Lack of Significant Drug Interactions for Sumanirole in Phase II Studies Using Population Pharmacokinetic Methods

Joel S. Owen, PhD[1], Kathryn Liolios, MA[1], Gwyn A. D'Souza, PhD[2], Barbara J. Carel, MS[3]
[1]Cognigen Corporation, Buffalo, NY, USA; [2]Pharmacia Corporation, High Wycombe, UK;
[3]Pharmacia Corporation, Kalamazoo, MI, USA

PHARMACIA

ABSTRACT

PURPOSE: Sumanirole is a highly D_2-selective dopamine receptor agonist that is in development for the treatment of Parkinson's disease (PD). Metabolism of sumanirole and in vitro data indicate that clinically significant pharmacokinetic (PK) drug-drug interactions are unlikely. This was further investigated using population pharmacokinetic (PPK) methodology.

METHODS: Data were obtained from 2 double-blind, placebo-controlled trials of sumanirole alone in early PD and sumanirole with levodopa in advanced PD. Patients received twice-daily extended-release oral sumanirole doses ranging from 2 to 48 mg/d. A one-compartment PPK model, with creatinine clearance (CrCL) and gender as covariates of clearance (CL/F), was used in NONMEM® to characterize the influence of concomitantly administered drugs on sumanirole PK. Use of a specialized case report form (CRF) page streamlined construction of the drug-interaction analysis dataset. Various single agents and classes of compounds were evaluated as a linear shift to the CL/F model. Univariate forward selection (α=0.05) was followed by backward elimination (α=0.001).

RESULTS: PPK data included 378 patients and 20 healthy subjects. Levodopa coadministration occurred in 111 subjects (200 sumanirole concentrations) and was absent for 287 subjects (2394 concentrations in early PD patients). Levodopa did not significantly (*P*=0.281) influence sumanirole PPK (<5% increase in mean CL/F). Selegiline was coadministered in 85 subjects and had an effect, but this did not reach statistical significance (*P*<0.001). The magnitude of the effect was small accounting for only a 10% decrease in CL/F for a patient with average CrCL. Other compounds and classes investigated, such as amantadine, aspirin, β-blockers, hypotensive agents, organic anion and cation transport substrates and inhibitors, renal anions, renal cations, and trihexyphenidyl, did not significantly alter sumanirole PK.

CONCLUSION: Sumanirole is not susceptible to drug interactions based on these PPK data. No single agent, including levodopa, or class of compounds studied, significantly altered sumanirole PK.

INTRODUCTION

- For many years, the mainstay of treatment for Parkinson's disease (PD) has consisted of dopamine replacement therapy; however, the occurrence of late side effects in patients on long-term levodopa prompted a search for novel antiparkinsonian drugs.
- Sumanirole (PNU-95666E), a selective D_2-receptor agonist within the D_2-receptor family, is currently in development. Because of its selectivity for the D_2 subtype, sumanirole is predicted to have fewer side effects than other dopaminergic agents used in the treatment of PD.
- Because sumanirole undergoes both renal excretion of unchanged drug and metabolism via multiple pathways, drug-drug interactions are unlikely. In vitro data support the hypothesis that clinically important pharmacokinetic (PK) drug-drug interactions are not anticipated.
- This Poster further describes the disposition of sumanirole based on population pharmacokinetic (PPK) analyses and subsequent assessment of the potential for drug-drug interactions.

OBJECTIVES

- To describe the PPK of sumanirole after oral administration in subjects with early and advanced PD.
- To use PPK methods to investigate the potential drug-drug interactions with selected medications likely to be administered concurrently in this patient population.

