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Clinical Pharmacology of Alendronate Sodium

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Abstract. Clinical studies have been performed to investigate the pharmacokinetics and pharmacodynamics of alendronate, an inhibitor of bone resorption for the treatment of osteoporosis. Alendronate is one of the most potent bisphosphonates currently undergoing clinical investigation (>100-fold more potent than etidronate in vivo). The pharmacokinetics of alendronate are similar to those of other bisphosphonates. After a 2-h intravenous infusion, plasma concentrations of alendronate decline rapidly to ~5% of initial values within 6 h. About 50% of a systemic dose is excreted unchanged in the urine in the 72 h following administration. By analogy to its behavior in animals the remainder is assumed to be taken up by the skeleton. After sequestration into bone, the elimination of alendronate is very prolonged. The terminal half-life was estimated to be greater than 10 years. Despite prolonged skeletal residence, the biological effects of alendronate begin to diminish post-treatment, since the duration of effect reflects factors besides dose and cumulative drug exposure. When taken after an overnight fast, 2 h before breakfast, the oral bioavailability of alendronate averages ~0.75% of dose with substantial variability (coefficient of variation 55%–75%) both between and within subjects. Reducing the wait before food from 2 h to 1 h, or even 30 min, produces a mean reduction in absorption of 40%. Since the clinical efficacy of alendronate is indistinguishable whether it is given 30 min, 1h, or 3 h before a meal, the observed variability in bioavailability within this range is of little consequence. Dosing up to at least 2 h after a meal dramatically reduces absorption (80%–90%).

Keywords: Alendronate; Bisphosphonates; Osteoporosis

Introduction

By virtue of its high affinity for hydroxyapatite, alendronate is rapidly taken up into the skeleton [1]. There it reduces bone resorption by inhibiting osteoclast function [2–4]. These properties of alendronate make it clinically useful for the treatment of disorders of bone metabolism [5–10], and have defined the approach taken to characterizing the pharmacokinetics and pharmacodynamics of this bisphosphonate in humans. The clinical pharmacology of alendronate provides a rationale for the therapeutic regimen recommended for the treatment and prevention of osteoporosis.

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Measurement of Alendronate in Biological Fluids

The pharmacokinetics of bisphosphonates have been characterized to a limited extent in humans. It is difficult to quantify the concentration of a bisphosphonate in biological fluids, especially plasma, following therapeutic doses of the more potent compounds such as alendronate.

Analytical determination of alendronate in biological samples is accomplished through high-performance liquid chromatography (HPLC) [11]. Alendronate is isolated from the sample by co-precipitation with naturally occurring phosphates by the addition of calcium under basic conditions. After re-solubilizing the pellet in acid, calcium is removed by solid phase extraction using a diethylamine cartridge. The eluate, containing alendronate, is alkalinized again and the drug is derivatized with 2,3-naphthalene dicarboxyaldehyde in the presence of *N*-acetyl-D-penicillamine. The resulting highly fluorescent derivative is then analyzed by HPLC. The limit of reliable quantification of this method of 1 ng/ml.

Pharmacokinetics of Alendronate in Animals

Prior to a discussion of the clinical pharmacokinetics of alendronate, it will be useful to review briefly the biopharmaceutics results in animals. The sequestration of drug in and its subsequent slow release from the skeleton, and the utility of studies with radiolabeled drug, make

such preclinical investigations particularly helpful in defining the unique pharmacokinetic properties of this compound.

Oral absorption of alendronate was estimated from the skeletal content of [^{14}C]alendronate and [^{3}H]alendronate following oral and intravenous dosing, respectively. Oral absorption of alendronate while fasting is less than 2% in all species tested (rats, dogs and monkeys), and absorption is virtually eliminated by dosing concurrently with food in rats [12]. Plasma concentrations following oral dosing were below the limit of detection.

Radiolabeled alendronate administered intravenously to rats is widely distributed initially. Residence in soft tissue, however, is brief; 5 min after administration of 1 mg/kg dose, 63% of the dose is in soft tissues, but within 1 h only 5% of the total dose and at 24 h less than 1% is still found in soft tissues [13]. In contrast, about 60%–70% of the dose is found in bone within 1 h and this is unchanged 71 h later. The remaining fraction of the dose (30%–40%) is eliminated in the urine [12,13]. In general, whole body retention is considered virtually synonymous with skeletal sequestration. The terminal half-life was found to be about 200 days in rats and greater than 1000 days in dogs [12].

