Effect of Herbal Medicines on the Pharmacokinetics of Donepezil

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BACKGROUND

- Donepezil is an acetylcholinesterase inhibitor (AChE-I) that is commonly used for the treatment of symptoms associated with Alzheimer's disease. It may be used concomitantly with herbal remedies (gamisoyo-san, banhasasim-tang, ojeok-san, bojungikki-tang) to manage associated symptoms.
- The frequent prescription of herbal remedies to the elderly for a variety of symptoms has given rise to a need for research to provide evidence for the co-administration of herbal medicines and donepezil. It is important to evaluate the impact of combining herbal remedies with donepezil on the pharmacokinetics (PK) and safety of donepezil.

OBJECTIVE

- The objective of this investigation was to ascertain the effects of Gamisoyo-san (A1), Banhasasim-tang (A2), Ojeok-san (A3), and Bojungikki-tang (A4) on the pharmacokinetics and safety of Donepezil (D).

METHODS

- **Study Design**
  A randomized, open-labe, multiple-dose, crossover study
- **Subjects**
  Healthy volunteers aged between 19 and 55 years
- **Primary Endpoint**
  $C_{max,ss}$, $AUC_{tau,ss}$ of donepezil
- **Secondary Endpoin**
  $AUC_{inf,ss}$, $AUC_{last,ss}$, $Tmax_{,ss}$, $t_{1/2}$, Vd_{ss}/F, CL_{ss}/F of donepezil
- **Steady-state PK parameters**
  Steady-state parameters for donepezil alone were obtained using a nonparametric nested method based on single-dose Period 1 data

- **Safety Assessment**
  Adverse events(AEs), physical examinations, vital signs, 12-lead ECGs, and clinical laboratory tests

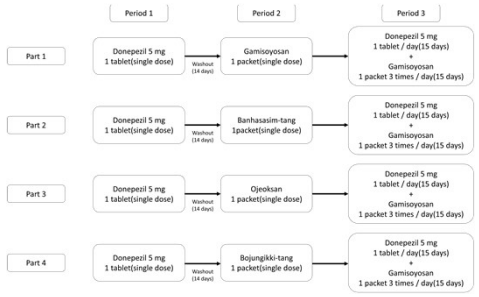

Figure 1. A schematic diagram of the study design

RESULTS

- **Study Subjects**

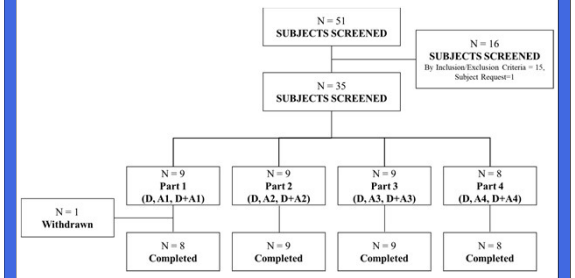

Figure 2. Disposition of study subjects

- **Pharmacokinetic Assessment**

Table 1. Summary of Donepezil PK parameter

Parameters	Arithmetic mean (SD)		GeoLSM		GMR (90% CI)
	D	D+A1	D	D+A1	D+A1/D
$C_{max,ss}$ (ng/mL)	2.35 (0.46)	3.65 (0.40)	2.31	3.63	1.57 (1.37-1.80)
$AUC_{tau,ss}$ (h·ng/mL)	42.22 (10.81)	61.77 (10.12)	41.16	61.06	1.48 (1.24-1.77)
	D	D+A2	D	D+A2	D+ A2/ D
$C_{max,ss}$ (ng/mL)	1.94 (0.59)	3.44 (0.90)	1.86	3.34	1.80 (1.43-2.27)
$AUC_{tau,ss}$ (h·ng/mL)	35.96 (13.80)	60.15 (14.92)	33.75	58.41	1.73 (1.32-2.26)
	D	D + A3	D	D+A3	D+A3/ D
$C_{max,ss}$ (ng/mL)	2.06 (0.57)	3.20 (0.47)	2.03	3.17	1.56 (1.31-1.85)
$AUC_{tau,ss}$ (h·ng/mL)	36.83 (11.19)	55.04 (10.42)	35.54	54.10	1.52 (1.25-1.85)
	D	D + A4	D	D+A4	D+A4/ D
$C_{max,ss}$ (ng/mL)	2.14 (0.80)	3.81 (0.61)	1.98	3.77	1.90 (1.42-2.54)
$AUC_{tau,ss}$ (h·ng/mL)	38.65 (15.78)	61.33 (11.70)	35.06	60.27	1.72 (1.22-2.42)

