Pharmacokinetics and Pharmacodynamics of Zileuton after Oral Administration of Single and Multiple Dose Regimens of Zileuton 600mg in Healthy Volunteers

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Summary

The pharmacokinetics and pharmacodynamics of zileuton were determined after oral administration of single dose (600mg) and multiple dose regimens [600mg every 8 hours (q8h regimen) and 600mg every 6 hours (q6h regimen)] in 12 healthy male subjects aged 18 to 50 years. Steady-state peak plasma concentration (Cmax), time to Cmax, apparent total plasma clearance, and apparent terminal phase volume of distribution values after the q8h and q6h regimens were 3.07 ± 1.13 and 4.37 ± 1.02 mg/L, 1.5 ± 0.9 and 1.5 ± 0.9 hours, 793 ± 233 and 579 ± 162 ml/min (47.6 and 34.7 L/h), and 179 ± 126 and 115 ± 29 L, respectively (mean ± SD). Trough zileuton plasma concentrations (Cmin) immediately before the morning dose were higher than Cmin immediately before the afternoon dose, suggesting a diurnal variation in the pharmacokinetics of zileuton. Accumulation of zileuton occurred with more frequent dose administration, although there was no unexpected accumulation of the parent drug or the N-dehydroxyzileuton metabolite. The q6h regimen of zileuton 600mg was superior to the q8h regimen in maintaining trough plasma concentrations of zileuton above 1.5 mg/L, corresponding to approximately 70 to 80% inhibition of leukotriene B4 biosynthesis.

5-Lipoxygenase is an enzyme that converts arachidonic acid to 5-hydroperoxyicosatetraenoic acid (5-HPETE) in the pathway leading to the production of leukotrienes.[11] Potentially, inhibition of leukotriene synthesis has many therapeutic benefits for conditions in which leukotriene synthesis is elevated, such as asthma, rheumatoid arthritis, allergic rhinitis, and inflammatory bowel disease.[2,3]

Zileuton (N-(1-benzo[b]thien-2-ylethyl)-N-hydroxyurea; Abbott-64077) is a potent, reversible, selective 5-lipoxygenase inhibitor in vitro and in vivo.[4-12] The drug exists as a racemate mixture and is currently under investigation in the treatment of asthma.

The pharmacokinetics of zileuton have been investigated in healthy human volunteers.[10] The results showed that zileuton 25 to 800mg was ab-
sorbed rapidly, with a time to peak plasma concentration ($t_{\text{max}}$) of 1 to 3 hours. The area under the plasma concentration-time curve (AUC) values increased linearly with dose, although the mean elimination half-life ($t_{1/2}$) of zileuton (approximately 2.3 hours) did not change over the dose range tested. However, estimation of half-life may be confounded by the flip-flop phenomenon as it applies to zileuton.\[13\]

Zileuton is extensively metabolised by the liver (Machinist JM, unpublished data) and about 80% of the administered dose is excreted in the urine in the form of conjugated glucuronides.\[14\] On the other hand, the $N$-dehydroxylated metabolite of zileuton (N-dehydroxyzileuton; Abbott-66193) is believed to result from enteric bacterial dehydroxylation of unabsorbed zileuton (data on file, Abbott Laboratories, USA).

The purpose of this study was to assess the pharmacokinetics and pharmacodynamics of zileuton after oral administration of single and multiple dose regimens of zileuton 600mg in healthy volunteers, and particularly to identify a multiple dose regimen that would sustain zileuton trough concentrations of 1.5 mg/L or greater, corresponding to approximately 80% inhibition of LTB$_4$ biosynthesis.

1. Materials and Methods

1.1 Study Design and Subjects

The study was designed in 2 parts, each comprising a randomised double-blind parallel placebo-controlled trial conducted at a separate study site. In both parts of the study, 6 or 7 subjects were randomised to receive zileuton administered orally [part 1 = zileuton 600mg administered every 8 hours (q8h regimen); part 2 = zileuton 600mg administered every 6 hours (q6h regimen)], while 3 subjects were randomised to receive identical placebo. Dose regimens were administered for 14 days, with only the morning doses being administered on study days 1 and 14. All subjects fasted for 8 hours before and 4 hours after morning drug administration on study days 1, 4, and 14. On all other study days, standardised breakfast, lunch, and dinner meals were served 1, 4, and 10 hours after the morning dose.

Caucasian males aged 18 to 50 years inclusive were eligible for study participation. Subjects were judged to be healthy on the basis of normal findings of a medical history, physical examination, clinical laboratory profile, and 12-lead electrocardiographic assessments; all subjects were non-smokers. The exclusion criteria included participation in any investigational drug trial within 30 days prior to the current study; receipt of any medications on a long term basis; a history of multiple drug hypersensitivity; hypersensitivity to aspirin or other nonsteroidal anti-inflammatory drugs; hepatitis; psychiatric illness; and active drug or alcohol abuse. Before participation, all subjects granted written, informed consent, as approved by the institutional review boards of the study sites.

1.2 Assays for Determining Zileuton, N-Dehydroxyzileuton and Leukotriene B$_4$ Concentrations in Plasma

1.2.1 Assay for Zileuton and N-Dehydroxyzileuton

Heparinised blood samples (5ml) were collected for zileuton and N-dehydroxyzileuton assay in parts 1 and 2 of the study as follows: immediately before and 1.5, 3, 4.5, 6, 8, 12, 16, 20 and 24 hours after the first dose on day 1; immediately before and 1.5, 3, 4.5, 6, 8, 9, 9.5, 11, 12.5, 14 and 16 hours after the morning dose (q8h regimen) or immediately before and 1.5, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours after the morning dose (q6h regimen) on day 4; immediately before and 3 hours after the morning dose on day 10; and at sampling times similar to day 1 on day 14. The samples were drawn before dose administration and prior to a meal when appropriate. After centrifugation of the blood samples, the resulting plasma samples were transferred into designated tubes and stored at $-10^\circ$C or colder until analysis.

Plasma zileuton and N-dehydroxyzileuton concentrations were quantified by a sensitive and specific high performance liquid chromatographic (HPLC) technique.\[15\]