Elimination of alendronate appears to be exclusively through urinary excretion. No biliary excretion is detectable in rats and chromatographic isolation revealed no metabolites of alendronate in the urine of dogs and rats, or in the skeleton of rats when the drug was extracted from bones and compared with authentic alendronate [12]. Renal clearance, at low systemic doses (1 mg/kg i.v.), is comparable to glomerular filtration rate in rats (Cl_r = 7.4 ml/min/kg). Since protein binding is >95% in this species, active secretion appears to be involved. However, secretion seems to involve neither the classical anionic nor cationic transport mechanisms, but instead appears to involve a distinct mechanism which can be inhibited by another bisphosphonate [14]. Similar findings have been reported for etidronate [15].

From a pharmacodynamic perspective, dose-dependent inhibition of bone resorption, without detrimental effects on bone mineralization, has been demonstrated in rats and baboons [16–21]. These findings apply to models of disuse osteoporosis [16,17], metabolic bone diseases such as hyperthyroidism [18], and bone loss associated with estrogen deprivation [19–21]. These studies have revealed that, despite continued drug administration, a plateau of the suppression of bone resorption is observed, on the basis of biochemical and histomorphometric indices. Furthermore, more frequent drug administration shows greater biological efficacy than widely dispersed dosing, given the same total dose [19].

Pharmacokinetics of Alendronate in Humans

Systemic Disposition

The systemic disposition and plasma pharmacokinetics of alendronate were studied following the intravenous infusion over 2 h of [^{14}C]alendronate (10 mg, 26.6 μCi) to patients with metastatic breast cancer [S Van Belle, unpublished observations]. Plasma concentrations decreased 95% within 6 h after the infusion. Elimination from plasma was multiphasic and plasma concentrations were undetectable beyond 12 h. Since elimination continues for much longer, a plasma terminal half-life could not be defined. Nearly 50% of the dose was recovered in urine within a 72 h period. That fraction of the dose remaining in the body is presumed to reflect skeletal deposition. There was essentially no fecal radioactivity, consistent with the absence of biliary excretion noted preclinically.

Renal clearance was estimated to average 71 ml/min with a volume of distribution (Vd_{ss}) estimated to be at least 28 l (exclusive of bone). This latter estimate is approximately double the extracellular fluid volume, consistent with the preclinical data that distribution of alendronate to soft tissues is not extensive. The mean plasma concentration versus time profiles for total radioactivity and unlabeled alendronate were nearly superimposable, providing strong evidence for the absence of circulating metabolites. Furthermore, no specific metabolites have been identified in urine.

In several studies, alendronate was administered as single or repeated intravenous doses (125 μg to 10 mg) to postmenopausal women. Recovery of alendronate in the urine for up to 72 h routinely averaged between 40% and 56% of the dose, and was independent of dose and duration of infusion. Disposition of alendronate after multiple doses was similar to that following administration of a single dose.

Long-Term Elimination

The rapid disappearance of detectable concentrations of alendronate in plasma following intravenous dosing, with persistent urinary excretion, suggests the slow redistribution of drug from a deep compartment, presumably bone. To obtain a better understanding of the long-term elimination of this drug in humans, women with postmenopausal osteoporosis were administered 30 mg intravenous alendronate (7.5 mg/day for 4 consecutive days) and urine collected at intervals over the subsequent 15 months. A preliminary analysis of 6 subjects revealed, as expected, that approximately 45% of total drug given was eliminated within 48 h of treatment completion. This was followed by a slower phase of excretion, over about the next 8 months, during which an additional 15% of the administered dose was excreted. Beyond this time excretion was very slow, providing an estimated terminal half-life of greater than 10 years [22].

