Use of opioids as one of the causes of fever in patients with advanced cancer

Michał Graczyk,[1] Małgorzata Krajnik,[1] Jarosław Woroń,[2,3]
Jerzy Wordliczek[4] and Małgorzata Malec-Milewska[5]

Dear Editor,

Opioid treatment involves the risk of undesirable symptoms. One of the extremely rare and still poorly known symptoms is fever caused by the use of this medicine.

Keeping an appropriate body temperature is one of the basic homeostatic functions that are critical to survival of the organism. A particular integrating role is played by the hypothalamus where all information concerning heat is integrated and, as a result, an autonomous, endocrine, motoric, and behavioral response is generated in order to adapt to the changes in the environment.[1] There are multiple hypotheses concerning thermoregulation. According to Romanowsky, maintaining a constant central body temperature is the result of interaction of independent thermoeffector loops that have their own impulsation pathways, both afferent and efferent.[2] Depending on whether a given factor increases or reduces the body temperature (leading to hyperthermia or hypothermia), it affects to the same extent the thermal value of the areas in the hypothalamus connected with the independent thermoeffector networks called term balance point (previously set point) which works as a "thermostat" and determines the central body temperature outside of the physiological values (the oscillation is in the range of 36.1–37.4°C).

The physiologically very complex process of maintaining a dynamic balance between heat production, preservation, and loss can be disrupted in many situations. It can be influenced by intake of medicine, presence of hormonal disorders or various medical conditions (e.g. cancer), as well as presence in disadvantageous environmental conditions (Table 1).[3] Diagnosis of fever and selection of the target procedure can be more difficult in the case of patients with simultaneous occurrence of many potential causes of thermoregulation disorders, including episodic ones. Below is a description of a patient with advanced pancreatic cancer, with numerous complications of the cancer and with thermoregulation disorders observed both during the attempt to include a strong opioid in the pain therapy and during the regular treatment with a weak opioid in the maximum dose.

A 67-year-old patient with progressing weakening, lack of appetite, weight loss, jaundice, and itch was diagnosed with pancreatic adenocarcinoma infiltrating the duodenum, in the T2N1Mx stadium (May 2010) (Figure 1).

Medical history revealed a condition after three removals of salivary gland tumors (1979, 1986, and 1989), benign prostatic hyperplasia, type 2 diabetes (treated with insulin), hypertension (second degree

[1]Department of Palliative Care, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland
[2]Department of Pain Treatment and Palliative Care, Jagiellonian University College of Medicine, Cracow, Poland
[3]Department of Clinical Pharmacology, Jagiellonian University College of Medicine, Cracow, Poland
[4]Department of Anesthesiology and Intensive Care, Jagiellonian University College of Medicine, Cracow, Poland
[5]Pain Clinic, Department of Anesthesiology and Intensive Care, Medical centre for Postgraduate Education, Warsaw, Poland

Corresponding author:
Małgorzata Malec-Milewska, Pain Clinic, Department of Anesthesiology and Intensive Care, Medical Centre for Postgraduate Education, Warsaw, Czerniakowska 231, 00-416 Poland.
Email: Lmilewski@post.pl

**Table 1.** Neurochemical influences that affect activity of thermoregulatory preoptic hypothalamic neurons.[3]

Influence	Effect	Clinical implications (examples)
Serotonin (5-HT$_2$ receptor)	Hyperthermia	Serotonin syndrome, IL-1β induced fever, antipsychotic-induced hypothermia*
Serotonin (5-HT$_1$ receptor)	Hypothermia	SSRI-induced sweating,† postoperative hypothermia, hypoxia-induced hypothermia
Dopamine (D$_2$ receptor)	Hypothermia	Bromocriptine-induced hypothermia, neuroleptic malignant syndrome‡
Norepinephrine (α$_1$ receptor)	Hypothermia	Isoflurane-induced hypothermia
Opioids		
μ receptor	Hyperthermia	Fentanyl reduces shivering threshold during epidural anesthesia
κ receptor	Hypothermia	Hypothermia during opioid overdose
Acidosis	Hyperthermia	Heat shock
Prostaglandin E$_2$	Hyperthermia	Fever

