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The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain

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Running head:

Tramadol and dihydrocodeine impact on QL of cancer pain patients

Abstract

Background: Tramadol and dihydrocodeine (DHC) are analgesics of step 2 WHO analgesic ladder (opioids for mild to moderate pain, weak opioids) frequently used in the treatment of cancer pain of moderate intensity. The aim of the study was to assess the impact of tramadol and DHC treatment on quality of life (QL) and performance status (PS) of patients with cancer pain.

Patients and methods: Randomized, cross-over, clinical study of 40 opioid-naive patients with nociceptive cancer pain who received tramadol or DHC controlled release tablets for 7 days, then drugs switched and administered for another 7 days. Pain was assessed by VAS (visual anlogue scale), QL by EORTC QLQ C 30; PS by ECOG and Karnofsky.

Results: From 40 patients recruited thirty completed the study. DHC treatment provided better analgesia (VAS). In QL functional scales better emotional functioning in tramadol group; better global QL and cognitive functioning in DHC group were observed. In symptom scales less fatigue, pain and sleep disturbances, less nausea and vomiting and better appetite in DHC group were noted. In tramadol group less constipation and less financial problems were observed. No differences in dyspnoea and diarrhoea were noted. ECOG and Karnofsky PS were low and did not differ between tramadol and DHC groups.

Conclusions: DHC treatment was associated with better global QL, cognitive functioning, analgesia and appetite, less fatigue, sleep disturbances, nausea and vomiting. Tramadol therapy was connected with better emotional functioning, less constipation and financial problems. PS deteriorated in both tramadol and DHC groups.

Key words: cancer pain, dihydrocodeine, performance status, quality of life, tramadol

What is already known on this topic?

Tramadol and dihydrocodeine are weak opioids used in the treatment of chronic and cancer pain of moderate intensity. Analgesic efficacy and adverse effects of both opioids were assessed in a number of clinical trials and in experimental studies. However equianalgesic doses of the drugs were not clearly established in clinical trials. The most common adverse effects of tramadol is nausea, sweating and diziness and of dihydrocdeine constipation, nausea and sedation.

What does this article add?

No studies in patients with cancer pain directly compared the drugs. This is the first clinical study that addresses analgesia, adverse effects and quality of life in patients with cancer pain treated with tramadol and dihydrocodeine in a cross-over design. Equianalgesic doses of tramadol and dihydrocdeine were established, the most common adverse effects of the analgesics identified and the guidelines of prophylaxis of tramadol and dihydrocodeine adverse effects were discussed

Introduction

Tramadol and dihydrocodeine (DHC) are analgesics of step 2 of the WHO analgesic ladder (opioids for mild to moderate pain, weak opioids), which are still frequently used in the treatment of cancer pain of moderate intensity. A number of studies indicate usefulness of weak opioids especially tramadol [1-3] and DHC [4-8]. A significant percentage of patients with cancer and chronic non malignant pain of moderate intensity may benefit from these drugs. However weak opioids are often neglected as a consequence of high efficacy of opioids for moderate to severe pain (opioids of step 3 WHO analgesic ladder, strong opioids) supported by clinical studies [9–12]. These studies are not quite convincing because of limited number of patients recruited. It seems also appropriate to administer weak opioids in moderate pain and strong opioids in patients with severe pain intensity. Studies comparing analgesia and adverse effects of high tramadol with low morphine doses indicate better global QL [13] and less adverse effects during tramadol treatment with similar analgesia [14,15]. Analgesic effect of weak opioids may be also improved by concomitant administration of NSAIDs, metamizole or paracetamol with tramadol, codeine or DHC [16].

Tramadol is an opioid agonist, which apart from opioid action activates pain inhibitory system (increase of noradrenaline and serotonin level). In comparison to other opioids (morphine, pethidine, buprenorphine) tramadol displays small affinity to mu opioid receptors, rarely causes respiratory and circulatory depression and physical dependence [1]. Tramadol in the dose 100 mg causes similar analgesia to 10 mg of morphine when the drugs are given orally [2]. The active metabolite O-desmethyltramadol possesses significant mu opioid receptor affinity and displays analgesic activity [3]. Tramadol is available in immediate and controlled release (CR) oral formulations.

