Pain Inventory (BPI) [12] by scoring the worst pain, the least pain, and average pain intensity during the previous 24 hours. The difference between worst and least pain was subsequently calculated at the end of the study as a measure of pain stability. The 3 pain intensity measures were scored on an 11-point NRS once daily. Measurements were recorded every evening for 1 week, at baseline, and at the end of the trial. The scale uses 0 to represent "no pain"