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ORIGINAL RESEARCH

Oxycodone and Naloxone Combination: A 12-Week Follow-up in 20 Patients Shows Effective Analgesia Without Opioid-Induced Bowel Dysfunction

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ABSTRACT

Introduction: Opioid analgesics are widely regarded to be highly effective but are equally known for their side effects on the bowel. A new combination of the opioid analgesic oxycodone and naloxone has been developed to combat opioid-induced bowel dysfunction (OIBD) whilst still being effective as an analgesic. The aim of this observational study was to assess the analgesic efficacy of this new combination and to analyze its effect on bowel function.

Methods: Twenty-six patients underwent a trial of this new combination, with 21 patients reaching week 8 and 18 reaching week 12.

Results: A significant reduction was seen in the pain severity score at weeks 4, 8, and 12 ($P < 0.05$), and a significant improvement in the bowel function index was again seen at these points ($P < 0.001$ at week 4 and 12, $P < 0.05$ at week 8). In the patients' global impression of change, 83.3% of patients rated the new medication as an improvement compared to their previous regimen, and 87.5% rated it overall as "good" or "very good."

Conclusion: This small single-center study suggests that the use of ONC in selected patients could lead to an improvement in pain severity and pain interference with a significant improvement in OIBD. Compliance with the combination is good, and it is generally well tolerated.

Keywords: Naloxone; Opioid-induced bowel dysfunction; Oxycodone and naloxone combination; Pain

INTRODUCTION

Opioid analgesics are known to be highly effective, but are equally known for their side effects on the bowel. As an example of this, it has been reported that around 41% of non-cancer patients treated for pain report constipation [1]. This constipation often requires the administration of sometimes multiple laxatives, which often do not satisfactorily relieve it. A new oral combination of oxycodone, an already proven

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and widely used analgesic, and naloxone in a ratio of 2:1 to combat opioid-induced bowel dysfunction (OIBD) is now available. Some of the data in this study have previously been published in abstract form in the proceedings of the World Institute of Pain conference, Maastricht, 2014, where it was featured in a poster [2].

METHODS

Recruitment was from a population of patients attending the chronic pain clinics at the Royal Preston Hospital following a protocol (Fig. 1). The oxycodone and naloxone combination (ONC) was already a licensed preparation and was approved by the Trust's drug and therapeutic committee for use within the trust with the intent of monitoring its efficacy on a small number of patients. As such, the sample size was determined by the number of patients who satisfied the protocol in the study period. There were no age inclusion or exclusion criteria. Twenty-six patients were recruited over the period 28 June 2012 to 11 November 2013. The medication and study were explained, and verbal informed consent to continue was obtained. As a baseline, a brief pain inventory as well as bowel function index were collected by a clinician on a pro forma designed by the Trust in conjunction with NAPP Pharmaceuticals. The ONC was then commenced as per the trust protocol (Fig. 1). Data were collected weekly via telephone on

