Reduced Single-dose Clearance of Clobazam in Elderly Men Predicts Increased Multiple-dose Accumulation

David J. Greenblatt, Marcia Divoll, Surendra K. Puri, Irwin Ho, Miguel A. Zinny and Richard I. Shader

Division of Clinical Pharmacology, Tufts-New England Medical Center, Boston; Department of Clinical Pharmacology, Hoechst-Roussel Pharmaceuticals, Somerville; and Medical and Technical Research Associates, Inc., Needham

The rate and extent of accumulation of clobazam and its major metabolite, desmethylclobazam, during multiple dosage with clobazam were evaluated in 4 similarly sized groups of young male, young female, elderly male, and elderly female volunteers. Subjects received single 10mg doses of clobazam daily for 22 consecutive days. Plasma levels were measured during and after the period of dosage. Compared with the young male subjects, elderly males had slower rates of clobazam accumulation and washout, higher steady-state plasma levels, and lower steady-state clearance. Accumulation of desmethylclobazam also was slower and more extensive in the elderly male group. Among females, however, age-related kinetic differences did not approach significance.

Among all subjects, pharmacokinetic variables for clobazam determined in a previous single-dose study were highly consistent with the multiple-dose pharmacokinetic profile. Single-dose vs post-multiple dosage half-life, single-dose vs steady-state clearance, observed vs predicted accumulation ratios, and observed vs predicted steady-state plasma concentrations were all highly correlated, with regression line slopes close to unity. Thus, reduced single-dose clearance of clobazam in elderly men leads to slower and more extensive accumulation during multiple dosage. The single-dose pharmacokinetic profile of clobazam is highly predictive of drug behaviour during repeated dosage, suggesting that clobazam kinetics are dose- and concentration-independent within the range studied, and that self-induction or inhibition of clearance is not evident during 3 weeks of dosage.

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Clobazam is a 1,5-benzodiazepine derivative used as an antianxiety agent (Brogden et al., 1980; Hanks et al., 1979; Hindmarch et al., 1982). Its major metabolic pathway involves hepatic N-demethylation, yielding the pharmacologically active metabolite, desmethylclobazam. A previous single-dose study of clobazam in the elderly demonstrated significantly reduced total clearance and prolonged elimination half-life in elderly men as opposed to young men (Greenblatt et al., 1981a). In women, however, age did not significantly influence elimination half-life or clearance.

The clinical implications of these findings are not established, since distribution rather than clearance probably determines the duration of action of benzodiazepines following single doses. However, the rate and extent of drug accumulation during multiple-dose therapy at any given dose are determined mainly by elimination half-life and clearance. Thus, reduction in clobazam clearance

![Graph displaying plasma concentrations of clobazam and desmethylclobazam](image)

**Fig. 1.** Plasma concentrations of clobazam and its major metabolite, desmethylclobazam, during single- and multiple-dose pharmacokinetic studies in a representative young male subject. Left, plasma concentrations during the single-dose study. Right, plasma concentrations during the multiple-dose study. Solid (\(\bullet\)) and dashed lines (\(\triangle\)) lines, respectively, represent computer-determined functions of best fit consistent with Equation 1. The horizontal dotted lines represent values of \(C_{ss}(\text{min})\) for clobazam desmethylclobazam. The vertical dotted line with the arrow indicates the last dose, followed by drug washout.