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Intravenous phentolamine infusion alleviates the pain of abdominal visceral cancer, including pancreatic carcinoma

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Abstract
This case report series describes eight patients (four patients with pancreatic carcinoma, one patient with hepatocellular carcinoma, one patient with gastric and rectal carcinoma, one with sigmoid colon cancer, and one with rectal cancer), whose abdominal cancer pain was treated with intravenous phentolamine infusion at 80 mg·day^{-1} for 2 days. All but one of the patients had already been treated with opioids. All eight patients complained of severe abdominal pain; in five patients the pain radiated to the back, and there was associated anal pain in two patients. Analgesia was achieved in three patients; pain alleviation was obtained in four patients, but was not sustained in two of these four patients; and the treatment in one patient could not be judged for efficacy because epidural morphine was used together with the phentolamine. Adverse effects of phentolamine were tachycardia and/or hypotension.

Key words Phentolamine · Abdominal cancer pain · Pancreatic carcinoma · Sympathectomy · Celiac plexus block

Introduction

In patients with pancreatic or other visceral neoplasms associated with a terminal condition, providing adequate pain control is difficult because of the compromise that has to be made between the benefits and side-effects of the therapeutic agents or procedures. Systemic medications, according to the World Health Organization analgesic ladder [1], are recommended to manage cancer pain. But, at times, systemic analgesics produce unpleasant side effects and compel us to stop their use. In these circumstances, invasive blocks such as celiac plexus block may provide excellent results, but they can be technician-dependent and are relatively expensive, and they have their own risks of side-effects.

A recent case report demonstrated the potentially useful analgesic effect of phentolamine infusion for the treatment of a patient having pain associated with pancreatic carcinoma [2]. Here we report our study of a series of patients with pain due to abdominal visceral cancer in whom we evaluated the efficacy of intravenous phentolamine infusion.

Patients and methods

In the present study, we included all eight consecutive patients treated with phentolamine infusion for abdominal visceral cancer pain between 1998 and 1999 (Table 1). Table 1 shows the patients' demographic details, diagnoses, and surgical history. Five patients (2, 3, 4, 6, 8) were inpatients and three (patients 1, 5 and 7) were outpatients. Except for patient 5, who had been treated with nonsteroidal anti-inflammatory drugs (NSAIDs), all patients had already been treated with opioids by their surgeons. We were consulted by our hospital surgeons about better control of their patients' visceral cancer pain, or about the impossibility of using opioids because of their side effects. Patient 1 was the first patient for whom we used an intravenous phentolamine infusion. She had inoperable pancreatic carcinoma and was in a terminal condition. Celiac plexus block was considered, but we were afraid that it had potential risks of serious side effects, and that its efficacy could be technician-dependent, and she could not sustain this procedure. Epidural morphine via a catheter was another option, but this method entails a risk of infection. We decided to try intravenous phentolamine infusion, as reported by McCleane [2].

All eight patients complained of severe abdominal pain; in five patients (patients 1, 3, 5, 7, and 8) pain

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Table 1. Patient details

Patient no.	Age (years)	Sex	Pain location	Diagnosis	Prior operation and treatment
1	73	F	Back and left lower abdomen	Pancreatic carcinoma	Pancreatico-duodenectomy, 7 months before
2	67	M	Lower abdomen	Pancreatic carcinoma	Gastrojejunostomy, 13 months before
3	65	M	Back and left upper abdomen	Pancreatic carcinoma	Stenting
4	66	M	Upper and lower abdomen	Gastric and rectal cancer Liver metastasis	Choledocho-jejunostomy, 10 months before, Gastrectomy, amputation of rectum
5	58	M	Back and upper abdomen	Pancreatic carcinoma	Gastro-jejunostomy, 5 months before
6	79	F	Lower abdomen and anus	Rectal cancer Lung metastasis	Amputation of rectum, 21 months before, Radiation
7	53	M	Back and abdomen	Sigmoid colon cancer Lung and liver metastasis	Sigmoidectomy, 3 months before Artificial anus
8	68	M	Back, upper abdomen, and anus	Hepatocellular carcinoma	Intraarterial chemotherapy

Table 2. Effects of phentolamine test and infusion

Patient no.	Pain intensity (VAS)		BP, pre-test PR, pre-test	During test During test	Infusion		Survival time (days)
	Pre-test	Post-test			Effect	Frequency	
1	7	0	124/70 72	108/60 108	Analgesia, appetite increase	1	42
2	7	3	130/72 64	122/70 84	Alleviation, but not sustained	2	45
3	4	2	124/70 72	90/0 84	Uncertain	1	19
4	5	5	122/70 80	96/56 92	Analgesia	1	34
5	5	0	98/50 72	86/46 102	Alleviation, appetite increase	2	190
6	7	4	120/70 96	120/70 124	Analgesia, voice normalized	1	240
7	8	Fell asleep	130/70 66	96/60 78	Alleviation, but not sustained	3	45
8	9	Fell asleep	138/80 78	104/60 102	Alleviation, appetite increase	2	80

