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Pyridostigmine bromide versus Fludrocortisone in the treatment of orthostatic hypotension in Parkinson`s disease – a randomized controlled trial

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Abstract

Background: Evidence for effective treatment options for orthostatic hypotension (OH) in Parkinson`s disease (PD) is scarce. Elevation of cholinergic tone with Pyridostigmine bromide has been reported as a way to improve blood pressure (bp) regulation in neurogenic hypotension without causing supine hypertension.

Methods: Double-centre, double blind, randomized, active-control, crossover, phase II non-inferiority trial of Pyridostigmine bromide for OH in PD (clinicaltrials.gov NCT01993680). Patients with confirmed OH were randomized to 14 days 3x60mg/d Pyridostigmine bromide or 1x0.2mg/d Fludrocortisone before crossover. Outcome was measured by peripheral and central bp monitoring during Schellong manoeuvre and questionnaires.

Results: Thirteen participants were enrolled between 04/2013 and 04/2015 with 9 participants completing each trial arm. Repeated-measures comparison showed a significant 37% improvement with Fludrocortisone for the primary outcome diastolic bp drop on orthostatic challenge (baseline 22.9±13.6 vs. Pyridostigmine bromide 22.1±17.0 vs. Fludrocortisone 14.0±12.6 mmHg; p=0.04), while Pyridostigmine bromide had no effect. Fludrocortisone caused an 11% peripheral systolic supine (baseline 128.4±12.8 vs. Pyridostigmine bromide 130.4±18.3 vs. Fludrocortisone 143.2±10.1; p=0.01) but no central mean arterial supine bp rise (baseline 107.2±7.8 vs. Pyridostigmine bromide 97.0±12.0 vs. Fludrocortisone 107.3±6.3; p=0.047). Subjective OH severity, motor score and quality of life remained unchanged by both study interventions.

Conclusions: Pyridostigmine bromide is inferior to Fludrocortisone in the treatment of OH in PD. This trial provides first objective evidence of efficacy of 0.2mg/d Fludrocortisone for OH in PD, causing minor peripheral but no central supine hypertension. In addition to peripheral bp, future trials should include central bp measurements, known to correlate more closely with cardiovascular risk.

Introduction

The disease burden by autonomic dysfunction in Parkinson`s disease (PD) is increasingly recognized. Orthostatic hypotension (OH) is reported to have an incidence of around 30% in PD (1) and a particular high influence on quality of life (2), while there is only Class III evidence for therapeutic interventions (3). Current treatment strategies anchor at behavioural adaptations, increasing overall blood pressure (bp) by elevation of plasma volume or administering vasoactive agents (4). Until now however, all of these interventions for OH in PD are viewed as *investigational* (5), reflecting the lack of randomized controlled trials.

In addition to decreased cardiovascular sympathetic innervation (6), impaired baroreflex function is a major factor for OH in PD (7). Elevation of cholinergic tone by Pyridostigmine bromide (PB) has been suggested to strengthen both limbs of the baroreflex without causing supine hypertension (8). Results from a trial in a cohort of patients with neurogenic OH were promising (8). We therefore aimed at studying the effect of PB on OH in a PD cohort. A non-inferiority design was chosen with Fludrocortisone (FC), a synthetic mineralocorticoid widely available and used, as an active comparator. Open-label studies in small samples have suggested that FC improves OH in multiple system atrophy (9) and in levodopa induced OH (10), while the only randomized controlled trial in PD showed an effect on subjective OH symptom severity but not blood pressure measurements (11).

Methods

This double-centre, double blind, randomized, active-control, crossover, phase II non-inferiority trial was conducted in accordance with national and international law and good clinical practice. It was registered locally and internationally (clinicaltrials.gov NCT01993680). The study protocol was approved by the Zurich cantonal ethics committee and the national medical regulatory body Swissmedic. All participants provided written informed consent for participation prior to inclusion. The study was designed with diastolic bp drop on Schellong maneuver (mmHg) as the primary outcome measure. Power calculations were based on effect sizes for PB in neurogenic OH (8) with a non-inferiority margin M of 50%. For an effect size of 2.45 and a calculated error probability of $\alpha = 0.05$ (resulting power $(1-\beta) = 0.95$), an overall sample size of n=10 participants was calculated to prove non-inferiority (critical t 1.86; actual power 0.97) – to increase power, we aimed at n=18.

