Newer Dopaminergic Agents Cause Minimal Endocrine Effects in Idiopathic Parkinson's Disease

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ABSTRACT

OBJECTIVE: We studied the prevalence of endocrine dysfunction in subjects with idiopathic Parkinson's disease (IPD) on newer dopaminergic agents (DA). DA are also used in endocrine hypersecretory states in small doses and we hypothesized that endocrine dysfunction was likely in IPD where DA were used in comparatively much higher dosage.

PATIENTS AND METHODS: Twenty-five subjects with IPD, established on DA, were recruited to this cross-sectional study. We measured insulin-like growth factor-1, prolactin, luteinizing hormone, follicle stimulating hormone, thyroid function, oestradiol or testosterone and cortisol levels following a short synachten test.

RESULTS: We studied 18 males and 7 females, whose median age was 72 years, and whose median time from diagnosis, and duration of treatment was 27 months (interquartile range 17–45 and 13–39 months, respectively). (1) Endocrine tests were normal in 19 of 25 subjects at recruitment. Minor abnormalities reverted to normal on repeat testing in three of six with initial abnormalities; two had persistent abnormalities and the third subject could not be further investigated. Therefore, 22 of 24 (92%) with IPD on DA therapy had normal endocrine profiles. (2) The cortisol response to ACTH was normal in 24 of 25 subjects (96%). (3) Eleven subjects (44%) had isolated PRL suppression. There were no differences between the suppressed PRL and "normal" PRL groups. However, a higher number of them were on non-ergoline-derived DA (83% vs 31%; $P < 0.05$).

CONCLUSIONS: We have demonstrated that newer non-ergoline DA therapy caused only minimal endocrine perturbations in subjects with IPD. Their clinical significance can only be speculative currently. The cortisol response to ACTH was normal in almost all but a significant minority had suppressed prolactin levels.

KEYWORDS: Parkinson's disease, endocrine dysfunction, dopaminergic agents

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Introduction

Idiopathic Parkinson's disease (IPD) is characterized by dopamine deficiency in the basal ganglia. Levodopa (a dopamine precursor) and dopaminergic agents (DA) are therefore useful in IPD treatment.[1] Dopamine is also an important hypothalamic neurotransmitter that has an important role in regulating hormones, some of which may be of relevance in IPD. Neurotransmitter deficiency in this region is therefore of considerable interest. The link between potential hormonal perturbations and the non-motor symptoms of IPD is of interest but currently remains speculative. Some of these may cause considerable morbidity in the form of autonomic, neuropsychiatric, cognitive and sleep disturbances, and weight loss. Some investigators have speculated about the loss of hormonal diurnal rhythmicity as a cause for these effects.[2–4]

In addition to hypothalamic neurotransmitter deficiency, hormone dysfunction may also result from DA use in treating IPD. These drugs act through dopamine receptors that are

widely distributed. Dopamine receptors are expressed in many normal endocrine and endocrine tumor cells, and therefore DA have the potential to inhibit hormone secretion. This feature is an advantage in hormone secreting pituitary adenomas.[5–9] The potential for such hormone dysfunction in IPD is high as significantly higher doses of DA are used in IPD.

There are only a limited number of prospective studies of long-term DA use and endocrine function in IPD,[10–13] and even fewer of the newer non-ergoline dopaminergic agents, eg pramipexole, ropinirole, and rotigotine. A few retrospective studies have produced conflicting results.[14–18] We felt that it was important to study endocrine function in such subjects as IPD medication-induced hormonal perturbations may worsen non-motor effects of IPD and contribute to a poor quality of life.

Subjects and Methods

Subjects. We recruited 25 consecutive subjects with IPD attending the Parkinson's disease clinic who gave informed consent. IPD was diagnosed clinically using the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.[19] Both male and female subjects aged 40 years or more, who had been on DA for more than six weeks, were eligible for recruitment. Subjects with diabetes mellitus, known pituitary, thyroid and malignant disease, bronchial asthma, stroke and those receiving beta blockers, hormone replacement, and neuroleptic therapy were excluded. The Aneurin Bevan University Health Board and the South East Wales Research Ethics Committee approved this study.

Study protocol. All subjects were studied between 9 and 9.30 am. Thirty minutes after inserting an intravenous cannula, blood was collected for insulin-like growth factor (IGF)-1, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone or oestradiol, thyroid stimulating hormone (TSH), free T4, cortisol, and prolactin assays. Immediately thereafter, 250 μg of synacthen (Alliance Pharmaceuticals Ltd., Wiltshire, UK) was given IV, and further, blood was collected 30 minutes later for cortisol assay. Samples were then centrifuged and plasma stored at −20°C until assayed.

Assays.

Cortisol. Cortisol was measured using the Abbott Architect immunoassay (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). The coefficient of variation (CV) was 6.9% at 222 nmol/L and 7.5% at 942 nmol/L.

