

**PAMIDRONATE**



*“The Hunt of Atalanta and Meleager”, (Detail) oil on canvas, 1634 - 39, Nicholas Poussin, Prado Museum, Madrid. Castor and Pollux lead the hunt.*

*“Now Castor and Pollux, the heavenly twins, before they were stars, came forward, both magnificent sights, both riding on horses whiter than gleaming snow, both proudly brandishing spears which quivered within their grasp as the metal tips, flashed in the sunlight...”*

*Ovid, The Metamorphoses, Book 8, 372-375, 8 A.D*

*The Dioskouroi (or Dioscuri) were the twin sons of their mother Leda, the wife of King Tyndareos of Sparta. Their names were Castor and Pollux. But they were only half brothers. Castor’s father was King Tyndareos, however the father of Pollux, was the supreme god, Zeus himself, making Castor a mortal and Pollux a demigod. The lustful*

*Zeus, had come to Leda in the form of a swan, and made to love her, which resulted in the birth of twins, Pollux and Helen, the most beautiful woman in the world, and cause of much future conflict!*

*Despite the great disparity in status and in fathers, Castor and Pollux grew up together as the greatest of friends, completely inseparable. They hunted together, both becoming very great horsemen and experts with the bow and the spear. They had many great adventures together. In the earliest days of the history of Rome, when it was a mere village, it was said that Castor and Pollux assisted the Romans in a civil war against King Tarquin the Proud, who had allied himself to the neighbouring Etruscans, mortal enemies of the people of Rome. The twins were reported as being seen in the Roman Forum, watering their horses, and celebrating with others the great victory over the Etruscans. Long after a Temple was built to their memory in the Forum, the Temple of Castor and Pollux. The twins, including Castor, who would be immortalized after his death by Zeus, became early revered battle gods of the Romans.*

*Among their many other adventures, the heroes also joined the crew of Jason as Argonauts, and assisted him in his great quest for the Golden Fleece. After their return from this epic voyage, to their home city of Sparta, the twins had become very famous throughout all of Greece and Italy. They were in very great demand by important monarchs, to assist in hazardous enterprises. Among one of the most famous of these was the hunt for the Calydonian boar. The arrogant Oeneus, king of Calydon, had neglected to sacrifice to the goddess Artemis, and this had so infuriated Artemis, the goddess of nature and the animals that she unleashed a monstrous boar into the kings lands, which ravaged the countryside and killed any who tried to hunt it down. It was clear that only a very special person or group could bring down this monstrous creature. Oeneus sent Meleager to gather up heroes from all over Greece to hunt down the boar. He included many heroes, but most remarkably of all, a woman was included as well. This was Atalanta, a great Amazonian huntress, who would ultimately, much to the shame of the male heroes, bring down the boar with her arrows. In the very vanguard of the hunting party, would be the striking figures of Castor and Pollux, leading the chase on dashing white horses. The great French Baroque painter, Nicolas Poussin captures the dramatic moment when the Calydonian Boar hunt begins, in a scene drawn from a version of the story in Ovid's Metamorphoses. The blond Amazonian warrior Atalanta appears dressed in a striking blue dress and helmet to the right. In the centre we see a statue of Artemis poised with her bow. In the vanguard leading the chase are the twin heroes on their great white horses - Castor and Pollux. A stunning example of Baroque Art that resides in the Prado Museum in Madrid, only ever once has it left its home ...for the city of Melbourne.*

*In the end the twins are undone over a matter of lust. After the hunt of the Calydonian Boar, the twins decide they should get married and settle down to a quieter family life. They have both long lusted after their female cousins, Phoebe and Hilaria, but unfortunately both had already been betrothed to two of the twins' other male cousins. On a pretext, they engineered a dispute with their cousins and confident of victory on account of the demigod Pollux, challenged them to a fight to the death, which the cousins outraged, duly accepted. In the ensuing battle Pollux, kills both of the rival cousins, but tragically one of them, before he dies, manages to land a mortal blow with his sword upon Castor. Pollux is inconsolable when Castor eventually dies. In desperation Pollux*

