ORIGINAL ARTICLE

Fexofenadine: Assessment of sleepiness potential using objective criteria

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Abstract : To evaluate the sedating effect of fexofenadine by subjective and objective assessment, 28 healthy male subjects were randomized to receive either placebo or fexofenadine 120 mg orally on day 1 or 2. Subjects were subjectively assessed for drowsiness on the basis of Stanford sleepiness scale (SSS) and visual analog scale (VAS). On day 2, multiple sleep latency tests were done at 0930, 1030, 1130, 1230, 1330, 1430, 1530 and 1700 hours. The procedure was repeated on day 3 and 4. Multiple sleep latency test (MSLT) (range) seen with placebo and fexofenadine is 14.36(± 2.83) and 13.5(± 3.66) minutes respectively. There was also no significant difference after fexofenadine and placebo between subjective sleepiness assessed by (VAS) (p=0.05) and (SSS) (p=0.412) respectively.

Keywords: fexofenadine; sleepiness scale; multiple sleep latency test

Introduction

The sedative effects of antihistaminics are believed to be related to the blocking of central H1 receptors [1]. However, some of them are not specific H1 receptor blockers and interaction with other receptors may lead to sedation. The low central effects of these drugs are believed to be due to their limited ability to cross the blood-brain barrier [2]. Many researchers have studied the effects of second generation antihistaminics on cognitive functions and pshychomotor skills [3, 4, 5, 6]. While it is true that second generation H1 receptor antagonists are in general only mildly sedative, these products are still liable to induce this central effect. Also, evidence of the cardiotoxicity in the form of prolongation of the QTc interval with possibility of ventricular arrhythmias similar to that seen with quinidine are seen with terfenadine and astemizole, though not with loratidine, putting these agents into disrepute [7].

The cardiotoxic potential of terfenadine and astemizole has prompted the search for an alternative antihistamine free of both central effects as well as cardiotoxicity. Hence, fexofenadine, a selective H1 antagonist not known to possess any other clinically relevant pharmacological activity after normal doses has been identified. Fexofenadine, is structurally identical to the active metabolite of terfenadine, except that it is a hydrochloride salt. After oral administration it is rapidly absorbed with time to maximum concentration occurring within 1-2 hours [8]. Elimination half life ranges from 13-16 hours. Single doses of 40 mg of the drug and above achieve more than 80% maximum inhibition of both the wheal and flare responses. The pharmacological effect starts 1-2 hours after dose administration and is sustained over 24 hour period. Fexofenadine does not produce any QTc prolongation as it is devoid of action on the myocardial potassium channel. In two long term studies on human volunteers in doses of 60 mg twice daily for 6 months and 240 mg once daliy for 12 months there was no prolongation of the QTc interval [9]. As the drug is a pharmacologically active metabolite of terfenadine, it is thought to be free of all central effects including sedation. Previous studies have analysed the effect of fexofenadine on psychomotor skills, cognitive performance and effect on actual driving performance [6, 10].

While evaluating the sedative potential of a drug, it is important to select adequate test methods and to keep in mind that psychometric approaches may be insensitive

as demonstrated by Moser [11] and Kulshrestha [12]. Only one study in the past has used Multiple Sleep Latency Tests (MSLT) as an objective method of assessing sleepiness after fexofenadine ingestion [6]. The present study aims to objectively assess sleepiness after consumption of the drug in therapeutic doses, using the Stanford Sleepiness Scale and performing Multiple Sleep Latency Tests in normal healthy young volunteers. Moreover, no definite studies demonstrating the non-sedating properties of fexofenadine have been done in Indian subjects.

Aims and objectives

To study the sedating effect of Tab. Fexofenadine 120 mg. when compared to a placebo in 28 healthy volunteers.

Methods

The subjects studied were 28 healthy volunteers. All subjects were male and their age ranged from 17- 46 (mean 26.21) years. Their mean BMI was 19.9 ± 2.61 kg/m^2 (range 16.5 – 26.6). They were not on any form of medication and gave an informed written consent to take part in the study, which was approved by the Ethics Committee. A detailed history regarding fever, viral illness, allergies in the recent past was obtained. History of snoring, excessive daytime somnolence to exclude patients with sleep disordered breathing was also taken. A detailed history of the number of hours and the quality of sleep in the past 48 hours was obtained. Subjects with night shift duties were excluded from the study. All subjects were non-alcoholics and had stopped smoking at least 12 hours prior to the study.

