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# Preliminary experience with the use of a new once-daily prolonged-release oral morphine capsules* in cancer patients with pain

## Abstract

**Background.** In an open, clinical study, preliminary assessment of analgesic efficacy and adverse effects of prolonged-release morphine sulphate capsules administered once-daily was conducted in patients with cancer whose pain required strong opioid analgesics administration.

**Material and methods.** Seventeen patients participated who were treated with capsules containing 20, 40 and 60 mg of the drug. The former treatment comprised morphine (8 patients): controlled-release (5), immediate-release (one), subcutaneous and the study drug (akin 1 patient), transdermal fentanyl (3), tramadol (2), non-opioid analgesics (3) and combination of transdermal buprenorphine with immediate-release morphine in one patient. Analgesia was assessed by NRS (Numerical Rating Scale: 0 — no pain, 10 — the most severe pain); the result 1–3 was assessed as good, 4–5 as satisfactory, over 5 as unsatisfactory. Adverse effects were assessed by verbal scale: 0 — none; 1 — mild; 2 — moderate; 3 — severe.

**Results.** Treatment lasted 7–161 (mean 50.47 ± 40.51) days; the daily dose range was 20–180 mg. Eleven patients (65%) assessed analgesia as good, 5 patients (30%) as partial, one patient (5%) had unsatisfactory analgesic effect. Adverse effects observed were as follows: constipation in 9 patients, drowsiness in two patients, nausea and vomiting in 2 patients, nausea alone in one patient, dry mouth in one patient.

**Conclusions.** This preliminary study demonstrated high analgesic efficacy of prolonged-release once-daily morphine capsules in the dose range 20–180 mg in cancer patients with pain requiring strong opioid analgesics administration. The treatment was well tolerated with no serious adverse effects observed.

**Key words:** pain, adverse effects, analgesic efficacy, morphine, opioids

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## Introduction

The treatment of pain in cancer is based on pharmacological approach according to the World Health Organisation (WHO) [1] and European Association for Palliative Care (EAPC) [2] recommendations with the use of analgesics according to three step WHO analgesic ladder [3]. Opioid analgesics should be administered along with appropriate for each type of pain adjuvant analgesics (co-analgesics). In majority of cancer patients with severe pain effective pain relief may be achieved thanks to strong opioids (opioids for moderate to severe pain) administered alone or in combination with adjuvant analgesics [4]. Several non-pharmacological methods may be used successfully in cancer patients with pain, namely neuromodulation procedures, acupuncture, physical treatment, the use of blockades and neurolytic blocks together with psychosocial and spiritual support [5].

In Poland controlled-release preparations of opioid analgesics are more often being used in cancer patients with pain. In spite of other strong opioids available in Poland (fentanyl, buprenorphine, oxycodone, methadone) morphine is still the most popular and an effective opioid for moderate to severe pain [6]. In a long-term therapy of chronic pain immediate-release morphine formulations (water solution and tablets) are most frequently substituted with regular administration of controlled-release morphine administered usually twice daily; the short-acting formulations are used for breakthrough pain management. A further progress in chronic pain management is the introduction of morphine sulphate controlled-release capsules (20, 40, 60, 120 and 200 mg strength) designed for once a day administration. The aim of the study was the preliminary assessment of analgesia and adverse effects during administration of morphine sulphate controlled-release capsules (20, 40, and 60 mg strength) designed for once a day administration in cancer patients with pain requiring opioid for moderate to severe pain treatment.

## Material and methods

An open clinical study conducted after registration of the study drug (Oramorph O.D.®, Molteni) in Poland. All patients had advanced cancer. Patients with renal impairment (serum creatinine level over 1.3 mg%) and with symptoms of delirium were excluded from the participation in the study. All patients were recruited from those treated at the Day Palliative Care Centre and those staying at home cared by a home palliative care team (Home Hospice) both attached to the Chair and Department of Palliative Medicine at Poznan University of Medical Sciences. The study drug was administered in three capsule strengths: 20, 40 and 60 mg, in daily doses up to 180 mg. Apart from regular administration of the study drug all patients were prescribed immediate-release oral morphine formulations (tablets or water solution) for breakthrough pain management at single doses 5–20 mg depending on the regular dose of morphine. The study medication was administered to 17 patients with cancer whose pain required strong opioid analgesics administration. The decision of the commence of therapy was made individually by a physician, after obtaining consent from patients.