Despite this long terminal half-life, as will be discussed below, the inhibition of bone resorption due to alendronate begins to diminish soon after the completion of treatment, suggesting that not all the alendronate sequestered in bone is biologically active. This is consistent with the preclinical findings that alendronate adsorbed to bone surfaces, which is not released by osteoclast activity, becomes buried as a result of new bone formation [4].

Oral Bioavailability

The oral absorption of alendronate was estimated by comparing the urinary excretion of drug after oral versus intravenous dosing. When taken after an overnight fast, 2 h before breakfast, the oral bioavailability averaged ~0.75% with a significant variability both within and between subjects (coefficient of variation 55% and 75% respectively). Oral absorption and disposition were linear with dose over the 5-80 mg dose range [23]. Reducing the wait before food from 2 h to 1 h, or even 30 min, reduces absorption by ~40%, but giving the drug with meals, or even 2 h after a large mixed meal, dramatically reduces absorption. These data, as well as results of clinical trials which included dosing 30 min or 1 h before food, indicate that a practical recommendation for dosing alendronate is after an overnight fast with water, delaying food by at least 30 min.

Drug Interaction Studies

Extensive drug interaction studies have not been performed with alendronate. This reflects in part the physicochemical and biological properties of alendronate, the absence of significant drug interactions reported for other bisphosphonates, and the experience reported from clinical trials with alendronate.

As noted previously, food dramatically impairs alendronate absorption and, given the propensity of alendronate to form insoluble complexes with multivalent cations (e.g. Ca^{2+}, Mg^{2+}), its concurrent administration with such supplements must be avoided. In addition, it was found that raising gastric pH to 6.0 by infusing an H_2-blocker increased the oral bioavailability of alendronate about two-fold compared with a fasting pH value of 2.0 [24].

The limited tissue distribution of alendronate in animals and humans, except for its uptake by bone, is consistent with the physicochemical properties of the drug which would limit transmembrane movement. Alendronate would therefore have limited access to sites of drug metabolism and thus would not be expected to alter the disposition of other drugs. Furthermore, the extremely low plasma concentrations and moderate plasma protein binding (78%) would not produce clinically important interactions with other drugs via competition for protein binding sites. Since alendronate is eliminated predominantly by renal glomerular filtration, with a presumed secretory component specific to bisphosphonates, the renal excretion of alendronate should not be altered substantively by other drugs, but may be decreased by a significant compromise of renal function.

Early Pharmacodynamic Studies

The early pharmacodynamic studies of alendronate were conducted in either pagetic patients or early postmenopausal women. These populations were relatively homogeneous, thereby optimizing the opportunity to define the dose-response for biochemical indices of bone turnover.

In the pagetic patients, a rising dose study investigated the safety and biochemical response over the 25-100 mg dose range (one group, $n = 10$, received placebo; the other, $n = 12$, received 25, 50, then 100 mg/day, each dose level for 5 days on each of 3 consecutive weeks) [25]. A significant mean reduction in urinary hydroxyproline (–33.3%, $p<0.05$ vs placebo) was evident by the second week. A maximum mean reduction of 43% in alkaline phosphatase was observed within 2 months of initiating therapy ($p < 0.01$)

In a randomized, double-masked, placebo-controlled trial of once-daily alendronate in early postmenopausal women, four groups of subjects received either 0, 5, 20, or 40 mg alendronate for 6 weeks [26]. Indices of bone resorption inhibition (urinary calcium, hydroxyproline, and pyridinium cross-links) were suppressed as early as 3 weeks into therapy, and this suppression appeared to plateau by week 3 of the treatment period at the higher doses. Despite the prolonged skeletal residence of the drug, these effects slowly resolved over the 7.5-month follow-up period [26].

Summary

The pharmacokinetics of alendronate have been investigated in several human study populations. The oral bioavailability of alendronate in fasting postmenopausal women is of the order of 1% or less. Delaying food by at least 30 min is necessary to ensure adequate absorption. About 40%–50% of the dose absorbed is rapidly excreted in the urine. A major portion of the drug initially retained in the body is slowly eliminated, presumably reflecting release of drug from the skeleton. Despite the long-term presence of drug in the skeleton, cumulative effects on bone resorption indices are not apparent and the biological effects slowly dissipate upon discontinuation of therapy.

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