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Pharmacology update: pamidronate for hypertrophic pulmonary osteoarthropathy in palliative care

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Abstract: Hypertrophic pulmonary osteoarthropathy (HPOA) is a rare syndrome that causes clubbed fingers, periostitis, and synovial effusions. It can adversely impact a patient's quality of life. It occurs secondary to pulmonary disease – most commonly pulmonary malignancy. The most effective treatment for HPOA is to treat the underlying disease, usually through surgical resection, chemotherapy, or radiation. However, symptomatic treatments rather than definitive treatments (surgical, chemotherapy, or radiation) are more appropriate for the palliative care patient. Pamidronate is a promising medication for the treatment of HPOA for its safety and rapid onset of action. Further research is indicated to determine whether pamidronate is consistently effective.

Plain Language Summary

Hypertrophic pulmonary osteoarthropathy (HPOA) is a rare syndrome that causes pain in the long bones and typical changes in the fingers, called 'clubbing'. It can adversely impact a patient's quality of life and occur secondary to lung disease – most commonly pulmonary cancers. The most effective treatment for HPOA is to treat the underlying disease, usually through surgical removal, chemotherapy, or radiation. However, treating the symptoms is often appropriate for the palliative care patient. Pamidronate is a promising medication for the treatment of HPOA for its safety and rapid onset of action. Further research is indicated to determine whether pamidronate is consistently effective.

Keywords: hypertrophic pulmonary osteoarthropathy, pamidronate

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Introduction

Hypertrophic pulmonary osteoarthropathy (HPOA) is a subcategory of hypertrophic osteoarthropathy (HOA) that is secondary to pulmonary disease, of which pulmonary malignancy is the most common. HPOA causes a variety of symptoms, which include painful swollen joints, digital clubbing, and periostitis. In the general population, HPOA is rare. Up to 80% of HPOA cases are due to a paraneoplastic process, usually due to lung adenocarcinoma and small-cell lung cancer.[1] HPOA can also be caused by nonpulmonary causes, such as hepatopulmonary disease of liver cirrhosis or cyanotic heart diseases.[2] It was first described in literature in 1889 by Eugen van Bamberger as a case report of two patients with HOA and bronchiectasis.[3] In 1890, the term was coined by Pierre Marie when he wrote a case report on a patient with HOA and pulmonary tuberculosis.[4] Interestingly, Hippocrates had described clubbing of the fingers as a sign of severe lung disease several millenniums ago – to this day, digital clubbing can be referred to as 'Hippocratic fingers'.

There are several theories as to why HPOA occurs. The first is deemed the 'neurogenic hypothesis', which is based on cases that improved following unilateral vagotomy on the side of tumor.[5] The second theory is called the 'biochemical hypothesis' and it hypothesizes that

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the tumor releases biochemical compounds, such as vascular endothelial growth factor (VEGF), growth hormone–releasing hormone, and gonadotropins.[6,7] The final theory is the 'mechanical hypothesis', which theorizes that arteriovenous shunting in the pulmonary system causes the release of vasoactive compounds into the peripheral circulation. For example, the production of cytokines that stimulate peripheral endothelial cells to produce platelet-derived growth factor (PDGF) and tissue growth factor. These compounds can become trapped in the peripheral microvasculature and release PDGF, VEGF, and other cytokines – which, in return, can cause tissue hypoxia, vasodilation, and cellular proliferation of distal digits. Current literature suggests that tumor production of VEGF and PDGF could be the critical factor in developing HPOA.[8,9]

There are a number underlying diseases are associated with HPOA, including malignancies, chronic respiratory diseases, congenital cyanotic heart disease, chronic inflammation, hepatic disorders, gastrointestinal disorders, and endocrine disorders.[1] Malignancy should always be ruled out when a patient presents with signs and symptoms of HPOA. While there are not any reported medications that cause HPOA, Voriconazole has been reported to cause periostitis that mimics HPOA in patients who received a lung transplant.[10] Complications of HPOA include pain, loss of range of motion, and osteoarthritis in longstanding cases.[11]

Treatment

Many treatments have been proposed for HPOA, including targeted therapy at the underlying cause (surgical procedures, chemotherapy, radiation), as well as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, tamoxifen, retinoids, and bisphosphonates.

Ideally, treatment should be directed at the specific cause of HPOA. However, in a patient who is receiving palliative care, this may not be possible. There are currently no medications with US Food and Drug Administration (FDA) approval for the treatment of HPOA.