Patients recruited for the study were formerly treated with strong opioids (12 patients), as well as five patients who were formerly treated with weak opioids, namely tramadol (two patients) or non-opioid analgesics (3 patients). In the first group 8 patients were previously treated with morphine: 5 patients received controlled-release preparations twice daily, one patient received immediate-release formulation every 4 h, one patient received morphine subcutaneously, and one patient was already receiving the study drug. All these patients while on former morphine formulations had effective analgesia, thus the same equivalent once daily morphine dose was prescribed (20–60 mg). Three patients were formerly treated with transdermal fentanyl (TF) and one with transdermal buprenorphine (TB) in a combination with immediate-release morphine administered every 4 h; in all these cases the treatment did not provide satisfactory analgesia. In one patient a dose of TF 37.5 $\mu$g/h was substituted with the study drug at a dose of 40 mg. In one patient the TF dose was 25 $\mu$g/h and the study drug was added at a dose of 20 mg. In another patient the TF 50 $\mu$g/h patch was substituted with the study drug at a dose of 60 mg. A patient who received TB at a dose 52.5 $\mu$g/h with immediate-release morphine 5 mg every 4 h the latter was substituted with the study drug at a dose of 60 mg while continuing TB treatment. In all patients who were formerly treated unsuccessfully with tramadol (at a dose of 200 mg daily with poor tolerance and 400 mg daily without satisfactory analgesia) or with non-opioid analgesics alone the study drug was started at a dose of 20 mg daily.

The patients had the following primary tumours: lung (6 patients), breast (3 patients), rectum (2 patients), prostate, palatine tonsil, mediastinum, uri-

nary bladder, pancreas, unknown primary tumour with bone metastases akin 1 patient. Most patients suffered from somatic bone pain (9 patients) somatic from soft tissues (2 patients), visceral pain (6 patients), neuropathic (5 patients) and pain due to raised intracranial pressure (1 patient). Eleven patients suffered from one type of pain; in 6 patients mixed pain syndromes were observed: bone and neuropathic (3 patients), bone and visceral, neuropathic and somatic from soft tissues, neuropathic and visceral akin 1 patient. Patients continued the former treatment with co-analgesics: antidepressants and anticonvulsants in neuropathic pain and non-steroid anti-inflammatory drugs and bisphosphonates in bone pain. In all patients who were opioid-naive or stopped tramadol metoclopramide 10 mg three times daily and lactulose twice daily 15 ml were administered. Analgesia was assessed twice a week by NRS (Numerical Rating Scale: 0 — no pain; 10 — the most severe pain). The score 1–3 was evaluated as good, 4–5 as satisfactory, over 5 as unsatisfactory. Pain intensity and adverse effects was assessed at baseline and every two days during the treatment. Adverse effects were assessed by a verbal scale: 0 — none; 1 — mild; 2 — moderate; 3 — severe. The study protocol was approved by the Regional Ethics Committee at the Poznan University of Medical Sciences.

## Results

The age of patients was 53–85 (the mean 68.53 ± 8.67), there were twelve men and 5 women. The time of the treatment was 7–161 (the mean 50.47 ± 40.51) days, the dose range 20–180 mg: the mean starting dose was 42.35 ± 19.26 mg and the mean final dose was 61.18 ± 42.55 mg. Eleven patients (65%) assessed analgesia as good, 5 patients (30%) as satisfactory, one patient (5%) had unsatisfactory analgesic effect. This patient with bone and neuropathic pain due to bone metastases from prostate cancer stopped the treatment due to ineffective analgesia after 7 days and returned to his former schedule with controlled-release morphine administered twice daily with good analgesia. Patients who had satisfactory analgesia were those two with bone metastases from unknown primary tumour and from lung cancer, one patient with lung cancer and oesophagus infiltration, one patient with lung cancer and local pain and a patient with somatic and neuropathic pain due to palatine tonsil cancer. The respective daily doses of the study drug were as follows: 20–120 mg, 20 mg, 60 mg, 60 mg, and 60–180 mg. Patients who experienced good analgesia were treated with the daily dose range of the study drug 20 mg (four patients), 40 mg (one patient), 60 mg (three patients), 20–40 mg (one patient), 60–80 mg (one patient), and 60–120 mg (one patient); two of those patients were treated concurrently with TF (25 $\mu$g/h) and TB (52.5 $\mu$g/h); the study drug daily doses were 20 mg and 60 mg, respectively.

