Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 13-22

Featured Article

First in human study with a prodrug of galantamine: Improved benefit-risk ratio?

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Abstract

Introduction: Gln-1062 (Memogain) is a pharmacologically inactive prodrug of galantamine. Owing to its lipophilic nature, it preferentially enters the brain, where it is cleaved into active galantamine. Gln-1062 is expected to have fewer peripheral side effects than other cholinesterase inhibitors, with improved effectiveness.

Methods: This was a double-blind, comparator and placebo-controlled, sequential cohort, single ascending dose study in 58 healthy subjects with Gln-1062 in doses of 5.5, 11, 22, 33, and 44 mg, compared with oral galantamine 16 mg and donepezil 10 mg. Safety, tolerability, pharmacokinetics, and pharmacodynamics were assessed.

Results: Gln-1062 doses up to 33 mg were well tolerated and induced a dose-dependent increase in the plasma concentrations of Gln-1062 and galantamine. Gln-1062 had a dose-dependent positive effect on verbal memory and attention, mainly in the first hours after drug administration.

Discussion: Gln-1062 was better tolerated than galantamine in doses with the same molarity and led to improved effects in cognitive tests. This is most likely caused by the more favorable distribution ratio between peripheral and central cholinesterase inhibition. These results give reason for further exploration of this compound.

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Keywords: Pharmacology; Galantamine; Donepezil; Side effects; Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia. Its pathogenesis involves the progressive development of amyloid plaques and tangles, loss of cholinergic neurons, and cholinergic deficiency. Recent trials with disease-modifying compounds, such as gamma secretase inhibitors and monoclonal antibodies against amyloid β, have had negative results [1–3]. Post hoc analysis of trial data of studies with solanezumab in patients with mild AD and the first results of trials with aducanumab in patients with mild or prodromal AD seem to underline the idea that disease modification might only be useful in earlier stages of the disease [4,5]. All trials in patients with moderate or severe AD with disease-modifying compounds have been negative so far. The first registered treatment in line for the symptoms of mild-to-moderate AD are cholinesterase inhibitors (ChEIs). Although not curative, ChEIs can reduce symptoms for 6–36 months [6]. However, this positive effect is only seen in 14%–36% of patients [7–11]. Administration of higher doses, for example, 24 mg of galantamine or 23 mg of donepezil, leads to an increase in peripheral side effects, such as nausea, vomiting, and diarrhea, which overshadows a possible positive effect on cognition and functioning in daily life [12,13]. As disease modification

D.G.K. and A.M. are employees of Neurodyn Inc and Galantos Pharma, respectively. All other authors report no conflicts of interest.

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http://dx.doi.org/10.1016/j.trci.2015.12.003
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has not yet been demonstrated for any drug in patients with AD, it is worthwhile to optimize the available symptomatic drugs. Therefore, Gln-1062 (Memogain) was developed as a modification of galantamine having much higher lipophilicity and hence higher preference for the brain than the parent drug. Gln-1062 was designed as an inactive prodrug (in casu a benzoic ester) of galantamine that, after entering the brain, is cleaved into active galantamine by a carboxy-esterase. Gln-1062 is administered intranasally to prevent cleavage to galantamine in the acidic environment of the stomach, and in the presence of carboxy-esterases known to be expressed in the intestines and the liver. In female Wistar rats, intravenous administration of 5.0-mg/kg Gln-1062 led to a maximum concentration (Cmax) of 650 ng/mL in blood with an AUC_{last} of 528 ng h/mL and a Cmax of 13,627 ng/mg in the brain with an AUC_{last} of 9717 ng h/g. The brain-to-blood AUC ratio of Gln-1062 was, therefore, 18.40. After intranasal administration of 5.0 mg/kg, this ratio was 8.1 and intranasal administration of 20.0 mg/kg resulted in a ratio of 10.2 (Supplementary Material).

