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Interactions between domperidone and ropinirole, a novel dopamine D_2-receptor agonist

C. de MEY, D. ENTERLING, I. MEINEKE & S. YEULET[1]
SK&F-Institute for Applied Clinical Pharmacology, Göttingen, Germany and [1]Department of Drug Metabolism, SK&F, Upper Merion, USA

1 Ropinirole, SK&F 101468 has been characterized preclinically as a specific dopamine D_2-receptor agonist. Nine male healthy subjects were investigated for the effects on supine and erect heart rate and blood pressure, catecholamines and prolactin, of a single dose of 800 μg ropinirole preceded by a single dose of 20 mg domperidone or domperidone-placebo, and those of a single dose of domperidone followed by ropinirole-placebo.

2 Single doses of 800 μg ropinirole did not cause clinically significant changes in supine resting heart rate and blood pressure. However, they caused postural faintness on 3 min immobile upright standing on 10/26 occasions.

3 Pretreatment with 20 mg domperidone 1 h before administration of ropinirole prevented the postural symptoms in all but one subject. It did not alter ropinirole's plasma pharmacokinetics.

4 Ropinirole did not alter supine or standing catecholamine concentrations.

5 Domperidone increased the plasma concentrations of prolactin whereas ropinirole administered alone reduced them. A single dose of 800 μg ropinirole did not attenuate the prolactin increase induced by a single dose of 20 mg domperidone administered 1 h earlier.

Keywords SK&F 101468 ropinirole domperidone dopamine prolactin

Introduction

Ropinirole, SK&F 101468, (4-[2-dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one, monochloride), is a novel non-phenolic indolone derivative which acts as a dopamine D_2-receptor agonist (Gallagher *et al.*, 1985). Previous studies in healthy subjects showed that single doses of ropinirole could cause nausea, orthostatic hypotension and prolactin inhibition (Acton & Broom, 1989; de Mey *et al.*, 1990).

Domperidone is a well established dopamine D_2-receptor antagonist practically devoid of central effects (Heykants *et al.*, 1981; Kohli *et al.*, 1983; Laduron & Leysen, 1979; Niemegeers *et al.*, 1980).

The present study was conducted to evaluate the clinical, pharmacokinetic and neuro-endocrine interaction between single doses of domperidone and ropinirole, in order to assess 1) whether the observed adverse events on acute dosing of ropinirole in normal man relate to peripheral D_2-receptor agonism, and 2) whether pretreatment with domperidone could prevent such undesired effects that occurred with acute doses of 800 to 1000 μg ropinirole in healthy volunteers.

Methods

Subjects and ethics

Ten male subjects (22 to 33 years of age) who on the basis of extensive investigation were judged to be healthy, participated. One subject was withdrawn from the study and the profilings were completed for the intended nine subjects. The study was conducted in accordance with the Declaration of Helsinki (Venice Amendment, 1983) and the German Drug Law (AMG). The subjects were informed about the study in detail, inclusive of their right to withdraw from the study at any time and on their initiative, and their consent was recorded in writing and in the presence of a witness. The protocol was approved by an independent Ethics Committee.

Materials

Tablets of 200 μg ropinirole (1/0.2-AFC1, batch 10) and matched placebo (3/1-AFC1-P-1, batch 2), supplied by SK&F Laboratories, Welwyn, UK, were used. Commercially available domperidone tablets of 10 mg

Correspondence: Dr C. de Mey, Zentrum für Kardiovaskuläre Pharmakologie, Alwinenstrasse 16, D-6200 Wiesbaden, Germany

(Motilium®, Ch.B.1801131 and Ch.B.370121) were used plus domperidone 'look-alikes' (batch 6887278) produced by SKD, Göttingen, FRG.

Study design

The subjects were studied on three occasions at least 1 week apart. On one occasion domperidone placebo was administered followed 1 h later by an active dose of 800 μg ropinirole (treatment PS), on another, an active dose of 20 mg domperidone, with an active dose of 800 μg ropinirole 1 h later (treatment DS), and on a further occasion, an active dose of 20 mg domperidone, with ropinirole placebo 1 h later (treatment DP). The three treatments were profiled in a double-blind fashion. The treatment sequences were randomly allocated in a period-balanced within-subject cross-over study design.