Free T4, TSH, IGF-1, prolactin, LH, FSH, oestradiol and testosterone. These were measured using an Abbott Architect automated analyzer (Abbott Diagnostics, Maidenhead, Berks, UK). The CV for free T4 was 7.2% at 9.9 pmol/L and 4.8% at 23.3 pmol/L; for TSH, 3.8% at 0.32 mU/L and 4.1% at 26.8 mU/L; for IGF1, 5.8% at 8.7 nmol/L and 6.2% at 27.3 nmol/L; for prolactin, 2.4% at 158 mIU/L, 2.6% at 850 mIU/L, and 2.2 at 1014 mIU/L; for LH, 2.9% at 3.3 IU/L, 2.5% at 34.9 IU/L, and 3.2% at 49.2; for FSH, 2.6%

at 3.5 IU/L, 3.0% at 25.1 IU/L, and 3.6% at 46.4 IU/L; for oestradiol, 7.9% at 196 pmol/L, 1.9% at 847 pmol/L, and 1.5% at 1256 pmol/L; and for testosterone, 6.6% at 2.9 nmol/L, 3.4% at 15.8 nmol/L, and 2.1% at 31.3 nmol/L.

Statistical analysis. Statistical advice on numbers to recruit and data analysis was obtained from the Statistical Advisor of the Aneurin Bevan University Health Board. Summary data that were assumed to be non-normally distributed were compared using non-parametric methods, and data tables were compared with the chi-squared test using IBM SPSS v 20.[20]

Results

There were 18 males and 7 females in the study with a median age of 72 years. The median time to study from IPD diagnosis was 27 months (interquartile range 17–45). They were on a variety of DA including pramipexole, ropinirole, rotigotine, and others (Table 1). The median duration of treatment was 27 months (range 13–39). A family history of IPD was present in only two (out of 22) subjects (Table 1).

Endocrine function.

(a) Endocrine function was entirely normal using the study protocol in 19 subjects at recruitment. In three of the six subjects with abnormalities, minor endocrine abnormalities reverted to normal on repeat testing. However, two of three subjects had persistent abnormalities: (1) elevated PRL level but a normal pituitary CT scan; (2) undetectable IGF-1 levels with normal endocrine tests, but the subject defaulted several times from pituitary imaging—a previous contrasted CT head scan for an unrelated indication, was reported as normal (although this was not pituitary specific). The third subject, who had hypogonadotrophic hypogonadism, undetectable IGF-1 levels, and an abnormal short synacthen test (SST) at

Table 1. Demographic details of subjects in this study.

DETAILS OF IPD SUBJECTS	RESULT
Gender	Male 18:Female 7
Median age (interquartile range)	72 (68–76) years
BMI	26.5 (23–28.6) Kg/m^2
Median time from diagnosis of IPD	27 (17–45) months
Median duration of dopaminergic therapy	27 (13–39) months
Dopaminergic agents used	Pramiprexole, Ropinirole, Rotigotine, Co-beneldopa, Co-careldopa, Selegeline, Entacapone
Subjects on combinations of DA	Single DA therapy = 13 Combination therapy Two DA = 10 Three DA = 2
Family history of IPD	2/22

Note: There was a male preponderance in this group of subjects with IPD who were treated for a median period of 27 months with DA.

Table 2. Details of six subjects with endocrine abnormalities at recruitment.

AGE AND GENDER	DOPAMINERGIC AGENT	ENDOCRINE ABNORMALITY*	FOLLOW UP
67, M	Pramipexole, co-beneldopa	HH (T 4.7; LH 1.1; FSH 5.1)	Repeat tests normal; normal pituitary MRI
72, M	Co-beneldopa, procyclidine	Raised PRL (PRL 851)	Repeat—PRL normal
64, M	Pramipexole, co-beneldopa	Subclinical hypothyroidism (TSH 5.71)	Repeat—TSH normal TPOAb positive
85, M	Co-careldopa, entacapone	Raised PRL (PRL 1187)	Repeat—PRL raised; normal pituitary CT
85, M	Co-beneldopa	Undetectable IGF1 (IGF < 3.3)	Repeat—IGF1 undetectable; defaulted from pituitary scanning
79, M	Co-careldopa	HH; undetectable IGF1; abnormal SST (T 2; LH 1.5; FSH 2.4; IGF < 3.3; cortisol 268 and 428)	Died before further tests could be done**

Notes: Endocrine function in 3 of 6 subjects normalized on repeat testing. Of the three subjects with persistent abnormalities, one died of unrelated causes before further tests could be done. **Died of unrelated causes.
Abbreviations: *HH, hypogonadotrophic hypogonadism; PRL, prolactin; IGF-1, insulin-like growth factor-1; SST, short synacthen test; TPOAb, thyroid peroxidase antibodies; T, testosterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone.

recruitment, died of unrelated causes before further investigations could be done (Table 2). Therefore, 22 out of 24 (92%) subjects in this study had normal endocrine profiles, and structurally normal pituitary glands on imaging done where clinically indicated. Further information was not available on the subject who died.

(b) The cortisol response to ACTH was normal in 24 of 25 subjects (96%) at recruitment, but could not be further investigated in the only subject who had a minor abnormality (cortisol at 0 minutes—266, at 30 minutes—428 pmol/L).

