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Zoledronic Acid

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Contents

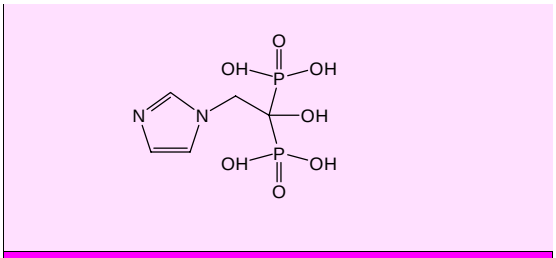
Abstract

▲ Zoledronic acid (zoledronate) is a new generation bisphosphonate that inhibits osteoclast bone resorption. It was much more potent than other bisphosphonates at inhibiting 1,25-dihydroxyvitamin D_3-induced hypercalcaemia in a rat model and calcium release *in vitro*.

▲ A single 5-minute intravenous infusion of zoledronic acid (4 or 8mg) was significantly more effective than a 2-hour infusion of pamidronic acid (pamidronic acid disodium, pamidronate disodium) [90mg] in normalising serum calcium levels in patients with hypercalcaemia of malignancy and resulted in a significantly longer median time to relapse (pooled analysis from 2 randomised, double-blind, parallel-group trials).

▲ There were no differences in tolerability between zoledronic acid and pamidronic acid in comparative trials; the most common events in pivotal trials were fever, anaemia, nausea, constipation and dyspnoea. Fever, hypophosphataemia and hypocalcaemia were the most common events in a small phase I trial.

Features and properties of zoledronic acid (CGP 42446, CGP 42446A, CGP42446B, zoledronate)	
Indication	
Hypercalcaemia of malignancy (tumour-induced hypercalcaemia)	
Mechanism of action	
Bisphosphonate	Inhibits bone resorption by inhibiting osteoclast formation
Dosage and administration	
Recommended dosage	4mg
Route of administration	Intravenous infusion (15 minutes)
Frequency of administration	Single dose
Pharmacokinetic profile (estimates from a population pharmacokinetic model based on single-dose administration of 4 to 16mg in patients with cancer)	
Total body clearance	4.4-5.6 L/h
Volume of distribution	6.1-10.8L
Elimination half-life	$t_{½\alpha}$ 0.23h $t_{½\beta}$ 1.75h $t_{½\gamma}$ 167h
Adverse events	
Most common	Fever, anaemia, nausea, constipation, dyspnoea, hypophosphataemia, asymptomatic hypocalcaemia



Zoledronic acid

Hypercalcaemia of malignancy is the most common life-threatening metabolic disorder observed in patients with cancer.[1] It predominantly results from increased calcium loss from bones. The balance between bone resorption and formation is disturbed when humoral and paracrine factors secreted by the tumour increase activity and proliferation of osteoclasts (which are associated with absorption and removal of bone) and inhibit activity of osteoblasts (which are associated with bone production). This results in increased calcium resorption from bone and a subsequent rapid rise in serum calcium levels.[1,2]

Bisphosphonates are the standard treatment for hypercalcaemia of malignancy. The characteristic P-C-P bond of these drugs enables them to bind to mineralised bone matrix and, in turn, inhibit osteoclast-mediated bone resorption thereby reducing serum calcium levels. The precise mechanism of action, relative potency and adverse effects differ among bisphosphonates depending on the structural modification of the side chain.[2]

Zoledronic acid (zoledronate) is a heterocyclic imidazole third-generation bisphosphonate which has proved more potent than other members of its class in preclinical studies and which can be administered as a short (15-minute) intravenous infusion.[3] This profile focuses on the efficacy and tolerability of zoledronic acid in the treatment of hypercalcaemia of malignancy, although this drug is also under investigation for the treatment and prevention of bone metastases and of skeletal complications associated with various cancers.[4]

