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Human pharmacokinetics of tiludronate.

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Abstract

Tiludronate is a bisphosphonate evaluated extensively as an osteoregulator in the treatment of metabolic bone disorders. It is highly polar and has a low and variable oral absorption similar to its related compounds. An absolute bioavailability of approximately 6% has been reported with large inter- and intra-subject variability. The extent of absorption is increased at doses above 400 mg and may be reduced by a factor of 5 when tiludronate is administered with, or within 2 h after, food or dairy products. Approximately 90% of tiludronate is bound to serum albumin, and the binding is linear in the concentration range 1-10 mg/L. Preliminary in vitro studies using human hepatocytes failed to show any evidence of biotransformation of tiludronate. The elimination half-life in patients with normal renal function is approximately 40-60 h, but is significantly increased in subjects with severe renal impairment. The renal clearance (0.7 L/h) is independent of dose and suggests that glomerular filtration is the mechanism responsible for elimination. Approximately 50% of the absorbed dose is bound to bone and the rate of release of the drug from this site is limited by bone turnover. In vitro experiments indicate that tiludronate is not an enzyme inducer or inhibitor. Drug interaction studies with the nonsteroidal agents acetylsalicylic acid, indomethacin, and diclofenac indicate that only with indomethacin was there any change in the pharmacokinetic parameters, and that these changes were minimal and unlikely to be of clinical significance. Tiludronate does not influence the pharmacokinetics of digoxin at steady state. Tiludronate appears to exhibit similar pharmacokinetic behavior to other bisphosphonates with the exception that its absolute bioavailability is significantly higher than that previously reported for clodronate and pamidronate. The impact of its pharmacokinetic properties on clinical outcome has yet to be determined.