Effects of a fixed herbal drug combination (Ze 185) to an experimental acute stress setting in healthy men – An explorative randomized placebo-controlled double-blind study

Sibylle Meier\textsuperscript{a,⁎}, Manuel Haschke\textsuperscript{b}, Catherine Zahner\textsuperscript{c}, Esther Kruttschnitt\textsuperscript{c}, Jürgen Drewe\textsuperscript{c}, Evangelia Liakonib, Felix Hammann\textsuperscript{b}, Jens Gaab\textsuperscript{a}

\textsuperscript{a} Division of Clinical Psychology and Psychotherapy, Faculty of Psychology, University of Basel, Missionstrasse 62, 4055 Basel, Switzerland
\textsuperscript{b} Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Habelstrasse 2, 4031 Basel, Switzerland
\textsuperscript{c} Max Zeller Söhne AG, Seeblickstrasse 4, 8590 Romanshorn, Switzerland

\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

\textit{Background:} Considering the negative effects of stress on health, there is a growing interest in stress-reducing interventions. The present study examines the effects of a fixed combination of valerian, passion flower, lemon balm, and butterbur extracts (Ze 185) on biological and affective responses to a standardized psychosocial stress paradigm.

\textit{Purpose:} The aim of the present study was to investigate the efficacy of Ze 185 on cortisol and anxiety stress responses to acute psychosocial stress in healthy subjects.

\textit{Study Design:} This study was a randomized, placebo-controlled, double blind study with 3 parallel groups.

\textit{Methods:} 72 healthy male participants were randomized to 3 groups (Ze 185, placebo or no treatment) during 4 days prior to a standardized psychosocial stress paradigm. Principle outcomes were salivary cortisol and self-reported anxiety responses to stress assessed at the fourth day.

\textit{Results:} The stress paradigm induced significant and large cortisol and self-reported anxiety responses. Groups did not differ significantly in their salivary cortisol response to stress, but participants in the Ze 185 condition showed significantly attenuated responses in self-reported anxiety in comparison to placebo (\(F(3, 41) = 3.33, p = 0.03\)) and no treatment (\(F(3, 43) = 2.77, p = 0.05\)).

\textit{Conclusion:} The results show that Ze 185 significantly attenuated the subjective emotional stress response during an acute stress situation, without affecting biological stress responses. Given that a circumscribed biological stress response is to be considered as an adaptive mechanism, Ze 185 reduces self-reported anxiety response to stress without affecting assumingly adaptive biological stress responses.

\textbf{Introduction}

While physiological and psychological responses in the face of adversities are both functional and necessary, biological, emotional as well as behavioral stress responses have been shown to negatively impact on mental and physical health in the long term (McEwen, 2012). Thus, approaches to mitigate stress-related health impairments become a matter of public health. Here, several randomized-controlled trials have shown that stress management trainings significantly attenuated acute cortisol stress responses in healthy subjects (Hammerfald et al., 2006; Storch et al., 2007). Also, several pharmacological substances have been shown to attenuate saliva cortisol responses to acute stress in healthy participants such as benzodiazepine (Fries et al., 2006) and opioid agonists (Bershad et al., 2015).

Considering the empirical status of herbal medicinal products for the treatment of stress and stress-reactivity, a number of randomized placebo-controlled trials indicate the potential of this approach in acute stress settings. In a randomized placebo-controlled study 600 mg of an extract combination of \textit{Melissa officinalis}\ L. leaves and \textit{Valeriana officinalis}\ L. roots reduced negative effects of the acute stress on ratings of anxiety.

\textit{Abbreviation:} AE, Adverse Event; AUC\textsubscript{i}, Area Under the Curve with respect to increase; AUC\textsubscript{g}, Area Under the Curve with respect to ground; BMI, Body Mass Index; HMPC, Committee on Herbal Medicinal Products; DER, Drug Extract Ratio; Ph. Eur., European Pharmacopoeia; FD, Flame Ionization Detector; GABA, Gamma-Aminobutyric acid; GC, Gas Chromatography; HPLC, High Performance Liquid Chromatography; HPA, Hypothalamic-Pituitary-Adrenal; ITT, Intention To Treat; PP, Per Protocol; SD, Standard Deviation; STAI-state, State Anxiety of the State-Trait Anxiety Inventory; STAI-trait, Trait anxiety of the State-Trait Anxiety Inventory; TSST, Trier Social Stress Test

\textsuperscript{⁎} Corresponding author.

\textit{E-mail address:} sibylle.meier@unibas.ch (S. Meier).
in healthy individuals undergoing cognitive tasks (Kennedy et al., 2006). Similarly, the fixed herbal drug combination Ze 185, containing extracts of Valeriana officinalis L. radix, Passiflora incarnata L. herba, Petasites hybridus (L.) P. Gaertn roots and Melissa officinalis L. folium, decreased anxiety levels in participants in response to cognitive tasks in a randomized-placebo controlled study (Steiner and Opwis, 2000). Herbal preparations containing Passiflora incarnata L., Melissa officinalis L. as well as Valeriana officinalis L. have been traditionally used for the relief of mild symptoms of mental stress, assessed by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (HMPC, 2013, 2014, 2016).

