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Anticholinergic Serum Levels and Cognitive Performance*

Ole J. Thienhaus, Alice Allen, Jerry A. Bennett, Yash M. Chopra, and Frank P. Zemlan

Laboratory of Geriatrics, Department of Psychiatry, University of Cincinnati, Cincinnati, OH 45267-0559, USA

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Summary. Integrity of central cholinergic neurotransmission is essential for adequate cognitive functioning. Many psychotherapeutic medications have anticholinergic side-effects. In order to determine the impact of circulating anticholinergic activity on cognitive performance, 28 geropsychiatric inpatients underwent cognitive testing at different levels of anticholinergic serum activity. In 10 subjects with a diagnosis of probable Alzheimer's disease, significant deterioration of selected cognitive functions was observed at anticholinergic serum levels that caused no dysfunction in the 18 non-demented subjects. The data suggest that non-demented elderly patients with psychiatric problems tolerate psychotropic pharmacotherapy without significant negative impact on their cognitive competency. By contrast, patients with Alzheimer's disease are at risk of additional impairment. The introduction of anticholinergic serum activity as a monitoring technique for safe psychopharmacotherapy in geriatric patients is discussed.

Key words: Anticholinergic – Dementia – Psychopharmacology – Geriatrics

Introduction

Compelling evidence has accumulated over the past decade indicating that integrity of central cholinergic neurotransmission is an important factor in maintaining adequate cognitive function (Drachman and Leavitt 1974; Bartus et al. 1982). Much of the pertinent data has come out of research in Alzheimer's disease. Substantial depletion of cholineacetyltransferase, the rate-limiting enzyme in the synthesis of acetylcholine, is widespread in brain tissue with the morphological signs of Alzheimer's disease (Davies 1977; Corkin 1981). Moreover, the severity of dementia at the time of death and the extent of histopathological change are directly correlated with the magnitude of cholinergic deficiency (Perry et al. 1978).

In the clinical setting, atropine and related substances have long been known to induce acute cognitive impairment (Davies et al. 1971; Potamianos and Kellett 1982). Older people are generally at increased risk of metabolic disequilibrium because of age-related ubiquitous decline in homeostatic reserve capacities. Consequently, primers on geriatric psychopharmacology emphasize the importance of anticholinergic side-effects associated with most psychotropic agents in clinical use (Salzman 1982).

Anticholinergic toxicity is clinically characterized by peripheral signs and symptoms of parasympatholysis, and an organic brain syndrome with decreased attention span, disorientation, psychotic features and psychomotor agitation. All these symptoms can lead to secondary functional impairment of various degrees. It is therefore generally recommended that anticholinergic load should be minimized in order to avoid compromising cognitive competency in the elderly patient (Drachman 1977).

The in vitro affinity of various psychopharmacological agents for central cholinergic receptors has been described (Snyder et al. 1974; Snyder and Yamamura 1977). Extrapolation from these studies to the clinical situation is of questionable validity because many psychotropic agents are metabolized to intermediate products that also have central anticholinergic properties. In addition, patients are often simultaneously maintained on more than one medication with anticholinergic properties. An individual may receive antidepressant, neuroleptic and antiparkinsonian drugs concurrently. In such a case, the total level of circulating anticholinergic activity can be expected to have more impact on cognitive function than the serum concentration of any one of the prescribed medications separately. It is proposed that a clearer understanding of the relationship between anticholinergic serum levels and cognitive-functional status could eventually improve our ability to use psychotropic and other anticholinergic drugs.

Offprint requests to: O. J. Thienhaus

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In accord with current usage, this paper will use the terms cholinergic and anticholinergic to refer to agents' affinity for central muscarinic receptors (Goyal 1989). In this sense they are synonymous with antimuscarinic. Activities related to nicotinic receptors are not considered.

Previous research has demonstrated the utility of measuring free anticholinergic serum levels and correlating them with clinically observable data (Tune and Coyle 1981). Anticholinergic serum activity showed a significant inverse correlation with extrapyramidal features. In other studies, young schizophrenic patients who were treated with antipsychotic medication showed an inverse correlation between anticholinergic serum activities and short-term memory (Tune et al. 1982; Perlick et al. 1986).