METHODS

Population Pharmacokinetic Model and Drug Interaction Assessment

Data

- Data were pooled from 2 Phase II trials. Data from 1 Phase I trial were also included for model development.
- Sampling design: Study 009—5 to 6 blood samples obtained after dose at Visit 8, 1 sample at Visit 9, and 1 (217 subjects) or 9 (50 subjects) samples at Visit 11; Study 010—single blood samples at Visits 9 and 11; Study 020—full profile (13 samples) after 5 days

Pharmacostatistical Model

- NONMEM®, version 5.1.1
- PK model: one-compartment model with first-order absorption and elimination
- Interindividual error determined by the exponential error model
- Residual variability determined with the proportional error model
- Creatinine clearance (CrCL) and gender were included as significant covariates of clearance (CL/F)
- CrCL estimated using the modified Cockcroft and Gault method1

Drug-Interaction Assessment

- A specialized case report form (CRF) page was used to efficiently construct the drug-interaction analysis dataset (Figure 3).
- Single agents and classes of concomitant medications evaluated as a linear shift to the CL/F model
- Univariate forward selection analyses performed, followed by stepwise backward elimination

Statistical Analyses

- Statistical significance: univariate forward-selection analyses: *P*=0.05; backward elimination: *P*=0.001
- Goodness-of-fit of each NONMEM® analysis assessed by examination of:
  - Scatterplots of predicted vs measured concentrations and vs weighted residuals
  - %SEMs of the parameter estimates
  - Changes in the estimates of the interindividual and residual variability

RESULTS

Population Pharmacokinetic Model and Drug Interactions

- Data were collected from 398 subjects: 111 subjects were coadministered levodopa (200 sumanirole concentration samples); 287 subjects received sumanirole monotherapy (2394 concentration samples) (Table 1, Figure 1).
- A one-compartment model with first-order absorption was used to describe the data (Table 2; Figure 2).
- Volume of distribution (V/F) was fixed to a constant 300 L because of correlation with the absorption-rate constant.
- Levodopa did not significantly influence sumanirole PPK (<5% increase in mean CL/F, P=0.281) (Table 3).
- Selegiline in 85 subjects resulted in the lowest *P* value for an effect on sumanirole CL/F (*P*=0.011), but the magnitude of effect was small (approximately 10% decrease in CL/F for a patient with average CrCL) and did not reach statistical significance.

Figure 1. Sumanirole concentrations versus time since last dose for all dose groups.

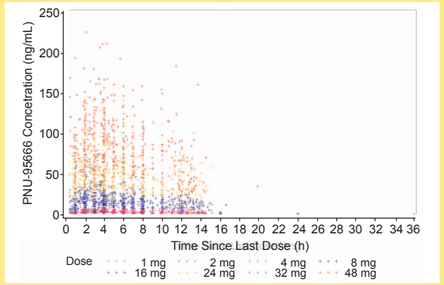


Table 1. Studies Included in the Population Analyses

Protocol	Study Design	Treatment Regimen
M/2760/0009	Double-blind, placebo-controlled, dose-response study of sumanirole tolerability, safety, and efficacy in patients with early PD	Dose escalating up to groups: 0 mg (placebo), 2, 8, 24 or 48 mg/d
M/2760/0010	Safety, tolerance, and efficacy evaluation of sumanirole as an adjuvant to levodopa in advanced PD	Dose escalating to any of 1, 2, 4, 8, 16, 24, 32, or 48 mg/d
666E-CNS-0075-020	A single-blind, placebo-controlled, randomized parallel group and crossover study to investigate pharmacokinetics and adverse event profile of sumanirole given in an extended release formulation to Caucasian healthy volunteers	Multiple-dose (twice daily) administration of placebo, 1-mg, or 2-mg doses

Figure 2. Individual predicted sumanirole concentrations vs measured sumanirole concentrations.