NSAIDs, such as COX-2 inhibitors indomethacin, ketorolac, and rofecoxib, have been reported to be helpful in some case reports.[12] Following cessation of NSAIDs, the patients' symptoms reoccurred and urinary metabolites of prostaglandins were markedly elevated.[13] Octreotide, a somatostatin analogue, has also been useful for symptomatic relief according to a few case reports.[14,15] It is theorized that octreotide is useful in the treatment of HPOA because of its inhibition of VEGF.[16]

Another treatment that has been proposed is the unilateral vagotomy. There are case reports/series that reported symptomatic relief following this procedure, as well as radiographic resolution of periostitis.[17,18] This treatment has largely been replaced by less invasive treatment methods.[19]

Finally, bisphosphonate drugs have been used for the treatment of HPOA. Besides pamidronate, which will be discussed in detail, zoledronic acid (ZA) has also been used to treat HPOA. In comparison with pamidronate, ZA has a higher response rate and longer duration of action when used for the treatment of hypercalcemia of malignancy.[20,21]

With regard to HPOA, the data are more limited for ZA than pamidronate. King *et al.*, described a case where a 48-year-old female who received a single dose of 4 mg ZA intravenously over 15 min; the patient reported significant relief of symptoms within 3 days and complete resolution within 7 days. She remained symptom free until her death approximately 3 weeks later without additional doses of ZA.[22] Thompson *et al.*[23] reported a case of a 45-year-old female who received 4 mg of ZA intravenously; the patient reported resolution of symptoms after two cycles of treatment (approx. 6–8 weeks).

Pamidronate

Pamidronate is a nitrogen-containing bisphosphonate. The proposed mechanism of action is binding to hydroxyapatite crystals in the bone matrix, which prevents osteoclast resorption.[24] Pamidronate also binds to and inhibits farnesyl pyrophosphate synthase, an enzyme that is essential for osteoclast function, which leads to the induction of apoptosis of osteoclasts. These actions stabilize the bone matrix and decrease the bone turnover rate.[19]

Pamidronate is currently FDA approved for the treatment of hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, osteolytic

lesions of multiple myeloma, and moderate to severe Paget disease.

Pamidronate has also been reported to be useful for the treatment of HPOA. Bernardo *et al.*[25] described a case report of a 63-year-old Caucasian male with stage IV non–small-cell lung cancer who showed complete resolution of symptoms 72 h after a single dose of intravenous (IV) pamidronate 90 mg.

Speden *et al.* reported successful treatment of HPOA in three patients with bronchogenic carcinoma. All three patients reported improvement of symptoms and reduction of pain. Two out of the three patients showed decreased radiolabel uptake on bone.[26]

Amital *et al.*[27] described a patient with HOA secondary to congenital cyanotic heart disease that was successfully treated with a single dose of 60 mg pamidronate. Garske and Bell[28] described a case of a patient with refractory HPOA who had complete resolution of symptoms following a single dose of pamidronate, which lasted for 3 months.

In another case report, a patient with primary breast cancer developed metastatic lesions in the lungs and she subsequently developed HPOA. Following treatment with IV pamidronate given every 2 weeks, there was a rapid resolution of her uncontrolled pain that was caused by HPOA.[29]

These case reports are summarized in Table 1.

With regard to the mechanism of action for patients with HPOA, there are several hypotheses. One is that the stabilization of the bone matrix through decreasing the bone turnover rate and inhibiting osteoclasts could explain some of the drug's success in treating HPOA. Furthermore, Santini *et al.* found that a single dose of pamidronate can cause a significant decrease of circulating VEGF levels in patients with advanced cancer and metastases.[30] Without a definite understanding of the pathogenesis, it is difficult to determine why pamidronate is successful in treating HPOA.

While considered generally a safe treatment for most patients, there are some important adverse reactions to be aware of when using pamidronate. A relatively rare, but widely known, adverse reaction is osteonecrosis of the jaw. In order to mitigate this risk, the American Association of Maxillofacial Surgeons (AAOMS) recommends that treatment with bisphosphonates be postponed until optimal dental health is attained and, once treatment begins, dental implants and other osseous injuries should be avoided.[31] Furthermore, large doses of pamidronate have been associated with renal deterioration progressing to renal failure and dialysis. This especially could be a potential risk in palliative care patients, who may have preexistent decline in renal function. This risk can be mitigated as long as a single dose of pamidronate does not exceed 90 mg. Further risk reduction can be achieved with longer infusion times (>2 h).[32]

While pamidronate has been available for decades, there have been no large studies to prove its effectiveness in HPOA. This could be due to several factors, including

1. No gold standard for the treatment of HPOA in palliative care patients who may not be treating the underlying cause;
2. The prevalence of the disease is rare in the general population;
3. Ethical concerns regarding withholding palliative treatment for the patients as a means of a control group.