The treatment with the study drug was continued until the end of life in three patients. In 4 patients morphine was administered subcutaneously due to general deterioration before death and inability to take medications orally. In another three patients therapy with the study drug was continued at the time of study evaluation; in 5 patients the treatment was stopped due to unavailability of the study drug and all these patients were switched to the treatment with controlled-release morphine administered twice daily. One patient was lost to follow up due to a stay in another hospital until her death. As mentioned above one patient stopped the treatment due to lack of efficacy of the study drug.

Adverse effects observed were as follows: constipation in 9 patients (in two severe demanding several enemas, in 5 moderate, in 2 mild), drowsiness in 2 patients (in one patient of mild and in another of moderate intensity), nausea and vomiting in two patients (moderate and mild akin 1), nausea alone in one patient, dry mouth also in one patient. In one patient choreatic movement exacerbated but the symptom was attributed to the Parkinson disease. No severe adverse effects were observed such as respiratory depression or allergy for the drug.

## Discussion

The results of the study indicate high analgesic efficacy of the new prolonged-release morphine formulation in the treatment of cancer patients with pain requiring strong opioids administration. In 11 from seventeen patients recruited analgesia was good, which concerned both patients treated formerly with morphine, fentanyl and two patients who required strong opioids administration due to ineffective analgesia and poorly tolerated tramadol treatment. Good analgesia was also observed in two patients who received concurrently TF and TB. Positive effects were achieved in patients with both receptor and neuropathic types of pain. Unsatisfactory analgesia was observed in one patient diagnosed with prostate cancer and bone metastases. In this patient the study drug was used at a dose of 60 mg per day; however, the

analgesic effect was unsatisfactory in the morning hours before the next dose administration. The patient returned to his former treatment schedule (one controlled-release morphine tablet at a dose 30 mg, every 12 h) and achieved satisfactory pain relief for 24 h; after several weeks of the treatment the dose was increased to 40 and then to 60 mg twice daily due to disease progression and more intense pain. Perhaps the cause of the treatment failure was accelerated gastrointestinal motility although special tests were not conducted. Five patients assessed analgesia as satisfactory; most of these patients suffered from bone or neuropathic pain and needed higher morphine doses although an uncontrolled study design and a small study sample does not allow drawing equivocal conclusions.

It should be emphasized that the tolerance of the treatment was generally good. Constipation was observed in 9 patients (in two severe demanding several enemas, in 5 moderate, in 2 mild), drowsiness in 2 patients (in one patient of mild and in another of moderate intensity), nausea and vomiting in two patients (moderate and mild akin 1), nausea alone in one patient, dry mouth also in one patient. All patients with constipation demanded laxatives administration (lactulose, senna and glycerine suppositories), which in most cases caused bowel movement every other day. However, in two patients constipation was severe and required enemas. Drowsiness was observed at the beginning of the treatment in one patient and disappeared without treatment; in another patient drowsiness was probably due to progressive cachexia that led to a patient's death. Nausea and vomiting was observed in a patient with brain metastases, which could have been the cause of the symptoms but also due to morphine administration. The symptoms were also apparent in a patient with advanced lung cancer and severe cachexia despite antiemetic administration. No severe adverse effects appeared especially respiratory depression or allergy to the drug. The low incidence and mild to moderate intensity of adverse effects was probably due to the fact that most patients were formerly treated with strong opioids including 8 patients treated with morphine at the same doses as the study drug and the prophylactic use of metoclopramide in opioid-naive patients and those who started the study drug after tramadol. Another factor could be that all patients recruited had normal renal function as in case of renal impairment morphine adverse effects are more frequent and more intense [7].