*appeals to his father Zeus, to intervene. He offers to forgo half of his immortality in order to be with his brother. Even though this is a most unusual request coming from an immortal, Zeus grants his immortal son Pollux his wish. From then on both brothers were reunited by living for six months in Olympus among the immortals and for the other six months of the year in Hades among the mortals. With time, Zeus, so overcome with grief that Pollux had to spend so much time away from him in Hades, decided to intervene. He placed both Castor and Pollux in the firmament of the stars, among the great Constellations of the Zodiac, as Gemini - the twins. We still see them today in the heavens holding hands together.*

*When we treat our patients who have life-threatening hypercalcaemia we may face a most difficult choice. A potentially lifesaving drug, pamidronate, is required but is relatively contraindicated in renal impairment. The story of Castor and Pollux tells us that an eventual happy outcome may be achieved by a compromise! As Pollux wished to save his brother from an eternity in Hades, he was prepared to give up half of his own immortality. So may we compromise! We may still be able to give pamidronate but accept that this may come at a cost – a further deterioration in renal function. This deterioration however can always be supported by dialysis if required, though a permanent place in the firmament among the Constellations will sadly not be our reward for these compromises.*



*Left: The ruins of the ancient Temple of Castor and Pollux, patron gods of war for the early Republican Romans, and the twins of the Zodiacal Constellation of Gemini. The temple supposedly stands on the very place where the twins watered their horses in the Forum.*

*Roman Forum, completed c. 495 B.C.*

## PAMIDRONATE

### Introduction

**Pamidronate** is an **intravenous bisphosphonate** used in the treatment of moderate to severe **hypercalcaemia**.

If patients with moderate to severe hypercalcaemia (irrespective of cause) do not respond adequately to rehydration, or have significant symptoms an intravenous bisphosphonate infusion such as pamidronate can be used to temporarily lower the serum calcium concentration.

The onset of action of disodium pamidronate is not immediate. Therefore, disodium pamidronate should be considered as only *one component* of the acute clinical management of tumour induced hypercalcaemia.

### Preparation

**Ampoules:** Disodium pamidronate: **30 mg, 90 mg.**

### Mechanism of Action

**Disodium pamidronate** is a potent inhibitor of osteoclastic bone resorption. This antiresorptive activity is responsible for its therapeutic effect.

The physicochemical interaction of disodium pamidronate with apatite crystals accounts for its *avid binding to bone* but the exact mechanism for its anti-osteoclastic activity at the cellular level is currently unknown.

### Pharmacokinetics

#### Absorption:

- Disodium pamidronate is given by intravenous infusion.
- Plasma concentrations of disodium pamidronate rise rapidly after the start of an infusion and fall rapidly when the infusion is stopped.

#### Distribution:

- Disodium pamidronate has a strong affinity for calcified tissues.

**Clinicians should be aware that some 50% of the infused material can remain within the patient's skeleton for years.**<sup>3</sup>

- Plasma protein binding is relatively low, at around 55%

- It is not known if disodium pamidronate crosses the human placenta.

### Metabolism and excretion:

- Disodium pamidronate is excreted intact **primarily via the kidney**

After an intravenous infusion, about 20 - 55% of the dose is recovered in the urine within 72 hours as unchanged disodium pamidronate

Within the timeframe of experimental studies **the remaining fraction of the dose is retained in the body**. The percentage of the dose retained in the body appears to be independent of both the total dose and the infusion rate.

- Hepatic and metabolic clearance of disodium pamidronate are insignificant.

Disodium pamidronate does not appear to be eliminated by biotransformation.

- The apparent half-life in plasma is about 0.8 hours.

Apparent steady-state concentrations are, therefore, achieved with infusions of more than about 2 to 3 hours duration.

### Pharmacodynamics

The onset of action of disodium pamidronate is not immediate.

Therefore, disodium pamidronate should be considered as only *one component* of the acute clinical management of tumour induced hypercalcaemia.

### Indications

*Indications in the ED include:*

- IV infusion for moderate to severe hypercalcaemia, unresponsive to fluid rehydration or causing significant symptoms.
  - ♥ It is most useful in hypercalcaemia due to malignant disease; however it can be used in hypercalcaemia due to any cause.
  - ♥ It is particularly useful for hypercalcaemia due to *osteolytic* bone metastases from breast cancer or advanced multiple myeloma.

