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Drowsiness and motor responses to consecutive daily doses of promethazine and loratadine

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HIGHLIGHTS

- Consecutive daily doses of first-generation antihistamine promethazine and second-generation antihistamine loratadine induce different behavioural responses following the initial dose compared to a follow-up dose 1 day later.
- Deficits in reaction time are less pronounced following a repeat dose for both antihistamines, whereas tremor responses are less affected with consecutive promethazine doses and exacerbated with consecutive loratadine doses.
- Future studies examining antihistaminergic and anticholinergic effects of such medications will benefit from examining drowsiness and movement responses following a single dose and also consecutive dosing.

ABSTRACT

Objectives: Limited information is available regarding sedation and motor function following repeat dosing of antihistamines. This study examined how promethazine and loratadine affect day-time drowsiness, the commencement of voluntary movement, and involuntary movement when administered on consecutive days.
Methods: Ten healthy young subjects (24 ± 5 years) were recruited into a double-blind, placebo-controlled, three-way crossover study. Subjects ingested either promethazine, loratadine or a placebo, and ingested the same drug 24 h later. Measures of drowsiness, simple reaction time (SRT), choice reaction time (CRT), and postural tremor were obtained pre-ingestion, 1 h post-ingestion and 2 h post-ingestion on each day.
Results: Consecutive daily doses of promethazine and loratadine affected SRT and CRT, respectively, whereby reaction time deficits were less pronounced following the repeat dose. A reduced tremor response was also observed following consecutive daily dosing of promethazine, in contrast to loratadine which caused an increase in tremor amplitude with the consecutive daily dose.
Conclusions: Reaction time and tremor responses differed following the single dose compared to consecutive doses.
Significance: Sufferers of allergic rhinitis often require antihistamine dosing regimens that continue over multiple days. Future studies will benefit from examining drowsiness and movement responses following single doses as well as consecutive dosing.

1. Introduction

Nearly two-thirds of allergy sufferers do not consult their doctor about their condition, instead choosing to self-medicate (Walls et al., 2005). Over-the-counter treatment options for allergic

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reactions often include an antihistamine or inhaled corticosteroid. As antihistamines are often employed to treat persistent conditions such as seasonal allergic rhinitis, self-medicated drug use may continue for days, weeks and even months at a time (Layton et al., 2009, 2011).

First-generation antihistamines, such as promethazine, possess a low molecular weight, are lipophilic, and are not substrates of the p-glycoprotein pump (PGP) which mediates the efflux of molecules across the blood–brain-barrier (BBB). Combined with their high binding affinity, these drugs are able to occupy more than 75% of H_1 receptors in the brain, which has strong links to increasing sedation and drowsiness (Yanai et al., 1995). As well as binding to H_1 receptors, first-generation antihistamines have the potential to block muscarinic (M) receptors in the central nervous system (CNS), which contribute to impairments of cognition and psychomotor performance (Hindmarch, 2002; Mahdy and Webster, 2011). The half-life of promethazine ranges from 9 to 16 h (Strenkoski-Nix et al., 2000), and following oral administration the drug can often remain in blood plasma for over 30 h in healthy adults (Taylor et al., 1983). Promethazine is usually dosed at 25–75 mg daily to treat allergic conditions, which can be administered as a single dose or split into smaller and more frequent doses. To ensure continual allergy relief, particularly during allergy seasons, repeated daily dosing is typically the preferred choice of treatment (van Cauwenberge et al., 2000). Therefore, there is a high probability that promethazine will remain in blood plasma to some extent when dosing occurs on the consecutive day.

Second-generation antihistamines, such as loratadine, are typically larger than first-generation antihistamines, are less lipophilic molecules, and are PGP substrates. As a result, the ability for second-generation antihistamines to cross the BBB and occupy H_1 and M receptors is restricted, resulting in a lower potential to cause adverse CNS effects than their first-generation counterparts (Gonzalez and Estes, 1998; Philpot, 2000). Loratadine is typically administered as a 10 mg single dose, and although the half-life of loratadine ranges from 3 h to 20 h (Salem et al., 2010; Simons, 2002) a single dose of 10 mg usually remains in blood plasma for less than 24 h (Sutherland et al., 2001). Interestingly, the active metabolite of loratadine, desloratadine, has a half-life ranging from 21 h to 27 h (Geha and Meltzer, 2001; Vuurman et al., 2004), can be present in plasma for up to 120 h (Ramanathan et al., 2007), and can affect aspects of voluntary and involuntary movement at therapeutic doses (Naicker et al., 2013). Given that both promethazine and loratadine can have adverse effects on voluntary and involuntary motor function following single doses (Kavanagh et al., 2012b; Naicker et al., 2013), consecutive-day dosing may exacerbate movement dysfunction on the second day due to an enhanced presence of the drug.