BP, blood pressure; during test, shows the lowest value during phentolamine test; PR, pulse rate; during test, shows the highest value during phentolamine test

radiated to the back, and in two patients (patients 6 and 8) there was associated anal pain. Three patients (patients 2, 5, and 8) had nausea and/or gagging and vomiting. Pain intensity was assessed for each patient, using a numerical rating scale of 0, no pain, to 10, the worst pain imaginable, on a 10-cm visual analog scale (VAS) shortly before and after a phentolamine challenge test. Blood pressure and pulse rates were monitored. A bolus of 2.5–5.0 mg of phentolamine (total dose, 10–20 mg) was repeatedly given very slowly via an intravenous line. When the phentolamine challenge test showed a decrease in pain of over 40%, we judged that it was effective. Subsequently, the eight patients received an infusion of 80 mg (8 ml) of phentolamine per day, with 112 ml of normal saline (infusion speed, 5 ml·h^{-1}) for 2 days, according to McCleane's report [2]. Lactated Ringer's solution, at 500 ml per day, was infused together with the phentolamine via a three-way stopcock.

Results

Pain intensity immediately after the phentolamine challenge test was lessened in five patients (patients 1, 2, 3, 5, and 6), was not changed in patient 4, and, in patients 7 and 8, we could not obtain a pain score because they fell asleep (Table 2). Excluding two patients (patients 7 and 8), the mean (SD) pain intensity before the test was 5.83 (1.33), and after the test it was 2.33 (2.07). The side-effects of phentolamine were hypotension and tachycardia (Table 2). The lower legs were elevated in four patients (patients 1, 2, 3, and 4) and intramuscular

ephedrine 20 mg was given to two patients (patients 3 and 4). Patient 4 showed transient arrhythmia. The morning after the challenge test, patient 4 had no abdominal pain and his appetite increased, so we judged phentolamine to be effective, and it was also judged to be effective for patients 7 and 8. Subsequently, all eight patients received an infusion of 80 mg per day of phentolamine for 2 days, and this produced complete relief of abdominal pain (analgesia) in three patients (patients 1, 4, and 6) and alleviation of pain in four patients (patients 2, 5, 7, and 8) but the alleviation was not sustained in patients 2 and 7. These four patients needed NSAIDs or opioids. Patients 1 and 4 remained pain-free without analgesics for 40 days and 30 days, respectively, until their demise. Patient 6 remained pain-free without analgesics for 96 days. Phentolamine infusion was repeated once in patients 2 and 8, and twice in patient 7, due to return of the abdominal pain to the pretest score, or a VAS of over 5/10, and once in patient 5, for social reasons. After the second infusion, the abdominal pain in patients 5 and 8 was alleviated to VAS 1/10 for 116 days and 62 days, respectively; patient 5 was taking morphine 10 mg orally twice a day and patient 8 had a diclofenac suppository (50 mg) given two or three times a day. Patient 3 was maintained on epidural morphine following stenting of the bile duct, done under thoracic epidural anesthesia, so we could not judge the efficacy of the phentolamine infusion. The back pain in five patients (patients 1, 3, 5, 7, and 8) and the anal pain in two patients (patients 6 and 8) was lessened. Appetite increased in three patients (patients 1, 5, and 8), and patient 6, who had been speaking weakly (whispering) was able to speak normally.

Side effects during the infusion were hypotension and tachycardia in patient 1, and tachycardia and arrhythmia in patient 4. The other patients showed no remarkable changes in vital signs. In patient 1, at the start of the phentolamine infusion, the blood pressure was 126/86 mmHg and pulse rate was 78 beats·min^{-1}, after 5 h of phentolamine infusion, these values were 89/65 mmHg and 115 beats·min^{-1}, but these signs improved spontaneously, and at the completion of the infusion (48 h after the start of the infusion), the blood pressure was 142/80 mmHg and pulse rate, 72 beats·min^{-1}. In patient 4, at the start of the phentolamine infusion, the blood pressure was 133/79 mmHg and pulse rate was 80 beats·min^{-1}. After 15 h of phentolamine infusion, the blood pressure was 126/70 mmHg, but the pulse rate had increased to 98 beats·min^{-1}, with no arrhythmia. Four hours later, the blood pressure was 124/77 mmHg, but the pulse rate had increased to 120 beats·min^{-1}, and arrhythmia appeared. At this time, his pulse rate transiently increased to 130–150 beats·min^{-1} when he walked. But these signs gradually improved until completion of the infusion. The blood pressure was 128/60 mmHg, and pulse rate was 90 beats·min^{-1}, with no arrhythmia, at the completion of the phentolamine infusion. In patient 7, continuous infusion of dopamine was needed to maintain normal blood pressure during the third phentolamine infusion. The survival time (from the date of the first infusion of phentolamine until the date of death) was 19 to 240 days (Table 2).