In the work presented here, we examined the impact of anticholinergic serum activity in both demented and non-demented elderly patients who were treated with heterocyclic antidepressants, neuroleptics or antiparkinsonian medications or any combination of these drugs. Specifically, the investigation sought to assess cognitive and functional status as a putative function of measurable serum levels of anticholinergic activity. The underlying assumption was that neither the pharmacodynamic designation of the psychotropic agents nor their dosage, but solely the cumulative muscarinic receptor blocking potency, constituted the relevant independent variable.

Patients and Methods

Patient Selection. The study was carried out in the geropsychiatric inpatient service at the University Hospital, Cincinnati. Among patients who were consecutively admitted to have psychotropic medication initiated or dosages adjusted, 28 elderly subjects were recruited. Most patients had either not been on medication, or were medication non-compliant prior to admission.

The sample consisted of two groups. One group comprised patients with probable Alzheimer's disease ($n = 10$), the other patients without significant cognitive impairment ($n = 18$). In order to be included in the non-demented group, subjects had to score at least 25 on the Mini-mental State Examination (MMS) (Folstein et al. 1975), and no higher than 2 on the Global Deterioration Scale (GDS) (Reisberg et al. 1982). The MMS is a screening instrument for cognitive impairment. The maximum attainable score of 30 represents absence of measurable cognitive impairment. Conventionally, scores below 25 are considered indicative of clinical dementia. The GDS quantifies functional incapacity on a numerical score ranging from 0 to 7. The maximum score of 7 reflects severe, observer-rated functional impairment.

The second group only included patients meeting criteria for probable Alzheimer's disease as developed by the work group of the National Institute of Neurological and Communicative Disorders and Stroke in collaboration with the Alzheimer's Disease and Related Disorders Association (McKhann et al. 1984). These subjects scored less than 25 on the MMS and 3 or more on the GDS. They fulfilled clinical criteria for a dementing illness as defined in the DMS-III-R (American Psychiatric Association 1987). An identifiable causative factor had been ruled out by history, physical, laboratory and neuroradiologic examinations. A summary description of the sample is provided in Table 1.

After patients' admission to the psychiatric inpatient service, pharmacologic treatment regimens with either a neuroleptic or an antidepressant medication, depending on the target symptomatology, were initiated or resumed. Antiparkinsonian agents were added as needed to control for extrapyramidal side-effects of neuroleptic drugs. The decision whether a patient needed medication, the choice of a specific drug, and the dose adjustments were at the discretion of the treating physician and determined by clinical needs. A summary of the medications prescribed for all study participants is contained in Table 2.

Table 1. Sample characteristics (all subjects were inpatients on a geropsychiatric hospital ward; educational level was at least 8 years of formal schooling)

	Non-demented subjects	Alzheimer subjects
Sample size	18	10
Mean age (± SD)	64 ± 8	66 ± 11
Male : female	3:15	1: 9
Black : white	3:15	3: 7
High school graduates	8	5
Some high school	10	5
Diagnoses		
Major depression	11	0
Bipolar affective disorder	3	0
Schizophrenia	1	0
Dementia	0	10
Other	3	0

Informed Consent. Informed consent in accordance with the University of Cincinnati's Institutional Review Board was obtained from all subjects. No patients on involuntary hospital status were included. Among the demented patients, substituted consent was obtained from court-appointed guardians if the patient had been declared legally incompetent.

Procedures. Venous blood samples were drawn at the time of a subject's entry into the protocol, and after a steady-state serum level of the prescribed psychopharmacologic regimen had been attained, i.e. at least 7 days after the final dose adjustment. All other medications prescribed had to be kept constant throughout the patients' participation in the study.

