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Acute tryptophan depletion and Lewy body dementias

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ABSTRACT

Background: Studies using acute tryptophan depletion (ATD) to examine the effects of a rapid reduction in serotonin function have shown a reduction in global cognitive status during ATD in Alzheimer's disease (AD) and Parkinson's disease (PD). Based on the severe cholinergic loss evident in dementia with Lewy bodies (DLB) and Parkinson's disease and dementia (PDD), we predicted that a reduction of global cognitive status during ATD would be greater in these conditions than in AD.

Methods: Patients having DLB or PDD underwent ATD in a double-blind, placebo-controlled, randomized, counterbalanced, crossover design.

Results: While the study intended to test 20 patients, the protocol was poorly tolerated and terminated after six patients attempted, but only four patients – three with DLB and one with PDD – completed the protocol. The Modified Mini-Mental State Examination (3MSE) score was reduced in all three DLB patients and unchanged in the PDD and dementia patient during ATD compared with placebo.

Conclusions: This reduction in global cognitive function and the poor tolerability may fit with the hypothesis that people with dementia with Lewy bodies have sensitivity to the effects of reduced serotonin function.

Key words: Parkinson's disease, dementia, memory, cognitive disorders, dementia with Lewy bodies

Introduction

ATD studies used to examine the effects of a rapid reduction in serotonin function have investigated the role of serotonin function in AD (Porter *et al.*, 2000; 2003), PD (Scholtissen *et al.*, 2006; Mace *et al.*, 2010a; 2010b), and recovered depression in the elderly (Porter *et al.*, 2005; 2007). These studies have found that ATD generally decreased global cognitive status (as measured by the MMSE) in patients compared with healthy controls. We have suggested that this may be a result of a sudden reduction in serotonin function compounding an impaired cholinergic system in these conditions.

There is evidence that cholinergic impairment is comparatively greater in PDD and DLB (Tiraboschi *et al.*, 2002; Bohnen *et al.*, 2003); thus, we predict that the effect of ATD on global cognitive status would be greater in dementia associated with Lewy body pathology than in AD.

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Methods

PDD and DLB patients, as defined by the Movement Disorders Society task force (Emre *et al.*, 2007) and the consensus guidelines for dementia with Lewy bodies (McKeith *et al.*, 1996), were recruited by a neurologist (TA) and old age psychiatrist (CC) in Christchurch, New Zealand. Patients had a recent physical and neurological examination. Exclusion criteria included a history of affective or other psychiatric disorder, serious medical disease, and serotonergic medication. All patients participated voluntarily and written informed consent was obtained. The study received ethical approval from the Upper South B Regional Ethics Committee, Christchurch. The design, procedure, and assessments have been described elsewhere (Mace, 2010a; 2010b). Cognitive status was measured using the Modified

Table 1. Patient characteristics at baseline

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Diagnosis	DLB	DLB	PDD	DLB
Age	72	71	71	79
Gender	Male	Female	Female	Male
PVIQ	100	102	101	102
MMSE	29	20	26	18
MADRS	10	0	10	6
UPDRS	25.8	22.5	38.5	46
H & Y	2.5	2.5	3	
Age of onset (yrs)	66	69	69	65
Side of onset	n/a	n/a	Right	n/a
Medication	Sinemet	Clozapine	Sinemet	Sinemet
	Aricept	Quetiapine	Quetiapine	Quetiapine
		Galantamine	Bromocriptine	Rivastigmine

Note. DLB = dementia with Lewy bodies; H & Y = Hoehn and Yahr (1967); MADRS = Montgomery–Asberg Depression Rating Scale; MMSE = Mini-Mental State Examination; PDD = Parkinson's disease and dementia; PVIQ = Predicted Verbal IQ (Nelson, 1982); UPDRS = United Parkinson's Disease Rating Scale.

Mini-Mental State test (3MS) (Teng and Chui, 1991). Practice effects were attenuated by using three different items for each registration and recall category as per the manual. Paired samples t-tests were used to compare results between placebo and depletion using SPSS for Windows Release 18 (SPSS, Chicago, Illinois).

Results

The study was designed to recruit 20 patients. However, the trial was terminated because of adverse events such that only four patients completed testing. Of the six patients recruited to the study, one female PDD patient, taking lisuride, sinemet, selegiline, procyclidine, and ranitidine, vomited at noon on the first test day and was taken home before testing. One female patient with DLB, taking rivastigmine, became obviously very confused during the late afternoon of the second visit (depletion) and meaningful testing could not be carried out. Confusion was not, in the weeks prior to the study, a significant part of her presentation. At follow-up, her nursing staff reported she had hallucinated on her way home. The characteristics of the four patients who completed two test days are presented in Table 1.