Participant Selection

PD patients diagnosed according to UK Brain bank criteria, 50-80 years of age, Hoehn & Yahr stages 2 and 3, with symptomatic, established OH (≥20 mmHg drop systolic or 10mmHg diastolic peripheral bp within 3 minutes of standing (12)) on routine follow-up were recruited from the outpatient clinics of participating centers. Patients on medication influencing bp regulation (antihypertensive drugs, mirtazapine, sertraline, paroxetine, fluoxetine, venlafaxine, trazodone, anticholinergics, etc.), depolarizing muscle relaxants, with systemic disease (diabetes, infection, renal or kidney failure, malignancy), pathological under- or overweight and conditions interfering with compliance were excluded. Furthermore, patients presenting with signs for cerebellar involvement or other clinical or imaging features suggestive of multiple system atrophy (MSA) were not included. Participants continued their dopaminergic medication and physical hypotension measures unchanged throughout the study.

Trial design and procedures

Study visits were conducted directly before the first and directly after the final dose of trial medication. Trial arms had 14 days duration and 21 days of washout before crossover, with the biological half-life being 36 (FC), respective 1.5 hours (PB). All study visits included the same procedures and were conducted in the same clinical trial suite at ambient room temperature from 9 AM after an overnight fast. Investigations were performed after a minimum of 20min supine rest at 30° head elevation. Non-invasive central bp measurements were performed using pulse wave analysis by applanation tonometry (13) (SphygmoCor; AtCor Medical Pty., Sydney, Australia) – measurements with an operator index <80% were excluded. Cardiovascular monitoring was recorded continuously during Schellong manoeuvre (Nihon Kohden, Cham, Switzerland; 10min supine, 10min standing). Motor (UPDRS III), cognitive (Montreal Cognitive Assessment (MoCA) and additional domains (Hospital Anxiety and Depression Scale, Zurich autonomic questionnaire, OH symptom assessment (OHSA) scale (14) and quality of life) assessments were recorded in a standardized way. Home bp measurements in sitting position consisted of repeat automated morning and evening measurements (WatchBPhome, microlife, Widnau, Switzerland) for 7 days before study visits.

Study medication was prepared in identical capsules by the Cantonal Pharmacy of the Canton of Zurich, which also performed independent randomization. Study medication was kept at 4°C by participants and was started at

3x30mg/d (PB) and 1x0.1mg (FC) + 2x placebo/d for 3 days before dose increment to 3x60mg/d and 1x0.2mg/d + 2x placebo/d. Compliance was monitored by drug calendars and collection of empty medication packaging.

Data analysis

All data are expressed as means and standard deviations. Data sets were included if trial arms were completed. Mixed linear model statistics were used for repeated measures comparison. Post-hoc analysis (LSD) was performed in case of significant differences between groups. A two-tailed p value of 0.05 was considered significant. Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY).

Results

Thirteen participants were enrolled between 04/2013 and 04/2015 – for clinical characteristics see Table 1. Before the final study visit, two subjects withdrew consent due to strenuous study procedures, one received DBS implantation and one dropped out due to a non-study related accident. After an interim analysis of the primary outcome measure after the ninth completed data set (subject 13) showing futility of the primary outcome measure for PB, the trial was terminated and data analyzed as intention to treat. Each trial arm was fully completed by 9 participants and medication compliance was 99%. The pre-defined non-inferiority margin M was missed and non-inferiority rejected.

Outcome variables of the intention-to treat analysis are displayed in Table 2 and Figure 1. FC improved the primary outcome measure diastolic bp drop on Schellong maneuver by 37% (p=0.016), as well as minimal mean arterial bp standing by 15% (p=0.02), whereas PB treatment had no significant effect (Figure 1A, B). Subjective symptom severity was not changed by any intervention (Figure 1E) and did not correlate with changes in bp drop on Schellong (*ns*). Peripheral systolic bp supine (Figure 1C) and systolic 7d home bp measurement sitting were increased by 11% after FC (p=0.004) but not PB treatment. Central mean supine bp was lowered by 9% by PB (p=0.03) but remained unchanged after FC treatment (Figure 1D). Neither drug had any influence on motor, cognitive and neuropsychiatric measure or quality of life. Stool consistency was significantly softened with PB treatment (p=0.015), while neither treatment had an influence on the subjective severity of other autonomic symptoms. While PB lowered Sodium levels (p=0.009), Potassium levels were unchanged in both trial arms (Figure 1F, G).

