Morphine poisoning in a patient with malignant peritoneal mesothelioma: A case report

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Abstract. Pain is one of the most common symptoms of malignant peritoneal mesothelioma. Therefore, analgesia serves an indispensable role in the treatment of this condition. Morphine is a representative opioid, which is widely used in clinical practice; however, excessive or unreasonable application can cause poisoning. Few cases of morphine poisoning have been reported, and cases of morphine poisoning in patients with malignant peritoneal mesothelioma are even more rare. Here, we present a case of morphine poisoning in a patient with malignant peritoneal mesothelioma. The patient had a high abdominal tumor load, hepatorenal insufficiency, and was treated with a combination of morphine and the sedative benzodiazepine, eventually leading to morphine poisoning. Therefore, for cancer pain, omni-directional and whole-process management should be emphasized. In patients with hepatorenal insufficiency, those treated with morphine combined with benzodiazepines, or those with a high abdominal tumor load, attention should be paid to drug absorption, excretion and interaction, and the drug dose during administration should be reduced to avoid drug poisoning. If poisoning symptoms occur, timely measures should be taken to reduce poison absorption and increase poison excretion, and antagonists should be used to reverse the poisoning and reduce the damage caused.

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Introduction

Cancer has become an important factor threatening human health. There are about 19.3 million new cancer cases worldwide each year, and about 10 million patients die of cancer (1). Although with the development of medicine, the quality of life of patients with common malignant tumors such as lung cancer, breast cancer, and esophageal cancer has been significantly improved, the treatment effect for patients with malignant tumors with a low incidence such as malignant peritoneal mesothelioma still not as good as it should be. Some patients had to resort to palliative care and end-of-life care (2). Pain is one of the most common symptoms of malignant peritoneal mesothelioma. It is reported that 92.7% of patients with this condition have experienced varying degrees of cancer pain. Therefore, analgesia plays an important role in the treatment of malignant peritoneal mesothelioma. Opioids are the first choice for the treatment of moderate and severe pain, but they also readily cause adverse reactions, such as constipation, nausea, urinary retention, respiratory depression, and addiction. Excessive or unreasonable administration can cause poisoning. This is mainly characterized by respiratory depression, pupillary constriction, a drop in blood pressure, and in severe cases, circulatory failure, shock, and even death. Few cases of morphine poisoning have been reported, and even fewer are cases of morphine poisoning in patients with malignant peritoneal mesothelioma. Here, we present a case of morphine poisoning in patients with malignant peritoneal mesothelioma in order to provide guidelines for clinical practice.

Case report

The patient, a 64-year-old man, had been diagnosed with malignant peritoneal mesothelioma 3 years and 5 months previously. He had undergone abdominal nodulectomy in May 2018. Postoperative biopsy pathology indicated poorly differentiated adenocarcinoma nodules, and malignant mesothelioma was considered (Fig. 1A and B). Immunohistochemistry indicated that the tumor was positive for AEI/AE3, calretinin, CK5/6, WT1, D2-40, and EMA and negative for Vim, CEA, and calponin. The Ki67 index was 10%. These findings were consistent with malignant mesothelioma. Because the patient was considered to have an advanced tumor and had a malignant abdominal effusion, he could not undergo surgery (Fig. 1C and D). There were no contraindications for chemotherapy. Therefore, the patient received a pemetrexed combined with platinum regimen for a total of 13 cycles, and the last cycle of chemotherapy was administered in September 2021. During chemotherapy, he was also treated with traditional Chinese medicine and gamma knife surgery in another hospital (the specific treatment is unknown). The patient had abdominal pain and poor sleep. Therefore, to alleviate cancer pain and insomnia, he began to take morphine hydrochloride sustained-release tablets (30-60 mg po q12h) in addition to estazolam tablets intermittently (1 mg po prn) (Fig. 2). He was admitted to the Fourth Hospital of Hebei Medical University in October 2021, for continued treatment.

