Frequency and Factors of Tremor, Palpitation, and Cramp in Patients with COPD and Asthma

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Abstract

Objective: To evaluate the frequency and predictability of side effects, including tremor, cramp, and palpitation, due to treatment in patients with chronic obstructive pulmonary disease and asthma.

Methods: We prepared a standard questionnaire for 299 patients concerning their diagnosis, treatment, and side effects of the treatment in February 2007 at Hacettepe University, Faculty of Medicine, Department of Pulmonary Diseases. We prospectively examined the clinical status of the patients and side effects of the treatment at the 15th, 30th, and 180th days of the treatment.

Results: In our study, there were 38 (12.7%) patients with drug-induced tremor. Of these, 27 (71.1%) had asthma (p=0.004) and 18 (47.4%) had anamnestic palpitation. Drug-induced tremor risk was 15.3 times higher in patients who used a beta-mimetic compared with those who used any drugs. Cramp risk increased with beta-mimetic use only. In our study, drug-induced tremor was still present at the 180th day of examination in 32 (84.2%) patients.

Conclusion: This study demonstrated that side effects, including tremor, palpitation, and cramp, were more common in our patients compared with those in other studies. These side effects were directly related to the primary disease and the use of beta-2-agonists. Another finding of our study is that tolerance did not develop as much as that reported in literature.

Keywords: Asthma, bronchodilator, COPD, cramp, palpitation, tremor

INTRODUCTION

Chronic respiratory diseases (CRD) are associated with airways and lung parenchyma as chronic obstructive pulmonary disease (COPD), asthma, occupational pulmonary diseases, and pulmonary hypertension. Worldwide, there are more than 1 billion people with CRD, of which 300 million people have asthma and 340 million people have COPD. More than 500 million patients live in developing countries. Prevalence increases with age (1). Early diagnosis and treatment of asthma and COPD are important because of their treatable nature. Asthma and COPD are chronic inflammatory airway diseases with different clinical presentations involving various cells and cellular mediators.

There is adequate evidence to indicate that the clinical symptoms of COPD and asthma can be controlled (symptoms such as sleep disorders, limitation of daily activities, disruption of pulmonary functions, and life-saving drug utilization) with appropriate treatment. Even though these diseases are controlled, recurrence of symptoms and severe inflammation may be observed (2, 3). The most common adverse effects are tremor, cramp, and palpitation. The adverse effects are caused by anti-inflammatory and bronchodilator treatments. Methylxanthines and long-acting inhaled β2-agonist treatment cause less systemic adverse effects than oral treatment.

These are cardiovascular stimulation, headache, skeletal muscle tremor, hypopotassemia, and cramp (4-15). Although the prevalence of adverse effects is reported as palpitation 1%-6.9%, tremor 1%-10.7%, and cramp 4%-5%, there is inadequate supporting data (5, 16). Undesirable effects of theophylline are gastrointestinal symptoms, soft defecation, cardiac arrhythmias, convulsive seizures, and mortality. The prevalence of adverse effects is tremor 11%-13% and cardiac arrhythmia 24%-29% (17-20).

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In our study, the prevalence of adverse effects, predictability of adverse effects, and characteristics of tachyphylaxis were surveyed. When the development of adverse effects related to bronchodilator therapy was carefully evaluated, false diagnose and treatment could be avoided in patients with asthma and COPD.

METHODS

Two hundred ninety-nine patients who presented to The Faculty of Medicine, Department of Pulmonary Diseases during February 2007 were considered for our cross-sectional study. There were included all applied patients to our polyclinic. They were requested to fill a questionnaire concerning their diagnoses, treatments, and several treatment-induced adverse effects. The patients were educated by only one chest physician regarding side effects. We prospectively examined the clinical status of the patients and side effects of the treatment at the 15th, 30th, and 180th days of the treatment either face to face or by phone.

The standard questionnaire included details on age, sex, diagnosis, smoking, alcohol use, drug utilization, tremor, cramp, and palpitation that were the most frequently encountered adverse effects. Spirometry results were recorded. Approval from the local ethics committee was received. Additionally, informed consent from the patients was received.