Dihydrocodeine (DHC) is a semi synthetic codeine derivative, which was formed by the hydrogenation of the double tie in the main chain of the codeine molecule. DHC exerts its analgesic action through affinity to mu, kappa and delta opioid receptors. After oral administration, 60 mg DHC analgesic activity is similar to 10 mg of morphine [4]. DHC and its metabolites: dihydromorphine, nordihydrocodeine and dihydrocodeine-6-glucuronide display analgesic activity mostly through mu opioid receptors activation [5]. DHC is available in CR tablets for oral administration. To our knowledge up to date no clinical studies in patients with cancer pain compared these analgesics. Quality of life (QL) assessment is increasingly important issue in patients with cancer pain. The aim of the

study was to explore the impact of tramadol and DHC treatment on QL of patients with nociceptive cancer pain.

Patients and methods

A randomized, cross-over, clinical study of patients treated either with CR tramadol (15 patients) or CR DHC tablets (15 patients) for 7 days; after this period drugs switched for another 7 days of treatment. All patients were treated at one in-patient palliative medicine unit; patients were recruited within the period of January 2007 – June 2008. To enter the study patients had to fulfill all inclusion criteria: cancer diagnosis, age over 18, opioid-naive, no history of drugs abuse, oral route of drug administration, ability of normal communication and filling questionnaires, nociceptive baseline pain intensity (VAS: 0 – no pain, 100 – the worst possible pain) over 40 during non-opioids (NSAIDs, paracetamol, metamizol) therapy, no renal impairment, if woman not pregnant and no lactation. Visceral pain was diagnosed in 17 patients, somatic in 13: in 9 bone, in 4 somatic from soft tissues and from the skin. Primary tumor localization was as follows: lung (4 patients), colon (4), stomach (3) and pallatinal tonsil (2); in one patient pharynx, esophagus, gall bladder, pancreas, thyroid and suprarenal glands, kidney, prostate, breast, skin, skin melanoma, myelodysplastic syndrome, Hodgkin disease, ovary, abdominal and pelvic tumors and bone metastases from unknown primary site.

Equianalgesic dose ratio of tramadol to DHC was 5:3 when drugs were switched after 7 days of the treatment (table 1) [6,7]. The starting dose of CR tramadol was 100 mg b.i.d., CR DHC 60 mg b.i.d. titrated according to the scheme (tab. 1) to satisfactory analgesia defined as pain intensity less than 40 or decrease by at least 20 (VAS). The maximal daily doses were for tramadol 600 mg and for DHC 360 mg. In case satisfactory analgesia was not achieved the treatment was stopped, patients were switched to strong opioids. Previous treatment with NSAIDs, paracetamol or metamizol was allowed. Patients did not receive prophylactic antiemetics and laxatives when starting treatment with tramdol or DHC. EORTC QLQ C 30 and performance status (PS ECOG and Karnofsky) were assessed at baseline, at the 7th day (before drug switch) and on the 14th day of therapy. At study completion patients were asked about the preferred analgesic. All patients provided written, informed consent prior to the study procedures. The trial was accepted by the Regional Bioethics Committee at the Poznan University of Medical Sciences and it was performed according to the Declaration of Helsinki.

The data were statistically analysed with a licensed statistical package (Statistica PL, version 8.0®). Pain intensity in both groups was assessed by VAS (mean and standard deviation); the t-test for paired data was used to compare analgesic effects. In descriptive statistics of functional and symptom scales of the EORTC QLQ C 30 (data not shown), ECOG and Karnofsky PS means and standard error were provided. Two-way ANOVA was used for the EORTC QLQ C 30, ECOG and Karnofsky PS results analysis. PS (ECOG and Karnofsky) results during treatment were compared to baseline by the the least significant difference (LSD) test. In all analyses p-value 0.05 was considered significant.

Results

At the entry of the trial 40 patients were recruited; thirty completed the study. From 10 patients who dropped out (data not included into results) four (1 from tramadol and three from DHC group) deteriorated during the first 7 days and could not received drugs orally, four patients treated with tramadol (tramadol/DHC group) and 2 treated with DHC (DHC/tramadol group) did not achieve satisfactory analgesia during titration (fig. 1). The mean age of patients was 70.47 ± 8.97; there were 19 women and 11 men. Results regarding adverse effects based on the modified ESAS (Edmonton Symptom Assessment System with two additional scales for vomiting and constipation) were reported in another paper [8]. No serious adverse events were observed with tramadol and with DHC treatment. The daily tramadol doses were 286.67 ± 157.35 mg and 256.20 ± 109.33 mg; for DHC 138.87 ± 40.77 mg and 172.53 ± 95.19 mg on the 7^{th} and on the 14^{th} day of the treatment respectively. The mean pain intensity at baseline was 63.07 ± 13.48 for tramadol and 57.73 ± 8.40 for DHC ($p > 0.2$). During all but two days DHC analgesic effect was superior to tramadol (tab. 2). More patients in the tramadol group (12) than in the DHC group (8 patients) used rescue analgesics. There were 19 patients who preferred DHC treatment and 4 patients in favour of tramadol therapy; 7 patients assessed both analgesics as equally effective.