The next day, the patient appeared to be in a deep coma, with constricted pupils, poor light reflex, and negative orbit compression reflex. The physical examination was difficult due to patients loss of consciousness and no response to voice command. ECG monitoring indicated the following results: Pulse: 122 beats/min, Respiratory rate: 13 times/min, and Blood pressure: 100/69 mmHg. Blood gas analysis indicated a pH of 7.290, PaCO2 of 59.4 mmHg, PaO2 of 33.5 mmHg, lactic acid of 1.61 mmol/l, and BE of 0.8 mmol/l. Liver and kidney function tests indicated an ALT level of 13.1 U/l, an AST level of 23 U/l, an SCR level of 136.1 μmol/l, and a urea level of 10.7 mmol/l. The blood chemical composition test detected a morphine component of 3.5 mg/l (therapeutic dose is less than 1.0 mg/l) and a diazepam component of 6.6 mg/l (therapeutic dose is less than 2.0 mg/l). Therefore, we diagnosed respiratory failure secondary to drug poisoning. The patient immediately underwent oral tracheal intubation and ventilator-assisted breathing, hypotension treatment, gastric lavage, acid inhibition to protect the gastric mucosa, and fluid replacement. At the same time, the patient is gave hemoperfusion twice by the doctor on duty, additionally, naloxone (0.4 mg) and flumazenil (0.3 mg) were injected into the patient by intravenous injection in order to promote awakening. After about 6 h, the patient's consciousness gradually recovered and his vital signs stabilized to a normal state. His status improved, and he was discharged from the hospital.

Discussion

Malignant tumors have become one of the main threats to human health. There were 19.3 million new cancer cases and nearly 10 million cancer-related deaths worldwide in 2020 (1). As the most common cancer symptom, pain seriously affects the quality of life of cancer patients. Previous studies have shown that approximately 55% of patients receiving anticancer therapy, and 66% of patients with advanced and metastatic malignant tumors experience pain (2). The goal of cancer pain management is to reduce pain to an acceptable level. In 1986, the WHO recommended a 'three-step treatment principle of cancer pain', which has played a vital role in cancer pain control in the past 35 years. However, because of the results of in-depth studies on cancer pain, analgesics are no longer required to be strictly administered in a step-by-step fashion. If patients present with moderate or severe pain, opioid painkillers can be administered immediately to avoid delay in treatment (3). Therefore, opioids, as the cornerstone of analgesic drugs, are widely used in clinical 'painless wards.' In this clinical setting, in order to relieve pain as one of the common symptoms of malignant peritoneal mesothelioma, morphine hydrochloride sustained-release tablets were given to this patient.

Opioid drugs used by humans to treat pain can be traced back to ancient Egypt (4). The pharmacological effects of opioid analgesics come from their complex interactions with three distinct opioid receptors (the μ, κ, and δ receptors) (5). When activated by opioid receptor agonists, these receptors indirectly inhibit voltage-dependent calcium channels, reduce the level of cAMP, and block pain neurotransmitters (such as glutamate and substance P), resulting in an analgesic effect (6).

The opioid morphine is widely used in clinical practice. Morphine can stimulate opioid receptors (mainly the μ receptor) on central and peripheral neurons, neuroendocrine (pituitary and adrenal), immune and ectodermal cells, to produce an analgesic effect (4,7,8). μ receptors are mainly expressed in the brainstem and medial thalamus (9,10). The μ receptor is encoded by the *Oprm*$_1$ gene and can be the μ_1, μ_2, or μ_3 subtypes. μ_1 is related to analgesia, euphoria, and sedation; μ_2 is related to inhibition of breathing, itching, stimulation of prolactin release, opioid dependence, pupil dilation, gastrointestinal motility (constipation), and sedation; and μ_3 is related to vasodilation (4,10). Morphine can also act on the κ and δ receptors. The κ receptor is mainly expressed in the marginal zone and other diencephalic regions, the brainstem, and the spinal cord, and is responsible for analgesia, sedation, diuresis, respiratory depression, and opioid dependence (4,10,11). The δ receptor is mainly expressed in the brain, and its effects may be related to analgesia, anxiety, and reduction of gastrointestinal motility (4,10). The roles of these opioid receptors explain the analgesic effect of morphine and its adverse reactions, such as respiratory depression, orthostatic hypotension and syncope, endocrine abnormalities, immune dysfunction, sleep and mood changes, SIADH, and addiction (10,12-14). This patient had obvious symptoms of the μ receptor.