Tremor was defined as the presence of trembling in hands, feet, voice, head, and chin; in performing tasks that require attention and ability; and in stretching hands forward. Family history, alcohol consumption, drinking tea and coffee, smoking as well as drug use, bronchodilator drug use history, and goiter history were asked in relation with tremor. Palpitation was defined as increased or irregular pulses in the chest. We asked if palpitation was related to drug use and drinking tea and coffee. Cramp was defined as an intermittently experienced painful muscle spasm. Its origin, time, and place were asked. Cramp was accepted as absent if it was rare (less than once a year).

Questionnaires and examinations were conducted by a chest physician. Tremor evaluation was carried out by spiral drawing and sentence writing in line with the recommendations of University Department of Neurology. The dominant hand was recorded, and spiral drawing and sentence writing were performed by the right and left hand. Scores were assigned based on four grades. Scores were 1: severe, 2: moderate, 3: insignificant, and 4: no tremor.

Statistical Analysis

Statistical analyses were done by Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 11.5 program. Mean±standard deviation median (minimum-maximum) for metric variables and frequency (percent) for categorical variables were given as descriptive statistics. In order to compare two independent groups in terms of metric variables, Mann-Whitney U test, that of categorical variables; Chi-square test was performed. Odds ratio (OR) with a 95% confidence interval (CI) was examined for risk evaluation. $p<0.05$ was considered as statistically significant.

RESULTS

Demographic characteristics of the 299 patients who participated in our study are given in Table 1. The mean (±SD) age of patients was 50.8±13.8 years (minimum: 16; maximum: 82); 60.5% of them were female. Asthma and COPD were the most frequent reasons for application with 49.5% and 23.7%, respectively. In our study, beta-mimetic use was present in 139 (46.5%) patients, theophylline use was present in 4 patients (1.3%), and concomitant use of theophylline and beta-mimetic was present in 11 patients (3.7%).

The mean age was identified as 48.9 years in patients with asthma and as 59.6 years in patients with COPD ($p<0.001$). There were 118 women (79.7%) and 30 men (20.3%) in patients with asthma; there were 16 women (22.5%) and 55 men (77.5%) in patients with COPD ($p<0.001$). Smoking and alcohol consumption were significantly higher in patients with COPD ($p<0.001$ and $p=0.005$, respectively). Beta-mimetic use was found to be 62.8% in patients with asthma and 54.9% in patients with COPD; theophylline use was found to be 2% in patients with asthma and 1.4% in patients with COPD (Table 2).

In our study, tremor was found in 100 (33.4%) patients at first application. Drug-induced tremor was detected in 38 (12.7%) patients. It was detected in 27 (71.1%) patients with asthma ($p=0.004$) and was detected together with anamnestic palpitation in 18 (47.4%) patients ($p=0.015$). Anamnestic palpitation was detected in 30.4% patients. Cramp was detected in 63.9% patients. Family history of tremor, alcohol consumption, and smoking did not increase the risk of drug-induced tremor (Table 3).

Table 1. Demographic characteristics of patients (n=299)

Descriptive statistics	
Age*	50.8±13.8 (16-82)
Sex (Female)	181 (60.5)
Asthma	148 (49.5)
Smoking	74 (24.7)
Regular alcohol consumption	13 (4.3)
Tremor presence	100 (33.4)
Drug-induced tremor presence	38 (12.7)
Anamnestic palpitation	91 (30.4)
Cramp	191 (63.9)
Drugs	
None	145 (48.5)
Beta-mimetic use	139 (46.5)
Theophylline use	4 (1.3)
Beta-mimetic and theophylline	11 (3.7)
Goiter	40 (13.4)
Parkinson's disease	4 (1.3)
Dominant hand (Right)	281 (94.0)
FEV %*	77.2±22.3 (11-163)
FVC %*	80.6±20.7 (11-148)
FEV_1/FVC*	79.5±11 (42-101)

Cells for variables with * represent mean±standard deviation (min-max), others represent frequency (percent)

FEV: Forced expiratory volume; FVC: forced vital capacity

Drug-induced tremor risk (OR) was 15.3 times (95% CI: 4.6-51.3) more in patients who used a beta-mimetic compared with those who used any drugs. The risk of drug-induced tremor was higher in concomitant beta-mimetic and theophylline users (OR: 4.7; 95% CI: 0.5-49.7); however, this estimate was not statistically significant (p=0.155).

