Psychoneuroendocrinology (2015) 51, 589—597

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: Randomized trial showing improved treatment retention and outcome

Rachel Yehuda[a,b,*], Linda M. Bierer[a,b], Laura C. Pratchett[a,b], Amy Lehrner[a,b], Erin C. Koch[a], Jaklyn A. Van Manen[a], Janine D. Flory[a,b], Iouri Makotkine[a,b], Tom Hildebrandt[b]

[a] *James J. Peters Veterans Affairs Medical Center, Bronx, New York, United States*
[b] *Traumatic Stress Studies Division, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States*

Received 21 May 2014; accepted 3 August 2014

KEYWORDS
PTSD;
Prolonged exposure;
Hydrocortisone;
Pharmacological augmentation strategies;
Psychotherapy;
Glucocorticoid receptor;
Veterans;
Treatment outcome

Summary
Background: Prolonged exposure (PE) therapy for post-traumatic stress disorder (PTSD) in military veterans has established efficacy, but is ineffective for a substantial number of patients. PE is also associated with high dropout rates. We hypothesized that hydrocortisone augmentation would enhance symptom improvement and reduce drop-out rates by diminishing the distressing effects of traumatic memories retrieved during imaginal exposure. We also hypothesized that in responders, hydrocortisone augmentation would be more effective in reversing glucocorticoid indices associated with PTSD than placebo augmentation.
Method: Twenty-four veterans were randomized to receive either 30 mg oral hydrocortisone or placebo prior to PE sessions 3—10 in a double-blind protocol. Glucocorticoid receptor sensitivity was assessed in cultured peripheral blood mononuclear cells (PBMC) using the *in vitro* lysozyme inhibition test and was determined before and after treatment. Intent-to-treat analysis was performed using latent growth curve modeling of treatment effects on change in PTSD severity over time. Veterans who no longer met diagnostic criteria for PTSD at post-treatment were designated as responders.

* Corresponding author at: James J. Peters VA Medical Center — 116/A, OOMH, 130 West Kingsbridge Road, Bronx, New York, United States. Tel.: +1 718 741 4000x6964; fax: +1 718 741 4703.
E-mail addresses: Rachel.yehuda@va.gov, rachel6964@gmail.com (R. Yehuda).

http://dx.doi.org/10.1016/j.psyneuen.2014.08.004
0306-4530/Published by Elsevier Ltd.

Results: Veterans randomized to hydrocortisone or placebo augmentation did not differ significantly in clinical severity or glucocorticoid sensitivity at pre-treatment. Hydrocortisone augmentation was associated with greater reduction in total PTSD symptoms compared to placebo, a finding that was explained by significantly greater patient retention in the hydrocortisone augmentation condition. A significant treatment condition by responder status interaction for glucocorticoid sensitivity indicated that responders to hydrocortisone augmentation had the highest pre-treatment glucocorticoid sensitivity (lowest lysozyme $IC_{50\text{-}DEX}$) that diminished over the course of treatment. There was a significant association between decline in glucocorticoid responsiveness and improvement in PTSD symptoms among hydrocortisone recipients.
Conclusions: The results of this pilot study suggest that hydrocortisone augmentation of PE may result in greater retention in treatment and thereby promote PTSD symptom improvement. Further, the results suggest that particularly elevated glucocorticoid responsiveness at pre-treatment may identify veterans likely to respond to PE combined with an intervention that targets glucocorticoid sensitivity. Confirmation of these findings will suggest that pharmacologic interventions that target PTSD-associated glucocorticoid dysregulation may be particularly helpful in promoting a positive clinical response to PTSD psychotherapy.
Published by Elsevier Ltd.

1. Introduction

Prolonged exposure (PE) is one of several cognitive behavioral treatments recommended by the U.S. Department of Defense and the Department of Veteran's Affairs for treatment of service members and veterans with PTSD (Ruzek et al., 2012; Susskind et al., 2012). This treatment is theorized to work by extinguishing fear responses to the emotions elicited by traumatic memories, reducing experiential and behavioral avoidance of trauma-related feelings, memories, and reminders, and facilitating new learning to correct cognitive distortions resulting from the traumatic exposure (Foa and Kozak, 1986; Hembree and Foa, 2000; Van Minnen and Foa, 2006).

Despite the efficacy of PE among treatment completers, high drop-out rates have been reported in clinical trials and in clinical practice. This is particularly evident for psychotherapies involving veterans. In randomized, controlled trials of PE in veterans, drop-out rates between 23% and 38% have been reported (Schnurr et al., 2007; Eftekhari et al., 2013; Simmons et al., 2013). Recent published analyses of patient charts found drop-out rates ranging from 27% to 44% (Jeffreys et al., 2013; Tuerk et al., 2011; Goodson et al., 2013) for veterans treated with PE by providers hired and trained as trauma specialists in VA specialized PTSD programs. Treatment drop-out has been theorized as a response to the early recounting of the trauma memory in therapy, which initially exacerbates symptoms, activates avoidance mechanisms, and may lead patients to withdraw from treatment (Schnurr et al., 2007; Leiner et al., 2012). It has therefore been of interest to develop strategies to use in tandem with PE to facilitate treatment gains by either accelerating improvement or increasing tolerability to prevent drop-outs. Some augmentation strategies, such as D-cycloserine, have focused on improving the rate of fear extinction, and have been successful in some reports (Rothbaum et al., 2014; for review, see de Kleine et al., 2013).

Hydrocortisone is a synthetic glucocorticoid with anti-inflammatory effects that is widely used in medical practice. The hypothesis that glucocorticoids might augment the therapeutic effect of PE is based on findings demonstrating that glucocorticoids facilitate extinction learning through their actions in potentiating effects of the glutamatergic N-methyl-D-aspartate (NMDA) receptors in the amygdala (Yang et al., 2005, 2007; Sakurai et al., 2007). Glucocorticoid administration is associated with decreased retrieval of fear memories in animals (Cordero et al., 2002; Roozendaal et al., 2004; Cai et al., 2006; Abrari et al., 2008; Kohda et al., 2007; Tronel and Alberini, 2007). Glucocorticoids also enhance memory consolidation and reconsolidation via interactions with brain noradrenergic systems, and therefore may promote the reframing of memories that forms the basis of posttraumatic recovery (Quirarte et al., 1997; Roozendaal, 2003; Nathan et al., 2004; Roozendaal et al., 2006). Patients receiving high doses of glucocorticoids for the treatment of septic shock were significantly less likely to suffer from traumatic recollections of the event or to develop PTSD (Schelling et al., 2004, 2006). Subsequent randomized trials confirmed that the effect of glucocorticoids such as hydrocortisone in the prevention of PTSD resulted from decreasing the traumatizing effects of memory (reviewed in de Quervain et al., 2009; Zohar et al., 2011). Further support for hydrocortisone augmentation of PE was provided by two randomized studies in which hydrocortisone was combined with exposure therapies for the treatment of anxiety disorders (Soravia et al., 2006; de Quervain et al., 2011). A case report of two PTSD patients showed results of hydrocortisone in comparison to placebo augmentation of PE for two combat veterans with similar pre-treatment symptom severity; the veteran receiving hydrocortisone showed an acceleration of symptom improvement and lower post-treatment PTSD severity (Yehuda et al., 2010a).

This pilot study was conducted to further examine the feasibility and potential benefit of hydrocortisone compared to placebo augmentation of PE for treatment seeking veterans with PTSD. It was hypothesized that, compared to placebo, hydrocortisone augmentation of PE would yield greater reduction in PTSD symptoms and full remission rates