Short report

Effect of naltrexone on senile dementia of the Alzheimer type

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SUMMARY Some reports have suggested that naloxone, a short-acting opiate receptor blocker given intravenously, has a beneficial effect on the symptoms of senile dementia of the Alzheimer type. We have performed a double-blind, crossover trial of naltrexone, an orally active, long acting opiate antagonist, in 17 Alzheimer-type dementia patients. None showed any improvement in assessments of day-to-day living skills or on a battery of neuropsychological tests. No side effects were noted. In the dosage used, naltrexone appears not to be useful in Alzheimer-type dementia.

Research on senile dementia of the Alzheimer type has uncovered defects in the noradrenergic, cholinergic, and somatostatinergic transmitter systems but the cause of the disease remains unknown,¹⁻⁴ and there is no effective treatment. Nonetheless, trials with cholinergic precursors and acetylcholinesterase inhibitors have resulted in some improvement and suggested that pharmacological intervention might be beneficial.⁵

Opiate antagonists can influence attention and memory and it has been hypothesised that they may be useful in Alzheimer-type dementia.⁶ Two reports described improvement in some patients with this disorder following intravenous administration of naloxone, a short-acting opiate antagonist.^{7,8} The results of subsequent trials, however, were disappointing.^{9,10} Possible causes for the failure of naloxone might include the short half-life of the substance (less than one hour) and the fact that intravenous administration will not maintain a continuous high blood level and a sustained opioid blockade. To find out if such limitations do indeed play a role, we undertook a double-blind cross-over study of naltrexone, a long acting opiate antagonist,¹¹ that can

be administered orally, and that produces a higher level of opiate blockade than naloxone at equivalent doses. The relatively long half-life of naltrexone, greater than 24 hours, suggests that opiate blockade can be maintained continuously for days when an oral dosing regimen is followed.

Methods

Subjects

Seventeen patients with Alzheimer-type dementia were recruited for this study (7 male; 10 female). All had extensive neurological, neuropsychological, and neuroradiological studies which were consistent with Alzheimer-type dementia. Only those patients who could understand and complete neuropsychological tests were included. Length of illness ranged from 1 to 15 years (4.4 ± 3.4 years, mean $\pm$ SE). Ages ranged from 57 to 81 years, with a mean of 67.5 years. Five had a positive family history for dementia. One patient did not attend the last session (placebo) because of agitation, apparently unrelated to the study.

Procedures

Informed consent was obtained from the patients and their families. Patients were given either 100 mg/day naltrexone HCl, by mouth (courtesy of Du Pont, Inc.) or placebo, each week, during a six-week double blind crossover study. Active medication was administered during either the second or fourth week of the study. Blood pressure, heart rate and weight were monitored at each session. Each week patients were also evaluated by a battery of neuropsychological tests, the family was interviewed to assess

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Table Effect of naltrexone and placebo on behavioural measures

Test	Scoring range (best to worst)	Difference due to naltrexone*			Difference due to placebo†		
		mean	SEM	t‡	mean	SEM	t‡
Daily living assessment	(0 to 57)	-0.57	0.85	-0.67	1.24	1.09	1.13
Temporal orientation	(0 to -113)	-3.16	4.34	-0.73	9.65	7.03	1.37
Recall of presidents	(7 to 0)	0.02	0.18	0.16	0.18	0.18	1.00
Personal information	(6 to 0)	-0.15	0.14	-1.12	0.24	0.26	0.89
Digit span	(16 to 0)	-0.90	0.47	-1.91	0.24	0.36	0.66
Line orientation	(10 to 0)	-0.08	0.28	-0.32	-0.25	0.40	-0.62
Verbal memory							
Trial 1 correct	(9 to 0)	-0.05	0.20	-0.30	0.00	0.26	0.00
errors	(0 to 9)	-0.00	0.28	-0.02	-1.00	0.43	-2.33
Trial 2 correct	(9 to 0)	0.04	0.27	0.18	0.24	0.33	0.72
errors	(0 to 9)	-0.05	0.26	-0.21	0.47	0.24	-1.93
Trial 3 correct	(9 to 0)	-0.18	0.33	-0.55	0.05	0.35	0.17
errors	(0 to 9)	0.38	0.29	1.30	-0.88	0.27	-3.27
Delay correct	(9 to 0)	-0.07	0.20	-0.38	-0.35	0.24	-1.46
errors	(0 to 9)	-0.02	0.27	-0.09	-1.06	0.53	-2.00
Recognition							
correct	(9 to 0)	0.15	0.54	0.27	-0.35	0.53	-0.66
errors	(0 to 9)	-0.45	0.51	-0.87	0.05	0.46	0.13
d'	(4.6 to -4.6)	0.24	0.29	0.84	-0.09	0.24	0.40
Perceptual speed	(21 to 0)	-1.17	0.65	-1.79	0.35	0.62	0.57
Visual retention							
correct	(5 to 0)	-0.14	0.19	-0.76	-0.06	0.19	-0.32
errors	(0 to 13)	0.42	0.43	0.98	0.00	0.50	0.00
Controlled oral word association	(60 to 0)	1.20	1.21	0.99	0.58	0.93	0.63

*Calculated as mean of placebo scores (n = 4) minus the naltrexone score.

