Poster number: Th-190

An open-label, parallel-group, repeat-dose study to investigate the effects of end-stage renal disease and haemodialysis on the pharmacokinetics of ropinirole

Debra J. Tompson,[1] Deborah Hewens,[1] Nancy Earl,[2] David Oliveira,[3] Jorg Taubel,[4] Suzanne Swan,[5] Luigi Giorgi[6]

[1]GlaxoSmithKline, Harlow, UK; [2]GlaxoSmithKline, Research Triangle Park, NC, USA*; [3]St George's University of London, London, UK; [4]Richmond Pharmacology Limited, St George's University of London, London, UK [5]Davita Clinical Research, Minneapolis, MN, USA; [6]GlaxoSmithKline, Greenford, UK

Introduction

Ropinirole is a dopamine (D-2) agonist approved for the treatment of Parkinson's disease (PD) and restless legs syndrome (RLS). Ropinirole is cleared predominantly by CYP1A2 metabolism in the liver to form two metabolites, SK&F-104557 and SK&F-89124, both of which are renally excreted. In subjects with normal renal function, systemic exposure to SK&F-104557 is slightly higher than ropinirole (ca 1.2-fold) whereas systemic exposure to SK&F-89124 is only 4% of that of ropinirole. SK&F-104557 is about 100-fold less potent than ropinirole, and SK&F-89124 possesses D-2 agonist activity similar to ropinirole. Hence neither metabolite contributes significantly to the pharmacological activity of the drug. This study (RRL 103628) investigates the effects of end-stage renal disease (ESRD) and haemodialysis on the pharmacokinetics (PK) of ropinirole and its metabolites.

Methods

Study design

- This was an open-label, parallel-group, repeat-dose study.
  - Subjects received a 14-hour controlled-release tablet formulation of ropinirole developed for restless legs syndrome (CR-RLS – no longer marketed) once-daily using an up-titration schedule starting at 0.5 mg in Week 1 and increasing weekly to a target dose of 2 mg/day (the minimum dose in healthy volunteers that allows the pharmacokinetic variables of SK&F-89124 to be determined) by Week 3.
- Dosing continued to the end of Week 4.
- For subjects with ESRD, if PK data collected during Week 1 predicted that a 2 mg/day dose would result in systemic exposure to ropinirole or its metabolites exceeding exposures in normal clinical practice, the dose could be capped at 0.5 or 1.0 mg/day.

Subjects

- Subjects were 11 individuals with ESRD on a stable haemodialysis regimen and 10 healthy, demographically matched controls with normal renal function.
  - Subjects were matched for age, body weight, gender, smoking status and females taking hormone replacement therapy.

Blood sampling

- At the end of Week 1, blood samples for PK analysis were collected over 24 hours on either Day 6 or Day 7 depending which was the "off-dialysis" day in subjects with ESRD.
- In Week 4, blood samples were collected from subjects with ESRD on one "off-dialysis" day and one "on-dialysis" day, with ropinirole being given 3 hours before dialysis.
- Samples were also drawn from the dialyser at the beginning, middle and end of the dialysis session.
- In healthy subjects, blood samples for PK analysis were drawn on the last day of ropinirole dosing in Week 4 only.
- On each PK assessment day, samples were collected before ropinirole dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post-dose.

PK analyses

- A non-compartmental analysis was used to compare the PK of ropinirole and its metabolites in subjects with ESRD *versus* healthy controls based on geometric mean ratios for steady–state 24 hours area under the curve ($AUC_{(0-24)}$) and maximum concentration (C_{max}) values normalized to a 1 mg dose.
- The concentration–time data for ropinirole and its metabolites were modelled using population pharmacokinetics.
  - Oral clearance (CL/F) was estimated for healthy controls and subjects with ESRD and the effect of haemodialysis on CL/F was estimated.
- The models were used to simulate the systemic exposure to ropinirole and its metabolites in subjects with ESRD (following various dosing regimens of ropinirole immediate release [IR]) compared with subjects with normal renal function for patients with RLS and for those with PD (at the maximum approved doses of ropinirole IR: 4 mg once daily in RLS and 8 mg three times daily [t.d.s] in PD).

Results

Ropinirole dosing

- All subjects with ESRD received ropinirole 0.5 mg daily in Week 1 and 1 mg daily in Week 2.
- The first four subjects with ESRD were maintained at 1 mg/day for Weeks 3 and 4 because PK data from the 0.5 mg dosing (Week 1) suggested slow clearance of SK&F-104557. Subsequent analysis of the 1 mg/day dose data predicted that a 2 mg dose would not exceed the systemic exposure levels observed in normal clinical practice; therefore, the remaining six subjects with ESRD received 2 mg/day in Weeks 3 and 4.
- All healthy controls received 0.5 mg/day ropinirole in Week 1, 1 mg/day in Week 2, and 2 mg/day in Week 3.