Although we did not find statistically significant results, the risk of anamnestic palpitation increased, regardless of the drugs used. However, the risk of cramp increased with only beta-mimetic use (p=0.020) and combined with theophylline (p=0.362) (Table 4).

In our study, drug-induced tremor disappeared in one (2.6%) patient on the 15th day, in one (2.6%) patient on the 30th day, and in three (7.9%) patients on the 180th day control. Drug-induced tremor continued in 33 (86.8%) patients. Cramp disappeared in one (2.6%) patient on the 15th day. Anamnestic palpitation disappeared in one (2.6%) patient on the 30th day. Two (5.3%) of the patients quit using drugs, and one (2.6%) patient died.

DISCUSSION

Asthma and COPD are globally important diseases. Significant improvements have been achieved in the treatment of asthma and COPD, which form a significant portion of CRD, compared with previous years. There is adequate evidence that clinical symptoms can be controlled with appropriate treatment in both diseases. Pharmacological treatment can cure and prevent symptoms, can decrease the severity and frequency of inflammations, and can increase exercise tolerance. This improves the quality of life. Although the natural history and treatment approaches of these two diseases are different, pharmaceutical groups used are substantially the same. Beta-mimetic, anticholinergic, methylxanthine, and steroids are the cornerstones of COPD and asthma treatment. In daily practice, more tremor, palpitation, and cramp adverse effects are experienced compared with those from literature reports. Adverse effect-induced tolerance (tachyphylaxis) is a very controversial issue.

In our study, the definitions of tremor, palpitation, and cramp were explicitly specified to decrease individual perceptions and changes due to cultural differences when filling the questionnaire. However, because of the lack of standard methods regarding the definition and follow-up of these adverse effects, definitions mentioned in the Method section were followed. Nevertheless, it may be controversial to compare figures reported regarding adverse effects in literature with the results found in our study.

Table 2. Demographic characteristics of patients with asthma and COPD (n=219)

	Asthma (n=148)	COPD (n=71)	p
Age*	48.9±13.3 [49 (16–77)]	59.6±10.1 [58 (32–82)]	<0.001
Sex			
Female	118 (79.7)	16 (22.5)	<0.001
Smoking	6 (4.1)	64 (90.1)	<0.001
Regular alcohol consumption	1 (0.7)	6 (8.5)	0.005
Tremor presence	58 (39.2)	21 (29.6)	0.166
Drug-induced tremor presence	27 (18.2)	8 (11.3)	0.187
Anamnestic palpitation	59 (39.9)	15 (21.1)	0.006
Cramp	96 (64.9)	48 (67.6)	0.689
Drugs			
None	51 (34.5)	22 (31.0)	
Beta-mimetic use	93 (62.8)	39 (54.9)	NA
Theophylline use	3 (2.0)	1 (1.4)	
Beta-mimetic+theophylline	1 (0.7)	9 (12.7)	
Goiter	23 (15.5)	6 (8.5)	0.147
Parkinson's disease	1 (0.7)	1 (1.4)	0.544
Dominant hand			
Right	136 (91.9)	68 (95.8)	
Left	6 (4.1)	2 (2.8)	NA
Bilateral	6 (4.1)	1 (1.4)	
FEV_1 %*	80.6±20.6 [83 (11–163)]	65.1±22.7 [65(23–112)]	<0.001
FVC %*	84.6±19.1 [87 (11–148)]	70.7±21.3 [70.5 (21–112)]	<0.001
FEV_1/FVC*	80±9.2 [82 (51–101)]	73.9±13.5 [76 (42–100)]	0.002

Cells for variables with * represent mean±standard deviation (min-max), others represent frequency (percent)
FEV: Forced expiratory volume; FVC: forced vital capacity; NA: not applicable

Table 3. The presence of the drug-induced tremor (n=299)