*Risperidone and other antipsychotic agents block 5-TH$_2$ receptors and could lead to hypothermia.
†Cyprocheptadine may reduce SSRI-induced sweating, presumably by blocking 5-TH$_1$ receptors.
‡This disorder may reflect blockade of D$_2$ receptors in hypothalamus.
SSRI, selective serotonin reuptake inhibitors.
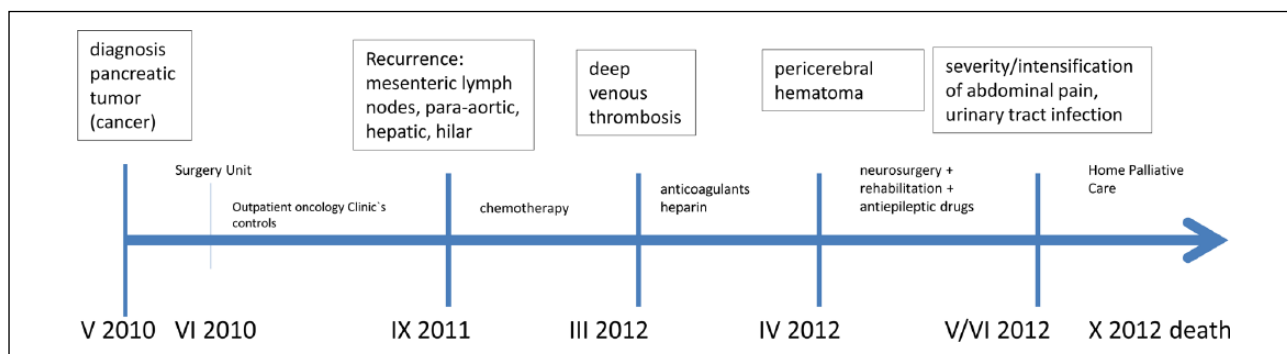
Figure 1. Diagram showing the history of the disease.

according to the Polish Society of Hypertension), and chronic kidney disease in the second stage. In the past (2006), due to aortic stenosis, vascular treatment was performed that included stent placement in the left renal artery and endarterectomy of the common carotid artery and the right internal carotid artery. After the cancer was diagnosed, pancreatoduodenectomy was performed on the patient using the Whipple method (June 2010). Once discharged from hospital, the patient attended regular checks at the Oncology Center in Bydgoszcz. After one year (September 2011), in FUSION PET (PET/CT) examination and in computed tomography (CT scans), recurrence was demonstrated. The patient was qualified for LFP chemotherapy (calcium folinate, fluorouracil, cisplatin). In a CT check in December 2011, no progression was demonstrated in relation to the previous check. During chemotherapy (March 2012), deep vein thrombosis in the

lower limbs and visceral vein thrombosis occurred. Anticoagulants were included and then discontinued because of occurrence of a peri-cerebral hematoma (subdural) in the forehead and left vertex area (April 2012). For this reason, in April 2012, an operation was performed on the patient to remove a subcaudal hematoma, with complications consisting of bleeding into the operating space that required reoperation and use of short respirotherapy with anti-edematous treatment in the Intensive Care Unit.

After efficient respiration was achieved, the patient was extubated and rehabilitation was implemented and continued at the Rehabilitation Unit (7–31 May 2012). Paresis of the right limbs was alleviated, the overall fitness and motor coordination were improved, but aphasia, mostly motor, remained. During that hospitalization, the patient experienced abdominal pain, localized

Table 2. Follow-up examinations.

	10 July 2012	23 August 2012	12 September 2012
WBC (thousand/μL)	6.12	7.38	16.53 ↑
HGB (g/dL)	9.2 ↓	8.4 ↓	9.5 ↓
PLT (thousand/μL)	180	105 ↓	121
creatinine (mg/dL)	1.70 ↑	1.51 ↑	1.24 ↑
eGFR	43	49	> 60
Na (mmol/L)	137.5	136.9	135.5
K (mmol/L)	3.97	4.13	4.30
Ca	2.35		
CRP (mg/L)		90.69 ↑	
AlAT (IU/L)		29.5	
AspAT (IU/L)		39.1	

↑- above reference values, ↓- below reference values.