Blood specimens were collected in untreated 10-ml tubes and allowed to clot at room temperature for 30 min. They were centrifuged at 2400 *g* for 10 min. Serum was removed and frozen at −20°C for up to 10 days prior to assay. Portions of the serum (200 µl) were assayed in triplicate for unbound anticholinergic activity utilizing the [^{3}H]-QNB radioreceptor assay described by Tune and Coyle (1981). The initial time point, associated with absent or low anticholinergic serum activity, was termed t_0, the time point of maximum anticholinergic activity t_1.

Cognitive Ratings. Subjects' cognitive and functional status was measured upon entry into the protocol and after attainment of medication steady state. The rater (A.A.) was blind as to the subject's measured blood level of anticholinergic activity. MMS scores served as screening measures of overall cognitive competency. The Digit Retention Span measures concentration by recording the highest number of single digits correctly repeated forward and in reverse by the subject (Buschke 1973). In assessing free recall, the score is obtained by computing the percentage of words, previously read to the subject, that are immediately remembered. In a similar manner, word recognition is tested. Given a written list of words, the subject is asked to identify which words he or she heard read out by the examiner. The score differentiates between hits, i.e. the number of correctly recognized words, and false alarms, i.e. the number of words "recognized" which had not been read before. False alarms represent a measure of intrusion error. Category retrieval measures knowledge memory (Battig and Montague 1969). The rater records the number of correctly associated words the subject spontaneously generates in response to a word stimulus over 90 s.

Table 2. Medications prescribed at t_1 for demented patients (probable Alzheimer's disease): dosages are total amount administerted in a 24-h period

	Diagnosis	Steady state medication
1	Dementia	Molindole 5 mg
2	Dementia	Perphenazine 64 mg and benztropine 1 mg
3	Dementia	Perphenazine 8 mg and diphenhydramine 25 mg
4	Dementia	Perphenazine 8 mg
5	Dementia	Loxapine 30 mg
6	Dementia	Fluphenazine 7.5 mg and desipramine 200 mg
7	Dementia	Desipramine 75 mg
8	Dementia	Nortriptyline 50 mg
9	Dementia	Desipramine 100 mg
10	Dementia	Perphenazine 2 mg and benztropine 2 mg
11	Major depression	Ipramine 150 mg
12	Major depression	Nortriptyline 75 mg
13	Major depression	Perphenazine 16 mg and desipramine 150 mg
14	Schizophrenia	Perphenazine 8 mg and diphenhydramine 75 mg
15	Bipolar disorder	Perphenazine 32 mg and benztropine 1 mg
16	Major depression	Protriptyline 20 mg and diphenhydramine 75 mg
17	Bipolar disorder	Perphenazine 8 mg
18	Agoraphobia	Desipramine 100 mg
19	Major depression	Diphenhydramine 50 mg
20	Bipolar disorder	Perphenazine 8 mg and benztropine 1 mg
21	Major depression	Desipramine 250 mg and perphenazine 16 mg
22	Major depression	Desipramine 75 mg and haloperidol 10 mg
23	Delusional disorder	Thiothixene 15 mg and diphenhydramine 50 mg
24	Major depression	Nortriptyline 75 mg
25	Major depression	Haloperidol 4 mg and benztropine 2 mg
26	Major depression	Nortriptyline 25 mg and perphenazine 24 mg
27	Major depression	Nortriptyline 75 mg
28	Bipolar disorder	Nortriptyline 75 mg

One of the testing instruments involved self-rating. The Self-rated Memory Scale (SRM) (Squire et al. 1979) reflects subjective evaluation of memory function on a Likert-type scale. A maximum score of 72 represents memory perceived as excellent. Four of the non-demented patients did not fill out the SRM questionnaire as instructed so that their responses could not be included in the data analysis. None of the Alzheimer patients were able to self-rate their memory.

Data Analysis. Ratings on each instrument were pooled across patients at each time point. A two-tailed paired *t*-test was used in order to determine significance of changes in rating scores between t_0 and t_1. Only for false alarms on word recognition testing was the Wilcoxon test used because the differences did not meet the assumption of a normal distribution. Correlation analysis was employed to determine Pearson's *r* representing the relationship between the independent variable, i.e. anticholinergic serum activity, and the dependent measures, i.e. cognitive rating scores. Linear regression analysis served to illustrate the relationship between measured atropine equivalents and conventional antidepressant blood levels, yielding both a regression equation and a coefficient of correlation.