ANOVA results for functional scales of EORTC QLQ C 30 are shown (tab. 3). No drug effect was observed. There was no treatment time effect in physical, role (work), cognitive, and social functioning. However treatment time effect was observed in emotional functioning ($p < 0.002$) and global QL ($p < 0.001$). There was no drug and treatment time interaction effect in physical, role (work) and social functioning but significant effect in cognitive functioning ($p = 0.05$), emotional functioning ($p < 0.013$) and global QL ($p < 0.006$). Higher scores of emotional functioning in tramadol group, higher global QL and better cognitive

functioning in DHC group were observed. A trend towards better physical functioning in DHC group was noted ($p = 0.063$ for treatment time; $p = 0.09$ for interaction of drug and treatment time).

ANOVA results for symptom scales of EORTC QLQ C 30 are shown (tab. 4). No drug effect was found, although in case of nausea and vomiting ($p = 0.072$) and sleep ($p = 0.06$) p-values were near significance. Treatment time effect was significant for fatigue ($p < 0.036$), pain ($p < 0.001$), sleep ($p < 0.001$) and finances ($p < 0.023$) with no effect in nausea and vomiting, dyspnoea, appetite, constipation and diarrhea. Interaction of drug and treatment time effect was observed for fatigue ($p < 0.01$), nausea and vomiting ($p < 0.001$), pain ($p < 0.001$), sleep ($p < 0.005$), appetite ($p < 0.039$) and constipation ($p < 0.001$) with no effect in dyspnoea, diarrhea and finances. Less intense fatigue, pain and sleep disturbances, nausea and vomiting and better appetite in DHC group were noted. In tramadol group less constipation and financial problems were observed. No differences in dyspnoea and diarrhoea were found.

ECOG PS of all patients deteriorated comparing baseline with day 7 ($p = 0.008$) and with day 14 ($p = 0.001$) (tab. 5). ANOVA revealed treatment time effect ($p < 0.001$) with no drug and no drug and treatment time interaction effect (tab. 6). No differences were found in ECOG PS between tramadol and DHC groups at baseline ($p > 0.2$), day 7 ($p > 0.6$) and day 14 ($p > 0.27$; LSD test). Karnofsky PS of all patients deteriorated comparing baseline with day 14 ($p = 0.001$). A trend was observed between baseline and day 7 ($p = 0.062$) (tab. 5). ANOVA revealed treatment time effect ($p < 0.001$) and a trend ($p = 0.087$) of drug and treatment time interaction with no drug influence (tab. 6). No differences were found in Karnofsky PS between tramadol and DHC groups at baseline ($p > 0.61$), day 7 ($p > 0.92$) and day 14 ($p > 0.61$; LSD test).

Discussion

To our knowledge no studies were performed to date comparing tramadol with DHC in patients with cancer pain. We observed better analgesic effect of DHC. A superior DHC analgesia was demonstrated in VAS, less consumption of rescue analgesics in DHC group and more patients who preferred DHC therapy. The study demonstrated possibility of tramadol to DHC and opposite way rotation, which in clinical practice may be indicated in case of adverse effects or insufficient analgesia during tramadol or DHC therapy using tramadol to DHC ratio for the oral route 5:3. A significant increase in daily tramadol doses (40%) and DHC doses (20%) in the first week of the treatment was observed. In the

second week daily doses were more stable taking into account the former analgesic dose at the 7th day (before switch) and the ratio used for drug rotation.

Tramadol and DHC were compared in few studies. Hummel et al. in a double-blind, cross-over, placebo-controlled experimental study demonstrated both drugs to be more effective when administered in the evening than in the morning; no equianalgesic tramadol/DHC dose was established [17]. Wilder – Smith et al. compared CR tramadol with CR DHC in osteoarthritis pain not responding to NSAIDs. Dose calculation was the same as in our study (CR tramadol 100 mg b.i.d. corresponded to CR DHC 60 mg b.i.d.). Analgesia was similar but tramadol caused more adverse effects and less constipation. This trial did not comprised QL evaluation and had a parallel design. Mean daily doses of analgesics were stable over the study period (209 mg and 203 mg for CR tramadol; 129 mg and 130 mg for CR DHC at the 1st and at the 28th day respectively) in contrast to the dose increments observed in our trial [6].

