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A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder

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ABSTRACT

Generalized and persistent anxiety, accompanied by nervousness and other symptoms (Generalised Anxiety Disorder, GAD) is frequent in the general population and leads to benzodiazepine usage. Unfortunately, these substances induce sedation and have a high potential for drug abuse, and there is thus a need for alternatives.

As the anxiolytic properties of lavender have already been demonstrated in pharmacological studies and small-scale clinical trials, it was postulated that lavender has a positive effect in GAD. A controlled clinical study was then performed to evaluate the efficacy of silexan, a new oral lavender oil capsule preparation, versus a benzodiazepine.

In this study, the efficacy of a 6-week-intake of silexan compared to lorazepam was investigated in adults with GAD. The primary target variable was the change in the Hamilton Anxiety Rating Scale (HAM-A-total score) as an objective measurement of the severity of anxiety between baseline and week 6. The results suggest that silexan effectively ameliorates generalized anxiety comparable to a common benzodiazepine (lorazepam). The mean of the HAM-A-total score decreased clearly and to a similar extent in both groups (by 11.3 ± 6.7 points (45%) in the silexan group and by 11.6 ± 6.6 points (46%) in the lorazepam group, from 25 ± 4 points at baseline in both groups). During the active treatment period, the two HAM-A subscores "somatic anxiety" (HAM-A subscore I) and "psychic anxiety" (HAM-A subscore II) also decreased clearly and to a similar extent in both groups.

The changes in other subscores measured during the study, such as the SAS (Self–rating Anxiety Scale), PSWQ-PW (Penn State Worry Questionnaire), SF 36 Health survey Questionnaire and Clinical Global Impressions of severity of disorder (CGI item 1, CGI item 2, CGI item 3), and the results of the sleep diary demonstrated comparable positive effects of the two compounds.

In conclusion, our results demonstrate that silexan is as effective as lorazepam in adults with GAD. The safety of silexan was also demonstrated. Since lavender oil showed no sedative effects in our study and has no potential for drug abuse, silexan appears to be an effective and well tolerated alternative to benzodiazepines for amelioration of generalised anxiety.

Introduction

Flowers of different species of lavender have been known for their wide therapeutic use for centuries. The main constituents of lavender oil are linalool, linalyl acetate, 1.8-cineole, β-ocimene, terpinen-4-ol and camphor (corresponding to GC chromatogram of lavender oil, European Pharmacopoeia 4th edition, 2002). The monograph in the Ph. Eur. 2002 describes a capillary gaschromatographic method and demands for the main terpenoids linalool, linalylacetate and terpinen-4-ol the %-values which must be in the range of 20.0-45.0, 25.0-46.0 and 1.2-6.0 respectively. These constituents can vary significantly in different oils.

The pure oil is most often used in aromatherapy and massage (Buchbauer et al. 1991). Despite its popularity and long tradition of use, only recently scientifically-based investigations into the biological activity of the various Lavandula species have been undertaken to a greater extent.

Small-scale studies have indicated that people with anxiety disorders might benefit from lavender massage. Lavender is able to decrease anxiety measured by the Hamilton rating scale (Itai et al. 2000) and can increase mood scores (Walsh and Wilson 1999). In another clinical study on 122 patients in a hospital intensive care

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unit, those subjects who received aromatherapy massage with Lavandula angustifolia oil reported a significant improvement in their perceived anxiety compared to patients with no aromatherapy (Dunn et al. 1995). A possible antidepressant effect of lavender has been investigated in smaller clinical trials (Diego et al. 1998; Vernet-Maury et al. 1999). However, no data on a lavender oil capsule formulation for oral application have been available until now.

Patients with a Generalised Anxiety Disorder (GAD, according to DSM-IV (300.02), ICD-10: F41.1) can experience excessive anxiety and worry associated with the stresses of everyday life. Most cases of GAD begin in childhood and can lead – without treatment – to a chronic condition, with fluctuating symptoms, often exacerbated by stressful life events (National Health Committee 1998; Wittchen and Hoyer 2001).

Treatment of GAD can be divided into psychotherapies and medicinal treatment. Pharmacotherapy is usually in the form of benzodiazepines, buspirone or antidepressants (Gliatto 2000).

Lorazepam is one of the common benzodiazepines and it acts on the gamma-aminobutyric acid (GABA)/benzodiazepine receptor complex. It suppresses activity in many limbic and other brain areas involved in anxiogenesis. The rapid onset of action is one of the advantages of the benzodiazepines, particularly in relieving the somatic symptoms of GAD. However, the benefits of short-term treatment are outweighed by the risks during long-term use of the substances (Tyrer and Murphy 1987). The disadvantages of taking benzodiazepines include a high risk of abuse or dependence, sedative effects, secondary symptoms of depression, psychomotor and cognitive impairment (Drug Monograph, 1995–2003). Withdrawal syndromes can occur during cessation after long term use.

