PAPER

Cholinesterase inhibitor use does not significantly influence the ability of ^{123}I-FP-CIT imaging to distinguish Alzheimer's disease from dementia with Lewy bodies

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Background: ^{123}I-labelled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) imaging is a diagnostic tool to help differentiate dementia with Lewy bodies (DLB) from Alzheimer's disease (AD). However, in animals, cholinesterase inhibitors (ChEi) have been reported to reduce radioligand binding to the striatal dopamine transporter. As ChEi are frequently used in people with dementia, it is important to determine whether their use affects ^{123}I-FP-CIT uptake in the striatum.
Objective: To clarify whether chronic ChEi therapy modulates striatal dopamine transporter binding measured by ^{123}I-FP-CIT in patients with AD, DLB and Parkinson's disease with dementia (PDD).
Design: Cross sectional study in 99 patients with AD (nine on ChEi, 25 not on ChEi), DLB (nine on ChEi, 19 not on ChEi) and PDD (six on ChEi, 31 not on ChEi) comparing ^{123}I-FP-CIT striatal binding (caudate, anterior and posterior putamen) in patients receiving compared with those not receiving ChEi, correcting for key clinical variables including diagnosis, age, sex, Mini-Mental State Examination score, severity of parkinsonism and concurrent antidepressant use.
Results: As previously described, ^{123}I-FP-CIT striatal uptake was lower in DLB and PDD subjects compared with those with AD. Median duration of ChEi use was 180 days. ^{123}I-FP-CIT uptake was not significantly reduced in subjects receiving ChEi compared those not receiving ChEi (mean percentage reduction: AD 4.3%; DLB 0.7%; PDD 6.1%; p = 0.40). ChEi use did not differentially affect striatal ^{123}FP-CIT uptake between patient groups (p = 0.83).
Conclusions: Use of ChEi does not significantly influence the ability of ^{123}I-FP-CIT imaging to distinguish AD from DLB.

Single photon emission computed tomography (SPECT) with the ligand ^{123}I-labelled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT), which binds to the dopamine transporter (DAT), has been shown to be useful in discriminating dementia with Lewy bodies (DLB) from Alzheimer's dementia (AD).[1 2]

However, the utility of ^{123}I-FP-CIT imaging may be undermined if individuals are taking medications that affect the striatal binding of ^{123}I-FP-CIT, particularly if such agents differentially influence ^{123}I-FP-CIT striatal binding between DLB and AD. A significant class of drugs which might impact on ^{123}I-FP-CIT binding in these patient groups are cholinesterase inhibitors (ChEi). In the monkey, DAT availability, assessed by [^{11}C] β-CFT positron emission tomography (PET), was reported to be acutely suppressed in a dose dependent manner by the ChEi donepezil.[3] Direct evidence that cholinesterase inhibition modulates DAT function in humans is currently lacking.

To determine whether chronic ChEi therapy influences striatal DAT binding by ^{123}I-FP-CIT in humans, we compared ^{123}I-FP-CIT striatal binding in patients with AD, DLB and Parkinson's disease with dementia (PDD) treated with ChEi with those not receiving these agents.

METHODS

Data from 93 subjects from a previous study published by our group were analysed.[2] Data from a further six subjects (five with DLB and one with PDD) were also included.

Detailed SPECT methodology and analysis are described elsewhere.[2] In brief, striatal binding was determined from the striatal:occipital activity ratios. Regions of interest (ROIs) were positioned at three distinct locations within the striatum to obtain measurements of the caudate, anterior putamen and posterior putamen. Striatal:occipital activity ratios for the three ROIs for each hemisphere were determined as:

$$^{123}\text{I-FP-CIT binding}_{\text{caudate, anterior putamen, posterior putamen}} = \text{Striatal uptake}_{\text{caudate, anterior putamen, posterior putamen}} / \text{Occipital uptake}$$

For analysis, an average of left and right hemisphere ^{123}I-FP-CIT uptake for each ROI was used.

