Combination of transdermal fentanyl with codeine or tramadol for the management of severe cancer pain

Zouka M, Zaralidou A, Maidatsi P, Andreopoulos K, Kokkonis G, Giala M

ABSTRACT

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The aim of this study was to examine and compare the efficacy and safety of combining strong opioids (transdermal fentanyl) with weak opioids (codeine or tramadol) for the management of severe cancer pain. Forty six patients (25 male / 21 female) aged 42-80 years were studied. According to an eleven-grade numeric rating scale (NRS; 0 = no pain, 10 = severe pain), they all had severe steady pain intensity greater than 5 (NRS >5) despite treatment with weak opioids and adjuvant drugs, as proposed by the 2nd step of the World Health Organization (WHO) analgesic ladder, at the maximum tolerated doses. Enrollment to the 3rd step of the ladder and initiation of transdermal fentanyl (fentanyl-TTS) was decided and informed consent was obtained by all subjects. They were randomly divided into 3 groups: group F (n=15), which constituted the control group, received fentanyl-TTS alone, group C (n=17) received combined codeine-acetaminophen (Lonalgal®) tablets in addition to fentanyl-TTS and group T (n=14) had tramadol capsules administered along with fentanyl-TTS. The above additional drugs were given at equipotent doses every 12 hours. All patients were informed so as to increase fentanyl-TTS dosage by 25μg/h/72h in cases of high steady pain intensity (NRS >4). Oral transmucosal fentanyl citrate was prescribed for possible acute pain episodes. A month later, the following parameters were recorded: pain intensity, final dosage of fentanyl-TTS, daily dosage of transmucosal fentanyl citrate, drug-related side effects and patients' judgment of treatment. Statistically significant results were recorded for pain intensity at the end of the study ($p<0.05$) compared to pain intensity immediately before enrollment but without significant differences among the studied groups ($p>0.05$), as well as for mean final dosage of fentanyl-TTS in groups C ($p<0.01$) and T ($p<0.05$) compared to the relative dosage in group F. Favorable but not statistically significant ($p>0.05$) results were recorded for the rest of the end-points apart from the adverse effects of the drugs used; nausea, vomiting and to a lesser extent constipation and somnolence were seen. In conclusion, the combination of either tramadol or codeine-acetaminophen with fentanyl-TTS were proven to be useful alternatives for long-term treatment of severe cancer pain for patients placed at the 3rd step of the WHO analgesic ladder, probably sparing the need for opioid switching or route rotation. Nevertheless, drug-related side effects were not limited. Moreover, due to lack of sufficient studied data we would not recommend any similar combinations for the management of severe cancer pain.

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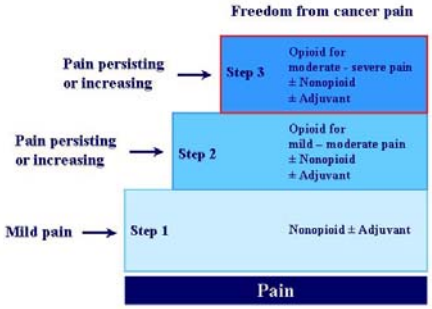
According to the international guidelines[1,2], weak and strong opioid combinations have not been recommended for the treatment of severe cancer pain, nor is there sufficient published data to support such management of cancer pain.

However, the effectiveness of transdermal fentanyl (fentanyl-TTS), a pure μ opioid agonist, is well-established[3-7]. It serves as a viable alternative to oral opioids, especially for patients with end-stage disease and impaired oral intake. The amount of drug released depends primarily on the surface area of the patch. A reservoir of drug established in the upper dermis delays systemic absorption for the first few hours, serum concentrations reaching the minimum effective and maximum in 1.2 to 40 hours and 12 to 48 hours of application, respectively[8]. The relative delay in reaching peak analgesic levels after dose escalation could be a problem in the setting of rapidly progressing disease accompanied with severe pain.