mostly in the epigastrium, which gradually increased. This is why, after his discharge from the hospital, the patient was treated by the oncologist with a mixture of analgesics (including papaverine, codeine, and metamizol). The pain treatment turned out to be insufficient and the patient was provided with home hospice care (Table 2). During the first visit on 6 June 2012, the palliative medicine physician recommended a 50-mg dose of tramadol every 6–8 h, orally (in a short-acting preparation). At that time, the patient was already taking anticonvulsant medication due to epileptic seizures after a neurosurgical procedure (valproate in a 2 × 500 mg dose). On 7 June 2012, the result of urine culture was obtained which demonstrated the presence of Morganella morganii (10^3–10^4); consequently, a decision was made to include ciprofloxacin in the 2 × 500 mg oral dose for a period of five days. Due to low tolerance of the therapy, the pharmacotherapy was modified and trimetoprim was used (240 mg/5 mL suspension, recommended 5 mL every 12 h), which was maintained for the next nine days (until 21 June 2012). Due to the deteriorating pain control, on 15 June 2012, the treatment was modified and morphine in a 0.5% water solution was included with the recommended dose of 0.5 mL of the solution (2.5 mg) orally as needed. Initially, the ad hoc doses resulted in good control of the pain and then, after six days, due to the recurring pain, oral morphine of regular doses (5 mg every 4 h) was started. On 21 June 2012 (the first day of regular morphine intake), after about 12 h, fever occurred (>38°C) without the characteristics of an infection. However, the practitioner decided that the most likely cause of the fever is infection of the urinary

tract; consequently, he recommended amoxycillin with clavulanic acid (2 × 1 g, orally) for seven days and, due to deteriorated verbal contact, dexamethasone was administered in the morning in the dose of 4 mg, subcutaneously. In spite of the therapy, the fever continued and caused a deterioration in the contact with the patient as well as strong shivers (also, an epileptic seizure cannot be excluded as, according to family members, a loss of consciousness also occurred). After morphine intake was discontinued (after less than 24 h of treatment) and use of tramadol was resumed in a larger doze than initially, the body temperature normalized. Three more attempts were made to include morphine (at intervals of 3–4 days) in regular doses taken every 4 h caused fever following strong shivers about 12 h after the first dose. In periods of high temperature, family members gave paracetamol and metamizole to the patient and applied cold compresses, which resulted in a reduction in the body temperature. For fear that the fever might occur again, morphine was discontinued and a tramadol dose of 50–75 mg in drops was resumed – most often given only as necessary. Later, a controlled release form was used up to the dose of 400 mg/day. After several days of regular administration of the maximum dose of tramadol, fever following shivers occurred again. On 7 August 2012, the opioid was replaced with controlled-release tablets of oxycodone, with the recommended dose of 2 × 10 mg. The pain-control effect was very good but after the third dose (1.5 days), high fever occurred with accompanying significant drowsiness, as well as deteriorated contact and apathy. Due to the undesirable effects and concern that they would intensify, tramadol

was used once again to control pain. Eventually, on 17 August 2012, morphine was used again in the initial dose of 10 mg a day, subcutaneously, administered every 4 h. Within four days, shivers and body temperature occurred again; their intensity was similar to the previous level (mostly low-grade fever up to the maximum temperature of 38°C). The symptoms were observed about 2 h after morphine was administrated. According to the family members' account, this was accompanied by slight muscle stiffness, which caused problems with getting out of bed, without any consciousness disruptions or convulsions. Administration of morphine was continued subcutaneously until death as needed (it sufficed for as long as 8 h) and later it was required at shorter intervals due to the end-of-dose pain (every 6 h). In the terminal phase of life, the patient did not receive antibiotics, despite the increased body temperature and leukocytosis determined in the last blood morphology test performed on 12 September 2012 (Table 2). The patient died on 24 October 2012.

While in care, the patient underwent follow-up examinations (presented in Table 2 below).

Discussion

There are different interpretations of the disturbances in thermoregulation in patients with advanced cancer. A definitive determination of the causes of fever in a patient suffering from advanced cancer may be difficult and, as the above case demonstrated, is often based on empirical analysis.

Potential factors that predispose patients in this population to have fever are changes in immunocompetence (the cancer itself, malnutrition, the implemented therapy), the mechanical effect of the cancer's progression (infiltration of tissues, fistulas, impact on natural biological barriers), placement of foreign objects and their impact on the mucosa, repeated antibiotic treatment, discontinuation of used medicines (opioids, benzodiazepines).[4]