1. Pharmacodynamic Properties

Studies in Patients with Cancer

- Zoledronic acid was reported to inhibit osteoclast-mediated bone resorption, as measured by urinary hydroxyproline and deoxypyridinoline (markers of bone resorption) in 58 patients with cancer (mainly multiple myeloma and breast carcinoma).[3] In a dose-ranging phase I trial, 5-minute intravenous infusions of zoledronic acid 0.1 to 8mg were administered 3 times at 4-week intervals. At 12 weeks, the median reduction from baseline for fasting urinary hydroxyproline and deoxypyridinoline was 0 to 42% and 4 to 53%, respectively. The decrease in deoxypyridinoline appeared dose-dependent, and for the 4 highest doses (1.5, 2, 4 and 8mg) the reduction ranged from 27 to 53% (measured at 12 weeks). A retrospective comparison suggested that zoledronic acid (2mg) had greater effects on the biochemical markers of bone resorption than pamidronic acid (pamidronic acid disodium, pamidronate disodium) 90mg (quantitative data were not provided). All data were obtained from a review article.[3]

- Zoledronic acid ≥2mg given as a single intravenous bolus injection over 30 to 60 seconds suppressed all measured markers of bone resorption throughout an 8-week dose-finding trial in 44 patients with cancer and metastatic bone disease.[5] At 8 weeks, the median reduction from baseline for urinary calcium/creatinine and N-telopeptide/creatinine ratios was 45 to 72% and 53 to 61%, respectively. Hydroxyproline/creatine, pyridinoline/creatinine and deoxypyridinoline/creatinine ratios were 16 to 46% below baseline values at 8 weeks after treatment with zoledronic acid at doses ≥2mg; however values for these markers were elevated above baseline levels at 8 weeks with the 1mg dose.[5]

Animal Studies

Effects on Calcium Levels

- Zoledronic acid was the most potent bisphosphonate tested (≥8 times more potent than comparators) in a study of 1,25-dihydroxyvitamin

D_3-induced hypercalcaemia in thyroparathyroidectomised (TPTX) rats (drug and inducer administered on 4 consecutive days).[6] Mean oral doses required for 50% inhibition of hypercalcaemia were 0.19 mg/kg for zoledronic acid compared with >50, >30, 23, 3.2, 2.0 and 1.6 mg/kg, respectively, for etidronic acid, clodronic acid, pamidronic acid, alendronic acid, risedronic acid and ibandronic acid. Values for subcutaneous administration (same drug order) were 0.072 versus >20 000, 1200, 61, 8.2, 1.7 and 1.4 μg/kg, respectively.[6]

- In a limited number of studies in TPTX rats (further details not reported), a single intravenously administered dose of zoledronic acid was 688 times more potent than pamidronic acid. The mean intravenous dose required for 50% inhibition of hypercalcaemia was 0.16 μg/kg for zoledronic acid versus 110 μg/kg for pamidronic acid.[6]

Effects on Bone Metabolism

- Histomorphometric analysis of the proximal tibia of rats revealed that zoledronic acid (0.028 to 2.8 μg/kg), given subcutaneously for 10 days, caused a dose-dependent increase in cancellous bone and a dose-dependent reduction of cancellous bone turnover and resorption. This was more pronounced in bone formed during rather than before treatment. Zoledronic acid was 100 times more potent than pamidronic acid.[7]

- In bone formed during treatment, zoledronic acid 2.8μg was reported to be significantly more effective than a corresponding dose of pamidronic acid (presumed to be 370μg) in reducing active bone resorption surface (5.5 *vs* 9% eroded surface).[7] In addition, zoledronic acid 2.8μg was reported to be significantly more effective than no treatment (control) for the bone resorption endpoint, and zoledronic acid 280ng and 2.8μg was significantly more effective than no treatment in increasing trabecular bone volume (40 and 66 *vs* 18% increase from baseline). All values are estimated from graphs; p-values were not reported.

