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Title: No Effect of Donepezil on Striatal Dopamine Release in Mild to Moderate Alzheimer's Disease

Running Title: Donepezil and Striatal Dopamine Release

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ABSTRACT

Objective: Work in experimental animals suggests that an interaction with dopaminergic networks might explain some of the therapeutic effects of the cholinesterase inhibitor class of drugs. This study aimed to test whether acute (single 5mg) or four to eight weeks (5 to 10mg) treatment with oral donepezil would elicit measurable striatal dopamine (DA) release in patients with mild to moderate Alzheimer's Disease (AD). A second aim was to establish whether any increase in DA levels would be associated with improvements in cognitive and motor function.

Methods: Percentage change in [¹¹C] Raclopride (RAC) binding potential (BP_{ND}) between baseline and treatment conditions was used to provide a measure of DA release. Repeated measures ANOVA was used to determine the effect of treatment upon [¹¹C] RAC BP_{ND} and neuropsychological test performance.

Results: Contrary to our prediction there was no significant change in [¹¹C] RAC BP_{ND} after acute or a mean of six weeks (range = 4-12) treatment with donepezil. Although motor speed (finger tapping) improved following 4-12 weeks treatment with donepezil ($F_{1,19} = 8.7, p = 0.009$) this was not associated with the degree of change in [¹¹C] RAC BP_{ND}.

Conclusions: Our findings provide no evidence that striatal DA levels are altered during the first 3 months of donepezil treatment. However we cannot rule out the possibility that extrastriatal effects may be occurring.

INTRODUCTION

Cholinesterase inhibitors such as donepezil are presumed to exert their therapeutic effects via the enhancement of cholinergic neurotransmission. However evidence suggests that this class of drugs may also enhance dopamine (DA) release by facilitating the desensitization and subsequent upregulation of nicotinic receptor sites.^{1, 2} Acute exposure to therapeutic doses of donepezil has been shown to significantly increase DA release in the rodent striatum,³ similar to the changes observed following exposure to low dose nicotine;⁴ and a four-fold increase in DA levels has been observed in the rodent hippocampus following 3 weeks treatment with oral donepezil.⁵ This study aimed to test the hypotheses that

- (i) Acute and/or four to eight weeks treatment with donepezil would increase striatal DA levels in people with mild to moderate AD
- (ii) The degree of change in [¹¹C] RAC BP_{ND} would correlate with changes in cognitive and motor function.

PATIENTS AND METHODS

Sample: Twenty four patients with probable late-onset AD (NINCDS-ADRDA)⁶ were recruited. All were eligible to receive donepezil, were not prescribed psychotropic or other medication that might interfere with DA function and had no motor symptoms. Written and verbal consent was obtained at the time of recruitment and repeated prior to the scanning procedure.

PET Procedure: [¹¹C]-Raclopride (RAC) is a PET radiotracer that competes with endogenous DA for striatal DA (D2) receptor sites. This competition has been utilized in

imaging paradigms that aim to estimate DA release following pharmacological challenge,⁷ a reduction in [¹¹C] RAC binding potential (BP_{ND})⁸ indicating DA release.

Baseline measures of [¹¹C] RAC BP_{ND} were compared to acute (4 hours post) and/or 4-8 weeks treatment with donepezil. A power calculation, based on the 5% reduction in [¹¹C] RAC BP_{ND} observed following low dose nicotine,⁹ indicated that a sample of 10 would allow a 4.7% reduction to be detected between scanning conditions (alpha = 0.05, power = 0.8), given the 4.7% test-retest reliability of [¹¹C] RAC BP_{ND}. Participants were scanned at rest on a 962-Siemens/CTI PET camera in 3D mode, using a bolus infusion technique (κbol = 60minutes; total administered activity 370 MBq per scan),¹⁰ a method which enables a state of dynamic equilibrium to be achieved, thus avoiding potential artefacts induced by blood flow changes. Head movement was corrected using a frame-by-frame realignment procedure, to create dynamic images. Region of interest (ROI) templates for striatal (limbic, associative and sensorimotor) and cerebellar areas were defined using previously described criteria:^{11, 12} Templates were applied to dynamic images to generate time-activity curves for striatal (region-of-interest) and cerebellar (reference) regions. The sampling period for calculation of BP_{ND} - once [¹¹C] RAC equilibrium had been established - was 35-60 minutes. Time activity curves were inspected to ensure that equilibrium had been achieved in all cases. For full details of the recruitment and scanning procedure see Reeves et al (2009).¹³

Neuropsychological Tests: In addition to a global measure of functioning - the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)¹⁴ - the following tests were carried out at baseline and after four to eight weeks treatment (i) Rapid Visual Information Processing (RVP) – a test of visual sustained attention from the

Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, UK) ¹⁵ (ii) Stockings of Cambridge (SOC) test of spatial planning (CANTAB) battery ¹⁵ (iii) Grooved Pegboard – a test of fine motor dexterity ¹⁶ (iv) Computerised Finger Tapping Task – a test of motor speed. ¹⁷

Statistical Analysis: Data were analysed using SPSS 15.0. Repeated measures ANOVA was used to determine the effect of treatment upon [¹¹C] RAC BP_{ND} and neuropsychological test performance. Correlational analysis was used to examine associations between changes in [¹¹C] RAC BP_{ND} and variables including mg/kg dose and treatment duration. Previously we reported higher BP_{ND} in men from this sample at baseline. ¹³ To control for this, an independent samples t-test was used to examine the impact of gender upon change in BP_{ND}.