QL was evaluated by EORTC QLQ C 30 an instrument with sound psychometric values [18] adapted in Poland [19]. In functional scales better global QL was associated with DHC and better emotional functioning with tramadol (treatment time effect and interaction of drug and treatment time). Better cognitive functioning was connected with DHC (interaction of drug and treatment time). Better global QL observed in patients treated with DHC might be a consequence of better analgesia, less fatigue, nausea and vomiting, and sleep disturbance in this group. Better emotional functioning in patients treated with tramadol might be connected with a possible antidepressant tramadol effect observed in some experimental studies [20] and less constipation [21]. A trend of better physical functioning in DHC group was noted ($p = 0.063$ for treatment time effect; $p = 0.09$ for interaction of drug and treatment time). There were no differences in role (work) and social functioning.

In symptom scales DHC therapy was associated with less pain, fatigue and sleep disturbance (treatment time effect and interaction of drug and treatment time), less nausea and vomiting, better appetite (interaction of drug and treatment time). Less constipation (interaction of drug and treatment time) and less financial problems (treatment time effect) were connected with tramadol therapy. No differences in dyspnoea and diarrhea were observed. Results of EORTC QLQ C 30 symptom scales are similar to those of modified ESAS, which comprised two additional scales for constipation and vomiting assessment [8]. This is the case for better analgesia and less intense nausea during DHC administration and

less constipation during tramadol treatment. The results might be associated with different mode of action of the drugs: tramadol displays significant non-opioid component [21] while DHC comparing to tramadol has significantly stronger affinity to mu opioid receptors [4] and thus may cause more intense constipation [5]. Nausea which is the most common tramadol adverse effect is connected with serotonin level increase [22]. All patients did not receive prophylactic antiemetic and laxative, which would influence the results. Patients treated with DHC experienced less sleep disturbance, which might be connected with better analgesia and less fatigue. Opposite to ESAS results no differences in dyspnoea measured by EORTC QLQ C 30 were observed in this study. In finances less problems in tramadol group was not connected with the analgesic type (both drugs were provided free of charge to all patients) but rather with patients' social situation.

Differences observed in QL may suggest prescription practice. Prophylactic antiemetic administration in patients starting tramadol and laxative therapy in patients commencing DHC should be considered. Laxatives administration in patients treated with tramadol may rely on the individual assessment of constipation risk as tramadol role is negligible with this regard [23]. Similar individual approach may concern antiemetic use when starting DHC. ECOG [24] and Karnofsky [25] PS was low and decreased due to general deterioration during the study period. A significant decrease of activity was the treatment time but not drug effect or drug and treatment time interaction. No differences in PS between patients treated with tramadol and DHC were found.

The results of the study should be interpreted with significant caution as we were not able to demonstrate drug effect in any of the EORTC QLQ C 30 functional or symptom scales, ECOG and Karnofsky PS. The treatment period with each analgesic was 7 days only. Another limitation of the study was non-blinded design and lack of wash-out period, which might have influenced the results after drug switch; however the latter approach might be justified by ethical reasons in cancer pain management. Patients with neuropathic pain component were excluded as they usually need strong opioids and adjuvant analgesics administration. The number of patients recruited was small; thus the results should be replicated in a controlled study with longer follow up.

In spite of these limitations to our knowledge this is the first clinical study evaluating the influence of CR tramadol and CR DHC treatment on QL of patients with cancer pain. To conclude in functional scales DHC treatment was associated with better global QL and cognitive functioning

and a trend of better physical functioning; tramadol therapy was connected with better emotional functioning; no differences in role and social functioning were found. In symptom scales DHC therapy was associated with better analgesia, less fatigue, sleep disturbances, nausea and vomiting, better appetite while tramadol treatment was connected with less constipation and financial problems; no differences in dyspnoea and diarrhea were found. All these differences were due to treatment time effect or drug and treatment time interaction with no drug influence. No differences in PS between tramadol and DHC treatment were found; in both groups ECOG and Karnofsky PS deteriorated as a result of the treatment time effect with no drug influence observed.

Conflict of Interest Disclosure Statement: We declare no conflict of interest connected with the article.