- In bone formed before treatment, zoledronic acid 2.8μg was reported to be significantly more effective than a corresponding dose of pamidronic acid (presumed to be 370μg) in reducing the active bone resorption surface (2 *vs* 6.5% eroded surface) and osteoclast number (0.15 *vs* 0.3/mm).[7] All zoledronic acid doses tested (28ng, 280ng and 2.8μg) were reported to be significantly more effective than no treatment (vehicle) for the resorption surface end-point; only the 2.8μg dose was significantly more effective than no treatment in increasing trabecular bone volume (19 *vs* 7% increase from baseline) and reducing osteoclast number (0.15 *vs* 1.2/mm). All values are estimated from graphs; p-values were not reported.

In Vitro Studies

- Zoledronic acid was the most potent bisphosphonate *in vitro*. The concentration required to inhibit 1,25-dihydroxyvitamin D_3-induced calcium release from mouse calvaria by 50% was 0.002 versus 4, 0.4, 0.2, 0.05, 0.02, and 0.01 μmol/L, respectively, for etidronic acid, clodronic acid, pamidronic acid, alendronic acid, ibandronic acid and risedronic acid.[6]

- In an *in vitro* study of fetal rat calvariae, zoledronic acid inhibited osteoclast formation (osteoclastogenesis) by inhibiting the fusion of more mature osteoclast precursor cells on the bone surface.[8] In cultures of 19-day calvariae (characterised by recruitment of precursor cells), zoledronic acid $\geq 2.5 \times 10^{-8}$ mol/L caused a marked reduction in osteoclast number. However, in cultures of 20-day calvariae (characterised by the fusing of more mature osteoclast precursor cells on the bone surface), all concentrations of zoledronic acid (2.5×10^{-6} to 2.5×10^{-10} mol/L) significantly reduced osteoclast number and size. Zoledronic acid had little effect on osteoblasts *in vitro* except at a high concentration (50 μmol/L).[8]

Effects on Renal Function

The possibility of impaired renal function has been raised in relation to rapid renal excretion of bisphosphonates, particularly in patients with malignancy and existing renal dysfunction who receive large intravenous doses.[9]

• No marked elevations in urinary malate dehydrogenase levels (an early marker of nephrotoxicity) were detected when zoledronic acid, alendronic acid, clodronic acid, etidronic acid, ibandronic acid, pamidronic acid or risedronic acid (1 mg/kg for 9 days) were administered subcutaneously to rats. Zoledronic acid had the highest therapeutic ratio [calculated by dividing the reciprocal of the ED_{50} (median effective dose for 50% inhibition of hypercalcaemia) value by the total units of malate dehydrogenase excreted] at ≥20 times that of the other drugs.[9]

• Single-dose intravenous administration of zoledronic acid or pamidronic acid (1.5 to 50 mg/ kg) produced a dose- and time-dependent increase in serum urea levels in rats. The change in urea level was statistically significant compared with that in control animals ($p < 0.05$) for zoledronic acid 50 mg/kg and pamidronic acid 15 and 50 mg/ kg at 2, 3 and 4 hours. The dose required to elevate serum urea level by 100% at 4 hours was 38 mg/kg for zoledronic acid and 10 mg/kg for pamidronic acid.[9]

2. Pharmacokinetic Properties

There are no pharmacokinetic data for zoledronic acid in patients with hypercalcaemia.[10] Data included in this section are predominantly from a preliminary report (in abstract form) of population pharmacokinetics from 2 studies (n = 32) in patients with cancer and bone metastases (aged 45 to 78 years). In study 1, zoledronic acid was given as a single 5- (4mg) or 15-minute (4, 8 and 16mg) intravenous infusion, and in study 2, as a single 5-minute (2, 4 and 8mg) intravenous infusion.[11]

• Plasma concentrations of zoledronic acid were linearly related to dose (dose range not specified). At 24 hours, plasma zoledronic acid concentration was <1% of that immediately after the end of the infusion following a rapid multiphasic decline. Zoledronic acid remained detectable to day 29 after the dose.[11]