Study procedures

On the day preceding each study day, the subjects abstained from alcohol-, xanthine-, or tyramine- containing foods or beverages. They were fasted from 22.00 h on the night prior to each profiling up to 8 h after dosing of ropinirole or placebo. The investigations started at about 07.30 h. The subjects were supine and resting for 1 h before the administration of domperidone or placebo (time $t = 0$ min). At 2 ($t = 180$ min), 4 ($t = 300$ min) and 6 h ($t = 420$ min) after dosing of ropinirole or its matched placebo ($t = 60$), the subjects stood upright and immobile for 3 min after a first minute sitting on the side of the bed with both feet hanging free. Except for these postural tests, the subjects remained recumbent and resting up to 8 h after dosing. Heart rate (HR) was monitored throughout, and blood pressure was measured every 10 min in the supine position, and every minute during sitting and standing.

Sampling and assays for ropinirole, prolactin and catecholamines

Venous blood was sampled for assay of plasma ropinirole, before dosing, and at 30, 60, 90, 120, 150, 180, 240, 300, 360, 480 and 600 min, and at 24 h after dosing. Plasma concentrations of ropinirole were assayed by a radioimmunoassay developed by SK&F. The antiserum used was raised in sheep to a diazo-derivative of ropinirole conjugated to bovine serum albumin and diluted 1:2500. The assay was shown to have a lower limit of quantification of 0.31 nmol l^{-1} (inter-assay CV < 11% accuracy ± 7%). Specificity for ropinirole was determined in the presence of a potential major metabolite in human plasma with which no significant cross-reaction was shown to occur at the concentrations studied.

Venous blood was sampled for assay of plasma prolactin, before dosing with domperidone, at 30 min after dosing with domperidone, at 60 min after dosing with domperidone (i.e. immediately prior to dosing with ropinirole) and at 60, 120, 180, 240, 300, 360, 480 and 600 min, and 24 h after administration of ropinirole. The plasma concentrations of prolactin were assayed by radioimmunoassay using a commerical kit (MAIA clone IRMA, Serono, UK). The concentrations were expressed in units of ng ml^{-1} NIH-F1.

Venous blood was sampled for assay of catecholamines immediately before dosing of domperidone ($t = 0$ min), immediately before dosing of ropinirole ($t = 60$ min), and then prior to ($t = 180$ and 420 min) and at the end of standing ($t = 184$ and 424 min) at 2 and 6 h after dosing of ropinirole. Blood for catecholamines was collected in heparinized chilled tubes which had been spiked with sodiummetabisulfite. Concentrations of noradrenaline and adrenaline in plasma were assayed by ion-exchange high performance liquid chromatography with electrochemical detection after a clean-up procedure which included liquid/liquid extraction and re-extraction in diluted acid (Meineke *et al.*, 1989). The limits of quantitation were 0.296 nmol l^{-1} and 0.027 nmol l^{-1} for noradrenaline (NE) and adrenaline (E), respectively.

Data format and analysis

The supine heart rate (HR) and blood pressure (SBP/DBP) data were summarized for each consecutive hourly time zone by the area under the time course of the variables.

Supine observations (circulatory variables, prolactin and catecholamines) subsequent to dosing were transformed as changed from the pre-dosing observations. Responses to standing were calculated as the postural change relative to the supine observations immediately prior to sitting and standing. These data were then assessed for subject, period and treatment related variance according to a general linear model. The residual variance was used to calculate the 95% confidence intervals around the estimated treatment differences for [PS-DP], [DS-DP] and [DS-PS] (Scheffés method for simultaneous evaluation of multiple comparisons, Scheffé, 1953).

Results

One of the 10 recruited subjects was withdrawn on his second study day, before dosing of ropinirole, because of sinoatrial dysfunction with pauses up to 2 s, occurring at 20–30 min after administration of 20 mg domperidone. This event was considered not to be drug related.

Supine heart rate and blood pressure

Little difference was observed between the treatments in terms of supine HR, SPB, DBP and MBP. There was a trend towards slightly higher mean supine HR-values beyond the first hour after administration of ropinirole, whether pre-treated with domperidone (treatment DS) or not (treatment PS). The effects relative to treatment DP (domperidone plus ropinirole placebo) were only about +1 to +4 beats min^{-1}, and even when reaching statistical significance for certain time zones, they were hardly likely to be clinically relevant. For instance, for the 4th hour after administration of ropinirole the mean treatment difference [DS-DP] was estimated to be +4.5 beats min^{-1}, 95% CI: 0.5 to 8.5 beats min^{-1}.

