The Influence of Corticosteroids and Theophylline on Cerebral Function*
A Review

James C. Schraa, Psy. D.;† and Jerald F. Dirks, Psy. D.‡

Evidence indicating that corticosteroid therapy may adversely affect attention and memory in asthmatic subjects is reviewed. The potential impact of corticosteroid dosage levels (high versus low) and treatment regimens (daily versus alternate day) on attention and memory is discussed. Findings indicate that the suppression of ACTH by corticosteroids may have different effects on attention and memory as a function of the sex of the asthmatic patient. The need to establish what the effects of theophylline-induced reductions of cerebral blood flow and cerebral oxygen tension are on higher cognitive processes are outlined. The importance of establishing whether or not medications commonly used for the treatment of asthma create deficits of memory or attention that interfere with medical compliance is emphasized.

The known complications of treatment of asthma with corticosteroids and theophylline have been discussed at length.1-3 However, a careful review of the literature on therapy with corticosteroids and adrenocorticotropic hormone (ACTH) reveals little discussion of the adverse effects that corticosteroids may have on cognitive processes. Similarly, while the literature on theophylline suggests it produces neurologic effects, the potential relationship between theophylline and cognitive functioning has also received little attention. The recent report4 of a sample of nine to 14-year-old asthmatic children who were significantly impaired on a battery of neuropsychologic tests and the interpretation that their impaired performance was due to hypoxia-induced brain damage, in spite of the fact that no controls for medications were included in the study, illustrates that there is a need for more understanding of how medications used in the treatment of asthma affect behavior. The high prevalence of impaired immediate recall of figural stimuli and impaired visuoconstructional skills in a sample of adult asthmatic patients with severe asthma5 underscores the immediate need to begin to develop a better understanding of the effects of asthma medications on higher cortical processes. The purpose of this paper is to review how corticosteroid therapy may influence attention and memory and to review the impact that theophylline may have on the central nervous system.

The Role of Steroids and ACTH

Corticosteroid treatment can cause suppression of the hypothalamic-pituitary-adrenal system.6 The synthesis of corticosteroids by the adrenal cortex is stimulated by ACTH.2 The release rate of ACTH from the basophil cells in the adenohypophysis is determined by a negative-feedback control system in which the corticosteroid secretions of the adrenal cortex play an inhibitory role and balance the excitatory effects of the nervous system.2,7 Optimal levels of endogenous corticosteroids will terminate ACTH release.7 Corticosteroid treatment affects the hypothalamus or anterior pituitary, and inhibits the release and, later, the synthesis of ACTH.6,8 In turn, the reduction in ACTH brings about reduced synthesis of corticosteroids by the adrenal cortex.8

The pattern and duration of the inhibition in the release and synthesis of ACTH will be determined by the characteristics of the corticosteroid treatment regimen. For example, studies of endogenous steroid concentrations in children have revealed that

*From the Medical Psychology Program, Division of Psychology, National Jewish Hospital/National Asthma Center, and the University of Colorado Health Sciences Center, Denver. Supported in part by Grants A1-15392 and HL-22065 from the National Institutes of Health.
†Adult Clinical Psychologist, Division of Psychology, National Jewish Hospital/National Asthma Center.
‡Chief, Clinical Psychology, Division of Psychology, National Jewish Hospital/National Asthma Center; Assistant Professor of Psychiatry.
Reprint requests: Dr. Schraa, National Jewish Hospital, 3800 East Colfax, Denver 80206
patients treated with more than 10 mg of predni-
sone on a daily basis have significantly lower con-
centrations of endogenous steroids than patients
treated on an alternate-day regimen. This obviously
suggests that a daily treatment regimen has
greater inhibitory effects on ACTH release than
does alternate-day therapy. High dose therapy
(more than 20 mg of prednisone on alternate days)
brings about significantly lower endogenous steroid
concentrations after 24 hours than does low dose
therapy (2.5 to 5 mg of prednisone on alternate
days). It is therefore reasonable to conclude that the
dosages used in corticosteroid therapy will
directly affect the amount of ACTH suppression.
The probable effects of ACTH suppression on high-
er cognitive processes, particularly attention and
memory, are illustrated by research on Cushing’s
syndrome and research on improving attention and
memory with ACTH fragments.

**Cushing’s Syndrome and ACTH**

Several recent articles on Cushing’s syndrome
have documented changes in cognitive functions as
a result of the spontaneous overproduction of corti-
costeroids. The direct relevance of these studies to
the discussion of the effects of corticosteroid therapy
is demonstrated by the fact that the signs and symp-
toms associated with prolonged exposure to inap-
propriately elevated plasma corticosteroid levels are
commonly used to define Cushing’s syndrome, re-
gardless of whether they occur endogenously or as
the result of therapy. A recent study utilized a
semi-structured interview technique to elucidate
the psychologic symptoms of 28 patients with Cus-
ching’s syndrome with high cortisol and high ACTH
levels and seven patients with Cushing’s syndrome
with high cortisol and low ACTH levels. Fifty
percent of the entire group of patients had a con-
stellation of symptoms consisting of impairment in
affect (depressed mood, crying), cognitive func-
tions (decreased concentration and memory), and
vegetative functions (insomnia and decreased libi-
do). Overall, 83 percent of the patients had impair-
ment in memory. Greater difficulties in concen-
tration were found to occur as the ratio of cortisol
to ACTH increased. Patients with memory im-
pairment frequently reported problems with the
registration of new information. In reviewing these
findings, the investigators pointed out that their
patients with Cushing’s syndrome did not have
levels of circulating cortisol as high as those fre-
quently found in corticosteroid therapy (20 mg of
prednisone).