Assessments

Data for all patients were limited and only complete data sets are shown in Table 2 and reported in text.

There was a significant difference in TRP at 4 hours when levels were lower after depletion (M = 775.00, SD = 427.20) and higher after the placebo (M = 5800.00, SD = 3496.67; $t_3 = 3.25$, p = 0.047).

3MSE scores were lower after depletion (M = 65, SD = 17.98) compared with placebo (M = 71, SD = 15.17; $t_3 = -2.64$, p = 0.08). The effect size (d) with all four patients was 1.38 (CI = −0.03 to 2.80). When restricted to the three DLB patients, d = 1.84 (CI = −0.22 to 3.91).

There was no significant difference in the change scores on Montgomery–Asberg Depression Rating Scale (MADRS), that is, the difference between baseline and 4.5 hours, after depletion (M = 5.5, SD = 4.51) compared to placebo (M = 2.25, SD = 3.60; $t_3 = 1.01$, p = 0.39).

Discussion

In the four patients who tolerated ATD, the procedure significantly lowered tryptophan levels by an average of 61% at 4 hours, which is in keeping with previous studies.

The patients in this study found the protocol difficult to tolerate and a decision was made to terminate the study early. This is in contrast to previous studies in the healthy elderly, including a group aged between 70 and 90 (Mace *et al.*, 2011), and studies mentioned previously in Alzheimer's and Parkinson's diseases in which ATD has been found to be relatively tolerable. The poor tolerability of ATD in this group could relate to the marked impairment in the cholinergic system found in DLB and PDD.

In particular, one patient became very confused and hallucinated during depletion. Although potentially related to ATD, we note the scale we used to assess fluctuations in consciousness

Table 2. Individual results for complete assessments

			PATIENT 1 ATD MEAN	(DLB) PLACEBO MEAN	PATIENT 2 ATD MEAN	(DLB) PLACEBO MEAN	PATIENT 3 ATD MEAN	(PDD) PLACEBO MEAN	PATIENT 5 ATD MEAN	(DLB) PLACEBO MEAN	p
Biological											
TRP 4 hours		ng/mL	700	6100	500	4300	1400	10500	500	2300	*
Global cognitive function											
3MSE		Total	84	89	42	52	73	73	61	70	
Mood											
MADRS	0 hours	Total	11	8	0	6	12	3	9	20	
	4.5 hours	Total	6	9	0	3	1	3	3	13	
	6.5 hours	Total	16	5			4	7	16	15	
Change score 0 hours–4.5 hours		Difference	5	1	0	3	11	0	6	7	
Working memory											
DigitsF		Total	7	4	2	3	9	7	5	0	
DigitsB		Total	5	4	1	0	3	2	1	2	
DOT		Total	5	2	0	0	1	2	0	1	
COWA		Total	18	15	0	0	24	27	6	14	
Visuoperception											
VOSP silhouettes		Total	9	8	0	3	10	7	7	7	
Psychomotor											
CRT time 1		Reaction time (ms)	530.74	507.84	3174.13	9532.15	876.58	689.76	809.5	2845.5	
CRT time 2		Reaction time (ms)	471.56	444.67	3506.82	4213.27	738.5	812.11	1024.24	1451.82	
Consciousness											
ODFAS		Total	4	8	15	12	6	1	6	10	

Note. ATD = Acute Tryptophan Depletion; COWA = Controlled Oral Word Association test; CRT = Choice Reaction Time; DigitsB = Digit Span Backward; DigitsF = Digit Span Forward; DLB = dementia with Lewy bodies; 3MSE = Modified Mini-Mental State Examination; ODFAS = One Day Fluctuation Assessment Scale; PDD = Parkinson's disease and dementia; TRP = plasma tryptophan; VOSP = Visual Object and Space Perception test.
*$p < 0.05$.