Transient, mild adverse events were reported during PB (dizziness, n=1; mouth dryness, n=1; transient increase of motor off phase n=1) and FC treatment (leg oedema, n=1) without leading to dose adjustment or drop-out. There was a weak positive correlation between motor and subjective OH symptoms among participants (Figure 1 H; r^2=0.38, p=0.03).

Discussion

Futility of Pyridostigmine bromide for OH in PD

OH is classically defined by a drop of more than 20 mmHg in systolic or 10mmHg in diastolic peripheral bp within 3 minutes of standing (12). Recently a mean bp (MBP) <75mmHg upon standing has been found to correlate better with OH symptoms in PD (15). In the present study, PB failed to display a positive effect for both OH definitions as well as for subjective severity of OH symptoms in PD patients. While 55% of patients had a net improvement of diastolic bp drop with PB (100% for FC, p=0.08), the overall mean effect size was negligible and did not reach the pre-set non-inferiority margin. Thus, in our homogeneous PD cohort, we could not reproduce the positive effect of PB on OH, as shown for a single dose of 60mg in a mixed cohort of patients with neurogenic OH (8) - follow-up studies of the initial report did not include PD patients (16,17). Possible explanations for this discrepancy could be either insufficient dosing or age- and disease-inherent factors. Previous studies have reported an effect of 30mg (18), 120mg (19) and 180mg (20) of PB on autonomic nervous system activity in healthy controls. Although having received 180mg PB per day, it cannot be excluded that this dose was insufficient for elevation of cholinergic tone in this population. On the other hand, the significant subjective softening of stool consistency and increased heart rate change on Schellong maneuver by PB suggests a clinically relevant effect on the autonomic nervous system. Alternatively, different OH disease mechanisms might influence the effect of PB on the baroreflex. The lesion site leading to OH is central and preganglionic in MSA, whereas it is peripheral and postganglionic in pure autonomic failure and PD (21). So far no difference in baroreflex testing has been reported between MSA and PD (22), suggesting that further studies into the exact pathophysiological mechanism of baroreflex dysfunction in these etiologies are warranted.

Our results indicate that a reasonable therapeutic effect on OH in PD might not be achievable with PB. Furthermore, the finding of hyponatremia is an additional caveat for its long-term application in PD, although the exact mechanism underlying this phenomenon remains elusive.

Beneficial effect of Fludrocortisone

In contrast, our data provide the first evidence for a significant improvement on both diastolic bp drop on orthostatic challenge (-37%) and MBP standing (+15%) by 0,2mg FC per day in PD. As MBP and diastolic bp have been shown to correlate closer with symptomatic OH than systolic bp (15), we consider OH therapy with FC can thus be considered successful. So far a significant effect has only been shown in cohorts of diabetic OH and Shy-Drager syndrome, i.e. MSA (9,23). In the single previous trial of FC for OH in PD, 0.1mg FC per day only improved subjective symptoms but did neither change bp drop on orthostatic challenge nor supine systolic bp (11). Together with our observations this supports a dose-dependent effect of FC on bp regulation. The fact that this positive effect with 0.2mg FC per day on objective bp regulation was not reflected by significant changes of subjective OH symptom perception might be either due to the limited sample size, low sensitivity of the OHSA score or a possible dissociation of subjective vs. objective OH symptoms in this population (24).

Treatment effects on central blood pressure

As expected, 0.2mg FC per day caused an overall increase of peripheral bp levels – systolic bp in sitting and supine position was raised by 11%. According to suggested criteria, this constitutes supine hypertension (15), quoted to be the most relevant side effect of FC treatment (4,15). Although frequently quoted, there is no clear definition of supine hypertension, leading to different cut off values applied to study data in the literature (15,25). Our finding of unchanged central bp with FC treatment however shed light on another, novel aspect in the interpretation of supine hypertension in PD. The elastic properties of the arterial system and its branches cause the central bp to be amplified in the periphery and while the bp in the central arteries directly governs the load on the heart, this is not directly reflected by peripheral bp (26). There is compelling empirical evidence showing that central bp is superior in predicting cardiovascular disease risk in comparison to peripheral bp (26,27). To our knowledge, central bp has not been reported in PD patients before (11,16,25). Although further studies into central bp in PD therefore seem warranted, the finding of unchanged central bp under FC treatment might indicate a more favorable side effect profile than anticipated. In contrast to previous reports, we did not observe any electrolyte disturbances and in particular hypokalemia with FC use.