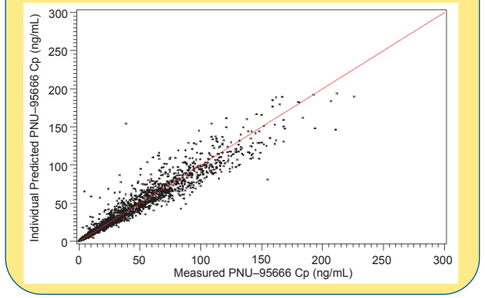
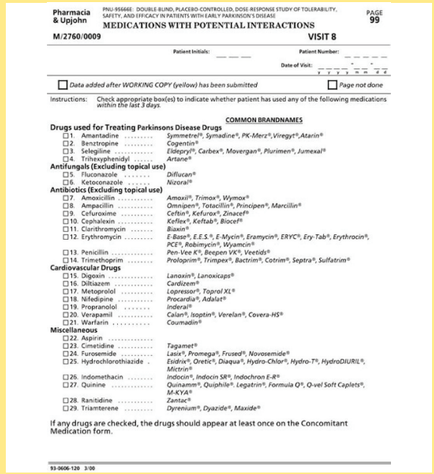


Figure 3. CRF for drug-interaction assessment


Pharmacia & Upjohn

PNU-95666E: DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY OF TOLERABILITY, SAFETY, AND EFFICACY IN PATIENTS WITH EARLY PARKINSON'S DISEASE

PAGE 99

M/2760/0009

MEDICATIONS WITH POTENTIAL INTERACTIONS

VISIT 8

Patient Initials: ___ ___ Patient Number: ___ ___ ___ ___

Date of Visit: ___ ___ / ___ ___ / ___ ___

☐ Data added after WORKING COPY (yellow) has been submitted ☐ Page not done

Instructions: Check appropriate box(es) to indicate whether patient has used any of the following medications within the last 3 days.

COMMON BRANDNAMES

Drugs used for Treating Parkinsons Disease Drugs
☐1. Amantadine ..... Symmetrel®, Symadine®, PK-Merz®, Virergy®, Atarin®
☐2. Benztropine ..... Cogentin®
☐3. Selegiline ..... Eldepryl®, Carbex®, Movergan®, Plurimen®, Jumexal®
☐4. Trihexyphenidyl ..... Artane®
Antifungals (Excluding topical use)
☐5. Fluconazole ..... Diflucan®
☐6. Ketoconazole ..... Nizoral®
Antibiotics (Excluding topical use)
☐7. Amoxicillin ..... Amoxil®, Trimox®, Wymox®
☐8. Ampacillin ..... Omnipen®, Totacillin®, Principen®, Marcillin®
☐9. Cefuroxime ..... Ceftin®, Kefurox®, Zinacef®
☐10. Cephalexin ..... Keflex®, Keftab®, Biocef®
☐11. Clarithromycin ..... Biaxin®
☐12. Erythromycin ..... E-Base®, E.E.S.®, E-Mycin®, Eramycin®, ERYC®, Ery-Tab®, Erythrocin®, PCE®, Robimycin®, Wyamicin®
Pen-Vee K®, Beepen VK®, Veetids®
☐13. Penicillin ..... Proloprim®, Trimpex®, Bactrim®, Cotrim®, Septra®, Sulfatrim®
☐14. Trimethoprim .....
Cardiovascular Drugs
☐15. Digoxin ..... Lanoxin®, Lanoxicaps®
☐16. Diltiazem ..... Cardizem®
☐17. Metoprolol ..... Lopressor®, Toprol XL®
☐18. Nifedipine ..... Procardia®, Adalat®
☐19. Propranolol ..... Inderal®
☐20. Verapamil ..... Calan®, Isoptin®, Verelan®, Covera-HS®
☐21. Warfarin ..... Coumadin®
Miscellaneous
☐22. Aspirin .....
☐23. Cimetidine ..... Tagamet®
☐24. Furosemide ..... Lasix®, Promega®, Frused®, Novosemide®
☐25. Hydrochlorothiazide ..... Esidrix®, Oretic®, Diaqua®, Hydro-Chlor®, Hydro-T®, HydroDIURIL®, Microtin®
☐26. Indomethacin ..... Indocin®, Indocin SR®, Indochron E-R®
☐27. Quinine ..... Quinamm®, Quiphile®, Legatrin®, Formula Q®, Q-vel Soft Caplets®, M-KYA®
☐28. Ranitidine ..... Zantac®
☐29. Triamterene ..... Dyrenium®, Dyazide®, Maxide®

If any drugs are checked, the drugs should appear at least once on the Concomitant Medication form.