The World Health Organization (WHO) places tramadol and codeine on step 2 of the analgesic ladder (figure 1) as alternative options for treating mild to moderate cancer pain. Tramadol is a centrally acting analgesic that shares properties of both opioids and tricyclic antidepressants, by weakly binding to the μ opioid receptors and inhibiting the reuptake of serotonin and noradrenaline, respectively[9,10]. Codeine is commonly used as a combination product with acetaminophen (Lonarid-N®, Lonalgal®) and once absorbed is only partly (10%) demethylated to morphine, which accounts for its weak analgesic properties[11].

Figure 1. World Health Organization 3-step analgesic ladder. Adapted and modified from: World Health Organization. Cancer pain relief and palliative care 2nd ed. WHO, Geneva 1996.



Therefore, we aimed to study and compare the efficacy and safety of combining weak opioids (tramadol or codeine) with strong opioids (fentanyl-TTS) for the treatment of severe cancer pain.

MATERIALS AND METHODS

Forty six patients (25 male and 21 female) aged 42-80 years were included in the study during a six-month period. Inclusion criteria were the presence of intractable cancer, as defined by specialist clinical evaluation and response to therapy, the presence of severe steady pain with intensity greater than 5 based on an eleven-grade numeric rating scale (NRS; 0 = no pain, 10 = very severe-unbearable pain) and the patient's ability for oral intake.

All patients were already under treatment with weak opioids and adjuvant drugs at the maximum tolerated doses according to the 2nd step of the WHO analgesic ladder. Informed consent was obtained by all patients prior to enrollment to the 3rd step of the ladder and initiation of fentanyl-TTS. The subjects were randomly divided by a blind observer into three groups: group F (n=15), group C (n=17) and group T (n=14). The former, which constituted the control group, received fentanyl-TTS alone, group C received combined codeine-acetaminophen tablets (Lonalgal®) in addition to fentanyl-TTS, and finally, group T patients were supplemented with the weak opioid tramadol in capsules. The additional drugs were given at equipotent doses every twelve hours. In cases of high steady pain intensity (NRS >4), all subjects were informed so as to increase fentanyl – TTS dosages by 25μg per hour, per 72 hours (25μg/h/72h). Oral transmucosal fentanyl citrate was prescribed for possible acute breakthrough pain episodes.

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One month after enrollment, the following end-points were recorded and analyzed for each group:

- pain intensity;
- mean final dosage of transdermal fentanyl;
- mean daily dosage of oral transmucosal fentanyl citrate;
- side effects potentially related to the studied drugs;
- patients' judgment of pain treatment, using a four-grade scale (grades 0-3, 0 representing poor outcome, whereas 3 assuming excellent pain relief).

Statistical analysis was performed using the Kruskal Wallis test for pain intensity and patients' judgment of pain treatment, while one-way ANOVA test was used for the rest of the parameters. $P<0.05$ was considered statistically significant. All means are given ± standard deviation.

RESULTS

Pain intensity at the beginning of the study was similar among the three groups of patients. The mean NRS score was reported to be 5.9±2.1 vs 6.4±2.9 vs 6.9±2.5 for groups F, C and T respectively. Significant pain relief ($p<0.05$) was seen at the end of the study in all subjects. The mean NRS score was 3.5±1.8 for group F, 2.9±0.9 for group C and 3.8±1.2 for group T. All three analgesic regimens provided a similar level of pain relief (Figure 2).

The dosage of fentanyl-TTS at the end of the study was significantly lower in patients who received codeine-acetaminophen ($p<0.01$) or tramadol ($p<0.05$) compared to those who received fentanyl-TTS alone. The mean dosage in group F was 80.1±20.2 μg/h/72h compared to 58.6±11.7 μg/h/72h in group C and 64.7±18.7 μg/h/72h in group T (Figure 3).

Dosages for oral transmucosal fentanyl citrate were equivalent in all three groups. They averaged 626.6±183μg/h vs 588.2±149.5μg/h vs 614.2±123.1μg/h for groups F, C and T respectively. The differences recorded were not statistically significant.

Figure 2. Mean numeric rating scale (NRS) scores before enrollment to the 3rd step of the analgesic ladder compared to the relative scores at the end of the study.