RESULTS

Changes in [¹¹C] RAC BP_{ND} Following Donepezil Treatment

Twenty four participants (11 men) were recruited to the imaging group (mean age 78.7+-6.1 years, mean MMSE 21.6 +- 2.9). Twenty one (88%) were right-handed.

Acute Treatment

Ten patients (4 men) were scanned 4.2 +-0.4 hours post 5mg donepezil (mean mg/kg dose = 0.08). Excessive movement during the scan led to the exclusion of one man. Compared to baseline, [¹¹C] RAC BP_{ND} increased by 1.6% (SD = 4.6) in the whole striatum ($F_{1,9} = 1.3$, $p = 0.28$), replicated in all subregions (Table 1). Neither age ($r = 0.02$, $p = 0.96$) nor mg/kg dose ($r = -0.16$, $p = 0.69$) correlated with change in BP_{ND}. Exclusion of a left handed individual did not alter the findings.

Four to Eight Weeks Treatment

Twenty patients (10 men) were scanned following 4 to 12 weeks treatment (5 to 10mg) with donepezil, longer duration of treatment in 3 participants occurring due to technical/scanner difficulties. Three participants were unable to tolerate donepezil and one dropped out of the study due to incidental physical health problems. Excessive movement during the scan led to the exclusion of one woman. Thirteen (68%) participants were prescribed 5mg donepezil. Mean duration of treatment was 42 +- 16.2 days (mean daily dose = 0.1 +-0.04 mg/kg). Compared to baseline, [¹¹C] RAC BP_{ND} increased by 2.2 +- 7.4% in the whole striatum ($F_{1,18} = 1.3$, $p = 0.26$) (Figure 1), replicated in all subregions (Table 1). Neither age ($r = 0.10$, $p = 0.67$), mg/kg dose ($r = 0.11$, $p = 0.66$), nor duration of treatment ($r = 0.09$, $p = 0.70$) correlated with percentage change in striatal BP_{ND}. There were no group differences in the change in BP_{ND} when separated by gender ($t_{17} = -0.9$, $p=0.38$) or donepezil (5mg versus 10mg) dose ($t_{17} = 0.64$, $p = 0.53$). Changes in neuropsychological test performance (Table 1) were not correlated with changes in BP_{ND}: ADAS-cog ($r = 0.07$, $p = 0.78$), spatial planning ($r = 0.22$, $p = 0.43$), grooved pegboard ($r = 0.26$, $p = 0.27$), finger tapping ($r = - 0.30$, $p = 0.21$), RVP ($r = - 0.47$, $p = 0.07$ - driven by two outliers).

DISCUSSION

Changes in [¹¹C] RAC BP_{ND} Following Donepezil

We found no change in [¹¹C] RAC BP_{ND} following acute or 4 to 12 weeks treatment with donepezil and there are several possible explanations for this. Our original hypothesis was based upon voltammetry data in rodents indicating an increase in striatal DA release following acute donepezil exposure.³ Oral administration of donepezil in our study inevitably introduced variability in plasma and brain donepezil concentrations; and whilst

mean (mg/kg) drug dosage was not correlated with change in [¹¹C] RAC BP_{ND}, differential responses to donepezil may have occurred within the striatum – as described by Zhang et al (2004).³

Other methodological considerations include the fact that PET measures are taken over a relatively long duration and are less sensitive to real-time changes in DA release than voltammetry techniques. Any net effect of (acute or 4 to 12 week) donepezil treatment over the scan duration may thus appear to be negligible. The modulatory influence of acetylcholine upon nicotinic cholinergic receptors is complex and dependent upon the activity state (firing frequency) of pre-synaptic neurones, leading to inhibition of DA release when in the tonic state and enhancement when in the phasic state.¹⁸ It is thus possible that our findings might reflect a predominantly inhibitory effect of donepezil upon striatal DA release in ‘at rest’ individuals.

