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Effect of two prednisone exposures on mood and declarative memory

E. Sherwood Brown *, Laura Beard, Alan B. Frol, A. John Rush

Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX 75390-8849, USA

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Abstract

Corticosteroids are essential for life and an integral part of the stress response. However, in excess, corticosteroids can be associated with a variety of effects on the brain including hippocampal atrophy and even neuronal death, mood changes, and declarative memory impairment. The magnitude of mood change in patients receiving prednisone is reportedly associated with previous lifetime corticosteroid exposure, consistent with a sensitization or kindling process whereby greater effects are observed with repeated exposure. To our knowledge, the effect of multiple corticosteroid exposures on mood and memory has not been previously examined prospectively in animals or humans. In this study, 30 human volunteers, with no history of systemic prescription corticosteroid therapy, were given (in random order using a crossover design) two 3-day exposures of prednisone (60 mg/day) and one of identical placebo, with 11-day washouts between each medication exposure. Before and after each 3-day prednisone/placebo exposure, declarative memory was assessed using different versions of the Rey Auditory Verbal Learning Test (RAVLT) to minimize practice or learning effects, while mood was assessed with the 21-item Hamilton Rating Scale for Depression, Young Mania Rating Scale and Internal State Scale. No significant mood changes were found. However, a significant decrease in aspects of RAVLT performance was observed after the first prednisone exposure consistent with a decline in declarative memory performance. The decline in RAVLT performance was significantly smaller after the second prednisone exposure as compared to the initial prednisone exposure. Thus, a second prednisone exposure was associated with an attenuated prednisone-effect on declarative memory. These data suggest tolerance or habituation, rather than sensitization, to prednisone effects on declarative memory during a second exposure. Implications and possible explanations for the findings are discussed.

Keywords: Corticosteroid; Sensitization; Mood; Memory; Habituation

1. Introduction

Prescription corticosteroids are associated with changes in mood and memory. The symptom presentation is variable, but brief corticosteroid therapy (days to weeks) may be primarily associated with manic or hypomanic symptomatology (Brown, Suppes, Khan, & Carmody, 2002; Naber, Sand, & Heigl, 1996) while longer therapy (months to years) may be more strongly associated with depressive symptoms (Brown et al., 2004; Gift, Wood, & Cahill, 1989). The effects of corticosteroids on memory are complex and dose dependent (Lupien & Lepage, 2001). Encoding of emotionally arousing memories may be enhanced (Buchanan & Lovallo, 2001) but memory retrieval decreased (Kuhlmann & Wolf, 2005) by corticosteroids. However, both short- and long-term exogenous corticosteroid exposures at supraphysiologic doses are associated with a decline in declarative memory for emotionally neutral material (Brown et al., 2004; Keenan et al., 1996; Newcomer et al., 1999; Wolkowitz et al., 1990).

In a study examining mood changes during brief prednisone "bursts" in asthma outpatients, we found a significant positive association between the number of prior lifetime courses of systemic corticosteroids and the increases in manic and depressive symptom rating scales during prednisone exposure (Brown et al., 2002). This finding is consistent with the possibility of a kindling or sensitization phenomenon in which the magnitude of mood change in

* Corresponding author. Fax: +1 214 645 6951.
E-mail address: Sherwood.Brown@UTSouthwestern.edu (E.S. Brown).

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response to corticosteroids incrementally increases over successive corticosteroid courses. Precedent for increases in behavioral responses to medications can be found with amphetamines (Strakowski, Sax, Rosenberg, DelBello, & Adler, 2001). Sensitization and kindling have been suggested as models for bipolar disorder where symptom severity may increase, and the role on stressors decrease, over multiple episodes (Post, Susan, & Weiss, 1992). Corticosteroids facilitate amygdala kindling (Karst, de Kloet, & Joels, 1999; Kling et al., 1993; Weiss, Castillo, & Fernandez, 1993) and amphetamine behavioral sensitization in animals (Deroche et al., 1995; Pauly, Robinson, & Collins, 1993; Rivet, Stinus, LeMoal, & Mormede, 1989), and thus might potentiate their own effects on mood and memory.

The primary aim of this study was to determine whether mood symptoms and declarative memory changes increased more during a second exposure to corticosteroids administered shortly after the first course of corticosteroids. A group of patients with atopic and allergic illnesses with no history of systemic prescription corticosteroid exposure was randomized to receive 3 days of prednisone on two separate occasions and one exposure to placebo with a washout period between exposures. In this placebo-controlled crossover design participants served as their own controls. Mood and short-term memory recall were assessed before and after each prednisone/placebo exposure.