Morphine is mainly metabolized by glucuronidation and demethylation in the liver. Glucuronidation, which produces morphine-6-glucuronide and morphine-3-glucuronide, is the main metabolic process (4,15,16). Morphine-6-glucuronide is thought to cause some of the analgesic effects of morphine (15), whereas morphine-3-glucuronide has no analgesic effect; some studies have even found that a sufficiently high concentration of morphine-3-glucuronide may lead to hyperalgesia (4,17). The metabolites of morphine are mainly eliminated by the kidneys, although small amounts are excreted in the bile and milk. With regard to the route of administration, morphine is

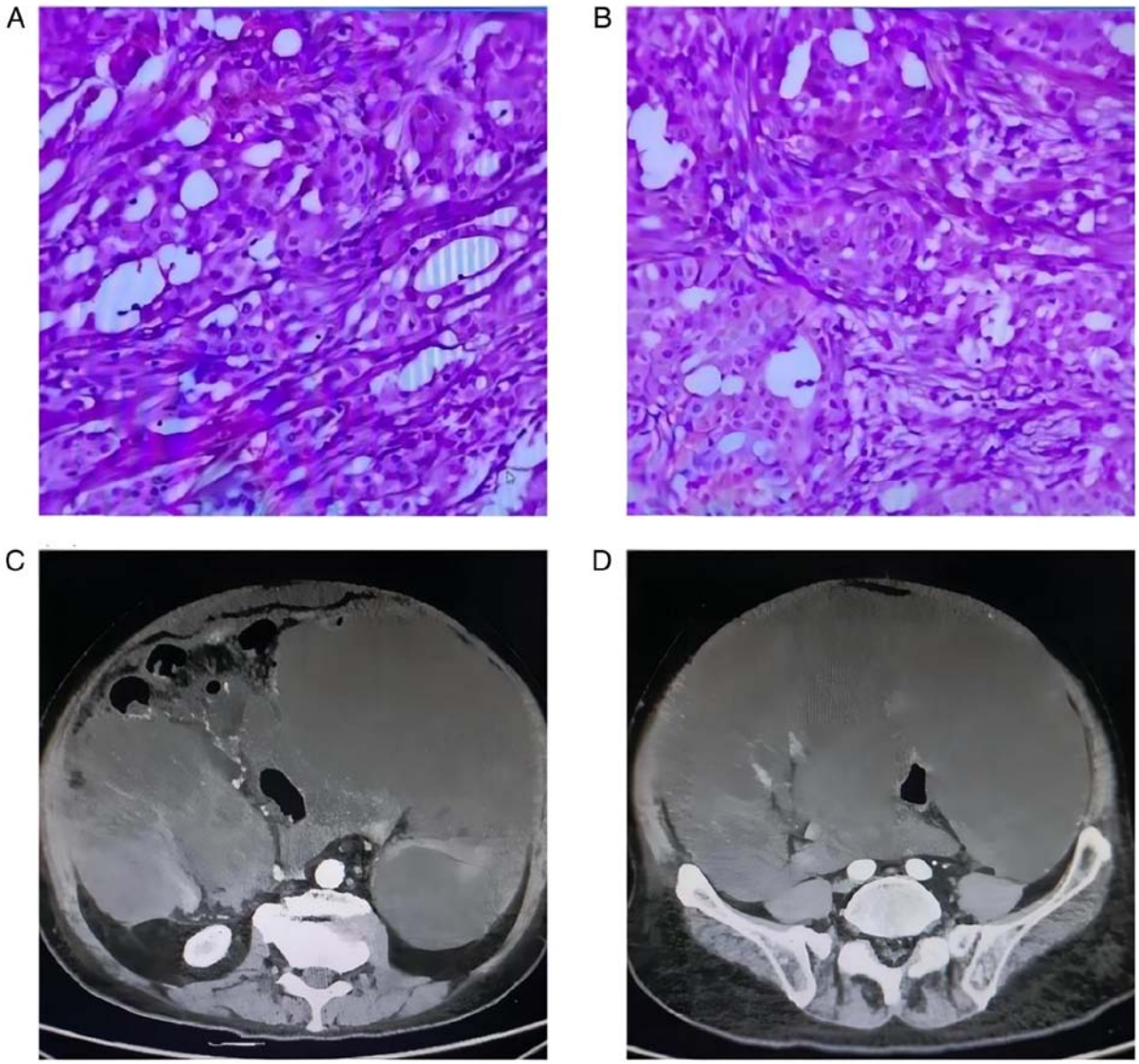

Figure 1. Initial patient data. (A and B) Postoperative biopsy pathology. Both (A) and (B) are pictures of two different areas of pathological sections with x100 microscopic magnification. (C and D) Abdominal CT was performed in October 2021 after the patient developed abdominal pain. Both (C) and (D) are pictures of two different levels of the same CT.

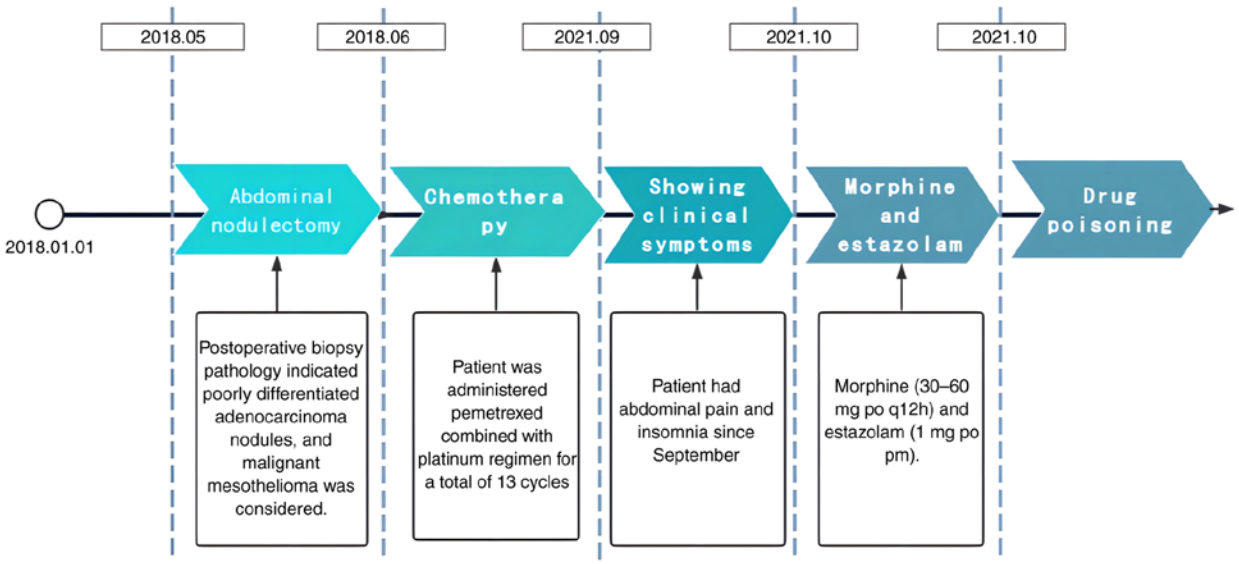

Figure 2. Diagnosis and treatment timeline.