To improve medical knowledge, a retrospective analysis comparing the effectiveness of pamidronate to the effectiveness of treating the underlying etiology (i.e. chemotherapy, radiation, surgery, etc.) alone could be considered. A randomized crossover trial could be attempted, but again the rarity of this condition would make this difficult.

Conclusion

HPOA is a relatively rare condition, but is distressing to those affected by it. The first step is to be able to recognize it. Other than treating the underlying condition that caused HPOA in the first place, the most rational treatment for HPOA is a pharmacologic approach with a single medication. Pamidronate is particularly attractive for patients in palliative care because it is not metabolized by the liver and is minimally bound to plasma proteins; thus, it can be used in patients with liver failure or in those with low plasma

Table 1. Summary of articles describing the use of pamidronate in the treatment of HPOA.

Authors	Title	Patient age, sex, and other information	Dosage of pamidronate	Repeat infusions?	Resolution of symptoms	Other
Bernardo *et al.*	Hypertrophic osteoarthropathy presenting as unilateral cellulitis with successful treatment using pamidronate disodium	63-year-old male with PMHx of stage IV non–small-cell lung cancer (NSCLC)	90 mg IV	No	Within 48 h – marked improvement. Within 72 h – complete resolution.	N/A
Speden *et al.*	The use of pamidronate in hypertrophic pulmonary osteoarthropathy (HPOA)	Patient 1: 65-year-old female with refractory HPOA Patient 2: 50-year-old female with adenocarcinoma of lung and refractory HPOA Patient 3: 72-year-old female with squamous cell carcinoma and refractory HPOA	Patient 1: 45 mg IV infusion over 8 h Patient 2: 15 mg IV infusion Patient 3: 30 mg IV infusion	Patient 1: No Patient 2: No Patient 3: Yes; two doses – 10 days apart	Patient 1: Resolution of symptoms after 8 days Patient 2: Resolution of symptoms when reviewed at 2-month follow-up Patient 3: Relief overnight which lasted for 7 days	Patient 1 and Patient 2 showed decreased radiolabel uptake on bone 2 months after therapy
Amital *et al.*	Hypertrophic pulmonary osteoarthropathy: control of pain and symptoms with pamidronate	50-year-old female with HOA secondary to congenital cyanotic heart disease	60 mg IV infusion over 1 h	No	Relief of symptoms 2 weeks after therapy, which continued for up to 4 months	Using the visual analogue scale for pain assessment (VAS score), the patient scored her pain as 100 mm prior to therapy and 37 mm (1 week) and 0 mm (4 weeks) following therapy
Garske and Bell	Pamidronate results in symptom control of hypertrophic pulmonary osteoarthropathy in cystic fibrosis	27-year-old female with Cystic Fibrosis and refractory HPOA	30 mg IV infusion	No	Complete resolution after 72 h which lasted for 3 months after single dose	N/A
Suzuma *et al.*	Pamidronate-induced remission of pain associated with hypertrophic pulmonary osteoarthropathy in chemoendocrine therapy-refractory inoperable metastatic breast carcinoma	44-year-old female with primary breast cancer with metastatic pulmonary lesions.	30 mg in 500 ml of 0.9% saline IV infusion over 3 h	Yes; dose every 2 weeks	Complete resolution within 7 days and remained pain free with 2-week administration	N/A

HOA, hypertrophic osteoarthropathy; HPOA, hypertrophic pulmonary osteoarthropathy.

proteins. Pamidronate also has few adverse effects and does not cause sedation. For Pamidronate (or ZA, for that matter) to have a greater role in treating HPOA, larger studies will need to be conducted as noted above.

Author contributions

Steven Baumrucker – Conceptualization; Project administration; Resources; Supervision; Validation; Writing - review & editing

Bethany Faust – Writing - original draft

Aaron Parkinson – Conceptualization; Data curation; Resources

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