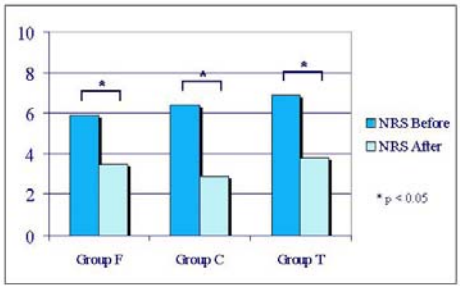
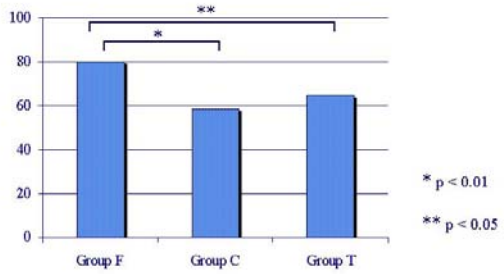


Figure 3. Mean final dosage of transdermal fentanyl in the three groups.



Adequacy of pain treatment was judged to be similar by all subjects. According to the four-grade scale the relative scores were 1.9±0.4, 2.1±0.4 and 1.9±0.7 for groups F, C and T respectively.

Nausea and vomiting were the most common side effects recorded in 5 subjects of the tramadol group, 3 of the codeine–acetaminophen group and 2 of the fentanyl-TTS group. Constipation and somnolence affected all patient groups in similar but smaller rates.

DISCUSSION

Our search of the medical electronic libraries revealed only 1 published study[12] concerning

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the combination of weak and strong opioids for the management of severe cancer pain, suggesting there is insufficient data on this particular subject. Our inclusion criteria were similar to those set by Marinangeli et al[12]. It was advocated though, that the authors provided limited demographic information regarding the subgroups and that differences in pain etiologies could have contributed to a differential response[13]. Cancer pain is multifaceted and can be described as acute, chronic, nociceptive (somatic), visceral, or neuropathic[11]. Alternatively, some have proposed just three prime categories: nociceptive, neuropathic, and psychogenic[14]. It is generally accepted that in cancer pain trials a distinction among nociceptive, neuropathic, and mixed pain is sufficient for patient classification[13]. Marinangeli et al[12] included only patients affected by chronic pain, while patients with prevalent neuropathic pain were excluded. Their trial was not powered to show the effect of combining weak with strong opioids on acute pain. In our study all subjects were affected by chronic mixed etiology pain; acute episodes were taken into account and managed by the administration of transmucosal fentanyl citrate.

Symptomatic treatment of severe cancer pain should begin with an opioid, regardless of the mechanism of pain[11]. Oral morphine has been widely used for treating pain of moderate to severe intensity, and remains the opioid of choice for its familiarity, availability, costs rather than proven superiority[15,16]. However, the importance of alternatives to morphine has been recognized for some years[17]. Fentanyl-TTS provides a similar extent of pain relief to sustained release morphine formulations and is probably accompanied by a lower risk of constipation[18]. Moreover, it constitutes an excellent alternative in cases of impaired oral intake. Despite application of the WHO 3-step analgesic ladder, advancing pain research, and expansive interventional modalities, as many as 50% of cancer patients with pain may remain undertreated[19]. Relevant reports persist in various clinical settings[20]. Fentanyl-TTS is available in fixed rate-controlled delivery systems (12.5, 25, 50, 75, 100μg/h), a fact that could lead to excessive dosage or inadequate pain control. These features, as Marinangeli et al[12] also stated, could be disadvantageous in allowing day-to-day titration of the analgesic dose in relation to changes of pain. Therefore, we supplemented fentanyl-TTS with weak opioids in order to determine whether the required strong opioid dose could be more accurately titrated and pain more efficiently relieved, probably sparing the need for rapid dose escalations. The statistically significant lower dosages of fentanyl-TTS in the tramadol and codeine-acetaminophen groups required to obtain equivalent levels of analgesia imply such an effect.