absorbed rapidly after subcutaneous and intramuscular injection and absorbed through the gastrointestinal tract after oral administration. It is then rapidly metabolized by microsomal enzymes through the liver, so that the blood concentration of morphine is relatively low. After absorption, it is distributed to the lung, liver, spleen, kidney, and other tissues. Only a small amount of morphine can pass through the blood-brain barrier, but it produces an efficient analgesic effect (4). This patient had extensive abdominal metastasis and high tumor load (Fig. 1C and D), resulting in slower intestinal peristalsis, prolonged drug retention time, increased absorption, and drug concentration accumulation. Simultaneously, morphine can also lead to the weakening of gastrointestinal peristalsis, which further aggravates the above effects. Another noteworthy problem is that this patient had normal renal function during initial treatment but he later developed renal insufficiency, as evidenced by a serum creatinine level of 136.1 μmol/l. This would reduce drug excretion and further increase the concentration of morphine in the blood.

Drug interactions must also be considered in patients receiving morphine. Morphine can reduce the peak blood concentration and efficacy of P2Y12 receptor antagonists by inhibiting gastrointestinal peristalsis and digestive juice secretion (18). Fine *et al* (19) reported a case of respiratory arrest, seizures, insanity, and general convulsions caused by cimetidine combined with morphine. However, Mojaverian *et al* (20) tested healthy individuals and found that cimetidine did not affect the metabolism and efficacy of morphine; no other adverse reactions were observed during the study. Shirooie *et al* (21) reported that long-term administration of metformin can improve morphine tolerance and dependence by inhibiting microglial activation and mTOR signaling. Okura *et al* (22) found that quinidine enhances the blood concentration of morphine by changing the activity of p-glycoprotein. Continuous oral administration of morphine combined with etoposide increases the blood concentration of etoposide, which may also be related to changes in intestinal p-glycoprotein activity (23). Manara *et al* (24) reported that oral administration of morphine and metoclopramide can accelerate the effect of morphine and enhance its analgesic effect. Morphine also prolongs the half-life of theophylline in rats and reduces the clearance rate by competing with theophylline for receptor binding (25). Some studies have shown that morphine may enhance the binding of benzodiazepines to GABAA receptors by acting on opioid receptors, thereby enhancing the efficacy of benzodiazepines (26). This patient took morphine and estazolam tablets at the same time, which may have led to poisoning due to drug interaction which enhanced each drug's effects.

Benzodiazepines, such as diazepam, midazolam and estazolam, are established first-line drugs for sedative-hypnotic, anxiolytic and antiseizure. Benzodiazepines are a family of drugs that exert their effects by allosterically modulating the activity of the ionotropic gamma-aminobutyric acid (GABA)-A receptor in the central nervous system . These drugs increase the probability that GABA binding to the receptor will open the associated Cl- channel. Thus, these drugs generally decrease neuronal excitation and exhibit sedative-hypnotic, anxiolytic and antiseizure (27). Estazolam is an s-triazolo benzodiazepine derivative whose structure is derived from the introduction of a triazole ring in the 1,2 position of the well-known diazepam structure. The plasma concentration of estazolam reached its peak 3 h after oral administration. It has a half-life of 10-24 h, which agree well with those reported by Mancinelli *et al* who described the human elimination of estazolam, determined in good agreement from the single- and multiple-dose studies, averaged 19 h (28). Pierce *et al* reported that estazolam 1.0 and 2.0 mg produce significant increases in total sleep time. Estazolam 0.25 and 0.5 mg are also effective, but the improvement in total sleep time may be too small to be clinically significant for most patients (29). Therefore, oral 1-2 mg Estazolam can play a good effect in the treatment of insomnia. The patient's oral 1 mg estazolam (safe dose) led to drug poisoning, so other factors were considered such as drug interaction, liver and kidney damage.

At present, the only drug approved by the FDA for the prevention and treatment of opioid overdose is naloxone (30). France *et al* (30) recently documented several new drugs or methods for treating opioid overdoses, including intranasal nalmefene, a competitive, reversible opioid receptor antagonist with a longer duration of action than naloxone; methocinnamox, a novel opioid receptor antagonist; covalent naloxone nanoparticles; serotonin$_{1A}$ receptor agonists; fentanyl-binding cyclodextrin scaffolds; detoxifying biomimetic 'nanosponge' decoy receptors; and antibody-based strategies. Thus, naloxone was administered to promote awakening.