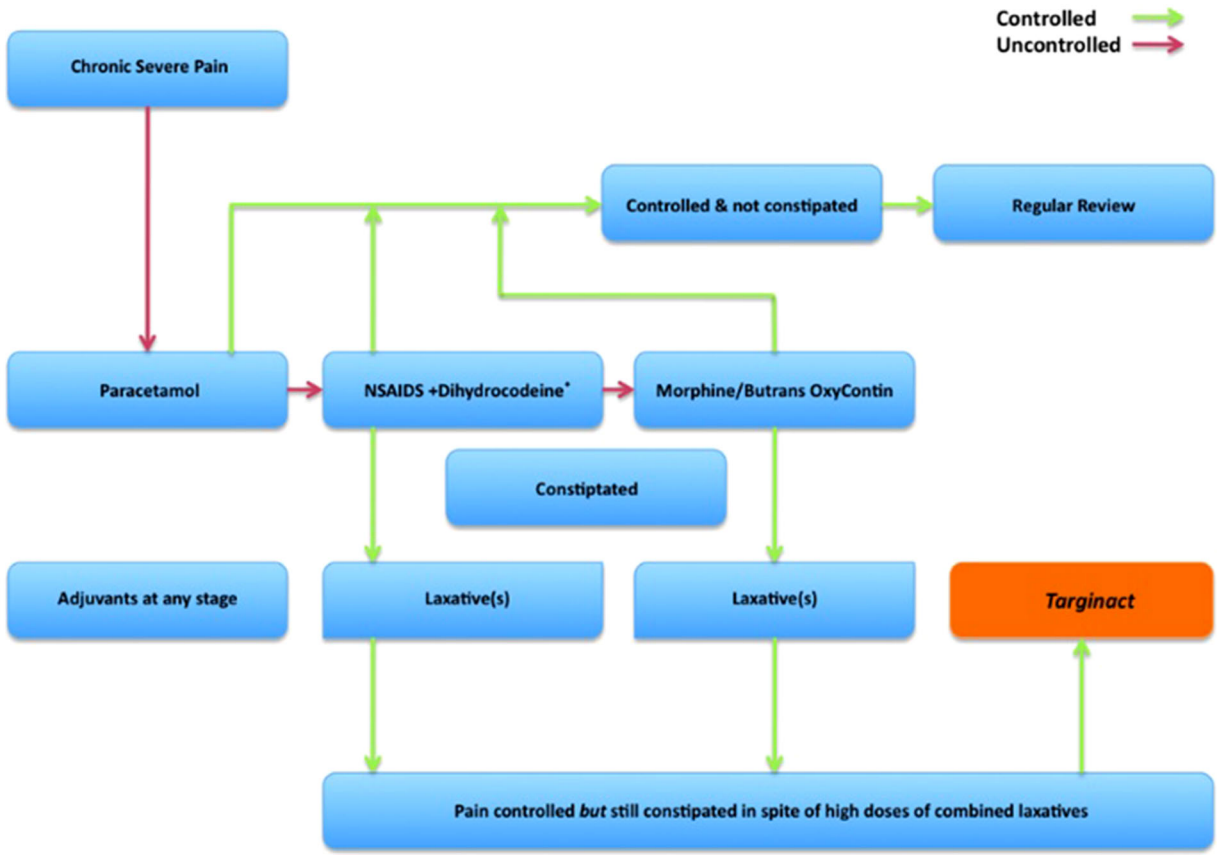

Fig. 1 Trust protocol for the initiation of the oxycodone and naloxone combination. *NSAIDS* nonsteroidal anti-inflammatory drugs

weeks 1, 2, 3, 5, 6, 7, 9, 10, and 11, which were entered onto the same pro forma as data collected in the clinic by a clinician on weeks 4 and 8 and at the end of the trial (11–12 weeks).

The data were then collated onto a spreadsheet for analysis, and descriptive statistical analyses of the group variables were calculated. The pain severity, pain interference, and bowel function indexes were tested for normality and compared using a paired Student's *t* test on SPSS (version 20; IBM Corp., Armonk, NY, USA) [3]. Patients were also asked to give the combination a rating at the end of the trial, which included patients' global impression of change (PGIC), general rating, and a rating in comparison to their previous analgesics, which were then analyzed using descriptive statistics.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed verbal consent was obtained from all patients for being included in the study, and this methodology was approved by Lancashire Teaching Hospitals NHS foundation trust drug and therapeutic committee.

RESULTS

Twenty-six patients started the trial. The mean (range) age of those starting the trial was 57.9 years (21–85 years). Eighteen patients (69.2%) completed the trial. A range of sites for the pain was represented in the sample; the largest group [14 (53.8%)] had lower back pain (±radiation), followed by widespread pain, leg pain, and then hip pain. Other areas also included the abdomen, perineum, thoracic region, hands, and coccyx. Twenty-five (96.2%) patients were taking opioid analgesia prior to the ONC, 11 (42.3%) of whom were taking strong opioid analgesia (oxycodone, morphine sulfate, fentanyl patch, buprenorphine patch), 13 (50%) were taking a weak opioid (tramadol, codeine or dihydrocodeine), and 1 patient was taking paracetamol only (due to OIBD). Twenty-two (84.6%) patients were taking laxatives at therapeutic levels, with 5 (19.2%) patients taking 2 different laxatives and 3 (11.5%) patients taking 3. A more detailed breakdown is available in Table 1.

