Clinical Trial > J Clin Pharmacol. 2002 Oct;42(10):1122-33.
doi: 10.1177/009127002401382731.

Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects

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PMID: 12362927 DOI: 10.1177/009127002401382731

Abstract

Safety and pharmacokinetics (PK) of the antiparasitic drug ivermectin, administered in higher and/or more frequent doses than currently approved for human use, were evaluated in a double-blind, placebo-controlled, dose escalation study. Subjects (n = 68) were assigned to one of four panels (3:1, ivermectin/placebo): 30 or 60 mg (three times a week) or 90 or 120 mg (single dose). The 30 mg panel (range: 34 7-594 microg/kg) also received a single dose with food after a 1-week washout. Safety assessments addressed both known ivermectin CNS effects and general toxicity. The primary safety endpoint was mydriasis, accurately quantitated by pupillometry. Ivermectin was generally well tolerated, with no indication of associated CNS toxicity for doses up to 10 times the highest FDA-approved dose of 200 microg/kg. All dose regimens had a mydriatic effect similar to placebo. Adverse experiences were similar between ivermectin and placebo and did not increase with dose. Following single doses of 30 to 120 mg, AUC and Cmax were generally dose proportional, with t(max) approximately 4 hours and t1/2 approximately 18 hours. The geometric mean AUC of 30 mg ivermectin was 2.6 times higher when administered with food. Geometric mean AUC ratios (day 7/day 1) were 1.24 and 1.40 for the 30 and 60 mg doses, respectively, indicating that the accumulation of ivermectin given every fourth day is minimal. This study demonstrated that ivermectin is generally well tolerated at these higher doses and more frequent regimens.

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