This study aimed to determine how promethazine and loratadine affect day time drowsiness, the commencement of voluntary movement (reaction time), and involuntary movement (postural tremor) when administered on consecutive days. It was hypothesised that drowsiness, reaction time, and postural tremor would be minimally affected the day after ingesting either promethazine or loratadine. However, it was hypothesised that ingesting a follow-up dose of loratadine, and in particular promethazine, a day after the initial dose would exacerbate any declines or dysfunction associated with measures of drowsiness reaction time and postural tremor.

2. Methods

2.1. Subjects

Ten healthy young adults (age 24 ± 5 years, 5 female) were recruited into the study. The exclusion criteria set for the study included any history of CNS disorders such as epilepsy, any present neuromuscular injury, pregnancy, or a history of regular antihistamine usage. Participants were asked to abstain from caffeine, alcohol, exercise, or any form of CNS stimulant or depressant for at least 6 h prior to testing. All subjects gave informed consent to the experimental procedures, which were approved by the local ethics committee and were in accordance with the Declaration of Helsinki.

2.2. Experiment design

The current study was a double-blind, placebo-controlled, repeat-dosing, 3-way crossover trial. All subjects were required to attend the laboratory on a total of 6 occasions. In this time, measures of drowsiness, reaction time, and postural tremor were employed for consecutive-day dosing of a first-generation sedating antihistamine, a second-generation non-sedating antihistamine, and a placebo. The order of drug administration was randomised, however all subjects ingested a drug at 1 pm on the day of testing (day 1), and ingested the same drug at 1 pm the following day (day 2). Data were collected pre-ingestion, 1 h post-ingestion and 2 h post-ingestion. A minimum of 7 days washout was given between testing and the next round of drug administration.

2.3. Antihistamine preparation

Standard white capsules were compounded with avicel filler and promethazine hydrochloride 25 mg (first-generation), and loratadine 10 mg (second-generation). The placebo capsule contained only the avicel filler.

2.4. Self-perceived assessment of drowsiness

The Stanford Sleepiness Scale (SSS) and a custom Visual Analogue Scale (VAS) were used to assess levels of drowsiness due to drug ingestion. A unipolar scale with end points of ‘not drowsy’ to ‘very drowsy’ was used for VAS so that subjects could focus on a single subjective perception.

2.5. Reaction time

Tests of SRT and CRT were undertaken by all subjects (Kavanagh et al., 2012b; Naicker et al., 2013). For all reaction time tests, subjects were seated in a comfortable position with their forearms and hands resting on a table. Subjects were required to place their index finger on a touch pad taped to the table (44 mm × 44 mm × 0.2 mm Interlink Force Sensing Resistors) and lift their finger in response to a visual cue presented at a random time interval between 0.5 and 5 s. Touch pads collected data at 1 kHz using custom-designed Labview software (v11.0, National Instruments) (Kavanagh et al., 2012a,b). For all tests, subjects were required to react as fast as possible, extending their index finger at the metacarpophalangeal joint only (i.e. not a multi-joint reaching movement). Twenty SRT trials were performed, where the index finger of the subjects preferred hand was placed on a single touch pad, and subjects reacted to a single visual cue (a green 40 mm circle). The CRT task was a two-choice design where the subject’s left and right index fingers were placed on separate left and right touch pads spaced 100 mm apart. A green circle flashed on the left or right of the PC screen to indicate which index finger was to be extended. The order of cue presentation was randomised and data were collected for 10 left and 10 right trials. All subjects practiced each reaction time task at least 5 times prior to data collection. Subjects were blinded to their performance, and trials were repeated if the subject anticipated or did not react to the visual stimulus.