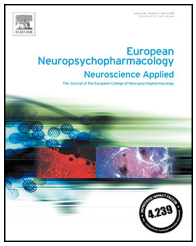
European Neuropsychopharmacology (2018) 000, 1–8



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Etifoxine impairs neither alertness nor cognitive functions of the elderly: A randomized, double-blind, placebo-controlled crossover study

D. Deplanque[a,b,*], F. Machuron[c], N. Waucquier[b], E. Jozefowicz[b], S. Duhem[b], S. Somers[b], O. Colin[a], A. Duhamel[c], R. Bordet[a]

[a] *Univ. Lille, Inserm, CHU Lille, U1171 - Degenerative & Vascular cognitive disorders, F-59000 Lille, France*
[b] *Univ. Lille, Inserm, CHU Lille, CIC 1403 - Centre d'Investigation Clinique, F-59000 Lille, France*
[c] *Univ. Lille, CHU Lille, EA 2694 - Santé publique: épidémiologie et qualité des soins, F-59000 Lille, France*

Received 22 December 2017; received in revised form 4 May 2018; accepted 17 May 2018
Available online xxx

KEYWORDS
Etifoxine;
Benzodiazepines;
Anxiolytic;
Cognition;
Elderly;
Geriatric psychiatry

Abstract
Etifoxine hydrochloride (Stresam®), a treatment indicated for psychosomatic manifestations of anxiety, could be an alternative to benzodiazepines. While no impact on alertness and cognitive functions has been proven among youth, data on elderly are lacking. The primary objective of this study was to measure the impact of etifoxine, lorazepam or placebo on alertness in the elderly. The secondary objectives were to evaluate cognitive performances and adverse effects. In this randomized, placebo-controlled, double-blind, 3-way crossover design, 30 healthy volunteers aged 65 to 75 years underwent three one-day sessions. After treatment intake, standardized cognitive tests were conducted using the Cambridge Neuropsychological Test Automated Batteries and other psychological tests (Stroop, Rey Auditory Verbal Learning Test, Digit

☆ **Registration:** EudraCT 2012-005530-11 and NCT 02147548

* Correspondence to: Department of medical Pharmacology, Faculty of Medicine, 1 place Verdun, 59045 Lille, France.
E-mail addresses: dominique.deplanque@univ-lille.fr, dominique.deplanque@chru-lille.fr (D. Deplanque).

https://doi.org/10.1016/j.euroneuro.2018.05.011

Please cite this article as: D. Deplanque et al., Etifoxine impairs neither alertness nor cognitive functions of the elderly: A randomized, double-blind, placebo-controlled crossover study, European Neuropsychopharmacology (2018), https://doi.org/10.1016/j.euroneuro.2018.05.011

Span). The reaction time (RTI) as primary endpoint was analysed using a 3×3 latin square variance analysis. A 100-mg dose of etifoxine has no deleterious impact on alertness and causes no cognitive disorders as compared to placebo (RTI: 744 ± 146 ms *versus* 770 ± 153 ms; $p = 1.00$). As expected, a 2-mg dose of lorazepam impairs alertness (RTI: 957 ± 251 ms *versus* placebo; $p < 0.0001$) and cognitive functions. A similar frequency of adverse events was observed with etifoxine and placebo while their incidence was 3-fold higher with lorazepam, drowsiness being the most frequent adverse event. No serious adverse events were observed. This study demonstrates in the elderly that a single dose of etifoxine does neither impair alertness nor any of the cognitive parameters evaluated. Etifoxine may be a good option when anxiolytic treatment is required, especially in elderly people.

1. Introduction

Elderly people of at least 65 years of age represent 8.5% (617 million) of the world's population and this proportion is expected to increase to 17% by 2050 (He et al., 2016). The elderly population is highly prone to develop psychiatric morbidities due to ageing of the brain, problems with physical health, cerebral pathologies, and factors such as a decrease in economic independence and the breakdown of family support systems (Varma et al., 2010). Anxiety is an important clinical concern in older adults, although little is known about its prevalence in this population. Adjustment disorder appears to be a significant cause of anxiety symptoms in community-dwelling elderly persons, especially those presenting personal health-related problems (Arbus et al., 2014).

Benzodiazepines (BZDs) are among the most widely prescribed psychotropic drugs for anxiety (Lagnaoui et al., 2004; Pringle et al., 2005). In France, 80-92.3% of BZDs are prescribed to people of at least 65 years of age (Lasserre et al., 2010), even though concerns have been raised about the adverse event profile of these agents, including cognitive dysfunction and the potential risk for dependence (Stewart, 2005; Tan et al., 2011; Picton et al., 2018).

Etifoxine (Stresam®) is an anxiolytic drug, which is currently prescribed for the treatment of psychosomatic symptoms of anxiety. Etifoxine is a benzoxazin that does not belong to the benzodiazepine family, but that has anxiolytic properties (Verleye and Gillardin, 2004). In previous randomized controlled trials, etifoxine demonstrated a similar anxiolytic effect to lorazepam and alprazolam in adult outpatients suffering from adjustment disorder with anxiety (Nguyen et al., 2006; Stein, 2015). The impact of etifoxine (50 and 100 mg, single dose) on vigilance or psychomotor impairments in healthy volunteers aged from 18 to 35 years was studied in a placebo-controlled trial and etifoxine showed no deleterious impact on cognitive functions (Micallef et al., 2001). However, there is little data concerning the cognitive effects of etifoxine in elderly subjects over 65 years of age.

The present study, ETILANCE, was conducted to evaluate the effects of a single oral administration of the usual 100 mg dose of etifoxine on alertness and cognitive functions in healthy elderly subjects between 65 and 75 years of age. The primary objective was to measure the impact of etifoxine as compared to a placebo on alertness. The secondary objectives were to evaluate the cognitive performances of subjects and describe any adverse effects. The lorazepam arm of the study was used as a positive control due to its previous well-described psychomotor and amnesic effects (Pomara et al., 2015; Loring et al., 2012).

2. Experimental procedures

ETILANCE was a randomized, double-blind, placebo-controlled, 3-way crossover study performed between December 2013 and October 2015 at the Clinical Investigation Centre 1403 INSERM of the Lille University Hospital (France). Both the French Health Authority (*Agence Nationale de Sécurité des Médicaments*, ANSM) and the Nord-Ouest IV Ethics Committee approved the study (EudraCT number 2012-005530-11). ETILANCE was performed in accordance with the Declaration of Helsinki and Good Clinical Practices. The participants were informed about the risks and requirements of the study and gave their written informed consent before any study procedure was done. The study was also registered at ClinicalTrials.gov (NCT02147548).

2.1. Subject selection

Right-handed men and women (according to Edinburgh Handedness Inventory) aged from 65 to 75, with no progressive neurological or psychiatric condition, and not usually receiving neither psychotropic treatment nor any other psychoactive substances, were eligible. Main exclusion criteria were anxiety (a score > 7 on the Hamilton Anxiety Rating Scale and/or a score > 51 for men and > 61 for women on Spielberger's anxiety scale), current treatment with drugs known to interfere with the metabolism of study drugs, previous allergic reactions to medicines, smoking, or excessive consumption of coffee or tea (> 4 cups/day) or alcohol ($> ½$ liter of wine or equivalent/day). Subjects were also able to carry out the cognitive tests and to understand instructions.

2.2. Study procedures and treatment

Participants underwent a total of 3 one-day sessions, according to a comparative, randomized placebo-controlled,

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