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Pharmacokinetic and clinical equivalence of oral and intravenous ibandronate for metastatic bone disease

B. Leyland-Jones

Department of Oncology, McGill University, Suite 701, 3655 Drummond Avenue, Montreal, Quebec Canada, H3G 1Y6

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Abstract

While monthly infusions of intravenous (i.v.) bisphosphonates effectively reduce skeletal complications of metastatic bone disease, regular hospital visits are inconvenient for patients and may reduce their quality of life. Daily oral bisphosphonate therapy would allow long-term patient management in the community setting. However, the use of oral bisphosphonate therapy (e.g. oral clodronate) is limited in clinical practice, due to its relatively low efficacy in comparison with i.v. agents, poor gastrointestinal tolerability, and a large tablet size that is difficult for patients to administer. Ibandronate is a highly potent, third-generation aminobisphosphonate that has been developed in an oral formulation with a small, easy-to-swallow tablet and convenient once-daily dosing. Pharmacokinetic evaluations of oral ibandronate have shown a linear dose-dependent increase in plasma concentrations that is non-saturable, and is proportional to its effect on bone-resorption markers. This ensures predictability of response to a given oral dose of ibandronate, reducing safety concerns. Bioavailability analysis suggests that oral ibandronate (50 mg) taken once daily, 30 min before food, provides comparable bone-surface exposure to i.v. ibandronate (6 mg) infused every 3–4 weeks i.e. the two formulations are dose-equivalent. The clinical equivalence of oral ibandronate (50 mg) and i.v. ibandronate (6 mg) is indicated by comparable reductions in the relative risk of skeletal events in phase III trials of patients with bone metastases from breast cancer.

1. Introduction

One of the main goals of palliative medicine is to ensure that patients lead as normal a life as possible. Infusion of i.v. bisphosphonates is the standard supportive care agent for the control of skeletal complications in patients with metastatic bone disease [1–5]. However, i.v. administration and patient monitoring (required to reduce the risk of side effects, particularly renal toxicity) results in lengthy hospital visits that can last several hours [6]. The need to return to hospital every 3–4 weeks for infusions is inconvenient for patients and impacts on their quality of life.

Conventional daily oral bisphosphonate therapy (e.g. clodronate) is available for patient management in the community setting. However, the use of first generation oral bisphosphonates is limited in clinical practice, as they are perceived to be less effective than i.v. agents. This perception is supported by clinical trial data showing that i.v. pamidronate is more effective than oral clodronate in reducing the risk of new bone events [5]. Oral clodronate has further disadvantages for clinical use, including poor gastrointestinal (GI) tolerability [7] and a large tablet that some patients find difficult to swallow. Clodronate is not the only oral bisphosphonate to be associated with tolerability problems: use of the oral formulation of pamidronate, for example, led to unacceptably high levels of upper GI side effects and subsequent drug discontinuation in clinical studies [8]. As a consequence of these side effects, pamidronate is administered by the i.v. route for the treatment of bone metastases.

The availability of an effective oral bisphosphonate would expand treatment choice for the management of metastatic bone disease. Ibandronate, a highly potent, third generation, aminobisphosphonate, has been developed in a small, easy-to-swallow tablet, with convenient once-daily dosing. This paper summarises the pharmacokinetic and clinical data showing the equivalence of dosing and efficacy with oral and i.v. ibandronate.

2. Determining dose equivalence

A phase III clinical trial of i.v. ibandronate provided strong evidence to show that a 6 mg infusion every 3–4

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weeks is highly effective in reducing skeletal complications due to breast cancer [9]. Pharmacokinetic and clinical investigations have been undertaken to determine the daily oral dose of ibandronate that would offer similar clinical efficacy to this i.v. regimen.

2.1. Oral ibandronate pharmacokinetics

Similarly to other oral bisphosphonates [10,11], the bioavailability of oral ibandronate is low and is not dose-dependent, with a large intrapatient (approximately 46%) and interpatient (approximately 70%) variability in the relationship between oral dose and plasma levels [11]. However, pharmacokinetic evaluations of oral ibandronate have shown a linear dose-dependent increase in plasma concentration that is non-saturable. This ensures predictability of response to a given oral dose, thus reducing safety concerns. It has also been found that the renal clearance rate of orally administered ibandronate is comparable to that of i.v. administered ibandronate, which is cleared at a rate of 90 ml/min [12].