Table 1 Listing of symptomatic events on 3 min immobile upright standing for those subjects with relevant findings

Subject	*Standing at 2 h*	*4 h*	*6 h*
Treatment DP: 20 mg domperidone + ropinirole placebo			
8	non-symptomatic hypotension	uneventful	uneventful
Treatment PS: domperidone placebo + 800 μg ropinirole			
1	nausea, hypotensive	nausea, hypotensive	uneventful
2	nausea	*	minimal symptoms
3	nausea, hypotensive	nausea, hypotensive	uneventful
4	malaise	uneventful	nausea
5	uneventful	malaise, hypotensive	uneventful
6	nausea	uneventful	uneventful
Treatment DS: 20 mg domperidone + 800 μg ropinirole			
3	nausea, hypotensive	*	nausea, hypotensive

*: subject not permitted to stand because of previous symptoms.

Observations on immobile upright standing

The clinical events on standing at 2, 4 and 6 h after administration of ropinirole or placebo are summarized in Table 1. Thus, orthostatic symptoms occurred on 10/26 occasions in 6/9 subjects after treatment PS (ropinirole preceded by domperidone placebo). These postural symptoms occurred after approximately 1 min standing in 2/10 incidents, after 2 min in 3/10 and at the end of 3 min standing in the remaining 5/10 incidents. Only one subject suffered 2 such events after administration of treatment DS (ropinirole preceded by 20 mg domperidone). In most cases faintness and a general non-specific feeling of 'not being well' ('malaise') were observed, with pallor, dizziness and sweatiness. Often the incidents were associated with yawning. In 9/11 incidents nausea was the main feature. Frank (SBP < 95 mm Hg or a drop of SBP > 20 mm Hg relative to the previous reading, or DBP < 50 mm Hg), relative or clinical hypotension (loss of ulnar pulsations) was observed in 7/11 of all symptomatic incidents, in the remaining 4, postural blood pressure responses appeared normal. None of these incidents was associated or followed by absolute or relative bradycardia. The reactions were essentially postural in nature and rapidly reversed after resuming the supine position. There was no indication of altered orthostatic heart rate and blood pressure control in those who could sustain standing uneventfully (this is exemplified in Table 2 for mean heart rate and blood pressure at t = 180 min).

Supine and standing catecholamines

There was no indication that any of the treatments altered the supine catecholamine concentrations in a clinically relevant fashion. The treatment means and contrasts for noradrenaline are shown in Table 3. There were furthermore no treatment effects with regard to the catecholamine responses to standing, even in those subjects who could not sustain standing (for those subjects the sample was taken immediately at onset of the symptoms).

Plasma prolactin

The time course of the median plasma prolactin concentrations is detailed in Figure 1. Plasma prolactin was clearly stimulated by domperidone. The largest effect was seen at 2 h after administration of domperidone (treatment DP: a mean rise of 38 ng ml^{-1} NIH-F1). Plasma prolactin was reduced relative to baseline after administration of ropinirole. The largest effect was seen at 3 h after dosing of ropinirole (treatment PS: a mean drop of 3.6 ng ml^{-1} NIH-F1). Administration of ropinirole 1 h after administration of domperidone tended to blunt the response of prolactin to domperidone, but the differences were small and not likely to be clinically relevant (for instance, at 2 h after administration of domperidone the mean treatment difference [DS-DP] was estimated to be −5 ng ml^{-1}, 95% CI: −15 to 3).

Table 2 Mean (s.d.) heart rate (HR) and blood pressure (SBP/DBP) before and during 3 min immobile erect standing at 2 h after dosing of ropinirole (t = 180 min). Data are reported for symptom-free standing only

	Heart rate (HR) (beats min^{-1})			*Systolic blood pressure (SBP) (mm Hg)*			*Diastolic blood pressure (DBP) (mm Hg)*		
Time	*DP*	*PS*	*DS*	*DP*	*PS*	*DS*	*DP*	*PS*	*DS*
Baseline	63 (13)	62 (11)	63 (9)	120 (9)	120 (9)	122 (7)	64 (12)	67 (11)	68 (9)
1 min	87 (13)	93 (11)	94 (11)	120 (13)	115 (12)	125 (16)	82 (12)	83 (14)	80 (14)
2 min	92 (15)	95 (13)	96 (15)	122 (14)	117 (10)	129 (8)	79 (11)	83 (13)	87 (11)
3 min	94 (16)	91 (9)	95 (14)	115 (15)	118 (10)	127 (12)	82 (15)	80 (8)	85 (11)

Only values recorded on symptom-free standing are reported. PS = Placebo + ropinirole; DS = Domperidone + ropinirole
DP = Domperidone + placebo.

