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Analgesia and serum assays of controlled-release dihydrocodeine and metabolites in cancer patients with pain

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Abstract:
Aim of the study was to assess dihydrocodeine (DHC) and metabolites concentrations and their correlations with DHC analgesia in cancer patients with pain. Thirty opioid-naive patients with nociceptive pain intensity assessed by VAS (visual analogue scale) > 40 received controlled-release DHC as the first (15 patients, 7 days) or as the second opioid (15 patients, 7 days). Blood samples were taken on day 2, 4 and 7 at each study period. DHC and its metabolites were assayed by HPLC. DHC provided satisfactory analgesia when administered as the first or the second opioid superior to that of tramadol. When DHC was the first opioid administered, DHC and dihydrocodeine-6-glucuronide (DHC-6-G) concentrations increased in the second and the third comparing to the first assay. A trend of nordihydromorphine (NDHM) level fall between the first and the third assay was noted; trends of dihydromorphine (DHM) level increase in the second relative to the first determination and decrease in the third compared to the second assay were observed. When DHC followed tramadol treatment a trend of DHC concentration increase in the second relative to the first assay was noted. DHC-6-G level increased in the second and in the third comparing to the first determination; NDHM and DHM concentrations were stable. DHC and DHC-6-G concentrations increased similarly during both treatment periods which suggest their prominent role in DHC analgesia. Few significant correlations were found between DHC dose, DHC and metabolites serum concentrations with analgesia suggesting the individual DHC dose titration.

Key words:
analgesia, cancer pain, dihydrocodeine, opioid, treatment

Abbreviations: ANOVA – analysis of variance, BPI-SF – Brief Pain Inventory – Short Form, NSAIDs – non steroidal anti-inflammatory drugs, DHC – dihydrocodeine, DHC-6-G – dihydrocodeine-6-glucuronide, DHM – dihydromorphine, DHM-3-G – dihydromorphine-3-glucuronide, DHM-6-G – dihydromorphine-6-glucuronide, NDHM – nordihydromorphine, NORDHC – nordihydrocodeine, NORDHC-6-G – nordihydrocodeine- 6-glucuronide, VAS – visual analogue scale

Introduction

Opioid analgesics are effective in chronic pain management that work through opioid receptors and the heterotrimeric guanine nucleotide binding proteins [27, 28]. DHC is an analgesic of step 2 of the WHO

analgesic ladder (opioids for mild to moderate pain) frequently used in Poland for the treatment of cancer and chronic non-malignant pain of moderate intensity [3]. DHC is a semi-synthetic codeine derivative formed by the hydrogenation of the double bond in the main chain of the codeine molecule [6]. Apart from being used as an analgesic and antitussive agent DHC is also used in the treatment of opioid addiction [18]. After subcutaneous administration of 30 mg DHC its analgesic activity is similar to that of 10 mg of morphine [6]. DHC metabolism is multidirectional: through CYP2D6 to DHM, which is further metabolized to 3-(DHM-3-G) and 6-glucuronides (DHM-6- G) and to NDHM; *via* CYP3A4 to NORDHC, which is further metabolized to NORDHC-6-G and to NDHM; and through glucuronidation to DHC-6-G (Fig. 1) [4, 19, 20, 24]. Due to the multidirectional metabolism, as opposed to tramadol [22, 23] and codeine [5, 17], CYP2D6 activity probably does not influence DHC analgesia [7, 26].

DHC exerts its analgesic action through affinity to predominantly μ and to less extent to κ and δ opioid receptors [8]. The highest affinity to μ opioid receptors displays DHM and DHM-6-G. The affinity of DHM and DHM-6-G to μ opioid receptor is 70 times more potent, whereas other metabolites possess less affinity in comparison to DHC. DHM-6-G possesses a little lower whereas DHM-3-G significantly lower affinity to μ opioid receptor in comparison to DHM. DHC and DHM display twice higher affinity than their 7,8 non-saturated analogues (codeine and morphine). DHC possesses twice higher affinity than DHC-6-G. Regarding δ opioid receptor, the affinity of explored compounds is 5–50 times lower than their affinity to μ opioid receptors with similar order as in the case of μ opioid receptor with the exception of DHC-6-G which possesses twice higher affinity in comparison to DHC. Regarding κ opioid receptor, DHC-6-G and DHM-6-G possess significantly lower affinity than their parent compounds (DHC and DHM, respectively). However, morphine and DHM, codeine and DHC display similar affinity to κ opioid receptors [19]. In Poland DHC is available only in controlled-release tablets for oral administration [11]. The aim of the study was to assess DHC analgesia and to evaluate correlations of DHC dose with analgesia, correlations of DHC and metabolites concentrations with analgesia and to assess the correlation of DHC dose with DHC and metabolites concentrations in cancer patients with pain.

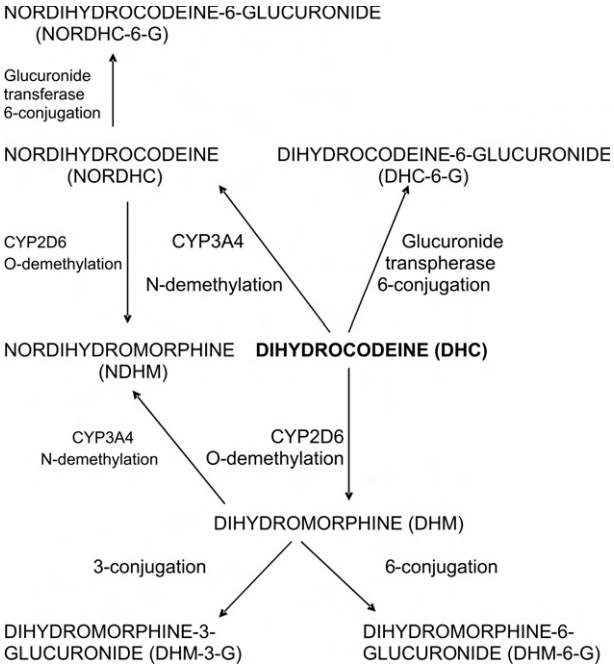

Fig. 1. Dihydrocodeine main metabolic pathways

Patients and Methods

Thirty opioid-naive patients with nociceptive pain (VAS > 40) received DHC for 7 days as the first opioid (15 patients; group 1) or as the second opioid administered also for 7 days after a switch from tramadol (15 patients; group 2). In group 1, the starting single dose of controlled-release DHC equalled 60 mg and was titrated to achieve satisfactory analgesia (VAS 40 mm or diminishing starting pain intensity by at least 15 mm in VAS) according to the following scheme: 60 mg, 90 mg, 120 and 180 mg administered twice daily. In group 1, after 7 days of DHC treatment, patients were switched to appropriate doses of tramadol. In group 2, the starting single dose of controlled-release tramadol equalled 100 mg and it was titrated to achieve satisfactory analgesia according to the following scheme: 100 mg, 150 mg, 200 and 300 mg administered twice daily. In group 2, the starting single dose of controlled-release DHC was 60 mg or higher depending on the previous tramadol dose. The equianalgesic doses of tramadol and DHC when drugs were switched are shown in Table 1. Break-