Silexan[1] contains a quality-selected, well-defined preparation from *Lavandula angustifolia* in an immediate release capsule. Silexan acts via the $GABA_A$ receptors (Aoshima and Hamamoto 1999), and pre-clinical data have suggested that it may have anxiolytic and antidepressant potential (Schwabe internal pharmacological reports, unpublished).

The aim of this study was to investigate the therapeutic efficacy and tolerability of silexan[1] compared to lorazepam in the treatment of patients with GAD. This multi-centre, double-blind, randomised study with 2 parallel treatment groups was conducted by general practitioners.

Materials and methods

Subjects and study design

The study protocol was approved by an independent ethics committee (Ethikkommission der Landesärztekammer Baden-Württemberg, Stuttgart, Germany) and all subjects gave their written informed consent. The study was performed according to legal requirements and (ICH) GCP guidelines.

In this study, patients (18 to 65 years) with a primary diagnosis of generalised anxiety disorder (GAD) according to DSM-IV (300.02) and outpatient treatment by a general practitioner were selected. In order to be eligible for study inclusion, all patients were required to have a HAM-A total score $\geq$ 18 *and* Item 1 "anxious mood" $\geq$ 2 *and* Item 2 "tension" $\geq$ 2.

During the one-week screening phase, all patients received placebo to ensure wash-out of any other drugs. Patients with a decrease of 25% or more of the HAM-A total score during this phase were to be excluded. Only patients who met the inclusion criteria were admitted to the treatment period.

During the 6 weeks of the double blind randomized treatment phase, patients received either 1×1 capsule filled with 80 mg silexan (SMC 7563, batch no. 0200202) *and* 1×1 capsule filled with lorazepam placebo (SMC 9059P, batch no. 0200203/0200301), representing the silexan group, or 1×1 capsule of 0.5 mg lorazepam (SMC 9059, batch no. 0200204) *and* 1×1 capsule filled with silexan placebo (SMC 7563P, batch no. 0200201), representing the lorazepam group.

Silexan is an essential oil produced from Lavandula angustifolia flowers by steam distillation. As a basic requirement, it complies with the monograph Lavender oil of the European Pharmacopeia with respect to all quality parameters. In addition, silexan exceeds the quality definition of the pharmacopoeial monograpph with respect to items that are important for efficacy and tolerability due to specific improvements in relevant steps of the manufacturing process. The uniformity of the specific composition of Silexan is warranted by continuous quality controls.

The random code was generated using a validated computer program.

The eligibility procedures were undertaken on the day of screening; efficacy assessments of primary and secondary outcome variables as well as of safety parameters were carried out at baseline, weeks 1, 2, 4 and 6, and after the discontinuation phase at week 8.

The discontinuation phase was of 2 weeks' duration (day 43 – day 56). On day 43, 45, 47, 50 and 53, patients received either 1×1 capsule filled with 80 mg silexan (SMC 7563, batch no. 0200202) *and* 1×1 capsule filled with lorazepam placebo (SMC 9059P, batch no. 0200203/0200301) in the silexan group, or 1×1 capsule of 0.5 mg lorazepam (SMC 9059, batch no. 0200204) *and* 1×1 capsule filled with silexan placebo (SMC 7563P, batch no. 0200201) in the lorazepam group. On the other days, both groups received one capsule of silexan placebo (SMC 7563P, batch no. 0200201) and one capsule filled with lorazepam placebo (SMC 9059P, batch no. 0200203/0200301) per day.

Methods

Statistical analysis

The primary target variable for the analysis of the therapeutic equivalence of silexan and lorazepam was the change in HAM-A total score between baseline and week 6.

The two therapies were compared by looking at the observed difference between the treamtment groups and the two-sided 90% confidence intervals for the difference of expected values.

The primary analysis was based on the full analysis set. Furthermore, a per protocol analysis was performed which included only patients without major protocol violations.

Evaluation of the primary and secondary efficacy variables

The efficacy assessments from baseline to week 6 were based on the Hamilton Anxiety Rating Scale (HAM-A) as an objective measure of the severity of anxiety symptoms. The change in score was evaluated as the primary efficacy parameter.

To compare the effects of silexan and lorazepam, responder and remission rates were assessed as secondary objectives. Response was defined as a reduction of at least 50% in HAM-A total score between baseline and the end of treatment. A HAM-A total score below 10 points at week 6 was defined as remission. In addition, the Clinical Global Impression (CGI) as an organised global assessment of severity (conducted by the investigator), the Zung's Self–rating Anxiety Scale (SAS) which measures how much a patient suffers from common anxiety symptoms, the Penn State Worry Questionnaire past week version total score (PSWQ-PW) as a measure of worry, the SF-36 Health Survey Questionnaire for documentation of quality of life and a Patient's Sleep Diary to

[1] Silexan is the active substance of LASEA® (W. Spitzner Arzneimittelfabrik GmbH, Ettlingen)