Objective data on the cognitive deficits associated
with Cushing’s syndrome were obtained in one in-
vestigation that utilized a battery of neuropsycholog-
ic tests. Twenty-two of the entire group of 35
patients with Cushing’s syndrome were found to
have at least mild impairment on the neuropsycholog-
ic measures. No relationship was found be-
tween the etiology of Cushing’s syndrome and the
overall severity of neuropsychologic deficits. Fif-
ten percent of the patients showed impairment on
a digit span test, and 37 percent were impaired on the
immediate recall of simple geometric designs. More
than 35 percent of the sample were also con-
sidered to be impaired on peg board completion
with the dominant hand, an arithmetic reasoning
task with a large concentration component, and se-
quential visual reasoning (Picture Arrangement, a
subtest of the Wechsler Adult Intelligence Scale).
Interestingly enough, there is one sketchily de-
scribed report which suggests that asthmatic chil-
dren are also impaired on immediate recall of geo-
metric designs.

**ACTH, Attention, and Memory**

Two types of research paradigms provide some
e elucidation of how ACTH may affect the ability
to attend to environmental events, and memory. First,
individuals with high levels of ACTH resulting from
chronic adrenal cortical insufficiency have been
found to have significantly enhanced acuity for ol-
factory, gustatory, and auditory stimuli. Second,
recent studies have also established that fragments
of ACTH can have direct effects on the central
nervous system and on behavior, without having
any of the alterations in endocrine function and
metabolic activity produced by the parent hor-
mon. Administration of the hormone fragment
ACTH 4-10 in healthy adult male volunteers repe-
tedly has been found to facilitate selective visual
attention and to improve visual memory. Other
studies with male volunteers have found that
ACTH 4-10 counteracts fatigue on a serial reaction
time task and reduces reaction times on an item
recognition task. In women, administration of
ACTH 4-10 has been found to significantly improve
performance on the logical memory and paired as-
sume subtests of the Wechsler Memory Scale. The
these findings provide a basis for the hypothesis
that corticosteroid treatment may, by suppressing
ACTH, adversely influence attention and memory.
Studies utilizing subjects other than healthy
young adults who typically have some form of dys-
function affecting higher cognitive processes yield
less convincing evidence for the conclusion that
ACTH and its fragments influence attention and
memory. Twelve geriatric outpatients with mild
cognitive impairment and 12 geriatric outpatients
with severe cognitive impairment failed to experience any significant improvement on a battery of memory and performance tests on the day they were treated with ACTH 4-10. However, the day after ACTH administration, the group with severe impairment improved significantly on the recognition of faces, and the group with mild impairment showed significant impairment on two tests of nonverbal memory. In another study, ACTH 4-10 was administered to a sample of healthy 65-to-80-year-old subjects. Statistically significant treatment effects were found only with subjects scoring below the mean on the Wechsler Memory Scale. For this group, ACTH 4-10 resulted in significant improvement on the visual memory and digits forward portions of the Wechsler Memory Scale. When the effects of ACTH were studied in a sample of 18 geriatric patients who were known to have significant cognitive impairment, no treatment effects were found on the Wechsler Memory Scale, the Bender-Gestalt test (a test of visuoconstructional skills), or a perceptual tracing task. However, a significant improvement was found on one time interval on a serial reaction time task. ACTH 4-10 failed to have any significant effects when studied in a sample of 20 hyperactive children with learning disabilities on measures of visual and auditory memory, new learning, impulsivity, attention, and perceptual motor skills. The authors also cite three other unpublished studies in which ACTH fragments had weak or inconsistent effects in aged or normal adults. In addition, one study with healthy male volunteers yielded the weak finding that ACTH 4-10 only improved performance on a digit span test.

The literature on the effects of treatment with ACTH 4-10 provides some suggestion that sex differences may be found in the types of abilities that may be impaired when male and female asthmatic patients experience ACTH suppression due to corticosteroid therapy. In men, visual attention and memory (as measured by the Benton Visual Retention Test) and concept formation have been consistently facilitated by treatment with ACTH 4-10. In women, ACTH 4-10 was found to improve verbal memory, to impair reversal learning on a concept formation task, and to have no effect on visual memory. The behavioral distinction present in this pattern of results was interpreted as the accentuation of dominant sex-related modalities by ACTH 4-10, where verbal modalities are seen as dominant over visuospatial modalities in females and the reverse is seen as being true in males. The findings on treatment studies with ACTH fragments suggest that the inhibition of ACTH by corticosteroids in asthmatic patients may have different effects on attention and memory depending upon the sex of the patient.