Procedure

Subjects were called on 4 consecutive days and were randomly given one tablet, either the drug Tab Fexofenadine 120 mg or Placebo at 0930 hours on Day 1 and were asked to retire at their normal bedtime that day. On Day 2 they were asked to report at 0900 hours. The subject was given the same tablet as on Day1 at 0930 hours and sleep latency tests were performed at 0930, 1030, 1130, 1230, 1330, 1430, 1530 and 1700 hours. The procedure was repeated with the other drug on Day 3 and Day 4. The subjects were asked to have a light breakfast before the test sessions and light lunch was offered at 1300 hours. The tests were done in a light proofed, sound attenuated, temperature controlled room.

Subjective and objective assessments of sleep latency:

Visual analog scale: -

Two hours after drug administration, sleepiness was assessed using a 100 mm visual analog scale, 0 being completely awake and 100 being grossly sleepy.

Stanford Sleepiness Scale: -

Sleepiness was assessed 2 hours after drug ingestion using the Stanford Sleepiness Scale [13]

Multiple Sleep Latency Tests: -

These were performed recording a 2 channel Electroencephalograph (EEG) activity, (C4-A1 and O1-A2) along with bilateral Electroocculogram (EOG) and submental Electromyogram (EMG) using Alice 3 v. 1.19 Healthdyne © Apreco 1995 sleep laboratory. Sleep onset was defined as recording of 3 consecutive epochs (30 secs each) of stage I or one epoch of Stage II, III, IV or REM sleep. Recording was terminated after sleep onset, or if sleep onset was not recorded, then after 20 mins. The sleep onset was determined independently by two analysts using standard criteria [14]. Both the analysts were blinded to the drug given.

Interpretation of MSLT [15]*:* Lower scores in MSLT indicate greater sleepiness and vice versa. Accepted rule of thumb has evolved from recommendations first made by Richardson et al. [16], which are, a mean daily score of < 5 mins indicates a pathological degree of sleepiness. This level is associated with impaired performance in patients and in sleep deprived normal controls [17, 18, 19, 20, 21]. Adult normal control volunteers usually score in the range of 10 – 20 mins [16, 22, 23, 24, 25], so that scores between pathological and normal ranges have become known as a diagnostic gray area [26].

Statistical methods

Keeping in view the size of the sample selected (n=28), no transformation was applied as used by other researchers of similar studies [1, 6] whose sample size was 6-7 cases. Since same subjects were used for Placebo & the drug fexofenadine on the same subjects with similar medical history (mentioned above), Student's paired t-test was applied to this data to test the significance of difference between mean values of the subjects under the influence of placebo and fexofenadine.

Results

There was no significant difference between the number of hours of sleep in the 48 hours preceding the experiment. The mean duration of sleep was 15.68± 1.68 hours in the 48 hours preceding the placebo experiment and 15.75 ± 1.55 hours before the fexofenadine study. Mean sleep latency time after ingestion of placebo is 14.36 ± 2.83 minutes while that after fexofenadine is 13.5 ± 3.66 minutes. This difference was found to be statistically significant (p= 0.02). Sleep latency after fexofenadine was shorter only at 4 hours post ingestion as compared to placebo (p = 0.008). There was no significant difference in sleep latency with fexofenadine at other times as compared to placebo. However, 3 of the 28 subjects (10.71%), had a sleep latency times < 5 mins at 1130 hours (peak blood levels of drug). These 3 subjects also tended to have lower sleep latency times at 0930 and 1030 hours on the same day.

There was also no significant difference after fexofenadine and placebo between subjective sleepiness assessed by the visual analog scale (VAS) and Stanford Sleepiness Scale after 2 hours of drug ingestion (peak blood levels of fexofenadine)

Table 1: Effect of drugs on sleep latency (means for 28 subjects).

Paired t – test

Variable	N	Mean (mins)	Standard Deviation	Standard Error	t	p
Mean SLP	28	14.3683	2.838	0.536	2.12	0.02*
Mean SLF	28	13.5000	3.661	0.692		
0930 P	28	13.1429	4.743	0.896	1.04	0.15
0930 F	28	12.3393	4.685	0.885		
1030 P	28	12.5714	5.374	1.016	- 0.47	0.32
1030 F	28	13.1429	5.042	0.953		
1130 P	28	12.5000	5.499	1.039	1.44	0.08
1130 F	28	10.9821	5.769	1.090		
1230 P	28	12.5357	6.508	1.230	- 0.62	0.27
1230 F	28	13.3393	6.400	1.210		
1330 P	28	15.1607	5.226	0.988	2.56	0.008**
1330 F	28	12.000	5.907	1.116		
1430 P	28	14.2143	6.296	1.190	0.24	0.40
1430 F	28	13.9286	7.106	1.343		
1530 P	28	16.9464	5.358	1.013	1.58	0.063
1530 F	28	15.2500	6.866	1.298		
1700 P	28	17.8750	4.729	0.894	1.06	0.14
1700 F	28	17.0179	5.087	0.961		

The variable column: Mean SLP & F indicate Mean sleep latency time with placebo and Fexofenadine respectively and 0930, 1030….indicate the time at which the study was done with P denoting placebo and F denoting fexofenadine.