(c) Eleven of 25 subjects (44%) had isolated suppressed PRL levels (reference range 40–530 IU/L). A comparison of subjects with suppressed PRL with those with "normal" PRL showed no significant differences in age, gender, weight, and BMI (Table 3). There was no significant difference in the time from diagnosis of IPD or duration of treatment for IPD between the two groups ($P = 0.09$ and $P = 0.44$, respectively). However, a significantly higher number of subjects with suppressed PRL levels were on DA therapy compared to the number of subjects with PRL in the reference range (83% vs 31%; $P < 0.05$).

Discussion

In this study, we have shown that the newer DA do not cause significant endocrine dysfunction in subjects with IPD, when given for a median period of 27 months. Ninety-two percent of our subjects had entirely normal endocrine function at recruitment or at repeat testing, together with normal pituitary structure when imaging was done. Furthermore, the cortisol response to ACTH during an SST was normal in 96% of our subjects. This should reassure physicians who use DA and particularly the newer non-ergoline agents such as pramipexole, ropinirole, and rotigotine, which have not previously been investigated in this manner.[21] This is particularly so because DA are given in significantly higher doses in IPD than that are used in the pituitary hypersecretory states mentioned earlier.

However, there was a significant suppression of PRL in 44% of these individuals; but within the reference range in 56% (Table 2). This is an expected effect of high-dose DA therapy. This appeared to be an isolated phenomenon with

Table 3. Comparison of subjects with IPD with suppressed and non-suppressed prolactin (PRL) levels.

	SUBJECTS WITH SUPPRESSED PRL (PRL <13, n = 7; 14–33, n = 4) (n = 11)	SUBJECTS WITH NON SUPPRESSED PRL (PRL 82–1187) (n = 14)
Median age (years)	71	73
Gender (M:F)	2:1	2.2:1
Median BMI (Kg/m²)	26.9	26.5
Median duration of IPD (months)	34.5	24*
Median duration of treatment (months)	34	25**
Subjects on pramipexole, ropinirole, rotigotine	83%	31%***

Notes: There was no significant difference in the demographic details, duration of IPD, or treatment in those with suppressed PRL compared to those with non-suppressed PRL levels. However, there was a significantly higher number treated with DA in the former group. *$P = 0.09$; **$P = 0.44$; ***$P < 0.05$.

no accompanying endocrine abnormalities. PRL has been linked to various physiological effects other than milk secretion in normal individuals and it is interesting to speculate whether this pathological PRL suppression could contribute to the non-motor effects commonly found in IPD.[22,23] PRL suppression has been demonstrated in other studies on IPD subjects too. There were two subjects in our study with elevated PRL—one normalized on repeat testing and the other with persistently elevated PRL had normal pituitary imaging and other hormone profiles (Table 2).

Reassuringly, we found the cortisol response to ACTH normal in all subjects except one (Table 2). The subject with the abnormal SST also had other pituitary abnormalities but died before further investigations could be arranged. Previous reports on the Hypothalmo-pituitary axis (HPA) in treatment naive and treated subjects with IPD have shown conflicting results.[14,15] Basal cortisol and Adrenocorticotrophic hormone (ACTH) levels were either normal[21] or low[14] in subjects in two studies on treatment naive subjects with IPD. Other studies have also demonstrated that basal anterior pituitary function was unaffected in treatment naive patients with IPD.[14,15,17,24,25] However, short-term dopaminergic therapy in normal humans[16–18,26] showed variable effects on anterior pituitary hormones but consistent PRL suppression. Similar PRL suppression has been demonstrated in subjects with IPD on chronic dopaminergic therapy.[25,27–29] A more recent study of chronic dopaminergic therapy in patients with IPD showed marked inhibition of PRL and peripheral growth hormone resistance.[21]

There were imitations to this study. (a) A larger number of subjects would have given more statistical credibility to the results; (b) the lack of dynamic pituitary tests (to detect subtle pituitary dysfunction); (c) and our inability to relate low prolactin levels to non-motor manifestations of IPD (because of study design), are some of them. However, we believe that these should not detract from its main message.

In conclusion, we have demonstrated that in patients with IPD on newer DA for a median period of 27 months, (a) there is only minimal endocrine dysfunction; (b) the cortisol response to ACTH remains normal in 96%; and (c) there was isolated PRL suppression in a significant percentage of individuals who also had a higher rate of exposure to newer DA. These data should reassure physicians who deal with these medications in treating patients with IPD.

Author Contributions

Conceived and designed the experiments: C D'S, CK, MAA, LDP. Analyzed the data: LDP. Wrote the first draft of the manuscript: LDP. Contributed to the writing of the manuscript: JSD, CK, MAA, LDP. Agree with manuscript results and conclusions: JSD, JPG, CK, C D'S, MAA, LDP. Jointly developed the structure and arguments for the paper: CK, MAA, LDP. Made critical revisions and approved final version: JSD, JPG, CK, C D'S, MAA, LDP.

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