In this case, the patient first received morphine for moderate and severe pain caused by peritoneal malignant mesothelioma. Morphine hydrochloride sustained-release tablets were administered because of their convenient use, definite analgesic effect, and long maintenance time. During the period of medication, the patient suddenly appeared in a deep coma with respiratory depression and pupil contraction (needle-like). Blood gas analysis showed hypoxia and CO_2 retention. A morphine component of 3.5 mg/l and a diazepam component of 6.6 mg/l were detected by blood sampling; therefore, we diagnosed respiratory failure caused by drug poisoning. We believe the following factors contributed to morphine poisoning in this patient: i) Both morphine and benzodiazepines have respiratory depression, and the combination of morphine and estazolam has an interaction, which enhances each other's efficacy. ii) Extensive metastasis in the abdominal cavity and high tumor burden lead to slow intestinal peristalsis and prolonged the retention time of the drug; the absorption rate increased, and the drug concentration accumulated. iii) Renal insufficiency occurred during medication, which may have prolonged the drug half-life and slowed down the excretion, thus further increasing the content of morphine in the blood. This case reminds us that it is very important to monitor the liver and kidney function during treatment. This patient's condition was improved after active treatment. The key to successful rescue lies in the application of effective comprehensive measures, such as the following: i) timely and rapid treatment, such as immediate endotracheal intubation and ventilation to assist breathing, through the most direct way to effectively supply oxygen and expel excess CO_2 from the body; ii) adequate intravenous infusion to dilute the effective concentration of absorbed toxic drugs in the blood and promote excretion; iii) timely administration of naloxone to block and replace the binding of morphine to opioid

receptors, quickly reversing the toxic state, promoting the recovery of spontaneous respiration, protecting the stability of cell membranes, antagonizing the production of inflammatory mediators, and reducing brain edema; and iv) timely administration of flumazenil to block the effect of benzodiazepines on the central nervous system and promoting awakening. Further, flumazenil and naloxone have a synergistic effect and can accelerate awakening.

In conclusion, for cancer pain, routine screening, standardized evaluation, and effective pain control should be performed, the indications and contraindications of drugs should be strictly grasped, omni-directional and whole-process management should be emphasized, and patients and their families should be well educated. For patients with high abdominal tumor load, physicians should consider the effect of the tumor on gastrointestinal peristalsis and drug absorption, and if necessary, when morphine is used in combination with benzodiazepines, attention should be paid to the interaction between drugs, resulting in enhanced respiratory depression. In addition, the effect of patients' liver and kidney function on drug metabolism and excretion should be fully evaluated before treatment, and the dynamic changes of patients' liver and kidney function should be monitored during treatment to adjust the dose in time. For this kind of patient, clinicians should consider reducing the drug dose at initial administration in order to avoid drug poisoning. At the same time, in the process of drug treatment, the general state and vital signs of patients should be monitored in time. If the patient displays poisoning symptoms, timely measures should be taken to reduce poison absorption, increase poison excretion, and administer antagonists to reverse the poisoning state, so as to reduce the damage caused by drug poisoning. Due to opioid dosage ranges widely, varies widely between individuals and patients using morphine and estazolam are both within the safe range, the relationship between dosages of opioid and Estazolam cannot be well discussed. Moreover, studies of the two drugs are rarely reported. We look forward to more studies reporting on the interaction between the two drug classes in the future.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

CZ, JB and FZ collected the patient data, reviewed relevant literature and wrote the original draft. XL and FZ conceived and designed the study, and suggested revisions to the manuscript. SJ, XZ, DG, DL, YW and SG reviewed the relevant literature, analyzed the patient data, proposed manuscript revisions and wrote the final version of the manuscript. All authors contributed to the article, and read and approved the final manuscript. CZ and FZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed written consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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