Results

Serum Assays

In order to characterize the present anticholinergic serum assay, IC_{50} values for several tricyclic antidepressants and haloperidol were determined in [^{3}-H]-QNB competition experiments. As seen in Table 3, the IC_{50} values calculated under the present assay conditions were highly correlated with those previously reported in the literature, indicating that the present [^{3}-H]-QNB assay conditions accurately reflected serum drug binding to cortical muscarinic receptors.

Tables 4 and 5 summarize the results of the serum assays. Initial mean anticholinergic serum activity (reported in atropine equivalents) in the non-demented group

Table 3. Computation of IC_{50} values for various commonly used drugs indicate consistent high correlation with IC_{50} values for the same agents reported previously (Snyder et al. 1974; Snyder and Yamamura 1977)

Drug	Present study [n*M*]	Literature [n*M*]
Amitriptyline	3.9	10.0
Protriptyline	6.2	–
Nortriptyline	24.0	57.0
Desipramine	58.0	170.0
Haloperidol	>10,000	48,000

Table 4. Cognitive ratings and anticholinergic serum activities in subjects without dementia (MMS > 24; GDS < 3)

	t_0	t_1	Mean change
MMS	27.7 ± 2.2	27.9 ± 1.9	NS
Digit span			
Forward	6.2 ± 2.1	6.1 ± 1.7	NS
Reverse	5.1 ± 3.8	4.3 ± 3.4	NS
Free recall	27.4 ± 15.5	31.8 ± 6.1	NS
Recognition			
Hits	12.4 ± 5.3	14.0 ± 6.1	NS
False alarms	4.1 ± 4.0	5.9 ± 6.1	NS
Retrieval	10.4 ± 4.0	10.5 ± 4.9	NS
Self-rated memory[a]	26.0 ± 38.4	27.2 ± 43.3	NS
Atropine equivalents	4.09 ± 4.83	6.66 ± 6.23	2.76[b]

All values are means ± standard deviation
[a] $n = 14$
[b] Paired *t*-test, two-tailed
MMS, Mini-mental State; NS, not significant; t_0, time of low anticholinergic serum activity; t_1, time of higher anticholinergic serum activity

Table 5. Cognitive ratings and anticholinergic serum activities in subjects with dementia, probable Alzheimer's disease (MMS < 25; GDS > 2)

	t_0	t_1	Mean change
MMS	19.2 ± 4.5	19.1 ± 4.7	NS
Digit span			
Forward	6.3 ± 1.2	4.8 ± 0.9	−1.5[a]
Reverse	1.8 ± 2.1	1.2 ± 1.0	NS
Free recall	17.5 ± 11.3	17.7 ± 8.9	NS
Recognition			
Hits	8.9 ± 7.8	7.1 ± 4.3	−1.8[a]
False alarms	2.4 ± 3.2	4.1 ± 6.0	+1.7[a]
Retrieval	7.3 ± 3.1	5.2 ± 2.8	−2.1[a]
Atropine equivalents	3.50 ± 2.39	6.17 ± 4.47	+2.67

All values are means ± standard deviation
[a] Paired *t*-test, two-tailed
MMS, Mini-mental State; NS, not significant; t_0, time of low anticholinergic serum activity; t_1, time of higher anticholinergic serum activity