Safety

- One subject with ESRD was withdrawn due to a non-serious adverse event (fall on standing up). All remaining subjects completed all study procedures.
- The proportion and severity of adverse events seen amongst subjects with ESRD was similar to that in the healthy control group.

Non-comp artmental analysis

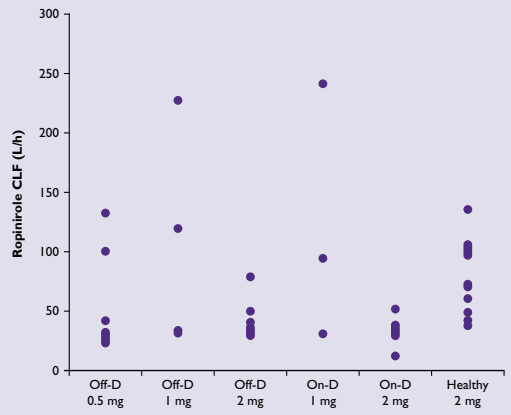
- Systemic exposures to ropinirole and both metabolites were higher in subjects with ESRD compared with healthy controls (**Table 1**).
- In subjects with ESRD, exposure to both metabolites was similar on "off-dialysis" days to "on-dialysis" days. For ropinirole, in the majority of subjects (8/10), dose normalized $AUC_{(0-24)}$ and C_{max} were similar on the "off-dialysis" and "on-dialysis" days. However, in two subjects the systemic exposure was substantially higher during the "on-dialysis" day. This higher exposure was attributed to a longer duration of time between the "off-dialysis" day and "on-dialysis" day in these two subjects, resulting in a more extensive accumulation of ropinirole compared with those subjects with more regular dialysis.
- Concentrations of ropinirole and SK&F-104557 leaving the dialysis machine were 30–40% lower than those entering, and for SK&F-89124 concentrations were 20–40% lower.
- CL/F of ropinirole and its metabolites was reduced in subjects with ESRD compared with healthy subjects. CL/F values did not appear to be affected by dose or dialysis (**Figures 1–3**).

Table 1. Comparison of dose-normalized $AUC_{(0-24)}$ and C_{max} values in subjects with ESRD and healthy controls and between "on-dialysis" and "off-dialysis".

	"Off-dialysis": healthy	"On-dialysis": "Off-dialysis"
Ropinirole CR-RLS		
$AUC_{(0-24)}$	1.27 (0.82, 1.98)	1.25 (1.03, 1.53)
C_{max}	1.15 (0.86, 1.54)	1.26 (1.08, 1.47)
SK&F-104557		
$AUC_{(0-24)}$	4.47 (3.74, 5.35)	0.97 (0.85, 1.10)
C_{max}	3.28 (2.78, 3.85)	1.02 (0.91, 1.14)
SK&F-89124		
$AUC_{(0-24)}$	2.14 (1.74, 2.61)	1.05 (0.93, 1.17)
C_{max}	1.61 (1.30, 1.99)	1.06 (0.95, 1.18)

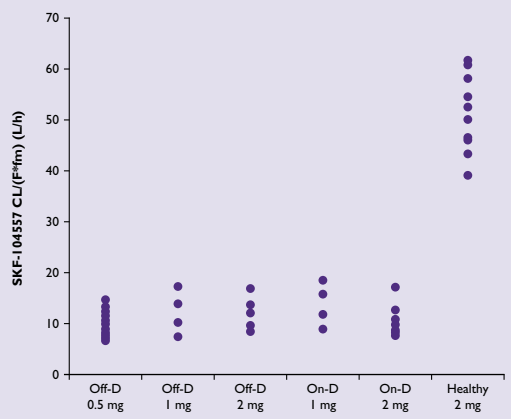
All values are geometric mean ratios and 90% confidence intervals. $AUC_{(0-24)}$ = steady-state 24 hours area under the curve, C_{max} = maximum concentration, CR-RLS = controlled-release formulation for restless legs syndrome, ESRD = end-stage renal disease.

Figure 1. Steady-state clearance of ropinirole (CL/F) in subjects with ESRD compared with healthy controls.



ESRD = end-stage renal disease, Off-D = "Off-dialysis" day, On-D = "On-dialysis" day.

Figure 2. Steady-state clearance SKF-104557 (CL/(F*fm)) in subjects with ESRD compared with healthy controls during daily dosing with ropinirole CR-RLS.