Analysis of the effect of medications on ^{123}I-FP-CIT striatal binding was tested using multivariate analysis of covariance (MANCOVA) with fixed factors of sex, diagnosis and concurrent antidepressant use, and covariates of age, Mini-Mental State Examination score, Unified Parkinson's Disease Rating Scale, subsection III (UPDRS III) score and duration of illness. In subjects on medications, time on ChEi was added into the model as an additional covariate.

RESULTS

Subject characteristics are summarised in table 1. Groups were broadly matched for sex, age and cognitive impairment

Abbreviations: AD, Alzheimer's disease; ChEi, cholinesterase inhibitors; DAT, dopamine transporter; DLB, dementia with Lewy bodies; ^{123}I-FP-CIT, ^{123}I-labelled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane; PDD, Parkinson's disease with dementia; PET, positron emission tomography; ROIs, regions of interest; SPECT, single photon emission computed tomography; UPDRS III, Unified Parkinson's Disease Rating Scale, subsection III

Table 1 Demographic and neuropsychological data on subjects studied using ^{123}I-FP-CIT SPECT

Variable	Subjects						p Value (diagnosis group)	p Value (ChEi status)
	With AD		With DLB		With PDD			
	No ChEi (n = 25)	ChEi (n = 9)	No ChEi (n = 19)	ChEi (n = 9)	No ChEi (n = 31)	ChEi (n = 6)		
Sex (M/F)	10/15	5/4	13/6	4/5	20/11	6/0	0.08	0.66
Age (y)	79.1 (5.7)	78.5 (5.6)	74.3 (6.6)	79.4 (6.7)	72.3 (5.3)	70.3 (6.3)	<0.001†	0.56
MMSE score (maximum score 30)	17.9 (5.1)	15.6 (4.0)	15.6 (6.1)	18.0 (4.3)	19.0 (5.2)	20.2 (7.9)	0.15	0.72
CAMCOG (maximum score 107)	59.8 (15.9)	49.3 (21.7)	59.6 (16.4)	61.5 (8.2)	63.8 (14.8)	64.3 (16.4)	0.09	0.64
UPDRS III (maximum score 108)	4.9 (3.9)	7.4 (7.0)	27.8 (14.1)	20.1 (9.8)	37.3 (11.6)	36.7 (11.8)	<0.001‡	0.44
Duration of Illness (months)	33.2 (20.1)	38.3 (13.5)	33.6 (25.9)	27.6 (25.0)	65.1 (39.0)	133 (96.0)	<0.001¶	0.01§
Time on ChEi prior to ^{123}I-FP-CIT (days)*	NA	99 (26–733)	NA	124 (35–520)	NA	388 (128–577)	0.07	NA
Antidepressant use (n)	2	3	3	1	8	1	0.47	0.70

AD, Alzheimer's disease; CAMCOG, Cambridge Cognitive Examination; ChEi, acetylcholinesterase inhibitor; DLB, dementia with Lewy bodies; ^{123}I-FP-CIT, ^{123}I-labelled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane; MMSE, Mini-Mental State Examination; NA, not applicable; PDD, Parkinson's disease with Lewy body dementia; UPDRS III, Unified Parkinson's Disease Rating Scale subsection III: motor function.
Data are mean (SD) unless stated otherwise.
*Data expressed as median (minimum to maximum).
†Gabriel post hoc tests showed that subjects with AD were older than PDD subjects ($p<0.001$) and subjects with DLB were older than PDD subjects ($p<0.02$).
‡Mann–Whitney post hoc tests showed that subjects with AD had lower UPDRS III scores than those with DLB ($p<0.001$) or PDD ($p<0.001$). Subjects with DLB had lower UPDRS III scores than those with PDD ($p<0.01$).
¶Mann-Whitney post hoc tests showed that subjects with PDD had longer illness duration than AD ($p<0.001$) or DLB ($p<0.001$).
§Interaction between diagnosis group and ChEi status was significant ($p<0.01$). Mann-Whitney post hoc tests showed that subjects with PDD and on ChEi had longer illness duration than PDD subjects not on ChEi ($p = 0.05$).