Owing to its more favorable brain-to-blood ratio, Gln-1062 is expected to have fewer peripheral side effects than galantamine and other ChEIs and a comparable, or possibly an improved, effectiveness in cognition enhancement. In this study, safety, pharmacokinetic, and pharmacodynamic effects of Gln-1062 were assessed and compared with orally administered galantamine and donepezil in healthy young and elderly male subjects.

2. Methods

2.1. Trial design and subjects

This was a double-blind, double dummy, double comparator, and placebo controlled, sequential cohort single ascending dose study (i.e., each subject received Gln-1062 nasal spray or placebo and capsules of either dummy or active substance for both comparator drugs). Five dose levels of intranasal Gln-1062, one dose level of oral galantamine, and one dose level of oral donepezil were tested in healthy, nonsmoking, male subjects. Main exclusion criteria were a mini-mental state examination of 27 or lower, impaired renal or liver function, use of interfering concomitant medication, and intranasal abnormalities. The first two cohorts each consisted of eight healthy young male subjects. In each cohort, six subjects received a single dose of intranasal Gln-1062 5.5 mg (cohort 1) or 11 mg (cohort 2) and two subjects received placebo. The last three cohorts each consisted of 14 healthy elderly male subjects. In each cohort, six subjects received a single dose of Gln-1062 22 mg (cohort 3), 33 mg (cohort 4), or 44 mg (cohort 5). Oral galantamine 16 mg was administered to 12 subjects in total (spread over cohorts 3 and 4) and oral donepezil 10 mg was administered to six subjects (cohort 5). In each cohort, two subjects received double placebo (six subjects in total; Fig. 1). In cohorts 3 and 4, all drugs were administered at the same time. In cohort 5, donepezil or placebo was administered 3 hours before administration of Gln-1062 or placebo to have the expected time of maximum concentration (Tmax) at approximately 3–4 hours after dosing at the same time point as the Tmax of Gln-1062, which was expected to be approximately 0.5–1 hour after dosing. All subjects gave written informed consent for participation in the study. The study was approved by the ethics committee of the Leiden University Hospital, the Netherlands. The study was conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and in compliance with Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. The trial was registered in the European Union Clinical Trials Register (2013-004354-25).

2.2. Dosing rationale

2.2.1. Gln-1062

In a 28-day intranasal toxicity study in Wistar rats, a NOAEL for intranasal Gln-1062 was observed at a dose level of 5 mg/kg. The human equivalent dose was estimated to be 48 mg. With a 10-fold safety margin, a starting dose of 5.5 mg was chosen.

2.2.2. Galantamine

The recommended starting regimen for galantamine (slow release formulation) in patients with AD is a titration period of 4 weeks on 8 mg daily after which the dose can be increased to 16 mg daily, and, if necessary, to 24 mg daily. In previous clinical trials, immediate release formulations without preceding dose titration have been given to healthy subjects as a single dose up to 15 mg [14,15]. Three of eight subjects not pretreated with a peripheral anticholinergic drug as antidote experienced nausea at a dose of 15 mg, and one of eight patients vomited. Because the main advantage of Gln-1062 would be a reduction of side effects, we chose to give a single oral dose of galantamine 16 mg.

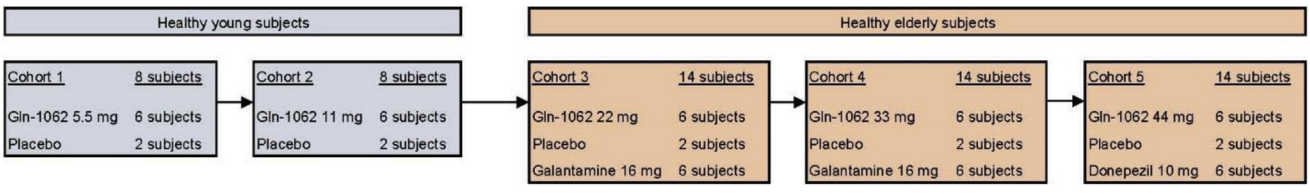

Fig. 1. Schematic overview of cohorts.

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