Discussion

The intravenous infusion of phentolamine, an antagonist of α-adrenergic receptors, has the potential to produce efficacy similar to that of sympathectomy. Raja et al. [3] reported a close correlation between the pain relief achieved with a diagnostic test using an intravenous infusion of phentolamine (total dose, 25–35 mg) in patients with sympathetically maintained pain (SMP), and that achieved by local anesthetic sympathetic block. Because these investigators observed that the pain gradually returned to near-baseline levels over the course of 7 h, they suggested that it was worth evaluating whether a series of pharmacologic sympathetic blockades, using an agent such as phentolamine, would result in long-term therapeutic benefit in patients with SMP. Galer [4] reported that, in patients with neuropathic pain who were administered 35-mg intravenous phentolamine over 30 min, the peak pain relief occurred most often at least 24 h after completion of the infusion and the pain relief was sustained for more than 2 days.

McCleane [2] demonstrated a potentially useful analgesic effect of intravenous phentolamine for patients with chronic pancreatitis and for the visceral pain associated with acute intermittent porphyria, and reported that this analgesic effect may mimic the analgesia caused by celiac plexus block and therefore could be useful in managing the abdominal pain in patients with pancreatic carcinoma. In one patient with pancreatic carcinoma, he administered a phentolamine infusion of 80 mg·day^{-1} for 2 days and reported effective pain relief. Our report shows that phentolamine infusion alleviates not only the abdominal pain associated with pancreatic carcinoma but also other abdominal visceral cancer pain where a celiac plexus block is often useful.

McCleane [2] reported that, after discontinuation of the first infusion the patient remained pain-free for 26 days, and was pain-free, for 12 weeks after the second infusion, until the patient's demise. In our case series, patients 1 and 4 remained pain-free without analgesics until their demise, and patient 6 remained pain-free for 96 days without analgesics. This point may be different from an investigation showing that, although neurolytic celiac plexus block improved pain relief in patients

with pancreatic cancer, vs optimized systemic anagesic therapy alone, opioid consumption was not significantly different between the two groups [5].

Galer et al. [6] describes that phentolamine infusion has advantages over other sympathetic blocks from the viewpoints that it is minimally invasive, is not technician-dependent, and has systemic activity that allows for treatment of multiple body regions in patients with SMP. On the other hand, it has been pointed out that it is unclear whether phentolamine shows a dose-response relationship; thus, some patients may need higher doses ($1\,mg{\cdot}kg^{-1}$) for an effect [7].

What mechanisms contribute to the efficacy of phentolamine infusion for visceral cancer pain? McCleane [2] pointed out that the analgesic effect of intravenous phentolamine may mimic the analgesia produced by celiac plexus block. Neurolytic celiac plexus block is useful in relieving severe intractable pain caused by cancer or chronic visceral disease, by blocking all the nociceptive (pain) pathways that supply the viscera in the upper abdomen [8]. Contrary to conventional teaching, it is now known that pain impulses arising from most viscera are transmitted to the dorsal horn by unmyelinated afferent fibers [9]. McCleane's report [2] and our present case series show that the sympathetic nervous system may play an important role in abdominal visceral pain conditions. Lindsay et al. [10] showed, in mice that developed pancreatic cancer, that peptidergic sensory (nonmyelinated) and sympathetic fibers in the pancreas increased with disease progression, but that pain became evident only in late-stage disease, as occurs in humans. With disease progression, the central area of the pancreas, where significant sprouting of peptidergic sensory and sympathetic fibers had previously been richly innervated, gradually became necrotic, resulting in destruction of the distal ends of the sensory and sympathetic fibers that had innervated these regions of the pancreas. Lindsay et al. [10] suggested that, as damage to even the distal ends of peripheral nerves can generate significant neuropathic pain, these processes of extensive sprouting and destruction of sensory and sympathetic fibers may contribute to the sensitization and activation of nerve fibers innervating the pancreas. Neuropathic pain is often maintained or augmented by efferent activity in the sympathetic nervous system, and SMP is mediated largely through α-adrenergic mechanisms, so the intravenous infusion of phentolamine has been described as a reliable, specific, and easy-to-do carry out diagnostic test for SMP [11]. It may be thought that the efficacy of phentolamine infusion for late-stage pancreatic cancer pain, shows, paradoxically, that late-stage pancreatic cancer is associated with neuropathic pain. Nevertheless, phentolamine's analgesic mechanism of action is unknown. It is not clear through which mechanism sympathectomy with systemic phentolamine alleviates abdominal visceral cancer pain.

The side effects of phentolamine in the present series were hypotension and/or tachycardia. During the challenge test, elevation of the lower legs and intramuscular injection of ephedrine were effective for counteracting these effects. During infusion, these signs spontaneously improved until completion of the infusion. However, the cardiovascular system in these patients with a terminal condition is very variable in response to phentolamine, so when the pulse rate tends to increase, early digitalization may be necessary.

In conclusion, intravenous phentolamine infusion is potentially a new significant option for the therapy of pain associated with abdominal cancers, including pancreatic carcinoma, due to its noninvasive nature and simplicity of use, especially relative to celiac plexus block.

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