although the PDD group were younger than the AD ($p<0.001$) and DLB ($p<0.02$) groups. As expected, the DLB and PDD groups had higher UPDRS III scores than the AD subjects (DLB vs AD, $p<0.001$; PDD vs AD, $p<0.001$). Analysis of illness duration showed that PDD subjects had a longer illness duration compared with AD ($p<0.001$) and DLB ($p<0.001$) subjects. Subject demographics for age, sex, degree of cognitive impairment or UPDRS III score did not differ by use of ChEi. Subjects with PDD taking ChEi had a longer illness duration ($p = 0.05$) and a trend to have been on their medication longer than subjects in the AD and DLB groups ($p = 0.07$). Concurrent antidepressant use was similar between diagnostic groups ($p = 0.47$) and cholinesterase status ($p = 0.70$).

Figure 1 shows graphically the mean and 95% CI for the striatal:occipital binding ratios of ^{123}I-FP-CIT for the three ROIs in subjects receiving ChEi and subjects not receiving ChEi. Striatal uptake differed between the groups (MANCOVA, Wilks Lambda, df = 6, $F = 3.87$, $p = 0.001$), after adjusting for fixed factors and covariates; specifically, the PDD group had lower striatal uptake in all three areas compared with the DLB ($p<0.001$) and AD ($p<0.001$) groups. DLB subjects had significantly lower uptake in all three striatal regions compared with the AD subjects ($p<0.001$). With regard to the effects of ChEi, across all three ROIs, there was a tendency for uptake to be reduced in those subjects on ChEi (mean magnitude of striatal:occipital binding reduction: AD 4.3%; DLB 0.7%; PDD 6.1%) but this reduction was not significant in the corrected multivariate analysis (MANCOVA, Wilks Lambda, df = 3, $F = 0.99$, $p = 0.40$). There was no significant interaction between the use of ChEi and diagnostic group in terms of striatal ^{123}I-FP-CIT uptake (MANCOVA, Wilks Lambda, df = 3, $F = 0.47$, $p = 0.83$). Similarly, antidepressant use did not significantly affect ^{123}I-FP-CIT uptake (MANCOVA, Wilks Lambda, df = 3, $F = 0.28$, $p = 0.84$) and there was no significant interaction between ChEi and concurrent antidepressant use (MANCOVA, Wilks Lambda, df = 3, $F = 0.26$, $p = 0.96$). In subjects taking ChEi, duration of prior ChEi use did not impact significantly on ^{123}I-FP-CIT uptake (MANCOVA, Wilks Lambda, df = 3, $F = 0.60$, $p = 0.54$).

DISCUSSION

^{123}I-FP-CIT SPECT imaging has been shown to have high sensitivity and specificity in distinguishing AD from DLB, even in DLB patients without clinical parkinsonism.[1 2 4 5] The main finding of this study is that concurrent use of ChEi does not significantly affect the results from ^{123}I-FP-CIT imaging.

There are conflicting reports on whether ChEi influence DAT binding by radioligands. In rats, Kilbourn *et al* showed that treatment with phenserine, a ChEi, produced a 24% decrease in radioligand DAT binding of d-threo-[^{3}H]methylphenidate.[6] In contrast, in a biodistribution study in rats, Knol *et al* did not observe any effect of donepezil or rivastigimine on DAT imaging with ^{123}I-FP-CIT.[7] Relevant to the present study is the primate study of Tsukada *et al* who observed that a single dose of

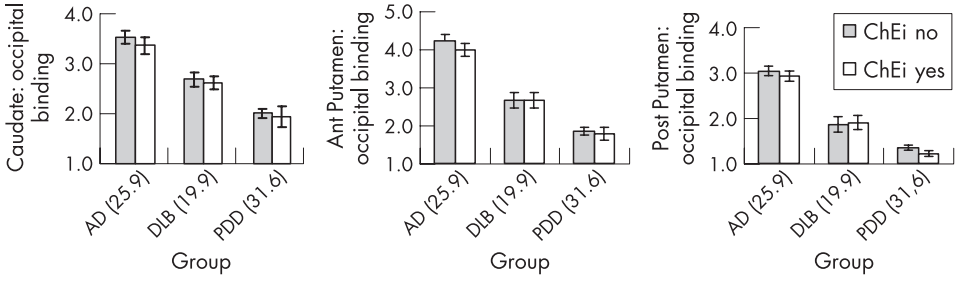

Figure 1 Striatal:occipital activity for subjects with Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) in the caudate nucleus, anterior putamen and the posterior putamen comparing subjects receiving cholinesterase inhibitors (ChEi) and those not receiving ChEi. Values are means (95% CI).