The most frequent cause of fever in this group of patients, in particular in those undergoing chemotherapy, is infection.[5] It is assumed that cases of fever in a patient with cancer (including neutropenic fever) should be associated with an infection and only once an infection has been excluded should another cause be looked for. The second most frequent cause of fever is cancer itself (27%).[6] Paraneoplastic fever can actually occur in patients

with any cancer, in particular during the progression of the disease. Although it has been known for years that cancer cells, despite lack of co-existing infection, produce pyrogens, the mechanism leading to paraneoplastic fever remains unknown. Factors that cause fever include interleukin 1α (IL-1α), interferon α (INF-α), tumor necrosis factor α (TNF-α), IL-6, oncostatin-M, cardiotrophin, and leukemia inhibitory factor. Pyrogens can act directly on the thermoregulatory center in the hypothalamus and, most of all, on the front preoptic nuclei, thus raising the thermal value by changing the activity of brain cyclooxygenasis (COX). In endothelial cells and cells surrounding vessel walls of the blood–brain barrier, post-inflammatory cytokines induce production of prostaglandin E_2. It is the basic central fever mediator and its synthesis is catalyzed by, among others, phospholipase A_2 and COX. In patients with metastases in the brain, paraneoplastic fever may also result from direct damage to the brain tissue and the ensuing activation of phospholipase A_2.[7]

It can be difficult to distinguish between infection-related fever and other types of fever, in particular paraneoplastic fever. In the case of infection-related fever, one rather expects temperature surges with accompanying shivers and sweating. In the case of paraneoplastic fever, more common is the constant sense of heat and sweating, generally without shivers, tachycardia, and mental (cognitive, consciousness) changes. Unlike infection-related fever, paraneoplastic fever does not respond to acetylsalicylic acid and acetaminophen. However, it recedes after naproxen is administered (naproxen test) and after other nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and diclofenac.[8–10] Chang's paraneoplastic fever diagnostic criteria are still considered to be up-to-date (Table 3).[11]

In the case described here, the influence of urinary tract infections and the cancer itself, as well as brain damage (as a result of bleeding into the central nervous system and two neurosurgical operations), venous thrombosis, and the medications taken, must not be excluded. In the initial period in particular, infection-related fever was very likely because of the "positive" urine culture. This is why another antibiotic was introduced (despite the lack of other symptoms indicating urinary tract infections), which did not result in a reduction of the fever.

Table 3. Criteria for paraneoplastic fever.[15]

I	Temperature over 37.8°C at least once each day
II	Duration of fever over two weeks
III	Lack of evidence of infection on:
	A. Physical examination
	B. Laboratory examinations, e.g. sputum smears or cultures, cultures of blood, urine, stool, bone marrow, spinal fluid, and discharge from local lesions
	C. Imaging studies, e.g. chest radiograph or CT scans of the head, abdomen, and pelvis
IV	Absence of allergic mechanisms, e.g. drug allergy, transfusion reaction, or radiation and chemotherapeutic drug reaction
V	Lack of response of fever to an empiric, adequate antibiotic therapy for at least seven days
VI	Prompt, complete lysis of fever by the naproxen test with sustained normal temperature while receiving naproxen

An analysis of the time relationship between the temperature increase incidents and the use of opioids indicates opioid-related fever. Opioid-related fever is an immensely rare phenomenon and therefore it is nearly impossible to define the typical course of the fever and the accompanying symptoms. Given the same mechanism of its occurrence, one can try to explain it in the following manner: stimulation of opioid receptors of the mi (μ) type on the immunocompetent cells in some genetically predisposed patients leads to expression of proinflammatory cytokines which, by increasing the production of endogenous pyrogen, can stimulate the hypothalamus to cause fever.

Also, it is possible that as a result of opioid use, changes may take place in the range of functioning of the central nervous system structures that are responsible for thermoregulation. The mechanism of hyperthermia induced by opioids can be compared to opioid-induced hyperalgesia (OIH). The latter, observed in certain patients treated with opioid, is manifested by increased sensitivity to pain stimuli despite increased doses.[12,13] One of the theories concerning OIH points at the emergence in the reticular formation of "on" type neurons instead of "off" type neurons. It is also possible that, due to the universal presence of opioid receptors in brain structures, opioids can also directly influence the centers responsible for thermoregulation. A partial explanation of this is the fact that a pure agonist of mi (μ) type receptors (without a ceiling effect) can induce hyperthermia, while opioids from the second step of the analgesic ladder, which do have the ceiling effect, do not demonstrate this ability.[14] In the case described here, the effectiveness of antipyretic drugs was observed, which possibly confirms this mechanism. Unfortunately, during fever occurrences, the patient's C-reactive protein (CRP), which is an unspecific marker of the acute phase of inflammation, was not regularly controlled. The only test was performed in August 2012 (after the incidents involving fever associated with administration of the opioid) and the measured value was about 90 mg/L. However, it is not known if earlier determinations of this marker would actually have proven to be helpful. In a prospective analysis covering patients with solid tumors mostly of the head and the neck, Penel et al. evaluated the diagnostic value of the CRP concentration. They found that CRP concentration was not significantly different in the case of infection-related fever and paraneoplastic fever.[15] An interesting observation pertains to differences in the increase of the CRP in patients without cancer and with cancer in the course of an infection.[1,15] In the former group, as early as in the first 8 h of the infection, the value often increases above 100 mg/L, and after 48 h of effective antibiotic therapy it drops quickly. On the other hand, in the latter group, both the increase of the CRP and its decrease during antibiotic therapy are not so significant. This is due, among others, to other groups of medicines used at the same time (steroids, NSAIDs, chemotherapy). Interestingly, high CRP values can be observed in some patients with advanced cancer without accompanying infections. Consequently, concentration of this acute-phase protein is nonspecific both in infections and in cancer, especially in the advanced stadium of the latter.