The mean final fentanyl dosage in group F was 80.1±20.2 μg/h/72h compared to 58.6±11.7 μg/h/72h in group C and 64.7±18.7 μg/h/72h in group T. These account for a sparing fentanyl effect of 21.5 μg/h in group C patients and 15.4 μg/h in the tramadol group. In oral morphine equivalents the above calculated sparing amounts should be approximately 51.5 mg in the first case and 37 mg in the second. Our results are in accordance with the results of the Marinangeli study[12]; the authors reported a 26.5 μg/h fentanyl sparing effect, the equivalent of about 60 mg of oral morphine. A synergistic effect of the drug combinations could be a reasonable explanation, as both tramadol and codeine act as weak opioids[11]. Tramadol's opioid agonist activity is expressed via activetion of special subtypes of opioid receptors, probably different than those fentanyl acts upon[21]. Its affinity for the μ receptors is about ten times weaker than that of codeine. Additionally, the mechanism of the analgesic action of tramadol comprises activation of both descending serotoninergic and noradrenergic pain pathways[22]. It is efficient mainly for the treatment of neuropathic cancer pain and has been shown to be more effective in this setting compared to other weak opioids[23]. Codeine acts on μ opiate receptors predominantly via its metabolite morphine. Once codeine is absorbed it is metabolized by the liver and 90% of its metabolites are primarily excreted as inactive forms in the urine. Only about 10% of the drug is converted to morphine, which accounts for its analgesic properties as well as its recommendation for the control of only mild to

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moderate cancer pain[11]. It is worth mentioning that genetic differences in the enzyme responsible for the conversion of codeine to morphine render codeine ineffective in about 10% of the Caucasian population[24]. Except for a synergistic effect, it has been proposed that factors including the possibility that tramadol is more potent than previous reports might suggest, or perhaps study-related issues, such as subgroup differences in spite of the randomization procedures, could be partly responsible for the sparing effect[13].

A phenomenon commonly seen when using opioids is tolerance. It is defined as the need for higher drug doses to accomplish the same analgesic effect, but its pathophysiology still remains unclear[25]. Disease-driven factors as well as pharmacological effects have been argued as possible mechanisms[26]. Neither overdosage, nor tolerance was observed in any group of our study. Moreover, the fact that combination of fentanyl-TTS with either tramadol or codeine-acetaminophen lead to significantly lower doses of the strong opioid, suggests a more gradual increase in fentanyl-TTS dosage; this even implies that the above mentioned adverse effects were less likely to have occurred in the combined therapy groups. The Marinangeli results[12] support our point of view. Even though there is lack of evidence to guide clinical practice, opioid switching is a therapeutic maneuver that seems to be effective, both in terms of improving pain relief and reducing opioid related adverse effects, such as overdosage and tolerance[27]. It includes change to different medication using the same administration route, maintaining the current medication but altering administration route (route rotation), or both[28,29]. No need for medication or route switching was recorded in our patients, as was also the case for Marinangeli et al[12].

Despite our favorable results, side effects of the therapeutic regimens were not limited. Nausea and vomiting, and to a lesser extent constipation and somnolence affected all groups of patients. Like in the Marinangeli trial[12], a greater incidence of nausea and vomiting was noted in the group of tramadol. Studies have previously demonstrated that at the relatively high doses of tramadol required to achieve adequate pain relief, the drug has a similar side effect and safety profile to strong opioids[30,31]. Nevertheless, there is insufficient literature data to support a possible synergistic interaction of fentanyl and tramadol regarding this side effect and further search is needed.

Finally, the combination of strong with weak opioids does not seem to have limited the acute pain episodes experienced by our patients. We found no literature data concerning this matter; further studies are needed to evaluate the effect of the above combined drugs on acute breakthrough pain.

CONCLUSIONS

According to our results, the combination of tramadol or codeine-acetaminophen with fentanyl-TTS are useful alternatives for long-term cancer pain treatment in patients placed on step 3 of the WHO analgesic ladder. Due to lack of sufficient studied data, we would not recommend any similar drug combinations. Adding weak opioids to strong opioid treatment regimens could probably limit tolerance and overdosing, thus avoiding opioid switching or route rotation. Nevertheless, opioid side effects do not appear to be less and still remain a problem.

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