Our hypothesis regarding 4 to 12 weeks treatment with donepezil presumed that nicotinic receptor upregulation would enhance DA release. However, whilst there is evidence that nicotinic receptor upregulation occurs within the cortex^{19, 20} this does not necessarily apply to other regions.^{21, 22} It is possible that variation in drug dosage and treatment duration reduced our ability to detect changes in striatal DA levels. Although neither duration of treatment nor mg/kg dosage correlated with mean change in [¹¹C] RAC BP_{ND}, only a small number (n = 6) were on optimal (10mg) treatment and we therefore cannot rule out the possibility of an effect on striatal DA at the higher dosage. Against this, our findings are in line with recently published SPECT data that showed no effect of chronic treatment with cholinesterase inhibitors upon striatal DA transporter availability.²³

The issue of statistical power needs to be addressed. It is not possible to directly extrapolate from voltammetry or microdialysis data to PET as the relationship is not a linear one and varies between drugs.^{24, 25} Although our sample size allowed us to detect changes as low as 3% after 4 to 12 weeks treatment, we were not powered to detect more subtle changes. In the absence of data on healthy older individuals, it is not possible to ascertain whether these findings are specific to AD. Furthermore our use of [¹¹C] RAC as a radiotracer meant that we were unable to measure changes in cortical DA levels and this will need to be investigated through the use of high affinity radiotracers that target extrastriatal DA (D2) receptor sites.

Disclosure/Conflict of Interest: All of the authors report no competing interests.

Professor Howard discloses that he has received honoraria as speaker's fee from Lundbeck and Pfizer-Eisai. Pfizer-Eisai and Lundbeck have provided medication and placebo for independently-funded randomised controlled trials on which Professor Howard is Chief Investigator; and Professor Grasby has served as an occasional consultant to GlaxoSmithKline, Merck and Pfizer.

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Ethics Approval: The study was approved by the Charing Cross and the Joint South London and Maudsley and Institute of Psychiatry NHS Research Ethics Committees. ARSAC (the Administration of Radioactive Substances Advisory Committee) granted permission to administer [¹¹C]-Raclopride

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Figure Legends

Figure 1

Individual changes in [¹¹C] RAC BP_{ND} between baseline and four to twelve weeks treatment with 5mg (shown as circles) or 10mg (shown as triangles) donepezil are plotted.

Table 1. Changes in [¹¹C] RAC BP_{ND} and Neuropsychological Tests Following Donepezil Treatment

Acute Dose (n = 9)	Mean (SD)	Mean (SD) :	Mean (SD); range % change	F_{df}
	Baseline	Single dose		
BP _{ND} <i>Striatum</i>	2.14 (0.13)	2.18 (0.16)	+1.5% (4.6); +8.6 to -7.5	1.3 _{1,8}
<i>Sensorimotor striatum</i>	2.55 (0.15)	2.57 (0.12)	+0.9% (2.8); +4.2 to -3.6	0.8 _{1,8}
<i>Associative striatum</i>	2.01 (0.15)	2.06 (0.20)	+2.4% (5.2); +10.4 to -8.6	2.4 _{1,8}
<i>Limbic striatum</i>	1.88 (0.16)	1.91 (0.24)	+1.4% (7.9); +12.1 to -15.7	0.41 _{1,8}
Four to Twelve Weeks (n = 19)	Mean (SD)	Mean (SD) :	Mean (SD) range % change	F_{df} (p)
	Baseline	4-12weeks		
BP _{ND} <i>Striatum</i>	2.17 (0.31)	2.21 (0.31)	+ 2.2 % (7.3); +22.6 to -9.8	1.3 _{1,18}
<i>Sensorimotor striatum</i>	2.54 (0.32)	2.58 (0.29)	+ 1.5 % (6.4); +16.6 to -11.7	0.6 _{1,18}
<i>Associative striatum</i>	2.02 (0.35)	2.07 (0.37)	+ 2.7 % (9.3); + 28.3 to -9.7	1.4 _{1,18}
<i>Limbic striatum</i>	1.95 (0.29)	2.00 (0.32)	+ 2.4 % (7.9); +22.8 to -10.6	1.6 _{1,18}
ADAS-cog [†]	21.3 (8.2)	18.7 (6.0)	-7.8 % (23.8); +35.7 to -40	4.91 _{1,18}
RVP: <i>Number of hits</i>	6.2 (2.2)	7.0 (2.2)	+ 26.4 % (80.9); + 300 to -57.1	1.2 _{1,14}
SOC: <i>Perfect Solutions</i>	7.1 (2.1)	6.9 (2.2)	+ 1.7 % (24.7); + 55 to -50	0.1 _{1,14}
Finger Tapping: <i>taps/s</i>	3.5 (0.9)	3.9 (0.8)	+ 14.1 % (23.7); + 93.9 to -15.2	6.8 _{1,18} *
Grooved Pegboard: <i>Time(s)</i> [†]	180.5 (75.3)	172.4 (80.9)	- 1.3 % (30.5); + 63.7 to -56.3	0.4 _{1,18}

* p< 0.05

[†] higher scores indicate poorer performance

Exclusion of non right-handed participants (n = 3), or participants scanned after eight weeks treatment (n = 3), did not alter the findings

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[¹¹C] RAC BP_{ND}

3.0
2.5
2.0

Baseline

Four to Twelve Weeks