For weeks 4 and 8, 21 patients had data for analysis. The pain severity score [standard deviation (SD)] was significantly lower than baseline 6.9 (1.2) to 6.0 (1.9) at week 4 ($P < 0.05$) and 5.6 (2.2) at week 8 ($p < 0.05$). A reduction was also seen in the pain interference score (SD) from 7.0 (1.5) at baseline to 6.2 (2.1) at week 4 ($P > 0.05$) and 5.6 (2.3) at week 8 ($P < 0.05$). The bowel function index (SD) dropped from an average of 69.7 (25.6) to 42.8 (31.9) at week 4 ($P < 0.001$) and to 46.6 (35.2) at week 8 ($P < 0.05$). The average starting dose (range) was 10.6 mg (5–40 mg) and the average dose (range) at the end of trial was 16.3 mg (5–40 mg). Thirteen (50.0%) patients required an increase in dose during the trial, of whom 7 (26.9%) required an increase of ≥10 mg and 2 (7.7%) required an increase of ≥20 mg.

Of 26 patients, a total of 18 had trial end data for analysis. The pain severity score (SD) was significantly lower than baseline 6.9 (1.4) at 5.4 (2.5; $P < 0.05$), the pain interference score (SD) 7.1 (1.7) to 5.5 (2.3; $P < 0.05$), and the bowel function index (SD) from 73.1 (26.8) to 35.6 (39.1; $P < 0.001$). Where stated, the main reason for discontinuation was intolerance of side effects. Side effects were reported by six (23.1%) patients during the trial, which

Table 1 Detailed breakdown of pre-study medications

Analgesia prior to study	*N*	Laxative prior to study	*N*
Paracetamol	1	None	4
Co/codamol	6	Senna	3
Dihydrocodeine/codeine phosphate	4	Macrogol	4
Tramadol	3	Lactulose	4
Tramadol and co-codamol	1	Ipsaghula husk	3
Bupenorphrine	4	Senna and macrogol	3
Bupenorphrine/co-codamol	1	Senna and bisacodyl	1
Bupenorphrine/morphine sulphate	1	Lactulose and ipsaghula husk	1
Fentanyl patch/co-codamol	1	Docusate, senna, and prucalopride	1
Morphine modified release	1	Senna, macrogol, and lactulose	1
Oxycodone	2	Senna, ipsaghula husk, and lactulose	1
Oxycodone/tramadol	1		

included sleep disturbance (nightmares and moving during sleep; $n = 1$), leg swelling/dry mouth ($n = 1$), agitation (jumpy/twitchy feeling described, particularly at a point where a dose is wearing off; $n = 1$), and cognition ($n = 1$) and mood changes (including mood lability, "dramatic mood changes," and mood swings; $n = 2$). Two of these patients had loss of inhibition after starting ONC necessitating its discontinuation, one of which was punching during their sleep.

In the PGIC, 15 of 18 (83.3%) patients rated the medication as an improvement, with 10 (55.6%) stating "much improved" or "very much improved" (Fig. 2). Eleven of 18 (61.1%) patients scored the combination as being better than their previous medications, 6 (33.3%) as the same and 1 (5.6%) as worse (Fig. 3). Patients were also asked to give a general rating, with 14 of 18 (87.5%) patients rating the combination as very good ($n = 9$) or good ($n = 5$), 3 patients could not decide between good and bad, and 1 patient rated it as bad.