D, Donepezil; A1, Gamisoyosan; A2, Banhasamin-tang; A3, Ojeoksan; A4, Bojungikki-tang

Table 2. Summary of Adverse Events

	Number of Subjects (%) [Number of adverse events]									
	D (N=35)	A1 (N=8)	D+A1 (N=8)	A2 (N=9)	D+A2 (N=9)	A3 (N=9)	D+A3 (N=9)	A4 (N=8)	D+A4 (N=8)	Total (N=34)
Subjects with any AE	3 (33.3) [3]	0 (0.0) [0]	4 (50.0) [6]	2 (22.2) [2]	1 (11.1) [1]	1 (11.1) [1]	3 (33.3) [3]	2 (25.0) [3]	0 (0.0) [0]	15 (44.1) [19]
Severity (all AEs)										
Mild	2 (22.2) [2]	-	4 (50.0) [6]	2 (22.2) [2]	-	1 (11.1) [1]	1 (11.1) [1]	2 (25.0) [3]	-	11 (32.4) [15]
Moderate	1 (11.1) [1]	-	-	-	1 (11.1) [1]	-	2 (22.2) [2]	-	-	4 (11.8) [4]
Severe	-	-	-	-	-	-	-	-	-	-
Relationship to study drug										
Related										
Definitely related	-	-	4 (50.0)	-	-	-	-	-	-	4 (11.8) [5]
Probably related	2 (22.2) [2]	-	1 (12.5) [1]	-	-	-	-	-	-	2 (5.9) [3]
Possibly related	-	-	-	-		-	-	-	-	-
Unlikely related	1 (11.1) [1]	-	4 (50.0) [5]	2 (22.2) [2]	-	1 (11.1) [1]	1 (11.1) [1]	2 (25.0) [3]	-	8 (23.6) [9]
Unassessable/ Unclassifiable	-	-	-	-	-	-	-	-	-	-
Not related										
Not related	-	-	-	-	1 (11.1) [1]	-	1 (11.1) [1]	-	-	2 (5.9) [3]

D, Donepezil; A1, Gamisoyosan; A2, Banhasamin-tang; A3, Ojeoksan; A4, Bojungikki-tang

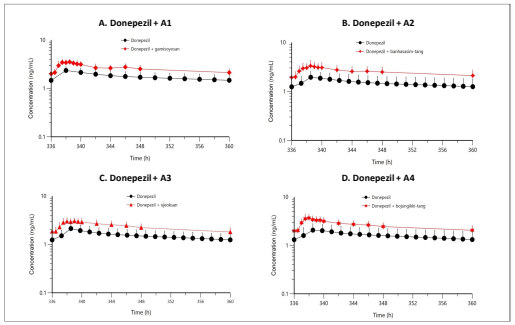

Figure 3. Mean Plasma Concentration of donepezil by administration groups

CONCLUSIONS

- The co-administration of donepezil with A1, A2, A3, and A4 resulted in a 1.56– to 1.90–fold increase in the $C_{max,ss}$ of donepezil and a 1.48- to 1.73-fold increase in $AUC_{tau,ss}$ of donepezil, respectively. In terms of safety, no serious adverse events were reported, and all adverse events were resolved without sequelae. Furthermore, the co-administration of donepezil and herbal medicines appeared to have a relatively good safety profile.

CITATIONS

[1] Kumar, A., Gupta, V., & Sharma, S. (2023, August 17). *Donepezil*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK513257/