Clinical Pharmacokinetics of Antidepressants in the Elderly
Therapeutic Implications

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Summary

The prevalence of depression in the elderly suggests that a substantial number of older patients will be treated with an antidepressant medication such as one of the tricyclics, trazodone, fluoxetine or lithium. The physiological changes that accompany aging raise the possibilities of altered pharmacokinetics, patterns of efficacy and adverse effect profiles. The literature addressing the subject of antidepressant use in the elderly has not provided a clear, consistent picture of how these drugs behave in this population in comparison with younger patients. Particularly in the case of the tricyclic antidepressants (TCAs), a large degree of interindividual variation in drug clearance (CL) confounds attempts to find differences attributable to age per se. Study design, however, is also a problem in that very few investigators include a young control group, choosing instead to compare their data with previously reported outcomes. Designations of statistical significance and positive correlation also differ among investigators, and the clinical significance of any finding is not always addressed.

The available data suggest that imipramine CL is reduced in the elderly and that amitriptyline
CL may be reduced. Desipramine CL does not appear to be affected by age, although decreased renal function in the elderly may lead to accumulation of the hydroxylated metabolite, the clinical importance of which is not known. Nortriptyline is the most thoroughly studied TCA in the elderly. CL seems decisively lower only in elderly patients with concurrent medical illness. The hydroxylated metabolite probably accumulates with diminishing renal function. Not enough data are available on doxepin to make a conclusion. Trazodone CL is diminished somewhat in elderly men. Lithium CL appears to diminish with the declining renal function associated with aging. Fluoxetine data are sparse. Available data do not show any decrease in CL of the parent drug; more information is needed on the metabolite norfluoxetine. Although knowledge of CL changes with aging can help the clinician more accurately achieve the desired steady-state concentration of a drug during long term therapy, much work is still needed to evaluate the relationships among drug concentrations at steady-state, efficacy and adverse effects in the elderly.

1. Depression in the Elderly

Depression is one of the most frequently encountered psychiatric syndromes in the elderly, with estimates that 10 to 20% of institutionalised elderly may have major depression and 10% of older persons in the community have depressive symptoms (Blazer 1989; Murphy et al. 1988; Regier et al. 1988; Small 1991; Uhlenhuth et al. 1983). Pharmacotherapy remains a fundamental component of treatment in this group, whose altered physiology resulting from normal aging and concomitant medical conditions may change the metabolic profile of psychotropic drugs (Greenblatt et al. 1982). Despite the obvious clinical relevance of data documenting the elderly's handling of antidepressant medications, there remain few strong studies on which the clinician can rely when tailoring antidepressant drug therapy to the older patient.

This article reviews principles of clinical pharmacology necessary for understanding pharmacokinetics of antidepressants in the elderly, and how the physiological differences between young and elderly persons have pharmacokinetic implications. The ages of participants in each study are given because of the differing definition of ‘elderly’ among investigators. We discuss some basic statistical points that were recurring areas of weakness in the analysis of data. All studies on antidepressant pharmacokinetics in the elderly located by using Medline search, review articles and bibliographies are reviewed in order to present those well supported conclusions having clinical implications (Gerson et al. 1988; Peabody et al. 1986; Plotkin et al. 1987; Potter et al. 1991; Rockwell et al. 1988; Sallee & Pollock 1990).

2. Methodological Issues
2.1 Pharmacokinetics in the Elderly

Clearance (CL) is a measure of drug elimination. It is an independent parameter that depends on intrinsic physiological function such as hepatic metabolism (biotransformation) or renal excretion (Greenblatt & Koch-Weser 1975). Volume of distribution (Vd) is a reflection of fixed physiological properties such as body size and extent of lean and nonlean body mass, and the drug's chemical properties, that determine solubility and protein binding. Elimination half-life (t1/2) for a given drug will be a function of both Vd and CL. If t1/2 is increased, it may be either that Vd is increased, with CL remaining constant, or that CL has decreased, or both. Sex can influence both Vd and CL, and age-related changes, or lack of changes, in one sex cannot be assumed to hold for the other.

Many studies involving drug administration in the elderly focus on the extent of accumulation during multiple oral dose therapy. The mean steady-state serum or plasma concentration (C^>50) depends directly on dosage rate and inversely on CL. That is, at any given dosage rate, C^>50 will increase if CL decreases. An increased t1/2 in a study group relative to a control group does not auto-