DISCUSSION

This study is a small single-center assessment of the initial use of this new combination within a Trust protocol. The sample size is small because of the timeframe and the strict protocol used, which makes it difficult to draw concrete conclusions. However, it did indicate that the combination could give superior analgesia with less OBID. This reduction in OIBD whilst providing effective analgesia with ONC has also been observed in a number of other studies [4–11] adding more evidence to support the efficacy of the combination in the reduction of OIBD. The numeric reduction in BFI has also been seen previously [5, 7]. The superior analgesic effects observed in this study could be attributed to a number of factors. First, this was not a case-control type study like a number of the studies referenced above and the two were not directly compared. Second, all of the studies mentioned above compared the combination to oxycodone, whereas this

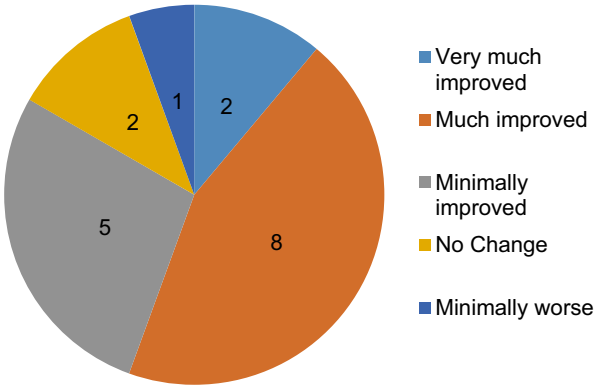

Fig. 2 Patient global impression of change rating

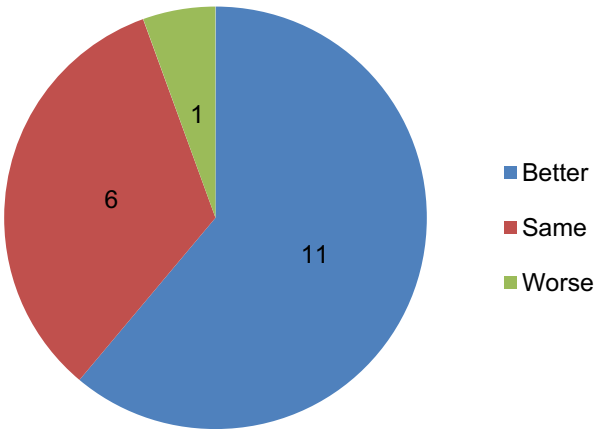

Fig. 3 Comparison to previous medications rating

group drew comparison with the patient's previous analgesia, which ranged from no analgesia to other opioid medications. As such, it could be suggested that the ONC is comparable in terms of analgesia to oxycodone and superior to other regimes, with an improvement in OIBD. Another factor that must be taken into account is the effect of OIBD on compliance. It was seen in this study that a number of patients were taking little or no analgesia through fear of OIBD and as a result were receiving inadequate analgesia. The introduction of this combination has allowed them to receive effective analgesia without OIBD. This can also be seen in patient ratings such as comparison to previous medication. More detailed collection of pre-trial medication data such as dose and actual compliance would have allowed a more robust comparison.

The patient ratings of the combination also revealed that it is effective. This study showed that a majority of patients feel that it is "good" or "very good". This has again been seen in another study that saw 50.0–72.5% of patients rating the combination as good or very good (range dependent on the dose) [12]. The combination was better tolerated in this study with the incidence of side effects lower at 23.1% than other studies, which saw rates of 55.8% [8] and 55.8% [4]; however, this could reflect the length of follow-up or smaller sample size.

CONCLUSIONS

This is a single-center observational study with small sample size. It suggested that the use of ONC in selected patients could lead to an improvement in pain severity and pain interference with a significant improvement in OIBD. Compliance with ONC is good, and less than one quarter of patients reported side effects. Most patients rated the combination as very good and found it better than their previous medications. The majority of the patients on ONC had an improvement in their condition. The results of this study could be used to assist the design of a larger, perhaps multicenter study or the data could be pooled for analysis.

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Disclosures. Gareth P. Jones and Shiva S. Tripathi have nothing to disclose.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed verbal consent was obtained from all patients for being included in the study, and this methodology was approved by Lancashire Teaching Hospitals NHS Foundation Trust Drug and Therapeutic Committee.

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