donepezil suppressed DAT availability, assessed using [^{11}C] β-CFT PET.[3] Tsukada *et al* proposed that this effect may occur either via transynaptic mechanisms or presynaptic receptor modulation. This observation is contrary to that observed in the present study. Dosage levels of ChEi in the study of Tsukada *et al* and the present study were comparable. Possible explanations for this discrepancy include the following.

Differences in ligands

^{123}I-FP-CIT reaches striatal binding equilibrium 3–6 h after injection. In contrast, [^{11}C]β-CFT reaches peak equilibrium within 1 h after injection.[8] Furthermore, ^{123}I-FP-CIT has an affinity for the serotonin reuptake transporter.[9] Therefore, it is feasible that differences in affinity and kinetic binding profiles between [^{11}C] β-CFT and ^{123}I-FP-CIT ligand may account for the disparity between our results and those of Tsukada *et al*.[3]

Differences in species, age and pathological status

Human DAT differs morphologically and functionally from DAT in other species.[10 11] Consequently, species differences in terms of ligand binding may be apposite. In addition, the monkeys used by Tsukada *et al* were young and healthy. Age related reductions in DAT have been noted in humans in both SPECT and PET studies and specifically in Lewy body disease, where there are significant losses of striatal DAT.[4 5 12 13] Therefore, it is possible that suppression of DAT activity as a result of ChEi use may not have been apparent in the present study because of floor effects.

Differences in duration of exposure to ChEi

The monkeys studied by Tsukada *et al* were treated acutely with an intravenous bolus of donepezil.[3] In contrast, in our study, patients had been receiving oral ChEi for a median of 180 days (minimum 26 days). It is plausible that prolonged exposure to ChEi might lead to a compensatory upregulation in DAT as a result of increased acetylcholine and therefore negation of any acute suppression. This is, in part, supported by evidence that the chronic administration of nicotinic agonists such as nicotine increase DAT mRNA expression in rats.[14] Furthermore, Padilla *et al* observed in rats that repeated bolus doses of chlorpyrifos, a ChEi insecticide, caused an increase in DAT density in the striatum after 6 months, although they did not observe any changes in DAT density with chronic low dose exposure to chlorpyrifos.[15]

Increases in ^{123}I-β-CIT striatal binding have been observed in subjects treated with the serotonin reuptake inhibitors, citalopram and paroxetine.[16 17] This increase may be caused by an interaction between serotonin and dopamine systems in the striatum[16] or increased ^{123}I-β-CIT availability secondary to peripheral serotonin reuptake transporter blockade and decreased central serotonin reuptake transporter availability.[17] Therefore, it could be argued that depression of striatal ^{123}I-FP-CIT uptake by ChEi might potentially be masked by concurrent antidepressant use. However, the proportions of subjects taking antidepressants in the present study were similar in those taking (20.8%) and not taking (17.3%) ChEi. Furthermore, we did not observe any significant interaction between antidepressant use and concurrent ChEi use in terms of ^{123}I-FP-CIT striatal binding.

The cross sectional nature of the present study cannot exclude subtle changes in ^{123}I-FP-CIT striatal uptake as a result of chronic use of ChEi. In addition, while currently most ^{123}I-FP-CIT imaging is carried out in patients with established dementia and on long term ChEi, the present study cannot determine the effect of acute/short term ChEi use. To answer these issues, a prospective blinded study comparing ^{123}I-FP-CIT binding before and after ChEi administration would be required. However, our study has important implications as it means that the prior use of ChEi does not affect the diagnostic discriminant validity of ^{123}I-FP-CIT imaging. This has clinical importance as it suggests that it is not necessary to withdraw ChEi prior to diagnostic ^{123}I-FP-CIT imaging, an action which could cause deleterious effects on patient's cognitive function and behaviour.

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