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Tab. 1. Equianalgesic doses of CR tramadol and CR DHC when drugs switched after 7 days of the treatment

Tramadol CR	DHC CR
2 x 100 mg	2 x 60 mg
2 x 150 mg	2 x 90 mg
2 x 200 mg	2 x 120 mg
2 x 300 mg	2 x 180 mg

CR – controlled release tablets

Tab. 2. Pain intensity (VAS) at baseline (before analgesics administration, day 0), during tramadol and DHC treatment (days 1 – 14; mean and standard deviation). Higher scores mean more intense pain

Day of the treatment	Tramadol	DHC	p-value*
0	63.07 ± 13.48	57.73 ± 8.40	P > 0.2
1	38.33 ± 19.27	10.20 ± 7.73	**0.001**
2	33.40 ± 23.86	11.47 ± 11.61	**0.003**
3	38.53 ± 20.93	8.13 ± 9.96	**0.001**
4	35.40 ± 19.83	7.80 ± 10.12	**0.001**
5	35.87 ± 18.86	7.80 ± 9.64	**0.001**
6	31.20 ± 22.10	8.07 ± 8.92	**0.001**
7	38.20 ± 16.27	8.80 ± 9.41	**0.001**
Analgesic switch			
8	30.93 ± 11.83	16.67 ± 13.72	**0.005**
9	30.93 ± 10.16	15.20 ± 15.24	**0.002**
10	27,60 ± 8,81	18,73 ± 16,95	0.087
11	28.67 ± 10.93	18.80 ± 16.23	0.062
12	35.47 ± 16.18	12.87 ± 12.46	**0.001**
13	32.33 ± 20.45	11.33 ± 12.30	**0.002**
14	37.93 ± 22.63	11.93 ± 13.70	**0.001**

* t-test for paired data

Tab. 3. Results of two-way ANOVA. Dependent variables: functional scales of EORTC QLQ C 30, independent variables: drug influence, time of QL measurement and interaction of drug and treatment time. Degree of freedom: for a drug 1, for the treatment time and interaction 2.

Functional scales of EORTC QLQ C 30	Drug influence	Treatment time effect	Drug and treatment time interaction
Physical functioning	P > 0.240	P = 0.063	P = 0.09
Role functioning (work)	P > 0.2	P > 0.1	P > 0.1
Cognitive functioning	P > 0.783	P > 0.1	**p = 0.05**
Emotional functioning	P > 0.508	**p < 0.002**	**p < 0.013**
Social functioning	P > 0.571	P > 0.260	P > 0.260
Global quality of life	P> 0.827	**p < 0.001**	**p < 0.006**

Tab. 4. Results of two-way ANOVA. Dependent variables: symptom scales of EORTC QLQ C 30, independent variables: drug influence, time of QL measurement and interaction of drug and treatment time. Degree of freedom: for a drug 1, for the treatment time and interaction 2.

Symptom scales of EORTC QLQ C 30	Drug influence	Treatment time effect	Drug and treatment time interaction
Fatigue	P > 0.6	**p < 0.036**	**p < 0.01**
Nausea and vomiting	p = 0.072	P > 0.486	**p < 0.001**
Pain	P > 0.558	**p < 0.001**	**p < 0.001**
Dyspnoea	P > 0.353	P > 0.222	P > 0.156
Sleep	p = 0.06	**p < 0.001**	**p < 0.005**
Appetite	P > 0.174	P > 0.26	**p < 0.039**
Constipation	P > 0.636	P > 0.222	**p < 0.001**
Diarrhea	P > 0.118	P > 0.437	P = 0.09
Finances	P > 0.796	**p < 0.023**	P = 0.092

Tab. 5. Performance status (ECOG and Karnofsky) statistical characteristics (mean, standard error) and the comparison of performance status at baseline with the treatment period

Performance status scale	Performance status assessment	Mean, standard error	p*
ECOG	0	2.90 ± 0.18	-
	1	3.10 ± 0.18	**0.008**
	2	3.20 ± 0.18	**0.001**
Karnofsky	0	5.03 ± 0.18	-
	1	4.90 ± 0.19	0.062
	2	4.77 ± 0.20	**0.001**

ECOG: Higher scores mean worse PS

Karnofsky: Higher scores mean better PS

Performance status assessment:

0 – at baseline
1 – at the 7th day of the treatment
2 – at the 14th day of the treatment

* The least significant difference test; p-values comparing performance status during the treatment period with the baseline assessment

Tab. 6. Results of two-way ANOVA. Dependent variables: ECOG and Karnofsky preformance status, independent variables: drug influence, treatment time effect and interaction of drug and treatment time. Degree of freedom for a drug 1, for the treatment time and interaction 2

Performance status scale	Drug influence	Treatment time effect	Interaction of drug and treatment time
ECOG	P > 0.316	**P < 0.001**	P > 0.162
Karnofsky	P > 0.516	**P < 0.001**	P = 0.087

Fig. 1. CONSORT diagram of the study