†Calculated as placebo score (session 2) minus the no medication score (session 1).

‡For 16 degrees of freedom, using Bonferroni's correction for multiple comparisons, $t_{crit} = 3.686$ ($p < 0.05$).

side effects and changes in day-to-day function, and a daily living assessment questionnaire was filled in by the family. The Hamilton depression and anxiety scales were (completed) at initial interview and after the second and fourth weeks.

The neuropsychological battery¹² included measures of: (1) *Orientation* to time, place and personal information; (2) *Immediate memory for digits* (digit span); (3) *Verbal learning and memory* in which subjects recalled a nine word list in a multiple trial, free recall format. Five minute delayed recall and recognition trials were included; (4) *Visual memory for designs* in which subjects were required to reproduce a geometric design after a 10 second exposure period. Five trials were adapted from the Visual Retention test; (5) *Visuospatial judgment* in which subjects were required to judge the orientation of lines in a matching to sample procedure. Ten trials were administered; (6) *Perceptual Speed* in which subjects were required to cross out a particular digit appearing 21 times among seven lines of 29 digits each. The dependent measure was number correct in 45 seconds; (7) *Controlled Oral Word Association* in which subjects orally generated words beginning with a given letter of the alphabet within a minute time period. Three letters were administered. This battery was designed in six parallel forms, and order of presentation of these forms was randomized for each patient.

For each patient, mean test scores were calculated from the four placebo trials. This mean was then compared to performance on the naltrexone trial by means of a *t* test. Level of statistical significance ($p < 0.05$) was adjusted using Bonferroni's correction for multiple comparisons. Difference scores were also computed for naltrexone vs placebo trials as well as for no medication (initial test ses-

sion) vs placebo trials. These scores were then analysed for the entire group of 17 patients by means of *t* tests, which were interpreted using Bonferroni's correction for multiple comparisons.

Results

As a group, the patients demonstrated no significant statistical change in performances on the neuropsychological battery, daily living questionnaire and Hamilton scales following naltrexone treatment. Family members did not report any consistent improvement during the week of naltrexone treatment. For example, during naltrexone treatment the results of the daily living questionnaire showed slight improvement in nine patients, worsening in seven, and no change in one. As a group, after treatment with naltrexone as compared to placebo, the patients' mean performance level was slightly higher on eight tasks of the neuropsychological battery and worse on 11 tasks; however, none of the difference scores reached statistical significance (table), even without correction for multiple comparisons. Similarly, comparison of performance at baseline (initial testing session, no medications) vs placebo (week 1) revealed no significant placebo effects.

Test scores after naltrexone therapy were also compared for each patient on an individual basis. In only one case was a significant difference found, and that one patient performed in the reverse direction,

Effect of naltrexone on senile dementia of the Alzheimer type

more poorly, on the digit span test after naltrexone than after placebo ($t = 10.1$, $p < 0.001$). This patient did not have significant differences on any other task.

The medication was well tolerated by all patients. No side effects were noted by the family or patients. No significant changes in heart rate, blood pressure, or weight occurred with naltrexone therapy, either in an individual patient or across the group.

Discussion

The effect of opiate antagonists on learning and memory is not yet fully understood. In young, normal volunteers high doses of naloxone (2 mg/kg, IV) has decreased performance on a delayed word recall and recognition task, but had no effect on immediate memory.¹³ Lower doses (0.03 mg/kg) of naloxone have been linked to increased selective attention in man.¹⁴ In the rat, naloxone has been shown to attenuate the amnesia caused by amygdaloid stimulation¹⁵ or electroconvulsive shock.¹⁶ Naltrexone has been shown to have an effect similar to naloxone, by increasing retention of passive avoidance tasks.¹⁷

In this study, we assessed the efficacy of naltrexone in the possible amelioration of memory and other cognitive deficits characteristic of Alzheimer-type dementia. Our results show that this intervention produced no improvement. Nonetheless, since our intervention was based on a single dosage schedule, for one week only, it remains possible that alternative dosage regimens may uncover some effect of long term opiate antagonists. Finally, we did not encounter any major side effects of naltrexone administration in this group of patients.

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