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# Is rivastigmine safe as pretreatment against nerve agents poisoning? A pharmacological, physiological and cognitive assessment in healthy young adult volunteers

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ABSTRACT

Rivastigmine, a reversible cholinesterase inhibitor, approved as a remedy in Alzheimer's disease, was suggested as pretreatment against nerve agents poisoning. We evaluated the pharmacokinetic, pharmacodynamic, physiologic, cognitive and emotional effects of repeated rivastigmine in young healthy male adults, in a double blind, placebo controlled crossover trial. Three groups completed 3 treatment periods: 0, 1.5 and 3 mg twice a day, for a total of 5 intakes. Parameters monitored were: vital signs, ECG, laboratory tests, sialometry, visual accommodation, inspiratory peak flow, and cognitive function tests. Adverse reactions were mild. Peak blood levels and peak cholinesterase inhibition increased with repeated intakes, and high variability and non-linear pharmacokinetics were demonstrated. In addition, two cognitive functions were affected (perceptual speed and dynamic tracking). The complicated pharmacological profile and the high inter-personal variability limit the potential use of rivastigmine as pretreatment for war fighters and first responders.



## 1. Introduction

The devastating effects of organophosphates (OP) nerve agents were recently demonstrated again in mass casualty events in Syria on August 2013 (Rosman et al., 2014). OP exposure results in the well-defined cholinergic crisis manifested as a dose dependent hyper-secretion, fasciculation, tremor, convulsions, coma, respiratory failure and death (Allon et al., 2011; Grauer et al., 2008; Markel et al., 2008; Munro, 1994; Rosman et al., 2014; Sidell et al., 2008). Pyridostigmine is commonly used as a pretreatment against OP nerve agent toxicity (Sidell et al., 2008), followed by an antidotal mixture of anticholinergic drugs and an oxime, administered after nerve agent exposure. Pyridostigmine pretreatment by itself provides only minor protection against OP poisoning, mainly through enhancement of the protection provided by the antidotal injection (Sidell et al., 2008). Pyridostigmine does not readily penetrate the blood brain barrier (BBB), hence does not protect from OP-induced major CNS symptoms.

Rivastigmine is a reversible ChE inhibitor that penetrates the BBB (Weinstock, 1999). It is approved for the treatment of mild to moderate dementia of the Alzheimer's type (AD) and dementia related to Parkinson's disease (Corey-Bloom et al., 1998; Emre et al., 2004; Finkel, 2004; Rösler et al., 1998, 1999). Rivastigmine was also found effective in counteracting cognitive damage following traumatic brain injury and focal ischemia in both animal

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and human (Chen et al., 1998a, 1998b; Cummings, 2000; Giladi et al., 2003; McKeith et al., 2000; Moretti et al., 2001; Silver et al., 2009; Tanaka et al., 1995; Tsujimoto et al., 1993; Wesnes et al., 2002), and was tested for its effects against cognitive deterioration in schizophrenia and drug abuse (Ribeiz et al., 2010; Sofuoglu, 2010; Theunissen et al., 2015). In animal studies, pretreatment with central ChE inhibitors were repeatedly demonstrated to protect against OP nerve agents induced damage (Albuquerque et al., 2006; Alexandrova et al., 2014; Grunwald et al., 2002; Haug et al., 2007; Harris et al., 1991; Janowsky et al., 2004, 2005; Lallement et al., 2001; Philippens et al., 2000).

The potential use of rivastigmine as pretreatment against OP exposure requires a careful analysis of its effects on the general population. Most of the clinical studies with rivastigmine included elderly and AD patients; only few studies tested its effects on young healthy volunteers.

In six young healthy volunteers aged 18–40 that were administered a single dose of 3 mg rivastigmine, inhibition of acetylcholinesterase (AChE) and buterycholinesterase (BuChE) activity in cerebrospinal fluid (CSF) was first observed 1.2 and 2 h, reached maximal effect of 39.4 and 9.7% inhibition, and lasted up to 8.4 and 3.6 h, respectively. Peripheral enzymes (RBC-AChE and Plasma-BuChE) were minimally inhibited (6–10%). No adverse effects were reported (Kennedy et al., 1999).

Tolerance and pharmacokinetics of rivastigmine (0.16– 4.6 mg) were assessed in 80 volunteers in a placebo-controlled study. Up to 3 mg of rivastigmine was well tolerated, but 4 out of 7 subjects treated with 4.6 mg reported nausea, vomiting, headache or dizziness. No peripheral hyper-cholinergic effects were observed (Enz et al., 1991). In another study with 12 young healthy volunteers, 1.3 and 2 mg induced an increase in the density of REM without affecting sleep quality (Holsboer-Trachler et al., 1993). Similar findings were obtained with healthy elderly volunteers (Schredl et al., 2000).