Table 3 Mean supine standing venous plasma noradrenaline concentrations and their contrast for treatments

*Data-format**	*Mean (DP)*	*Mean (PS)*	*Mean (DS)*	*[PS–DP] (95% CI)*	*[DS–DP] (95% CI)*	*[DS–PS] (95% CI)*
Supine (0)	813	824	820	11 (−159, +181)	7 (−163, +177)	−4 (−174, +166)
Supine (60)–Supine (0)	−16	+94	+42	+110 (−104, +324)	+59 (−156, +273)	−52 (−266, +163)
Supine (180)–Supine (60)	+79	−5	+51	−84 (−331, +163)	−29 (−276, +218)	+55 (−192, +302)
Stand (184)–Supine (180)	+1361	+1159	+1371	−202 (−1027, +623)	+10 (−815, +835)	+212 (−613, +1037)
Supine (420)–Supine (60)	+33	+24	−1	−9 (−262, +245)	−34 (−287, +220)	−25 (−279, +228)
Stand (424)–Supine (420)	+1411	+1309	+1269	−102 (−698, +493)	−142 (−738, +453)	−40 (−636, +555)

* For each time point the data are presented as the change from the corresponding baseline. All times are in minutes and refer to the actual time of sampling.
Time 0 min: dosing of domperidone or placebo, time 60 min: dosing of ropinirole or placebo.
DP: domperidone + placebo, PS: placebo + ropinirole, and DS: domperidone + ropinirole.

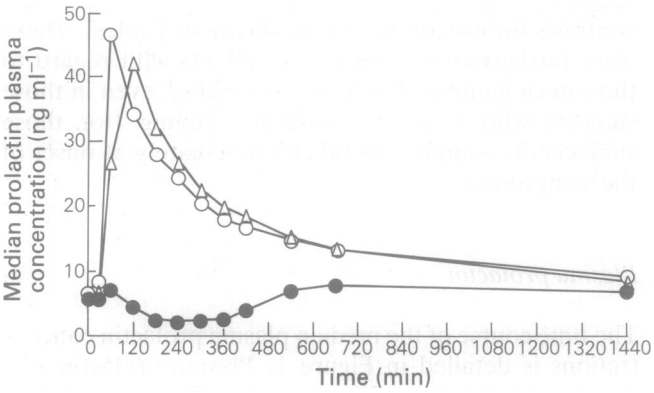

Figure 1 Time course of the median plasma prolactin concentrations for treatments PS: placebo + ropinirole (•), DS: domperidone + ropinirole (○), and DP: domperidone + placebo (△). Domperidone or its placebo was administered at time $t = 0$; ropinirole or its placebo were administered at time $t = 60$ min.

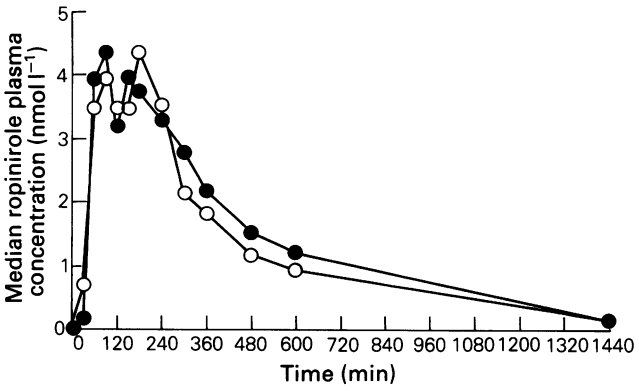

Figure 2 Time course of the median plasma concentrations of ropinirole for treatments PS: placebo + ropinirole (•), and DS: domperidone + ropinirole (○).

Plasma pharmacokinetics of ropinirole

The time course of the median plasma concentrations of ropinirole is detailed for treatments PS and DS in Figure 2. The curves were often characterized by multiple peaks, and appropriate points failed to estimate the terminal slope with reasonable accuracy. The maximum observed plasma concentration, C_{max}, ranged from 3.57 to 12.6 nmol l^{-1} (mean: 6.24) and from 3.48 to 13.4 nmol l^{-1} (mean: 7.05) for treatments PS and DS, respectively. The 95% interval estimate of the true ratio DS/PS was 0.96 to 1.14. The area under the time course of the quantifiable plasma concentrations, AUC, ranged from 11.6 to 48.0 nmol l^{-1} h (mean: 26.7) and from 10.1 to 68.1 nnmol l^{-1} g (mean: 28.4) for treatments PS and DS, respectively. The 95% interval estimate of the true ratio DS/PS was 0.77 to 1.28. There thus was no indication that pretreatment with domperidone altered ropinirole's plasma pharmacokinetics.

Discussion

Ropinirole is a novel dopaminergic agonist with a relatively high selectivity for dopamine D_2-receptor sites. The drug might therefore be devoid of adverse effects related to dopaminergic D_1-receptor agonism and α-adrenergic effects, often seen with less selective dopaminomimetics.