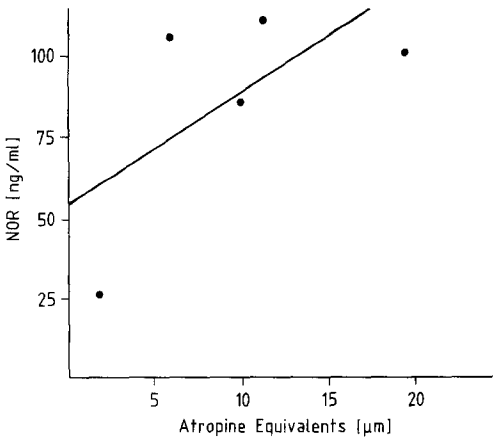

Fig. 1. Correlation between nortriptyline serum concentration and free anticholinergic serum activity. The coefficient of correlation is $r = 0.61$; the regression equation is [NOR] = 54 + 2.9 × [AE], where [NOR] is the serum concentration of nortriptyline in ng/ml, and [AE] is the level of circulating anticholinergic activity in µ*M* atropine equivalence

Table 6. Blood levels of nortriptyline and associated anticholinergic serum activities

Case no.	Medication	Serum concentration [ng/ml]	Atropine equivalents [n*M*/ml]
2	Nortriptyline	100	5.6
10	Nortriptyline	25	1.4
3	Nortriptyline	96	19.9
6	Nortriptyline	105	10.0
8	Nortriptyline	80	9.4

was 4.09 ± 4.83 µ*M* (mean ± SD) and 3.50 ± 2.89 µ*M* in the Alzheimer subjects. After achievement of pharmacokinetic steady state, mean anticholinergic serum activity was 6.66 ± 6.23 µ*M* (non-demented) and 6.17 ± 4.47 µ*M* (Alzheimer group) respectively. The difference between the two activity levels is significant for each group ($t = 4.54$; $df = 17$; $P < 0.01$ and $t = 2.95$; $df = 9$; $P < 0.02$).

In some subjects, we could use antidepressant blood levels, routinely obtained for clinical purposes, to standardize the atropine equivalence units of the QNB assays. Applicability of this internal test was limited because it could only be meaningfully employed in cases of monotherapy with secondary amines. Results are summarized in Table 6. Linear regression analysis, as indicated in Fig. 1, revealed a coefficient of correlation between the two measures of $r = 0.61$.

Cognitive Assessments

While cognitive performance remained unchanged in the non-demented group (cf. Table 4), the demented subjects displayed significant further impairment in association with higher anticholinergic serum activities (cf. Table 5). Only selected measures of cognitive performance showed this change. Specifically, measures of recognition showed a significant effect of circulating anticholinergic activity, with the rate of recognition "hits" at higher serum atropine equivalence being 20% below that at the lower anticholinergic activity level ($t = 3.2$; $df = 9$; $P < 0.02$). In the Alzheimer group, the incidence of false alarms on word recognition testing increased substantially with the attainment of higher serum anticholinergic activity ($t = 3.5$; $df = 9$; $P < 0.01$), while total free recall remained unaffected. Concentration deteriorated as assessed by forward digit span ($t = 3.4$; $df = 9$; $P < 0.01$). The performance deterioration was correlated with the increase in anticholinergic serum concentration at $r = 0.29$.

Reverse digit span, which was minimal even at the lower anticholinergic serum levels, showed no significant change. Category retrieval capacity changed significantly between the two assessment points ($t = 3.7$; $df = 9$; $P < 0.01$), representing additional deterioration of knowledge memory with increased circulating atropine equivalents.

Discussion

The preliminary data presented suggests that geropsychiatric patients with no preexisting dementia tolerate the anticholinergic properties of psychotropic medications at therapeutic dosages without measurable impairment of their cognitive-functional status. This finding is compatible with a report by Sunderland and associates, who found that non-demented geropsychiatric subjects were significantly less vulnerable to the cognitive effects of a standardized scopolamine challenge than their Alzheimer counterparts (Sunderland et al. 1987). It is also consistent with previous data our group obtained in non-demented geropsychiatric patients in a pilot study preceding the present work (Thienhaus et al., in press).

Obviously, all results reported here have to be interpreted with due caution. Small sample size and methodologic limitations characterize the investigation as a pilot study. The design was not truly experimental, but

by necessity used the naturalistic clinical setting. Confounding variables include the nature of the subjects' psychopathology and non-specific other (i.e. not anticholinergic-related) influences of prescribed psychotherapeutic medications or non-pharmacological interventions on cognitive function. Thus, for future reference we raise the question whether a control group like ours can be assumed to be sufficiently homogeneous. While the majority of control subjects may diagnostically belong to the spectrum of affective disorders, the group does comprise patients with a variety of diagnoses.