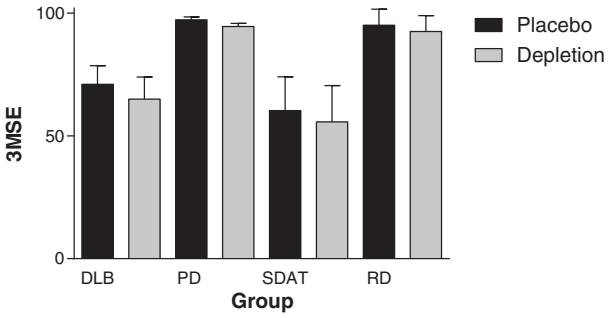

Figure 1. Effects of ATD on global cognitive function in DLB/PDD (current data), PD (Mace *et al.*, 2010b), senile dementia of the Alzheimer's type (SDAT) (Porter *et al.*, 2000) and recovered depression in the elderly (RD) (Porter *et al.*, 2005).

during the day – which was designed to assess fluctuations in DLB (Walker *et al.*, 2000) – did not show a consistent difference between ATD and placebo in the other patients. In this patient, there was uncertainty regarding the nursing home's administration of her usual rivastigmine on that morning and, although clinically significant confusion is not generally a sequela of missing a dose of a cholinesterase inhibitor, the confusion could possibly have been secondary to this omission. This patient was only taking rivastigmine, making interactions between current therapy and the effects of ATD less complicated than in the other patients. Confusion had not been a particular clinical problem in the weeks prior to depletion.

Based on previous studies and the marked cholinergic deficit in DLB/PDD, we hypothesized that ATD would reduce global cognitive status in DLB/PDD. Given the small sample size, it is not surprising that results were not significant. However, three of the four patients did have a lower 3MSE during depletion, while in the fourth patient it was unchanged. A reduction in 3MSE is in line with the results of previous studies as illustrated in Figure 1 and is compatible with the explanation that an overall cholinergic deficit, combined with a profound reduction in serotonin function caused by ATD, gives rise to a global cognitive impairment. One study referred to in Figure 1 was conducted in recovered elderly depressed subjects in whom cholinergic deficit has not been well described. However in PD at least, depression does seem to be associated with greater cholinergic deficit (Bohnen *et al.*, 2007). The magnitude of the change in 3MSE obviously depends on the severity of cognitive impairment at baseline. In unimpaired groups, the 3MSE is likely to be relatively insensitive to change because subjects are operating at close to ceiling. As can be seen from Figure 1, the magnitude of change is greater in the DLB/PDD and the Alzheimer's (senile dementia of the Alzheimer's type) groups, both of whom have a much lower baseline. Variability of scores is of course also much greater in these groups and it is important to note once again the low number of patients tested in the current study and the variability that this introduces. The small number of subjects with variable test results also makes it very difficult to draw any further conclusions from the more detailed neuropsychological testing. The results of more detailed testing have not been consistent in the previous studies described.

Surprisingly, none of the studies described have shown a significant differential effect on mood in the patient groups despite all being more vulnerable to depression than healthy subjects. In this small group of patients with DLB/PDD, there was no clear effect on MADRS scores.

The changes in cognitive status which appear to have occurred in this study, in response to ATD, may not be a direct result of reduced central serotonin function. Young *et al.* (2013) review a number of other effects of ATD to which the patients in this study, by virtue of their neurodegenerative brain impairment, may be more vulnerable.

A further complicating factor in this study is that patients were on a range of medication including three patients who were taking a combination of L-dopa and a peripheral decarboxylase inhibitor and three who were on quetiapine. It is beyond the scope of this paper to review all the possible implications of this especially given the small number of patients. However, of particular note may be the data suggesting that the upregulation of $5HT_2$ receptors during ATD is important (Price *et al.*, 1997). The $5HT_2$ antagonist effect of quetiapine could significantly alter this effect.

The adverse effects seen in this study raise further concern regarding the ethics of administering compounds that may cause even a temporary deterioration in a patient group. The possible information gained, given uncertainty regarding the specificity of the method, must be weighed against the possible side effects. If, following this assessment, symptom provocation studies such as this one are contemplated, we agree with the recommendation of Young *et al.* (2013) that vulnerable participants be carefully observed (including a post-test follow-up) and administered 1 gram of tryptophan at the end of the study day to restore tryptophan levels.

The small number of patients completing the current study and uncertainties regarding the ATD method makes it impossible to draw firm conclusions. However, important results are that the protocol was poorly tolerated in this group and that there was a trend towards a reduction

in global cognitive status during ATD possibly suggesting that, as hypothesized, this group is particularly susceptible to a sudden reduction in serotonin function. Clinically, it is difficult to draw conclusions from a small experimental study such as this. In our practice however, this study has increased our caution and degree of monitoring when withdrawing SSRI medication in this group of patients.

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Conflict of interest

None.

Description of authors' roles

Design of study – all authors. Data collection – J Mace. Supervision of data collection – R Porter, T Anderson. Patient recruitment – C Collins, T Anderson. Statistical design and analysis – J Mace, R Porter. Writing of article – all authors.

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