2.2. Dose-finding study

An important step in determining the most appropriate oral dose for clinical use was to compare the effect of different doses on laboratory markers of bone resorption. In a phase I parallel group dose finding-study (MF 4346/4353), a clear linear dose–response relationship could be seen in terms of change from baseline on several bone resorption markers (urinary calcium excretion, urinary C-terminal telopeptide of type I collagen [CTx], urinary N-terminal telopeptide of type I collagen [NTx], and urinary pyridinium crosslinks [Fig. 1]) with the 50 mg daily dose having a greater effect than 5 mg, 10 mg or 20 mg ibandronate [13].

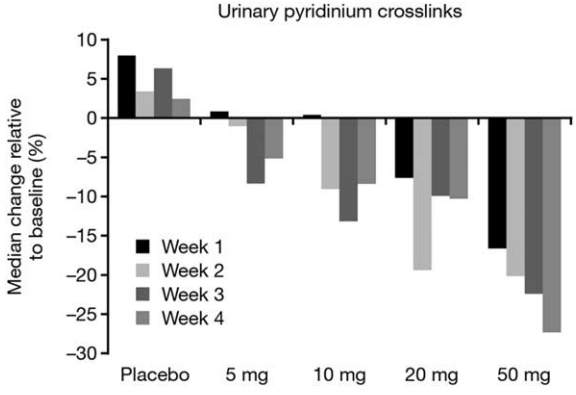

Fig. 1. Relationship between dose of oral ibandronate and change in urinary pyridinium crosslinks as a marker of bone resorption [13].

2.3. Impact of food intake on bioavailability

The absorption of any oral bisphosphonate is impaired by the intake of food or calcium-containing liquids. Therefore, a study of 20 healthy volunteers was conducted to investigate the relationship between meal timing and the plasma concentration of oral ibandronate (50 mg) [12]. Subjects received a standard meal at the following times: 2 h before receiving ibandronate, immediately before receiving ibandronate, or 1, 2 or 3 h after administration of ibandronate.

Peak plasma concentrations of ibandronate were highest when drug was administered in the 1–3 h period just before food intake when patients were in a 'fasting' state (Fig. 2). In contrast, drug taken immediately after a meal was poorly absorbed, with the area under the curve (AUC) plasma concentrations reduced by around 90%.

In clinical practice, where many patients may not be fully compliant with dosing instructions, a gap of 30 min before a meal is more practical and realistic than a 1-h interval. Pharmacokinetic data demonstrate that a 30-min fasting period would result in a bioavailability of 0.44% for a 50 mg daily oral dose, and the resulting plasma concentration of the drug would match that achieved by monthly administration of i.v. ibandronate 6 mg (Table 1). The similarity of the AUC values for the i.v. 6 mg dose and the oral 50 mg dose given 30 min before food indicates that these formulations have similar effects on bone resorption, suggesting that they are dose-equivalent [12].

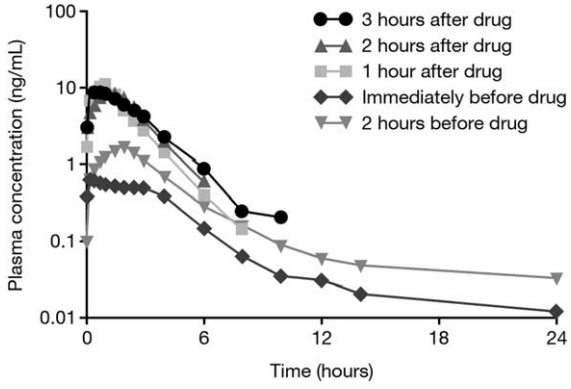

Fig. 2. Effect of timing of food intake on mean plasma levels of ibandronate following oral dosing [12].