*: significant (p < 0.05) **: highly significant (p < 0.01)

Table 2: Effect of drugs on subjective sleepiness (means for 28 subjects).

Paired t – test

VAS (P & F) – Visual analog scale using placebo and fexofenadine
SSS (P & F) – Stanford Sleepiness Scale using placebo and fexofenadine
p = 0.05

Discussion

The present study was done on 28 normal healthy young volunteers from the general population. In our study, the mean sleep latency time was lower after ingestion of fexofenadine (13.5 mins) as compared to placebo (14.368 mins). Sleep latency times were lower with fexofenadine as compared to placebo at most times during the day, including at 1130 hours corresponding to the peak blood drug levels. However, this difference was not statistically significant, except at 1330 hours when sleep latency was 10.98 mins with fexofenadine as compared to 12.50 mins with placebo. The study to assess the sleepiness potential of fexofenadine using MSLT by Nicholson et al [6] was limited by the small number of subjects on which the tests were performed. Moreover, these subjects were basically pilots, which is a highly specialized subset of general population with very high degree of physical fitness and mental acuity. The results of the Nicholson's study [6] therefore, cannot be extrapolated to the general population. The Nicholson study [6] also had demonstrated a reduction in sleep latency times in the immediate post lunch sessions, though; the reduction was same as that seen with placebo. The lower sleep latency at 1330 hours with fexofenadine as compared to placebo, in our study, needs to be viewed against this background and considered significant. Hence, the fact that fexofenadine has more sleepiness potential as compared to placebo cannot be ignored. However, as mentioned above in the interpretation of MSLT [15], the sleep latency time of normal healthy volunteers is between 10-20 min and only sleep latency times of < 5min are considered pathological and are associated with impaired performance [17-21]. Thus, even if there was a reduction in mean sleep latency times after fexofenadine ingestion as compared to placebo, the values were well within the normal range of 10-20 min, suggesting that the sleepiness produced by fexofenadine is not clinically

relevant [15]. As against fexofenadine, cetrizine at doses of 10 mg and above caused reduction in sleep latency times to less than 5 min in the afternoon hours, thus making its use unsafe in subjects involved in highly skilled activity [1]. In our study, though there was no significant reduction in sleep latency time, as compared to placebo at 2 hours after fexofenadine ingestion coinciding with the peak blood concentration of the drug, 3 of the 28 subjects (10.71%), with low baseline sleep latencies had sleep latency time of < 5 min at peak blood levels of fexofenadine. On detailed retrospective evaluation of their sleep history, it was appreciated that these subjects had chronic sleep debts, thus accounting for their low baseline sleep latencies. These observations tend to suggest that, in subjects with history of sleep deprivation or chronic sleep debt, fexofenadine can cause pathological decrease in sleep latency times [24, 25]. Similar extrapolations can also be made for patients with other causes of excessive daytime sleepiness like obstructive sleep syndromes and narcolepsy [16, 17]. These observations, though, need to be confirmed by further studies on sleep deprived individuals and patients with excessive daytime sleepiness.

Though no performance tests were used to test sleepiness potential in this study, other studies [6, 10] have demonstrated that fexofenadine in therapeutic doses has no effect on performance of highly skilled activities. Similarly, no significant difference in subjective assessments of sleepiness as recorded was noted with the use of fexofenadine 120 mg at times coinciding with peak blood levels of the drug. However, as proved in other studies the subjective evaluation of sleepiness is not as sensitive as MSLT in evaluation of central effects of antihistaminics [1].

In conclusion, although the specificity of fexofenadine to H1 receptors and its limited ability to cross the blood brain barrier would suggest that the drug may have little or no sedative properties, the present study has shown that fexofenadine has the potential to cause slight increase in sleepiness, as compared to placebo, throughout the day. However, this degree of sleepiness is neither clinically relevant nor pathological, thus making the drug safe to be used in persons involved in highly skilled activity. The tendency of this drug to cause pathological decreases in sleep latency times in sleep deprived individuals, though, needs to be studied further.

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