Hypothesized Mechanisms

Two major types of hypotheses (improved retrieval or enhanced ability to attend to the environment) have been proposed to account for the beneficial behavioral effects of ACTH fragments. The hypothesis that ACTH improves retrieval has received only limited attention from researchers. In a sketchily described study, volunteers who were required to learn lists of letter-word combinations and were treated with ACTH 4-10 a week later, had significantly improved recall of the stimuli. However, a recent study found that a single dose of ACTH 4-10 failed to improve retrieval and to alleviate the retrograde amnesic effects of unilateral ECT in 20 depressed patients. Retrieval of information also failed to be enhanced in a sample of healthy women when ACTH 4-10 was administered after acquisition and 30 minutes before recall.

A variety of investigators have concluded that ACTH 4-10 enhances the ability to attend to the environment and thus only indirectly improves memory. They have based their conclusions upon findings that ACTH 4-10 counteracts fatigue on reaction time tasks, improves performance on tasks involving concept formation, and improves performance on a complex item recognition task (the Sternberg task) in a manner that is suggestive of improved attention rather than improved memory. The mechanism through which ACTH fragments enhance the ability to attend to the environment has not yet been clearly established, but either increased generalized alertness or a form of selective attention are possibilities. A recent study found no significant effects when ACTH 4-10 was administered in a paradigm designed to enhance consolidation of information into longterm memory. Therefore, at this time, it would appear most promising to hypothesize that the suppression of ACTH by corticosteroid therapy detrimentally affects attention and, therefore, only indirectly affects memory. Furthermore, it is reasonable to hypothesize that individuals on daily corticosteroid treatment will have greater impairment than individuals on alternate-day treatment regimens, and that higher doses of corticosteroids will produce greater impairment than lower doses.

On the basis of animal experimentation, VanRiezen, Rigter, and DeWied postulated that ACTH and ACTH fragments activate the brainstem and reticololimbic system, and that corticosteroids inhibit such activation. It has also been found that
cortisol decreases the amplitude of average evoked potentials produced by a significant stimulus, but does not alter the average evoked potential produced by an insignificant stimulus. On the basis of these findings, it was concluded that cortisol reduces the processing of important information and decreases the signal-to-noise ratio.

The majority of the findings reviewed to this point would appear to suggest that corticosteroid therapy may have important effects on attention and memory that have been overlooked to date. To better establish the relationship between corticosteroid therapy and higher cognitive functions, research on the following questions, among others, is in order: (1) Do patients on alternate-day steroid therapy experience impairment of attention and/or memory on days they take steroids relative to days they do not? (2) Is there greater impairment of higher cortical functions as dosages of corticosteroids are increased? (3) Do asthmatic patients (particularly school children) experience impairment of cognitive functions when they are placed on therapy with corticosteroids? Research on these questions would establish if physicians should screen patients being treated with corticosteroids for attentional deficits or memory problems.

Theophylline and the Central Nervous System

It is well known that therapeutic plasma concentrations of theophylline (5 to 20 mg/L) are efficacious in relieving bronchoconstriction in asthmatic adults and children. The most frequent side effects of theophylline are gastrointestinal; however, symptoms associated with excitation of the central nervous system also occur including headache, nervousness, anxiety, irritability, decreased ability to concentrate, and even seizures. These side effects infrequently occur at concentrations between 15 and 20 mg/L (within the therapeutic range), and improvement in the side effects typically occurs with a small reduction in dose. The frequency of side effects increases markedly with theophylline levels of more than 20 mg/L. However, some patients cannot tolerate oral theophylline preparations even when their concentrations are well within the therapeutic range (less than 15 mg/L), and occasional patients are noted who can tolerate very high levels of theophylline with minimal or no side effects. The central nervous system side effects of theophylline are particularly important for those asthmatic patients whose inability to tolerate optimal serum concentrations of theophylline necessitates higher and more frequent (daily versus alternate day) doses of steroids.

At the present time, only a limited amount of research has been done on the mechanism(s) of theophylline-induced central nervous system side effects. It is known that theophylline or aminophylline (theophylline ethylenediamine), the most widely used of the soluble theophylline salts, cause a decrease in cerebral blood flow and in the oxygen tension of the brain. Even within the range of therapeutic plasma concentrations, decreases in cerebral blood flow have been demonstrated. It has been argued that the reduction in cerebral oxygen tension brought about by theophylline and continued metabolic demands for oxygen may bring about a real anoxia of brain tissues. The mechanism of theophylline-induced cerebral anoxia has been cited as a probable cause of theophylline-induced seizures which occur with excessively high serum theophylline levels (common at concentrations greater than 40 mg/L).

Currently, the relationship between serum concentrations of theophylline and measures of cognitive processes are unknown. One practical outcome of research on cognitive processes and theophylline levels would be to determine if neuropsychologic measures that are highly sensitive to drug effects could detect the adverse influence of theophylline on the central nervous system before more blatant side effects occur. Since it has been reported that theophylline interferes with concentration, it would also be appropriate to establish if there is a relationship between theophylline levels and the ability to attend to and retain information.

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