Table 1
Pharmacokinetic parameters of iv and oral ibandronate [12]

Pharmacokinetics (28-day equivalent)	i.v. ibandronate 6 mg	Oral ibandronate 50 mg (30-min fast)
Mean AUC (ng.h/mL	1250	1960
Median AUC (ng.h/mL)	1155	1548
Dose exposure	6 mg	6.2 mg

Once-daily dosing of oral ibandronate 50 mg has potential compliance benefits for patients, as the convenience of a 30-min pre-food fasting period would maximise the likelihood that patients will consistently receive an effective bisphosphonate dose.

3. Data from phase III clinical trials showing the equivalence of oral and i.v. ibandronate

Three multicentre, randomised, double-blind, placebo-controlled phase III studies have investigated the efficacy and safety of ibandronate in metastatic bone disease from breast cancer (one study of i.v. ibandronate 6 mg, MF 4265 and pooled data from two trials of oral ibandronate 50 mg, MF 4414/4434). Patient demographics and baseline characteristics were generally comparable between studies, and between the ibandronate and placebo groups in each trial. The primary endpoint was the Skeletal Morbidity Period Rate (SMPR), which assesses the incidence of skeletal events (incorporating vertebral fractures, non-vertebral fractures, radiotherapy to bone and bone surgery) occurring during 12-week observation periods. The results demonstrated that both i.v. and oral ibandronate are effective against skeletal complications, with significant reductions in overall SMPR versus placebo ($P = 0.004$ for both formulations) [14]. Using Poisson regression multivariate analyses, it was possible to determine and compare the relative risk of new bone events with i.v. and oral ibandronate compared with placebo. The mean reduction in the relative risk of new bone events was 38% with oral ibandronate 50 mg (RR 0.62, $P < 0.001$ versus placebo) and 40% with i.v. ibandronate 6 mg (RR 0.60, $P = 0.0033$ versus placebo) (Fig. 3) [14]. Oral ibandronate was well-tolerated in the phase III studies, with a similar GI tolerability profile to placebo [15].

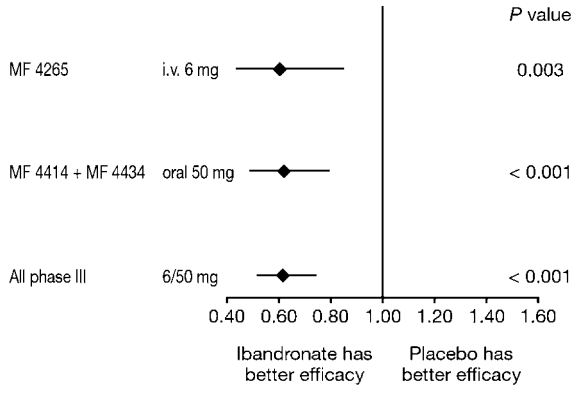

Fig. 3. Relative risk of skeletal events with i.v. and oral ibandronate: phase III trial results [14].

4. Implications for clinical practice

As the only bisphosphonate to offer i.v. efficacy in a convenient, once-daily oral formulation, oral ibandronate offers improved treatment flexibility. Clinicians would be able to prescribe i.v. or oral treatment whilst patients are in hospital (or visiting hospital for chemotherapy), followed by oral dosing on an out-patient basis, according to clinical need and circumstances. Patients receiving oral ibandronate would no longer experience the unwelcome disruption associated with monthly bisphosphonate infusions. Hospitals would benefit from greater availability of inpatient beds and an associated reduction in the costs of patient care.

5. Summary

The use of oral bisphosphonate therapy has previously been limited by low efficacy, poor GI toxicity and difficulty of administration. Ibandronate offers an oral formulation that has a small, easy-to-swallow tablet and convenient once-daily dosing. Pharmacokinetic evaluations of oral ibandronate have shown a linear dose-dependent increase in plasma concentrations that is non-saturable, and is proportional to its effect on bone-resorption markers. The predictability of response to a given oral dose of ibandronate reduces safety concerns. Oral ibandronate 50 mg taken once daily, 30 min before food, provides comparable bone-surface exposure to i.v. ibandronate 6 mg infused every 3–4 weeks i.e. the two formulations are dose-equivalent. The clinical equivalence of oral and i.v. ibandronate is supported by comparable reductions in the risk of skeletal-related events versus placebo, suggesting that oral ibandronate will provide a viable alternative to i.v. treatment for metastatic bone disease.

Acknowledgements

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