Cholinesterase Inhibitors: Applying Pharmacokinetics to Clinical Decision Making

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ABSTRACT

Background: Cholinesterase inhibitors are indicated for the treatment of Alzheimer-type dementia. There are few direct comparative studies of adverse effects or studies to suggest clinical superiority of one inhibitor over the others.

Objective: The objective of this study was to relate pharmacokinetic differences among the agents to potential clinical considerations.

Methods: Population pharmacokinetics were obtained from US Food and Drug Administration–approved label information and published literature. Plasma concentration–time profiles were derived from these parameters using noncompartmental pharmacokinetic modeling.

Results: Plasma concentration profiles differed significantly among different agents and between different formulations of the same agent.

Conclusions: The initial choice among the various cholinesterase inhibitors requires consideration to adherence and cost. Consideration to differences in pharmacokinetics among these drugs provides a better understanding for the clinical practice of dose titration, identification and management of drug-related side effects, and lapses in therapy. Pharmacokinetic considerations among the various agents and formulations provide the clinician with options to enhance therapy when these agents are chosen for treatment of patients with Alzheimer-type dementia. (*Am J Geriatr Pharmacother*. 2011;9:259–263)

Key words: adverse reaction, donepezil, galantamine, pharmacokinetics, rivastigmine.

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Table. Selected pharmacokinetic characteristics of cholinesterase inhibitors.

Pharmacokinetic Parameter	Galantamine 12 mg IR BID	Galantamine 24 mg ER Once Daily	Rivastigmine 6 mg BID	Rivastigmine 9.5 mg Patch Daily	Donepezil 10 mg IR BID	Donepezil 23 mg SR Once Daily
Bioavailability, %	90	90	70	70–100 (site dependent)	100	92
T_{max}, h	0.5–2.0	4–6	0.8–1.7	8.1	3–5	8
V_d, L/kg	2.5	2.5	1.8–2.7	1.8–2.7	12	12
CL/F, L/kg/h	0.26	0.26	1.54	2.50	0.13	0.13
$t_{1/2}$, h	5–7	5–7	0.6–2	N/A	50–70	50–70
$C_{max,ss}$, μg/L	84.7	65.0	18.8	7.9	95.9	103.2
$C_{min,ss}$, μg/L	29.0	21.0	Approaches zero	3.5	86.9	86.6
Peak-to-trough ratio	2.9	3.1	Very large	2.3	1.1	1.2
Fluctuation index (C_{max}–C_{min}/C_{avg})	1.2	1.0	>2.2	0.8	0.1	0.2

CL = clearance; ER = extended release; IR = immediate release; SR = sustained release.

INTRODUCTION

Cholinesterase inhibitors are indicated for the treatment of Alzheimer-type dementia. There are few direct comparative studies of adverse effects or studies to suggest clinical superiority of one inhibitor over the others.[1–5] Nevertheless, we propose that pharmacokinetic differences among the agents are accompanied by clinical considerations worthy of review.

In this paper, relevant pharmacokinetic parameters are derived and differences among these drugs are applied to considerations of adherence, suspected adverse drug events,[6] both during initiation and maintenance therapy, as well as temporary lapses in drug therapy.

METHODS

Population pharmacokinetics were obtained from US Food and Drug Administration approved label information[7–11] and published literature.[12–18] Plasma concentration–time profiles were derived from these parameters using noncompartmental pharmacokinetic modeling.

RESULTS

Pharmacokinetic parameters of interest among the currently available drugs are listed in the **Table**. Plasma concentration time profiles for the 3 currently available cholinesterase inhibitor agents are illustrated in the **Figure**.

DISCUSSION

Clearance, Half-Life, and Adherence

Drugs with relatively faster clearances have shorter half-lives. In order to achieve plasma levels which do not vary as much over time between doses, short half-life oral drugs require more frequent dosing compared with drugs with longer half-lives. Therefore, fluctuations in once-daily donepezil plasma concentrations (ie, peak-to-trough plasma concentration ratios) remain smaller than fluctuations with twice-daily conventional rivastigmine and galantamine because of the much longer half-life of donepezil (**Table** and **Figure**).

Adherence with relatively short half-life drugs requiring twice-daily oral dosing (eg, galantamine or rivastigmine immediate-release tablets) will be more challenging, especially for patients with dementia and/or their caregivers, compared with longer half-life drugs and

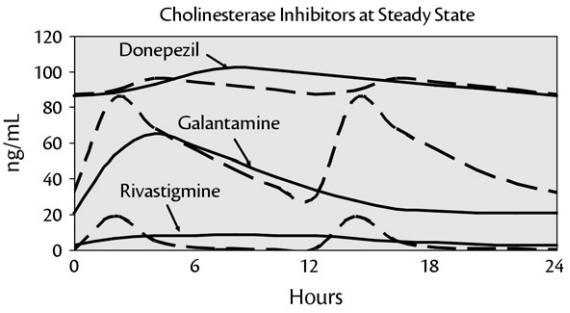

Figure. Pharmacokinetic-derived steady state plasma concentration–time curves for donepezil 23 mg SR once daily versus 10 mg immediate release BID; galantamine 24 mg extended release once daily versus 12 mg BID; and rivastigmine patch 9.5 mg daily versus 6 mg PO BID (solid vs broken line curves, respectively).