*Indications outside the ED:*

- Symptomatic Paget's disease of bone

## Contraindications/ Precautions

1. Known hypersensitivity to disodium pamidronate or to other bisphosphonates.
2. Significant renal impairment:
  - Note that pamidronate is not recommended in cases of severe renal impairment (**Creatinine clearance < 30 mL/minute**).

However in cases of **life-threatening** hypercalcaemia the benefit probably outweighs the potential risk<sup>2,3</sup> and this should be discussed with ICU. In any case the patient can be later dialyzed if required.
3. Pamidronate should not be added to intravenous infusion fluids containing *calcium*, such as Ringer's solution or Hartmann's solution.
4. Previous thyroid surgery:
  - Patients who have undergone thyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.

## Pregnancy

Pamidronate is a category B3 class drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

## Breast feeding

Caution, insufficient data.<sup>1</sup>

## Adverse Effects

These include:

1. Nonspecific constitutional symptoms:
  - Intravenous bisphosphonates have been associated with transient influenza-like symptoms, (i.e. myalgias, mild fever, malaise, and headache).

- These are generally mild and usually resolve spontaneously (within 48 hours)

2. Thrombophlebitis:

- Pamidronate should never be given as a rapid bolus injection, as severe local thrombophlebitis may occur.

**It should always be diluted and then given as a slow intravenous infusion.**

3. Osteonecrosis of the jaw:

- Antiresorptive drugs (bisphosphonates and denosumab) have been associated with osteonecrosis of the jaw (or “ARONJ” i.e. antiresorptive agent-induced osteonecrosis of the jaw).
- This is a rare complication.
- It has mainly occurred in patients receiving **intravenous** bisphosphonates for multiple myeloma or metastatic breast cancer.

Many of these patients were **also** receiving **chemotherapy** and **corticosteroids**. Many had signs of local infection including established osteomyelitis, and so the relative contribution of pamidronate is unclear.

Presentation may include jaw pain, toothache, exposed bone, altered sensation and local infection, including osteomyelitis. The condition may result in chronic pain, may be resistant to treatment and, in serious cases, may result in disfigurement.

4. Deterioration of renal function:

- Renal deterioration and progression to renal failure has been reported in patients after a single dose of disodium pamidronate.
- Deterioration of renal function (including renal failure) has also been reported following **long-term** treatment with disodium pamidronate in patients with multiple myeloma, though this could be due in part also to the disease process itself.

5. Electrolyte disturbances:

- Hypocalcaemia, with excessive use.

*Less commonly the following may also be seen:*

- Hypomagnesaemia, hypokalaemia, hypophosphataemia.

5. Allergic reactions (rare).

### **Dosing**

**Patients should receive prior adequate IV rehydration.**

Give pamidronate **60 - 90 mg IV** over **2- 4 hours**; (slower rates are used for those with renal impairment) with the starting dose depending on severity of the hypercalcaemia.

The infusion **rate** should not exceed 60 mg/hour (1 mg/min).<sup>3</sup>

It is preferable to give the infusion into a *larger peripheral vein* to minimize the risk of thrombophlebitis.

**Dilute in 250 - 500 mls sodium chloride 0.9% or glucose 5%, (not calcium containing solutions such as Hartman's).**

In significant renal or hepatic impairment infusions should be slowed (< 20 mg/hour).

*Blood should be taken beforehand to measure the parathyroid hormone concentration, when the diagnosis is unknown.*

Renal function and serum concentrations of calcium, phosphate and magnesium should be monitored during treatment with intravenous bisphosphonates.

**If hypercalcaemia recurs or plasma calcium concentration does not decrease within 48 hours, further infusions may be given.**<sup>2</sup>



*The constellation of Gemini, (from the Southern hemisphere). To the right are the brilliant stars of Alpha Geminorum and Beta Geminorum - otherwise known as Castor and Pollux. The twins are seen holding hands together.*

### References

1. eTG - July 2014
2. Pamidromate in Australian Medicines Handbook, October 2013
3. Pamidromate in MIMs 1 July 2014.

Dr J. Hayes  
August 2014.