2. Methods

Thirty participants with asthma, atopic dermatitis or allergic disorders were recruited from local clinics and with posted fliers. Participants were not acutely symptomatic at the time of study entry. Therefore, the study included otherwise healthy participants between the ages of 18–55 years old, men or post-menopausal or ovariectomized women. Ovulating women were excluded due to concern that different phases of the menstrual cycle might be associated with different mood or memory responses to prednisone resulting in enrollment of fewer women than men in the study. However, recent data, not available to us during the study, suggest that menstrual cycle phase does not affect declarative memory changes with corticosteroids (Kuhlmann & Wolf, 2005). Exclusion criteria included lifetime oral or intravenous corticosteroid use, major depressive disorder, bipolar disorder, schizophrenia, and drug or alcohol abuse or dependence based on a Structured Clinical Interview for DSM IV-Clinician Version (SCID) (First, Spitzer, Gibbon, & Williams, 1995), as well as neurological disorders such as stroke or dementia. Additional exclusion criteria included disorders that might increase risk of side effects with corticosteroids (e.g., infection, compromised immune system), current treatment with mood stabilizers (e.g., anticonvulsants, antipsychotics) or medications with drug–drug interactions with prednisone (e.g., carbamazepine). All participants signed a UT Southwestern IRB-approved written informed consent.

Participants were randomized to one of three groups that received prednisone and placebo exposures in different orders in a crossover design (Fig. 1). Each participant received prednisone twice and placebo once in a double-blind fashion in which neither participant nor rater was aware of whether the participant was receiving prednisone or placebo. In this crossover design the participants served as their own controls. Seven participants dropped out at various times during the study. Their data are included in the analyses up to the point of study exit. Baseline mood was assessed with the 21-item Hamilton Rating Scale for Depression ($HRSD_{21}$) (Hamilton, 1960), a clinician-rated assessment of depressive symptoms in the past week, Young Mania Rating Scale (YMRS) (Young, Biggs, & Meyer, 1978), a clinician-rated assessment of manic or hypomanic symptoms in the past week, and the activation (ACT) subscale of the Internal State Scale (ISS) (Bauer et al., 1991), a self-report measure of manic/hypomanic symptoms in the past 24 h that is highly sensitive to prednisone effects (Bolanos et al., 2004; Brown, Bauer, Suppes, Khan, & Carmody, 2000). Declarative memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) (Rosenberg, Ryan, & Prifitera, 1984) using alternative versions given in a random order to minimize practice or learning effects (Crawford, Stewart, & Moore, 1989; Ryan, Geisser, Randall, & Georgemiller, 1986). No participant received the same RAVLT version twice.

Each participant was given two 3-day exposures to prednisone (60 mg/day) and one 3-day exposure to an identical appearing placebo in a double-blind fashion with an 11-day washout period between each exposure. The third and final study drug dose during each of the three exposures was to be taken at 09:00 h on the day of mood and cognitive assessment (Fig. 1). An 11-day washout between study drug exposures was selected based on prior research showing that this is sufficient to see a return to baseline mood and memory performance following corticosteroid therapy (Brown et al., 2002; Newcomer et al., 1999). Mood and declarative memory were assessed by blinded raters at each appointment. Pill counts were conducted to assure study drug adherence. Assessments were typically in the early afternoon with mean times of 1410 ± 2.13 h (assessment 1), 1435 ± 2.08 h (assessment 2), 1409 ± 2.34 h (assessment 3), 1335 ± 2.48 h (assessment 4), 1347 ± 2.38 h (assessment 5), 1346 ± 2.37 h (assessment 6), and 1423 ± 2.05 h (assessment 7). RAVLT, YMRS, and $HRSD_{21}$ scores did not correlate with time of assessment at any of the seven study assessments. ACT scores showed a significant correlation (Pearson's correlation coefficient $r = -.48$, $p = .02$) with time of assessment at assessment 7 but not at assessments 1–6.

2.1. Statistical analysis

Participant characteristics between the three groups were analyzed with either a one-way analysis of variance (ANOVA) for continuous measures (e.g., age) or Chi-Square (χ^2) for discrete measures (e.g., gender). Contrasts between raw scores or change scores (pre to post) for memory and mood continuous measures were analyzed with either independent (between groups) or dependent (within groups) 2-sided t tests. Significance was accepted at $p \leqslant .05$ for all analyses. The number of measures was limited to three memory measures (total words recalled over five learning trials; delayed recall after twenty minutes; and discrimination, a delayed recognition measure calculated by subtracting correct responses from errors on delayed recognition) and three mood measures ($HRSD_{21}$, YMRS, ACT).

3. Results

Demographic information on the participants is given in Table 1. Participant characteristics were not significantly different between groups with the exception of gender ($\chi^2 = 6.7$, $p = .04$) since all three women were in group II. Baseline memory and mood measures were not significantly different between the three groups with the exception of YMRS scores ($F = 4.7$, $p = .02$) with mean values ranging from 0.6 to 3.3. These differences are not considered clinically significant given the range of possible scores of between 0 and 60 on the YMRS. These findings supported collapsing groups, regardless of presentation order of medication, and placebo, to increase the number of subjects for subsequent analyses.

3.1. Effect of first exposure to prednisone on mood and declarative memory

The data from the first prednisone exposure from groups I, II, and III were combined. A within subjects analysis, comparing data from all three randomization groups