Limitations and Conclusion

We acknowledge the number of participants and dropout rate in this trial as a weakness that warrants replication. Future trials with similarly strict in- and exclusion criteria will likely need a multi-center approach (25), as recruitment was more difficult than anticipated. Although we excluded alternative pharmacological influence on

bp, dopaminergic medication of course influenced bp regulation (28). However, measurements in the OFF state were deemed unfeasible and we think that measurements in the ON state more closely resemble clinical reality. Independent of this it is important that pharmacological therapy of OH should always be preceded by the exhaustion of non-pharmacological measures.

This trial however provides first evidence for the efficacy of 0.2mg/d FC for OH in PD, which is a confirmation of frequent clinical practice. The observed effect size with FC treatment is of note compared to recent much larger trials for OH in PD that did not show a persistent benefit on bp regulation (25). We also show first evidence that supine hypertension in the periphery might not reflect central bp changes in PD. Additional studies are needed to clarify the significance of central bp and supine hypertension in the cardiovascular risk assessment in PD.

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Figure and Table captions:

Fig.1 Effect of study medication on diastolic blood pressure drop standing (a), minimal mean blood pressure standing (b), supine systolic peripheral (c) and supine mean central (d) blood pressure, severity of subjective OH symptoms (e) and electrolyte levels (f, g). Parkinson´s disease motor symptoms correlated weakly with subjective OH symptoms (h).

Table 1 Study population baseline characteristics.

Table 2 Effect of Pyridostigmine bromide and Fludrocortisone on blood pressure regulation, motor symptoms and other autonomic domains in study participants (n=13)

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Table 1 Study population baseline characteristics

No.	Sex/age	UPDRSIII ON	MoCA	LED (mg/d)	Diastolic bp drop on Schellong (mmHg)	minimum standing mean bp	OHSA
1	M / 73	15	26	865	27	67	10
2	F / 77	17	29	600	15	110	9
3	M / 78	19	24	1000	10	87	23
4	M / 65	15	25	600	24	66	9
5	M / 72	25	26	1165	21	77	11
6	M / 60	18	29	990	30	58	9
7	M / 79	45	20	1264	17	65	32
8	M / 75	22	22	1250	57	32	13
9	F / 73	23	21	685	15	86	30
10	M / 66	29	20	1197	39	52	22
11	M / 67	21	22	550	27	67	24
12	M / 72	33	20	1412	18	70	17
13	M / 70	32	27	785	17	81	18
Mean ± SD	71.3 ± 5.6	24.2 ± 8.6	23.9 ± 3.3	947 ± 295	22.9 ± 13.6	70.7 ± 18.8	17.8 ± 8.4

Abbreviations: UPDRSIII – United Parkinson`s disease rating scale part III; MoCA - Montreal Cognitive Assessment; LED – levodopa equivalent dose (according to (29));

Table 2 Effect of Pyridostigmine bromide and Fludrocortisone on blood pressure regulation, motor symptoms and other autonomic domains in Parkison`s disease patients with symptomatic orthostatic hypotension (n=13)

	Baseline	Pyridostigmin bromide	Fludrocortisone	Mixed linear repeated measures comparison	LSD post hoc comparison
Peripheral blood pressure on Schellong manoeuvre					
Diastolic bp drop § (mmHg)	22.9 ± 13.6	22.1 ± 17.0	14.0 ± 12.6	p=0.036	‡ p=0.016
Systolic bp drop § (mmHg)	41.1 ± 16.9	36.4 ± 11.1	34.6 ± 15.2	p=0.26	n.a.
Mean systolic bd standing (mmHg)	105.0 ± 16.8	100.2 ± 18.8	112.0 ± 21.8	p=0.34	n.a.
Mean diastolic bd standing (mmHg)	71.6 ± 1.4	68.6 ±13.9	73.3 ± 15.7	p=0.62	n.a.
Rate of improvement on diastolic bp drop	n.a.	5/9 (55%)	9/9 (100%)	Fisher`s Exact Test p=0.08	n.a.
Lowest mean arterial bp (MBP) standing §	70.7 ± 18.8	69.9 ± 16.4	83.9 ± 17.3	p=0.038	‡ p=0.021, © p=0.029

