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CLINICAL REVIEW

Effect of hypnotic drugs on body balance and standing steadiness

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SUMMARY

Background: Disturbed body balance and standing steadiness are problematic for those who wake up at night or in the morning after using hypnotic drugs. As a result, falls and hip fractures are frequently reported in patients using sleep medication.
Methods: A literature search was performed to identify double blind, placebo-controlled clinical trials that examined body balance and standing steadiness. Drugs that were searched were nitrazepam, triazolam, lorazepam, temazepam, loprazolam, flunitrazepam, flurazepam, and the Z-drugs zopiclone, zolpidem and zaleplon.
Results: A total of 57 studies were eligible for inclusion. Results showed that both benzodiazepine hypnotics and the Z-drugs significantly impair body balance and standing steadiness after single dose administration. Impairments correlate significantly with blood plasma levels and are greatest at peak plasma concentrations, but are sometimes still present upon awakening. Balance problems were dose-related and most pronounced in elderly. Co-administration of alcohol aggravated the impairment. After repeated daily use of hypnotic drugs partial tolerance develops to the impairing effects on standing steadiness.
Conclusion: Single dose administration of benzodiazepine hypnotics and Z-drugs significantly impair body balance in a dose-dependent manner. Zolpidem and zopiclone produced similar significant impairment as benzodiazepine hypnotics. Zaleplon significantly impaired balance up to 2 h after intake. Partial tolerance develops after repeated daily use. In conclusion, patients should be warned about the possible risk of imbalance and falls due to the use of sleep medication.

Introduction

Most falls occur during daytime and are related to imbalance and postural instability. Slippery sidewalks, irregular surfaces (e.g., a bobbling carpet) and bad luck account for the majority of falls.[1,2] Approximately 20% of falls occur at night. Falls are most common among elderly; about 30% of elderly experience at least one fall yearly. The majority of these falls have no serious consequences, but 20–30% of falls result in injury, hip-factures or even death. For example, in 2001, over 15,000 deaths from falls were reported in the USA. In contrast to young adults, elderly recover much slower from injury, if at all. Indeed, increased mortality rates have been reported in elderly who have been involved in falling accidents resulting in hip fracture.[3–5]The economic burden of non-fatal falls is significant. For the USA, it has been estimated that over 20 billion dollars yearly are spend on medical costs related to falls.[6,7] Various studies have associated the use of hypnotic drugs, including benzodiazepines and zopiclone, with postural instability and an increased risk of falls and hip fractures.[8,9] Hypnotic drugs can have an effect on functions that are not related to sleep. Some of these may be of importance in postural control, which is governed by a number of processes such as sensory, cognitive and motor processes.[2] This review discusses the clinical trials that examined the effects of hypnotics on body balance and postural stability.

Measurement of balance and body sway

Ability to stand upright on one foot

A method to measure body balance that does not require special equipment is recording the time a person is able to maintain balance on one foot. This method has been very popular in the first experiments that wanted to measure effects of hypnotics on body balance. In the test, subjects are instructed to stand on one foot, with hands held horizontally and with eyes closed.[10–18] Subsequently, the time until the second foot touches the ground is used as a measure of body balance. Tests are generally performed for 30–60 s, and for each foot. Unfortunately, this test gives a rather crude

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measure of body balance. In modern research, it is therefore largely replaced by electronic measurements of body balance.

The ataxiameter and other swaymeters

The ataxiameter is a simple electronic device introduced to measure body sway.[19] Subjects are instructed to stand upright on two feet, placed apart. A cord from the recording device is attached to the subject. Body sway is measured by determining the angular movement of the body around the ankle joint. In other versions of this test such as the swaymeter, the cord is attached to the subject's waist and displacements of the body are measured.[20]

Force platforms

Measurements using electronic force platforms are based on changes of the Center of Pressure (COP), which is the point where the resultant of all ground reaction forces act, e.g., the center of mass and the torque on the surface. Subjects are placed on the platform and are instructed to stand steady. Duration of the test usually varies from 20 s to 3 min. Often, tests are carried out with eyes closed and with eyes open. In the latter case, having the subject fixate at a target positioned 2–3 m in front of the subject controls head position. This is illustrated in Fig. 1.

Two types of platforms are used: static and dynamic platforms. On dynamic platforms such as the stabilometer, the platform is unstable. Hence, subjects need to adapt posture to attain balance. In addition, situations can be created in which movement of the platform or the environment compromises the use of sensory information to control balance.[21] Static platforms are fixed in a horizontal plane. Subjects are instructed to maintain a steady postural balance. The force platform is connected to a computer and records small movements made by the subject. The three most commonly used statistics of sway are: 1) path length of the COP; 2) the circular area encompassing 100% of data points (Area Circ) and 3) the area of the ellipse encompassing 95% of the data points (if normally distributed; Area95). A typical example of results from a test using the Area95 to measure balance after administration of placebo (Fig. 2A) and zopiclone (Fig. 2B) is shown in Fig. 2.

Methods

A literature search was performed using Medline (from 1966), Embase (from 1974) and the Cochrane clinical trials database (searched May 15th, 2009), to collect clinical trials that examined body balance or postural sway. Keywords were 'balance', 'body sway', 'coordination', 'body equilibrium', 'postural sway', 'musculoskeletal equilibrium', and 'imbalance'. Hypnotic drugs that were searched were nitrazepam, triazolam, lorazepam, temazepam, loprazolam, flunitrazepam, flurazepam, zopiclone, zolpidem, and zaleplon. Fig. 3 gives an overview of the search process.

For 549 articles the abstract was examined. Since only clinical trials were included, most papers were not relevant for this review ($N = 459$). Of 87 papers, the full text was obtained. Cross-references yielded an additional 19 papers. After reviewing these 106 papers, 49 were excluded. The excluded papers included no balance test ($N = 22$), did not test hypnotics or specify which drugs were tested ($N = 16$), or were review articles ($N = 11$). Results from 57 papers were included and are discussed in this review. The Jadad score (0 = poor quality, 5 = excellent quality) was computed to illustrate the average quality of the included articles.[22] The average Jadad score equaled 3.2. We carefully inspected the data from each clinical trial in order to see whether it was possible to conduct a meta-analysis. Unfortunately, in most papers vital data were lacking. In general, balance test results were poorly reported, presumably because the test was not regarded as the most important measurement of the clinical trial. The data therefore do not allow conducting a meta-analysis.

Results

Single dose in young healthy volunteers

The results from studies testing the effects of a single dose on body balance in healthy young volunteers are summarized in Fig. 4.

Fig. 1. Balance test using an electronic platform. Subjects are instructed to stand right up (see panel left) for 1 min with eyes closed and 1 min with eyes open, focusing on a target point (see right panel). Reprinted with permission from QinetiQ.