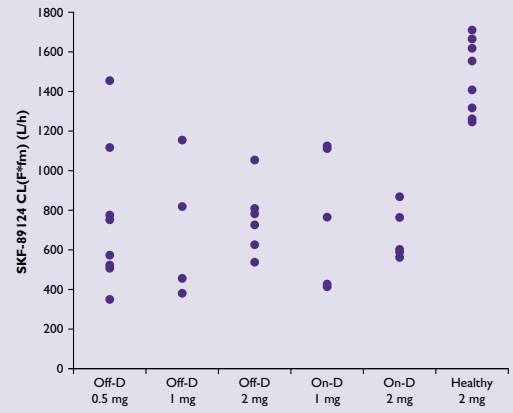


CR-RLS = controlled-release formulation for restless legs syndrome, ESRD = end-stage renal disease, Off-D = "Off-dialysis" day, On-D = "On-dialysis" day.

Population PK analyses

- CL/F of ropinirole and its metabolites was reduced in subjects with ESRD compared with healthy subjects (**Table 2**). CL/F was reduced by 30% for ropinirole, 80% for SK&F-104557 and 60% for SK&F-89124.
- The simulation results from this study are applicable to all formulations of ropinirole, as the ratios of metabolite to parent in subjects with normal renal function are comparable across the different tablet formulations (IR, CR-RLS and prolonged release [PR/XL]).

Figure 3. Steady-state clearance of SKF-89124 (CL/(F*fm)) in subjects with ESRD compared with healthy controls during daily dosing with ropinirole CR-RLS.



CR-RLS = controlled-release formulation for restless legs syndrome, ESRD = end-stage renal disease, Off-D = "Off-dialysis" day, On-D = "On-dialysis" day.

Table 2. Apparent clearance of ropinirole and its metabolites in healthy subjects and subjects with ESRD, and impact of dialysis on clearance.

	Healthy subjects	Clearance in healthy subjects (L/h)	Clearance in ESRD subjects (L/h)	Clearance ratio ESRD: healthy subjects
Ropinirole CR-RLS	67.2 (9.1)	47.7 (9.9)	+13.7 (7.6)	0.71
SK&F-104557	48.3 (2.37)	8.87 (0.635)	+32.2 (2.54)	0.18
SK&F-89124	1480 (50.8)	559 (71.8)	+988 (310)	0.38

Values are litres/hour (standard error). CR-RLS = controlled-release formulation for restless legs syndrome, ESRD = end-stage renal disease.

PK modelling: RLS

- The population PK model for ropinirole and its metabolites predicted that once-daily administration of 3 mg ropinirole IR in subjects with ESRD would provide similar ropinirole exposure to 4 mg once-daily ropinirole IR in subjects with normal renal function, with a similar PK profile, but higher exposure to both metabolites.

PK modelling: PD

- The population PK model was used to predict exposure to ropinirole and its metabolites at doses of ropinirole IR from 3 mg t.d.s. to 8 mg t.d.s. in subjects with ESRD compared with 8 mg t.d.s. in subjects with normal renal function.
- A dose of 6 mg t.d.s. in subjects with ESRD was predicted to provide a similar ropinirole exposure to 8 mg t.d.s. in subjects with normal renal function, with a similar PK profile, but a higher exposure to both ropinirole metabolites.

Conclusion

- CL/F was reduced, on average, by 30% for ropinirole, 80% for SK&F-104557 and 60% for SK&F-89124. Dialysis had minimal impact on the CL/F of ropinirole or its metabolites, therefore supplemental dosing of ropinirole is not required after dialysis.
- The PK simulations using the model derived from this study, enable the following dose recommendations to be made for subjects with ESRD.
  - The maximum dose of ropinirole should be reduced by 25% compared with those recommended for subjects with normal renal function. A 25% dose reduction represents a more straightforward dosage regimen in terms of available tablet strength, compared with a 30% dose reduction.
  - Therefore, the daily maximum dose in ESRD should be limited to 3 mg daily of ropinirole IR for subjects with RLS and 6 mg t.d.s. of ropinirole IR for subjects with PD.
  - It has been previously shown that on a dose-for-dose basis, $AUC_{(0-24)}$ and C_{min} values are similar for once-daily ropinirole PR/XL and ropinirole IR t.d.s., and that the PK profiles over 24 hours of the PRXL and IR formulations are similar.[1] Therefore a maximum daily dose of 18 mg is also recommended for PR/XL.
  - Adjustment of the ropinirole dose is not required during the up-titration.
  - As in subjects with normal renal function, individual dose-titration for efficacy and tolerability is recommended.

Reference

1. Tompson D, Vearer D. *Clin Ther* 2007;29:2654–66.

Acknowledgements

Study supported by GlaxoSmithKline Research and Development.

Disclosures and conflicts of interest

D Tompson, D Hewens and L Giorgi are employees of GlaxoSmithKline. *N Earl is a former employee of GlaxoSmithKline. D Oliveira, J Taubel and S Swan have no conflicts of interest.