• Modelling using a nonlinear mixed effects model with a 3-compartment first-order population pharmacokinetic model indicated that total body clearance from plasma (CL) was 5.6, 4.4 and 5.4 L/h, and volume of distribution of the vascular central compartment was 10.0, 10.8 and 6.1L, for Caucasian, Black and Oriental populations, respectively. Half-lives for the 3 phases of elimination were 0.23 ($t_{½\alpha}$), 1.75 ($t_{½\beta}$) and 167 ($t_{½\gamma}$) hours. There was a positive correlation between CL and creatinine clearance (CL_{CR}). Renal clearance of zoledronic acid was 82% of CL_{CR}.[11]

• *In vitro* zoledronic acid is not metabolised and it does not inhibit human cytochrome P450 enzymes.[10] Less than 3% of the administered dose of zoledronic acid (dose not stated) was recovered in the faeces in animal studies. There are no pharmacokinetic data on this drug in patients with hepatic insufficiency.[10]

3. Therapeutic Trials

The efficacy of zoledronic acid in the treatment of moderate to severe hypercalcaemia of malignancy has been compared with that of pamidronic

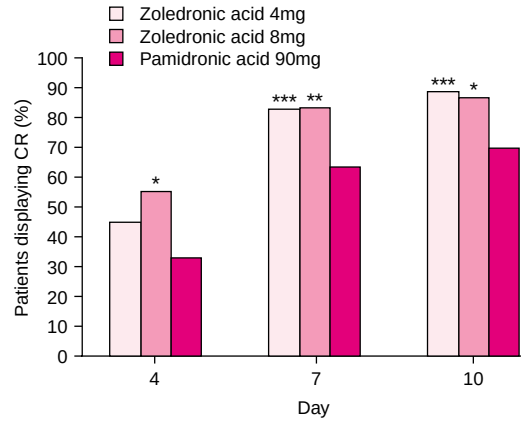


Fig. 1. Response rates with zoledronic acid and pamidronic acid in patients with hypercalcaemia of malignancy. Pooled data from 2 double-blind, randomised, parallel-group trials (n = 275 evaluable patients).[12] Zoledronic acid was given as a single dose of 4 or 8mg in a 5-minute infusion, while 90mg of pamidronic acid was given as a 2-hour infusion. Complete response (CR) was defined as corrected serum calcium level ≤2.7 mmol/L. * $p < 0.05$, ** $p = 0.01$, *** $p \leq 0.005$ *vs* pamidronic acid.

acid (the gold standard) in 2 pivotal randomised, double-blind. parallel-group trials from which data were pooled for analysis (n = 287).[12] The evaluable patient group (n = 275) included 144 individuals with bone metastases and 131 without. Zoledronic acid (4 or 8mg) was administered via a 5-minute intravenous infusion and pamidronic acid (90mg) was given as a 2-hour intravenous infusion.[12] Additional efficacy data have been reported from a multicentre, phase I dose-finding trial.[13] The primary clinical end-point for all trials was normocalcaemia [complete response (CR)], defined as serum calcium levels ≤2.7 mmol/L in the 2 pivotal trials[12] and ≤2.6 mmol/L in the phase I trial.[13] Other clinical end-points studied in the 2 pivotal trials included duration of CR and time to relapse. The efficacy of the 8mg dose in the retreatment of patients who had relapsed after achieving CR or who were refractory to treatment was also evaluated.[12]

- In the pivotal trials, both dose levels of zoledronic acid (4 and 8mg) were significantly more effective than pamidronic acid according to CR (normocalcaemia) rates at 7 and 10 days ($p \leq 0.015$) [fig. 1]; the higher dose was also significantly more effective than pamidronic acid at 4 days ($p = 0.021$).[12] The relative improvement in response versus pamidronic acid at 10 days was 27% (4mg) and 24% (8mg). There was no significant difference in the proportion of patients experiencing CR with zoledronic acid 4 versus 8mg.[12]