(mmHg)					
Systolic bp supine (mmHg)	128.4 ± 12.8	130.4 ± 18.3	143.2 ± 10.1	p=0.012	‡ p=0.004; © p=0.03
Diastolic bp supine (mmHg)	79.9 ± 6.7	79.0 ± 9.0	84.6 ± 6.8	p=0.23	n.a.
Heart rate increase on standing §	10.1 ± 3.1	12.5 ± 4.0	9.2 ± 4.0	p=0.028	# p=0.038; © p=0.011
Central supine blood pressure					
Central mean bp (mmHg)	107.3 ± 7.8	97.0 ± 12.0	107.3 ± 6.3	p=0.047	# p=0.034; © p=0.029
Central systolic bp (mmHg)	134.0 ± 14.8	122.7 ± 17.6	137.3 ± 15.3	p=0.16	n.a.
Central diastolic bp (mmHg)	88.7 ± 6.8	80.8 ± 10.6	89.0 ± 4.3	p=0.056	n.a.
7d Home bp measurement sitting					
Systolic bp (mmHg)	123.9 ± 16.6	127.7 ± 12.0	139.9 ± 11.0	p=0.002	‡ p=0.002; © p=0.002
Diastolic bp (mmHg)	74.6 ± 9.3	74.6 ± 9.8	82.3 ± 9.3	p=0.017	‡ p= 0.031; © p=0.038
Heart rate (bpm)	73.0 ± 7.8	69.6 ± 9.3	71.3 ± 6.9	p=0.73	n.a.
Overall motor, cognitive and neuropsychiatric functioning and Quality of life					
UPDRSIII	24.2 ± 8.6	24.0 ± 10.5	22.1 ± 10.7	p=0.93	n.a.

MoCA	23.9 ±3.3	24.1 ± 5.0	25.3 ± 2.7	p=0.61	n.a.
HADS A	5.1 ± 2.9	4.13 ± 2.7	5.6 ± 5.2	p=0.89	n.a.
PDQ-39 sum index	24.9 ± 18.6	22.6 ± 12.8	22.3 ± 17.7	p=0.55	n.a.
Subjective severity of autonomic symptoms					
OHSA	17.8 ± 8.4	16.0 ± 10.8	16.6 ± 14.3	p=0.96	n.a.
OHDAS	11.5 ± 6.6	10.9 ± 5.0	12.4 ± 10.6	p=0.75	n.a.
Stool consistency $	3.2 ± 1.5	1.8 ± 0.9	2.8 ± 1.2	p=0.028	# p=0.015; © □=0.07
Stool frequency per day	0.4 ± 0.7	0.9 ± 0.8	0.9 ± 0.9	p=0.34	n.a.
Urinary urgency †	3.1 ± 0.9	3.0 ± 0.9	3.5 ± 1.2	p=0.77	n.a.
Urinary frequency per day	5.3 ± 1.4	6.1 ± 2.2	4.8 ± 2.6	p=0.54	n.a.
Subjective drooling †	2.2 ± 1.0	2.4 ± 1.3	2.0 ± 1.2	p=0.29	n.a.
Dizziness on rising †	2.9 ± 0.8	2.4 ± 0.9	2.3 ± 1.0	p=0.14	n.a.
Electrolytes					
Potassium (mmol/l; norm: 3.3 - 4.5)	3.9 ± 0.29	4.0 ± 0.29	4.0 ± 0.17	p=0.64	n.a.
Sodium (mmol/l; norm: 136 - 145)	139.7 ± 2.0	136.7 ± 4.1	139.7 ± 2.6	p=0.013	# p=0.009; © p=0.01

baseline vs. Pyridostigmine bromide; ‡ baseline vs. Fludrocortisone; © Pyridostigmine bromide vs. Fludrocortisone; Abbreviations: UPDRSIII – Unified Parkinson`s disease rating scale part III; MoCA - Montreal Cognitive Assessment; LED – levodopa equivalent dose (according to (29)); OHSA – Orthostatic Hypotension Severity Assessment;

OHDAS - Orthostatic Hypotension Daily Activity Scale; § between 0 and 3 min standing; Zurich Autonomic Questionnaire using a 5 point likert scale from 0 to 5 indicating soft to hard ($), respectively little to severe symptom intensity (†) ;