Our results are comparable to the experience of other authors who used controlled-release morphine sulphate tablets and capsules administered twice daily that were effective in most cancer patients with pain requiring strong opioid administration [8]. The convenience of the new morphine capsules formulation that demand once daily administration every 24 h should be emphasized. Similarly as in the case of morphine controlled-release capsules designed for twice daily administration [9] the advantage of the new morphine capsule formulation designed for once daily administration is the possibility of opening the capsule and administration of the content (microcapsules) with pap-like food without disturbing the controlled-release system of drug. This was confirmed in our large, multicenter study conducted in patients with cancer and chronic, non-malignant pain [10]. It is important for patients with dysphagia and for those fed by nasogastric tube and gastrostomy with 16 FG or bigger diameter. It is also an advantage of the study drug in comparison to morphine tablets administered once-daily [11, 12]. According to the manufacturer drug recommendations morphine sulphate prolonged-release capsules designed for once-daily administration may be given to patients formerly treated with immediate-release or controlled-release morphine administered every 4–6 h or every 12 h, respectively [13]. In the light of our observation it seems feasible to administer the study drug in patients who were formerly treated with TF at doses 37.5 and 50 $\mu$g/h. It was also possible to concurrently treat patients with TF 25 $\mu$g/h or TB 52.5 $\mu$g/h with the study drug at daily doses 20 mg and 60 mg (in this case instead of regularly administered immediate-release morphine), respectively [14, 15] with good analgesic effects. The treatment was also successful in patients treated formerly with weak opioids namely tramadol who did not achieve satisfactory analgesia at a full dose (400 mg). It was also possible to administer successfully the study drug in opioid-naive patients who suffer from severe pain demanding opioids for moderate to severe pain administration. In all these cases the starting dose was 20 mg once daily, although these approaches need more data. Due to a possible negative interaction of the concurrent study drug administration and alcohol intake (dr Arleta Kaczmarek, dr Wojciech Stanek, Molteni Poland, personal communication) and unavailability of the study medication the treatment was completed in five patients who were switched to the controlled-release morphine administered twice daily. However, in vitro studies did not demonstrate increased release of morphine from prolonged-release tablets in the presence of ethanol 4–40% [16].

Several limitations of the study should be addressed. It was a pilot survey with a small study sample recruited; moreover, it was a heterogenic group of patients with different primary tumours, different types of pain and different pain medications administered before entering the study. However, due to these features it was more alike to everyday clinical practice situation rather the clinical trial. Due to these limitations the results achieved need verification in a larger patient group with a controlled study design. Further limitations include an open design without comparators and lack of a control group. Most patients recruited were those treated formerly with other morphine formulations that provided satisfactory analgesia. The observation was limited to analgesia and adverse effects reported by patients without the use of more precise tools such as pain, adverse effects and quality of life questionnaires. The time of the treatment was quite different in individual patients. The study was conducted in one centre and all patients were treated at out-patient palliative care clinic, day care centre or at home. In spite of numerous limitations preliminary results indicate on the usefulness of morphine sulphate prolonged-release capsules (20, 40, and 60 mg strength) designed for once-daily administration in cancer patients with pain requiring opioids for moderate to severe pain treatment. Both satisfactory analgesia as well as beneficial profile of adverse effects encourages further comparative studies with other strong opioids taking into consideration analgesia, adverse effects, pharmacokinetic profiles of drugs studied and patients' quality of life.

In conclusions the use of morphine sulphate prolonged-release capsules (20, 40, and 60 mg strength) administered once-daily in cancer patients with pain requiring treatment with opioid for moderate to severe pain in the daily dose range 20–180 mg provided in all but one patient good or satisfactory analgesia. It refers to strong-opioid tolerant patients as well as those treated formerly unsuccessfully with weak opioids (tramadol) and opioid-naive patients. The tolerance of the treatment was good; the observed adverse effects were constipation, drowsiness, nausea and vomiting in most cases of mild to moderate intensity with no serious adverse effects.

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*The production of the medicine has been halted and it is no longer available (Ed.).

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