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

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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 renal clearance and minimal systemic exposure to ropinirole and both metabolites were higher in subjects with end-stage renal disease (ESRD), both of which are markedly reduced in subjects with normal renal function, systemic exposure to SK&F-104557 is a slightly higher than ropinirole (as 1:2.6-fold) whereas systemic exposure to SK&F-89124 is only 1% 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 where systemic exposure to SK&F-89124 is only 4% of that of ropinirole. SK&F-104557 has been developed for restless legs syndrome (CR-RLS – no longer marketed) once-daily using population pharmacokinetics.

Methods

Study design

The open-label, parallel-group, repeat-dose study was conducted to characterize the pharmacokinetics of ropinirole and its metabolites in subjects with ESRD, compared with healthy controls. Subjects were matched for age, body weight, gender, smoking status and having undergone haemodialysis replacement therapy.

Blood sampling

At the end of Week 1, blood samples for PK analysis were collected over 24 hours on either Day 1 or Day 7 depending on which was the “off-dialysis” day in subjects with ESRD.

Table 1

Comparison of dose-normalized AUC(0–24) and Cmax values in subjects with ESRD and healthy controls. CL/F was reduced by 30% for the maximum dose of ropinirole 4 mg once daily in ESRD compared with healthy controls.

Table 2

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

Results

Ropinirole dosing

All subjects with ESRD received ropinirole 0.5 mg daily in Week 1 and 1 mg daily in Week 2.

Conclusions

– 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 35% dose reduction.

– The maximum dose of ropinirole should be limited to 3 mg daily of ropinirole IR for subjects with PD and 6 mg t.d.s. of ropinirole IR for subjects with PD.

– It has been previously shown that a dose-for-dose basis, Cmax and C0 values are similar for once-daily ropinirole CR-RLS and ropinirole IR t.d.s., and that the PK profiles over 24 hours of the PR XL and IR formulations are similar. 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.

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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.

Reference