- The median time to relapse with zoledronic acid was 13 days (4mg) or 23 days (8mg) longer than that for pamidronic acid ($p = 0.001$ and $p = 0.007$, respectively), and there was a trend to a longer median duration of CR with zoledronic acid [≈1.8 (4mg) and 2.4 (8mg) times that with pamidronic acid; fig. 2]. 69 of 70 patients who relapsed or were refractory to initial treatment were retreated with the 8mg dose of zoledronic acid in the pivotal trial; 52% of patients experienced CR by day 10.[12] Median duration of CR was 12.8 days and median time to relapse was 10.4 days.[12]

- Zoledronic acid 0.02 and 0.04 mg/kg were the most effective doses (dose range: 0.002 to 0.04 mg/kg) in a multicentre, nonblind, dose-finding study in 30 patients with hypercalcaemia of malignancy (defined as serum calcium levels ≥2.75 and ≤3.75 mmol/L).[13] Normocalcaemia was achieved in 5 of 5 and 14 of 15 patients at these doses; lower doses were much less effective (normocalcaemia was achieved by 1 of 3 patients at 0.002 or 0.005 mg/kg and 1 of 4 patients at 0.01 mg/kg).

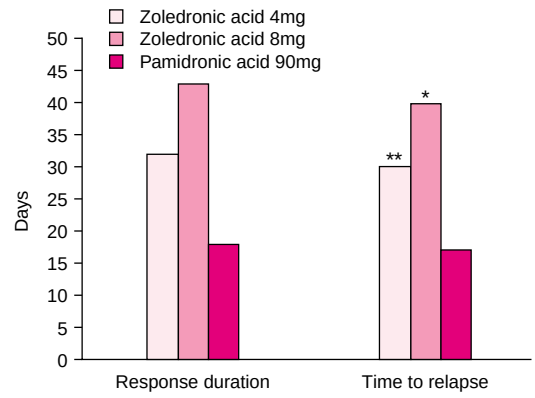


Fig. 2. Median duration of complete response and time to relapse with zoledronic acid and pamidronic acid in patients with hypercalcaemia of malignancy. Pooled data from 2 double-blind, randomised, parallel-group trials.[12] Zoledronic acid was given as a single dose of 4 or 8mg in a 5-minute infusion, while 90mg of pamidronic acid was given as a 2-hour infusion. Median duration of complete response was defined as period from onset of complete response until last corrected serum calcium measurement ≤2.7 mmol/L, and median time to relapse as the time from drug infusion until last corrected serum calcium measurement ≤2.9 mmol/L. * $p = 0.007$, ** $p = 0.001$ *vs* pamidronic acid.

4. Tolerability

- Fever, anaemia, nausea, constipation and dyspnoea were the most common adverse events reported by patients with hypercalcaemia of malignancy in the 2 pivotal clinical trials (n = 275; data were pooled) [fig. 3; see section 3 for detailed methodology].[12] There was no significant difference in adverse events among those receiving single dose zoledronic acid 4 or 8mg or pamidronic