Ropinirole affects both central and peripheral dopamine D_2-receptor sites. The former effects are determinant of the drug's potential therapeutic value in Parkinson's disease. The latter are responsible for the inhibition of prolactin by ropinirole observed here and reported previously (Acton & Broom, 1989; de Mey *et al.*, 1990). Indeed, modulation of prolactin release is considered to be a 'peripheral' function because of its anatomical substrate which is not sealed off by the

blood-brain barrier (Clemens *et al.*, 1974; Lemberger & Crabtree, 1979; Thorner & Vance, 1989). This agrees with the finding that domperidone increases prolactin as also seen here. The lack of evident effect of ropinirole on the prolactin stimulation by domperidone administered 1 h earlier does not permit conclusions to be drawn regarding the relative affinity of domperidone and ropinirole for these receptors. Further experiments with different sequence and timing of the drugs would be required to elucidate this.

Nausea and emesis are frequently reported side effects of dopaminomimetic drugs (Ho & Thorner, 1988; Rinne 1988), also thought to be related to essentially peripheral dopaminergic effects (Caine & Kebabian, 1987). These effects are usually transient, can be prevented by prior food ingestion and by commencing treatment with low doses followed by gradual increments (Ho & Thorner, 1988).

Acute doses of ropinirole were found to cause mild nausea, but no vomiting, in supine healthy subjects (Acton & Broom, 1989; de Mey *et al.*, 1990). In the present study nausea was not observed in supine subjects but nausea and malaise were the main features of the orthostatic symptoms that occurred when ropinirole was administered without pretreatment with domperidone.

Blood pressure reduction, especially on standing, has often been observed with dopaminomimetics. The reports on the effects of domperidone *vs* these dopaminomimetic hypotensive reactions are equivocal (Pollak *et al.*, 1981; Quinn *et al.*, 1981; Rinne, 1983). In the present study supine blood pressure was not affected by the treatments. A small rise in supine heart rate was seen which confirms our previous findings (Acton & Broom, 1989; de Mey *et al.*, 1990). Symptomatic events were observed on immobile upright standing. The reactions were different from the variant responses sometimes observed with postural stress in normotensives (de Mey & Enterling, 1988), and none of the incidents was associated with or followed by absolute or relative bradycardia as had been previously the case (Acton & Broom, 1989). Therefore, these postural events were probably not vasovagal in nature. Pretreatment with domperidone prevented the orthostatic reactions in all but one subject. This indicates that the reactions are most likely related to peripheral dopaminergic agonism. The volunteer who was refractory to domperidone pretreatment was studied in parallel to other subjects one of whom suffered an orthostatic reaction. A psychological witness effect might have occurred.

Clinical experience in 22 Parkinsonian patients pretreated with domperidone showed that acute doses of ropinirole up to 10 mg were well tolerated and did not cause similar postural distress. Chronic incremental dosing with weekly dose increases up to 8 mg twice daily did not produce significant orthostatic symptoms, indicating the possible development of tolerance to these events.

It is generally accepted that the hypotensive effects of dopaminomimetics might relate to central and/or peripheral pre-synaptic D_2-dopaminergic effects resulting in a decreased neurogenic noradrenaline release (Clark *et al.*, 1978; Fuxe *et al.*, 1974; Kalsner & Chan, 1980; Kolloch *et al.*, 1980; Lokhandwala & Jandyala, 1979; Mohanty *et al.*, 1985; Sowers *et al.*, 1982; Whitfield *et al.*, 1985). We previously reported that single oral doses of 400, 800 and 1000 μg ropinirole blunt the noradrenaline responses to immobile erect standing at 200 min after dosing (de Mey *et al.*, 1990). In the present study there was little treatment effect in terms of venous plasma catecholamines, both in the supine resting position and in response to standing. The noradrenaline responses could not be judged deficient in symptomatic subjects. However, this does not per se exclude inadequacy of the postural neurogenic noradrenaline release, as peripheral venous catecholamines are quite crude estimates of sympathetic activity (Folkow *et al.*, 1983; Goldstein *et al.*, 1983; Hjemdahl, 1988; Johnson *et al.*, 1977).

We therefore conclude that single doses of 800 μg ropinirole could cause faintness and malaise on 3 min immobile erect standing in young healthy subjects. Pretreatment with a single dose of 20 mg domperidone prevented these events in all but one subject. The observed reactions are probably related to the peripheral dopaminergic agonistic action of ropinirole.

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