93-0606-120 3/98

Table 2. Predicted Parameter Estimates from the Final Pharmacokinetic Model

Parameter	Population Mean Estimate	%SEM*
CL/F coefficient (L/h)†	20.1	2.8%
Power for CrCL effect on CL/F†	0.622	10.0%
CL/F shift for males‡ (1/h)	2.96	27.6%
V/F (L)	300	Fixed
ka (1/h)	0.379	4.6%
IIV‡ CL/F (%CV)	32.6%	12.3%
IIV‡ ka (%CV)	39.1%	30.8%
Residual variability (%CV)	21.1%	7.7%

* % SEM = Standard error of the estimate divided by the population mean estimate times 100%, a measure of the relative precision of estimates

† $CL/F = \left[\theta_1 \bullet \left(\frac{CrCL}{75.8}\right)^{\theta_2} + \theta_3 \bullet SEXM\right] * e^{\eta_1} = \left[20.1 \bullet \left(\frac{CrCL}{75.8}\right)^{0.622} + 2.96 \bullet SEXM\right] * e^{\eta_1}$

‡ IIV = Interindividual variability

Table 3. Summary of Drug Interaction Evaluation

Drug	Change in Mean CL/F	% of the SEM	Univariate *P* Value	Number of Subjects on Concomitant Drug	Number of Observations With Concomitant Drug
Amantadine	0.434	440.1	0.629	71	407
Aspirin	0.601	196.3	0.349	77	496
β-Blockers*	2.22	154.1	0.066	22	144
Hypotensive agents†	0.0943	1124.1	0.882	128	815
Levodopa‡	0.907	100.0	0.281	111	200
Organic anion transport inhibitors§	0.450	251.1	0.462	86	549
Organic anion transport substrates‖	0.797	204.5	0.336	83	465
Organic cation transport inhibitors¶	-0.172	1866.3	0.938	7	47
Organic cation transport substrates#	1.77	123.7	0.067	35	237
Renal anions**	1.06	106.6	0.059	150	906
Renal cations††	1.51	127.2	0.093	42	284
Selegiline	-2.09	32.7	0.011	85	540
Trihexyphenidyl	-0.446	287	0.725	36	187

* β–blockers included: propranolol and metoprolol.
† Hypotensive agents included: diltiazem, furosemide, hydrochlorothiazide, metoprolol, nifedipine, propranolol, selegiline, triamterene, trimethoprim, and verapamil.
‡ Interaction for levodopa assumes all Study 010 subjects/concentrations had concomitant levodopa and no Study 009 or 020 subject concentrations had concomitant levodopa.
§ Organic anion transport (OAT) inhibitors included: aspirin, furosemide, indomethacin, and verapamil.
‖ Organic anion transport substrates included: amantadine, ampicillin, cephalexin, cimetidine, and hydrochlorothiazide.
¶ Organic cation transport (OCT) inhibitors included: cimetidine and verapamil.
# Organic cation transport substrates included: metoprolol, propranolol triamterene, trimethoprim, and ranitidine.
** Renal anions included the combined list of OAT substrates and OAT inhibitors.
†† Renal cations included the combined list of OCT substrates and OCT inhibitors.

CONCLUSIONS

- The population pharmacokinetics of sumanirole were best described using a one-compartment model with first-order absorption and elimination.
- This population analysis indicates that sumanirole is not susceptible to PK drug-drug interactions and confirms previous observations.
- No single agent, including levodopa, nor pharmacologic class of medications explored, significantly (P<0.001) altered sumanirole PK.

REFERENCE

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Presented at the November 2002 annual meeting of the American Association of Pharmaceutical Scientists.