Repeated administration of rivastigmine was well tolerated in AD patients (Sramek et al., 1996). In another study with AD patients, repeated administration of 3 mg induced 46% AChE inhibition and 77% BuChE inhibition in the CSF with 35% BuChE inhibition in plasma (Cutler et al., 1998). Chronic treatment with 3–4 mg of rivastigmine for 3–12 months induced 20–30% inhibition of ChE, with CSF AChE inhibition slightly higher than that in plasma (Darreh-Shori et al., 2002). PET studies in AD patients following 3–5 months of rivastigmine treatment showed differential ChE inhibition of 27–37% in various cortical areas and demonstrate the high affinity of rivastigmine to central cholinergic sites (Kaasinen et al., 2002).

The repeated demonstration of the central effects of rivastigmine suggests likely alteration of cognitive and emotional behaviors. If the drug is to be used as prophylactic treatment against OP poisoning, the target population may consist of otherwise healthy people (e.g. first responders) that may be adversely affected by these cholinergic alterations. Thus, a careful, objective analysis of cognitive and physiological changes following single and repeated administration of rivastigmine is required.

The objectives of the presented study were to assess the safety and tolerability of single and repeated rivastigmine administration (1.5 and 3 mg) in healthy young male volunteers, to determine the pharmacokinetic and pharmacodynamic profile, and to assess physiological and behavioral effects following, in correlation with plasma rivastigmine concentrations and whole blood ChE inhibition in these subjects.

## 2. Methods

This was a single-center, double-blind, placebo-controlled, cross-over study, designed to assess the pharmacokinetic and pharmacodynamic profile and the physiological and behavioral effects following a single and repeated rivastigmine administration in healthy male volunteers. The institutional review boards of Tel-Aviv Medical Center and IDF Medical Corps approved the study. The study was registered in the NIH clinical trials registry (number CT00624663).

### 2.1. Subjects

19 healthy Caucasian males 18–40 years old were recruited by the Clinical Research Center at the Tel-Aviv Sorasky Medical Center. Four of the 19 volunteers were excluded before the initiation of dosing (3 developed flu-like symptoms and one retracted his consent). The remaining 15 subjects participated in the study. Sample size was determined by Power/Sample size calculator, based on the requirement of at least 20% differences in means of the behavioral tests performance (power = 0.80, two-tailed, $\alpha$ + 0.05).

### 2.2. Inclusion criteria

No known history of significant neurological, renal, cardiovascular, respiratory, endocrinology, gastrointestinal, hematopoietic disease, neoplasm or any other clinically significant medical disorder; BMI (body mass index) range 18–29; non-smoking (by declaration) for a period of at least 6 months; and no history of drug or alcohol abuse.

### 2.3. Exclusion criteria

Known hypersensitivity to the drug or other carbamates; any history of or currently active cardiac, pulmonary, gastrointestinal, urinary or neurological disease or disorder; significant abnormalities in screening physical exam; abnormal clinical laboratory parameters or electrocardiogram (ECG) within 21 days of the start of the study; significant allergic response to other drugs; adherence (for whatever reason) to an abnormal diet during the 4 weeks prior to the study; recent significant change in body weight; use of any prescription or over-the-counter (OTC) medications, including vitamins and herbal or dietary supplements within 7 days prior to the first study dosing or during the study; history of blood donation in the 3 months preceding the first study dosing or intention to make blood donation during the study, or within the three months following the study completion; history of transfusion of blood or plasma derivatives in the 3 months preceding the first study dosing; participation in another clinical trial of a drug within 3 months prior first study dosing; Inability to communicate well with the investigators and medical staff (i.e., language problem, poor mental development or impaired cerebral performance); difficulty fasting or consuming the standard meals that will be provided; and any acute medical situation (e.g. acute infection) within 48 h of study onset, which is considered of significance by the Principal Investigator.

### 2.4. Test drug

Rivastigmine (Exelon, Novartis) capsules were purchased and their content was re-packaged by Concept for Pharmacy (Kfar Sava, Israel) in unmarked capsules for ingestion containing 1.5 mg rivastigmine. Identical capsules containing the non-active excipients were also prepared and served as the placebo medication.

### 2.5. Regimens

Three rivastigmine regimens were evaluated: 0 mg (2 placebo capsules) BID, 1.5 mg (1 rivastigmine capsule and 1 placebo