A useful marker to distinguish the causes of temperature increase in patients with advanced cancer appears to be procalcytonin (PCT) (which was not determined in the case described herein), whose significantly higher concentrations were found to be present in infection-related fever.[15] However, in no patients with paraneoplastic fever did the concentration reach the value of 2 ng/mL; consequently, in the opinion of the researcher, the

predictive value of PCT in diagnostics of this type of fever is 100% negative.

Interactions between different neurotransmitters and neuromodulators, such as norepinephrine, dopamine, serotonin, acetylcholine, prostaglandin E_1, GABA, and opioids, are important to the regulation of body temperature on the central level. If the opioid system takes part in thermoregulation control in mammals, then endogenous opioid peptides and opioid medicines, such as morphine, can influence the body temperature. Hyperthermia and hypothermia caused by an opioid are the effects of actions on the opioid receptor by the μ, κ, and delta receptor agonists; therefore, both these phenomena can be blocked by the antagonists. Also, in both cases tolerance and cross-tolerance may develop.[16]

Morphine administered (in the room temperature of the laboratory) in small doses caused hyperthermia in rats by activating the mi receptors, while in larger doses it causes hypothermia by stimulating the kappa type receptors (κ).[17–20] Perhaps this impact on the mi receptors could explain the presence of hyperthermia in the patient described herein. Tramadol, morphine, and oxycodone (the latter two in low doses) are antagonists that act mainly through opioid receptors of the mi (μ) type.

The fever mechanism must also include pathology within the central nervous system which was present in the patient described herein. Tests on animals have demonstrated that interactions between opioid receptors and the stimulating and inhibitory amino acids are important to the survival of the cells damaged by induced hyperthermia and, consequently, to the functioning of the brain.[21] Tests performed on rats indicate that blocking of opioid receptors significantly changes the neurotransmission of amino acids and causes neuroprotection. On the other hand, breaking of the blood–brain barrier increases the risk of cognitive dysfunction of the brain, cerebral edema, and brain damage induced by hyperthermia.[21] One can suspect that in the patient described herein the damage to the blood–brain barrier caused by the pericerebral hematoma and the two neurosurgical operations were conducive to the aggravation of the symptoms of hyperthermia (cognitive disruptions, strong shivers, and loss of conscience) and to the occurrence of fever as a result of small doses of agonists of the mi opioid receptor.

In conclusion, diagnosis of fever and selection of the target procedure can be difficult in the case of patients with advanced cancer and simultaneous occurrence of many potential causes of thermoregulation disorders. At present, opioid-related fever can only be diagnosed by way of elimination (in particular of infection-related fever and paraneoplastic fever) and is based on an analysis of the time relationship between the use and discontinuation of use of opioids and the disturbances in thermoregulation. One must also consider whether another attempt to use a drug (a provocation attempt) causes similar symptoms and whether discontinuation of a drug results in remission of the problem and if so, then after what time. In the patient described herein, repeated use of morphine (but also oxycodone and tramadol, the latter in the maximum dose) caused the occurrence of the same symptoms after three successive doses of the medicine administered at 4-h intervals (after about 12 h). Clinically, most often the temperature increased above 38°C, with accompanying disruptions in the central nervous system in the form of deteriorated contact with the surroundings. In patients with advanced pancreatic cancer, fever may occur spontaneously without any relation to a potential infection factor, which is confirmed by lack of leukocytosis with an increase of the CRP.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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