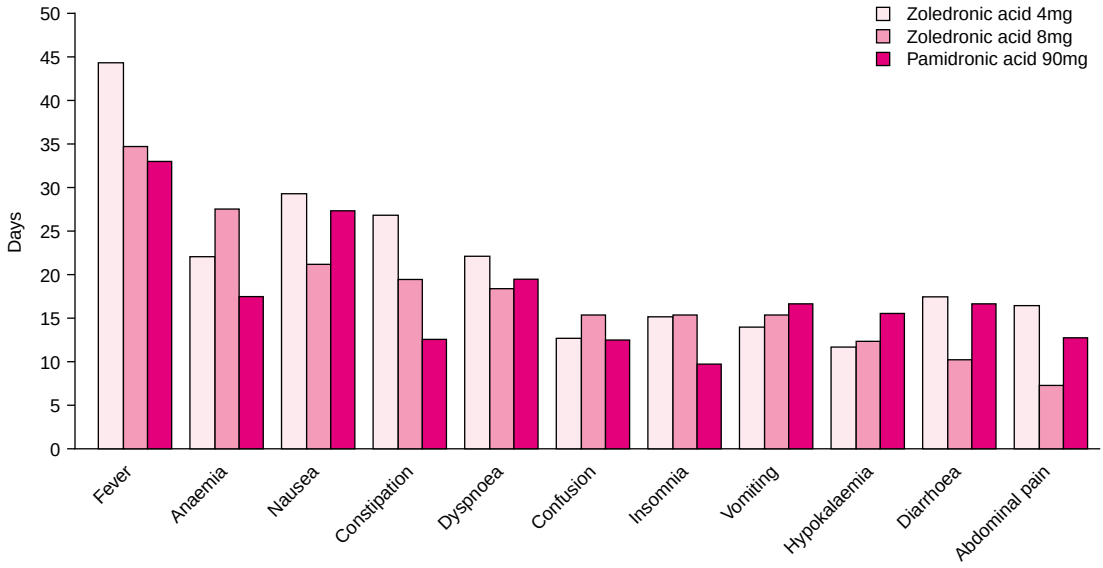


Fig. 3. Adverse events occurring in >5% of patients with hypercalcaemia of malignancy after zoledronic acid or pamidronic acid treatment. Pooled data from 2 double-blind, randomised, parallel-group trials; adverse events were assessed over 10 days.[12] 86 and 98 patients, respectively, received zoledronic acid as a single dose of 4 or 8mg in a 5-minute infusion, and 103 patients received pamidronic acid 90mg as a 2-hour infusion.

acid 90mg (fig. 3). Suspected drug-related adverse events included fever, hypophosphataemia and asymptomatic hypocalcaemia.[12]

- Elevated serum creatinine levels were observed in a few patients from each of the 3 treatment groups; 2 patients treated with zoledronic acid 8mg and 1 patient with pamidronic acid 90mg developed grade 4 serum creatinine values. In addition, 2 and 3 patients who received zoledronic acid 4 or 8mg and 3 patients treated with pamidronic acid 90mg developed grade 3 creatinine changes.[12] Due to concerns over renal function, the 8mg dose of zoledronic acid has been eliminated from ongoing clinical trials.[14] Other serious adverse events were confusion and hallucination experienced by 1 patient taking zoledronic acid 4mg and thrombocytopenia which developed in 1 patient treated with pamidronic acid.

- Fever, which was generally moderate and transient, was the only clinically detectable adverse event in a phase I dose-ranging trial of single-dose zoledronic acid 0.002 to 0.04mg (see section 3 for detailed methodology).[13] Ten of 33 patients experienced an increase in body temperature after treatment with zoledronic acid; 7 of these patients had received the highest dose (0.04 mg/kg).

- Seven of 33 patients developed transient hypophosphataemia; 6 of the 7 patients were treated with zoledronic acid 0.04 mg/kg and 1 received a lower (unspecified) dose.[13] Three patients developed transient hypocalcaemia after receiving zoledronic acid 0.04 mg/kg and 1 developed hypomagnesaemia after an unspecified dose. One patient receiving zoledronic acid 0.04 mg/kg had liver dysfunction as indicated by laboratory tests (further details were not reported).[13]

5. Zoledronic Acid: Current Status

Zoledronic acid was more effective than pamidronic acid in the treatment of hypercalcaemia of

malignancy according to pooled data from 2 phase III trials. This agent can be administered as a 15-minute intravenous infusion compared with the 2-hour infusion time for pamidronic acid. Zoledronic acid has been approved for use in patients with hypercalcaemia of malignancy in several countries world wide. Large phase III trials are currently under way or being initiated to investigate zoledronic acid for the treatment and prevention of bone metastases in patients with breast and prostate cancer and of skeletal complications associated with cancer.

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