Despite this caveat, the hypothesis that cognitive function in non-demented elderly psychiatric inpatients deteriorates with therapeutically obtained antimuscarinic plasma activities is not supported by our data. This result appears to be inconsistent with other reports which described impairment of recent memory in younger age schizophrenics treated with antipsychotics (Tune et al. 1982; Perlick et al. 1986) and more global cognitive deterioration in healthy elderly volunteers after administration of benztropine (McEvoy et al. 1987).

Part of the discrepancy may be related to the differences between the populations sampled. One of the previous studies investigated much younger patients. Relationships between mental illness, anticholinergic activities and cognitive integrity are likely to be different depending on age group. Our sample consisted of elderly subjects with a serious mental illness, most often a mood disorder (cf. Table 1). We speculate that subclinical cognitive impairment, associated with mental illness in geriatric patients (Wells 1979; McAllister 1982; Freeman et al. 1985), may respond to the therapeutic action of the medication, and that this curative effect more than offsets any potential antimuscarinic-induced disturbance.

The study which reported that elderly individuals treated with benztropine showed cognitive deterioration used oral dosage, not anticholinergic serum activity levels, as a reference variable. This difference makes a direct comparison of that report to our data problematic. Also, that study was based on healthy volunteers, not psychiatric patients. In these subjects, the proposed effect of subclinical pseudodementia would not have been operative.

We recorded some degree of anticholinergic activity in our subjects even when, reportedly, they had not been taking any medication for several days. This finding probably reflects the delayed elimination of psychotropic drugs that is a characteristic pharmacokinetic phenomenon in the elderly. Some of the subjects in the study had minor impairment at point t_0, which did not qualify for dementia. Such minor impairments (for instance, an initial MMS score between 25 and 30) in several cases seemed to improve after establishment of drug therapy. None of these changes, however, were significant.

In contrast to the cognitively intact control subjects, patients who meet diagnostic criteria for dementia present a different vulnerability, especially if the dementia is related to central cholinergic deficiency. In these patients, i.e. patients with a diagnosis of probable Alzheimer's disease, the monitoring of anticholinergic plasma levels may assume practical relevance. Our data indicate that anticholinergic activity of 6.2 μM atropine equivalence can be associated with significant added cognitive dysfunction. When the anticholinergic monitoring of a psychopharmacologically treated Alzheimer patient shows that such an activity level is approached, corrective adjustment could be made in the pharmacologic management. Dosage could be reduced, or less atropinic drugs could be substituted. In that way, the risk of iatrogenic anticholinergic overload may effectively be reduced.

Conversely, if on attainment of moderate anticholinergic serum activities during psychopharmacologic treatment significant cognitive deterioration is observed, a primary diagnosis of a dementing illness should be entertained. The boundaries between dementia and affective disorders are blurred in the geropsychiatric population so that clinical differentiation is often impossible (Reynolds et al. 1988). The simultaneous monitoring of anticholinergic serum activity and cognitive status may ultimately help to enhance our differential diagnostic acuity.

Only selected measures of specific aspects of cognitive competence were affected. A global screening device such as the widely used MMS showed no significant change while tests of short-term memory, concentration, knowledge memory and intrusion error indicated deteriorations as anticholinergic load increased. All instruments were clinically easy to use. Further research would need to examine our findings with more sophisticated neuropsychological methods in order to establish the pertinent validity of bedside rating scales. In addition, the potential clinical significance of our data warrants replication with a more stringent research design. This would involve repeated pre-treatment testing on standardized neuropsychological batteries to determine a consistent baseline for each subject, greater homogeneity in diagnoses and treatments of probands, and possibly the inclusion of a placebo group. If our data were validated in a truly experimental protocol, the immediate implications for clinical practice could become compelling.

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