However, data regarding the effects of the herbal extracts used in Ze 185 on psychophysiological responses including the assessment of the activation of one of the major biological stress systems, namely the hypothalamic-pituitary-adrenal (HPA) axis with neuroendocrine cortisol stress responses, under acute psychosocial stress is missing. A previous study investigated physiological and psychological stress responses in participants completing cognitive tasks under the intake of Ze 185 and placebo (Steiner and Opwis, 2000). In other studies, Ze 185 was investigated as treatment for psychosomatic complaints in comparison of oxazepam (Schellenberg et al., 2004) and for somatoform disorders (Melzer et al., 2009). The aim of the present study was therefore to investigate the efficacy of Ze 185, a fixed herbal drug combination, regarding neuroendocrine and psychological responses to acute psychosocial stress in healthy subjects. Considering the previous research with Ze 185 (Melzer et al., 2009; Schellenberg et al., 2004; Steiner and Opwis, 2000) we assume that Ze 185 will reduce the emotional responses to the stress tests, with possible attenuation of neuroendocrine responses in consequence.

Material and methods

To observe the effects on neuroendocrine responses, the primary outcome was salivary cortisol secretion as the HPA axis is one of the major biological stress response systems. Previous research shows that the Trier Social Stress Test (TSST; see below; Kirschbaum et al., 1993) – protocol is a reliable tool to experimentally evoke HPA axis stress responses (Allen et al., 2014). As secondary outcome, we chose self-reported state anxiety as a measure of psychological stress response. Furthermore, safety and compliance of Ze 185 and placebo were assessed with laboratory tests, physical examination, assessment of Adverse Events (AEs) and drug accountability.

Study medication

Active ingredients of the herbal medicinal product Ze 185, a fixed herbal drug combination, were 90 mg of a 90% (w/w) ethanolic extract of Petasites hybridus (L.) P. Gaertn., B. Mey. et Scherb. (Drug Extract Ratio; DER 7–14:1); 90 mg of a 45% (w/w) methanolic extract of Valeriana officinalis L. roots (DER 4–6:1); 90 mg of a 50% (w/w) ethanolic extract of Passiflora incarnata L. herb (DER 3–6:1); 60 mg of a 20% (w/w) ethanolic extract of Melissa officinalis L. leaves (DER 2.5–3.9:1) per film-coated tablet. The extract has been registered in Switzerland since 1970. The herbal medicinal products containing Ze 185 are indicated for the following complaints: nervousness, tension, restlessness and exam nerves. These can lead to the following symptoms, amongst others: spasmodic gastrointestinal complaints, increased irritability and occasional trouble falling asleep and sleeping through the night. High performance liquid chromatography (HPLC) fingerprints of one extract batch of each extract of Ze 185 are shown in Figs. 1–4. For the study, the commercially available formulation of Zeller Entspannung film coated tablets was used. Placebo was identical in presentation, color, and shape.

Participants

85 participants were screened, of which 13 met one or more of the exclusion criteria. The remaining 72 participants were randomized to namely Ze 185 (n = 24), placebo (n = 24), and no treatment (n = 24) groups (see Fig. 5). We included a no treatment group to be able to detect a possible placebo effect (i.e. difference between placebo and no treatment) in the placebo response (i.e. absolute effects of placebo administration). Inclusion criteria for the study were age between 18 and 45 years, male gender, and written informed consent. Previous research on the influence of age on cortisol responses is inconsistent (Agrigoroaei et al., 2013; Rohleder et al., 2002). However, Allen et al. (2014) point out the consideration that the testing environment of the standardized stress test (see below) itself might be more stressful for older participants compared to a younger population. Previous research has shown a broad moderating effect of gender on cortisol responses as well as has suggested a different behavioral stress response pattern in men and women (Allen et al., 2014; Taylor et al., 2000). Smoking, presence of somatic or psychiatric disorders, or any other clinically relevant diseases like hepatic, renal, cardiac respiratory disorders, alcohol or drug abuse, as well as previous participation in a TSST and in any psychotherapy were counted among the main exclusion criteria together with the use of defined concomitant medication. To check for exclusion criteria the screening procedures included ana- nalysis of medical and psychiatric history and urinalysis for cotinine and drug use. All participants gave written informed consent. Randomized participants were financially compensated for their participation in the study. The study was approved by the local Ethics Committee and Swiss Agency for Therapeutic Products (Swissmedic, trial number: ZE185-4-2014-02) and registered on clinicaltrials.gov (ID: NCT02189239) and in the supplementary federal database (Swiss National Clinical Trials Portal; ID: SNCTP00001075). The study followed the guidelines of the Declaration of Helsinki and Tokyo for humans.

Procedure

At the screening visit, electrocardiogram, physical examinations, blood samples for hematological and clinical chemistry parameters, and the vital signs were assessed for safety analyses and to detect any clinically relevant abnormalities. All those procedures were conducted by a physician, and his team at the University Hospital of Basel. Participants completed 3 visits (baseline: day 1, stress test: day 4, and end of study). At baseline (day 1) eligible participants were randomized to one of the study groups. Randomization was provided centrally with randomly permuted blocks of variable length with equal numbers of assignments to the 3 arms. The random code was supplied by an external provider using a validated random program. Participants were instructed to orally administer 3 film-coated tablets per day for the following 3 days, i.e. one tablet every morning, midday, and evening on days 1, 2 and 3. On day 4, all participants underwent a standardized psychosocial stress test. On this day, participants took 2 film-coated tablets, i.e. in the morning and midday. The end of study visit was scheduled 3 to 5 days later and included a physical examination and laboratory tests. AEs were assessed throughout the study from giving informed consent signature until last visit and were evaluated by a medical doctor.

Stress test

On day 4 all participants were subjected to the TSST at the division of Psychology and Psychotherapy of the University Basel. The stress paradigm has repeatedly been found to induce profound psychobiological stress responses in 70–80% of subjects (Kudielka et al., 2007). After 50 min upon arrival including cortisol baseline assessment, participants were taken to the testing room and introduced to the TSST. The TSST procedure involves giving a free speech and a serially
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