	Absent (n=261)	Present (n=38)	p
Age*	51.4±13.2 (21–82)	46.9±17.4 (16–80)	0.118
Sex			
Female	156 (59.8)	25 (65.8)	0.478
Male	105 (40.2)	13 (34.2)	
Asthma	121 (46.4)	27 (71.1)	0.004
COPD	63 (24.1)	8 (21.1)	0.676
Smoking	67 (25.7)	7 (18.4)	0.333
Regular alcohol consumption	13 (5)	-	0.385
Anamnestic palpitation	73 (28)	18 (47.4)	0.015
Cramp	162 (62.1)	29 (76.3)	0.088
Drugs			
None	142 (54.4)	3 (7.9)	NA
Beta-mimetic use	105 (40.2)	34 (89.5)	
Theophylline use	4 (1.5)	-	
Beta-mimetic+Theophylline	10 (3.8)	1 (2.6)	
Goiter	35 (13.4)	5 (13.2)	0.966
Dominant hand			
Right	246 (94.3)	35 (92.1)	NA
Left	7(2.7)	3(7.9)	
Bilateral	8(3.1)	-	
Family history of tremor	42 (16.1)	6 (15.8)	0.962

Cells for variables with * represent mean±standard deviation (min-max), others represent frequency (percent)
COPD: Chronic obstructive pulmonary disease; NA: not applicable

Generally it is reported that tremor is detected in approximately 14.5% patients, cramp in approximately 36%, and palpitation in approximately 7%-24% in conducted studies (5, 11, 21-26). In our study, tremor, cramp, and palpitation were found in 33.4%, 63.9%, and 30.4% of the patients, respectively, which were higher percentages compared with previous studies. Moreover, drug-induced tremor was found in 12.7% of the patients. In a recent study, beta-mimetic-induced tremor and palpitation were found to be very low (often in <1% of patients), and muscle cramp was found in 5% of patients (12). The University Faculty of Medicine Hospital is a tertiary health care provider. In other words, notwithstanding that it is incorrect on an individual basis, it can be considered that more comorbid patients come or are sent here generally from primary or secondary health care centers. This may be the factor explaining the increase in adverse effects. It is necessary to repeat these adverse effect studies in primary and secondary healthcare centers in order to prove the accuracy of this idea.

In literature, tolerance (tachyphylaxis development) was reported for these adverse effects. The adverse effects are considered insignificant. In a cohort study conducted by Mann et al. (4) with 15,407 patients, tachyphylaxis developed within 2-6 months. In another study, Newhouse et al. (27) showed that systemic beta-receptor subsensitivity develops when the salbutamol cumulative dose was over 4000 mcg. In their study, Bartow et al. (26) observed tachyphylaxis development due to a reduction in the number of β2 receptors. Tachyphylaxis developed after 2-4 weeks against the adverse effects that formoterol induced, such as tremor, palpitation, and cramp, on patients with asthma. In our study, the patients were called or evaluated face to face for controls on the 15th, 30th and 180th days. Drug-induced tremor disappeared in one (2.6%) patient on the 15th day, in one (2.6%) patient on the 30th day, and in three (7.9%) patients on the 180th day control. Drug-induced tremor continued in 33 (86.8%) patients. Cramp disappeared in one (2.6%) patient on the 15th day. Anamnestic palpitation disappeared in one (2.6%) patient on the 30th day. In our study, tachyphylaxis did not significantly develop by the 15th, 30th, and 180th days.

It was established that adverse effects such as tremor, cramp, and palpitation were directly related with the disease itself and beta-mimetic use. In our study, drug-induced tremor development increased 15.3 times because of beta-mimetic use in patients. Beta-mimetic use was more frequent in patients with asthma. Concomitant use of beta-mimetic with theophylline was more frequent in patients with COPD. The frequency of adverse effects in patients with asthma was significantly more than in that in patients with COPD. This took placed despite the characteristics of patients with

Table 4. Drug-related other adverse effects

Drugs	Anamnestic palpitation			Cramp		
	Frequency (Percent)	OR (95% CI)	p	Frequency (Percent)	OR (95% CI)	p
None	38 (26.2)	Reference	-	83 (57.2)	Reference	-
Beta-mimetic use	47 (33.8)	1.4(0.7–2.4)	0.16	98 (70.5)	1.8 (1.1–2.9)	0.02
Theophylline use	3 (75)	8.4 (0.9–83.7)	0.06	2 (50)	0.7 (0.1–5.5)	1.00
Beta-mimetic and Theophylline	3 (27.3)	1.1 (0.3–4.2)	1.00	8 (72.7)	2 (0.5–7.8)	0.36

CI: Confidence interval; OR: odds ratio

COPD being advanced age, smoking and alcohol consumption, and prominent male gender. These patient characteristics significantly increase tremor, cramp, and palpitation. Maybe, adverse effects are effected disease itself. Wenning et al. (22) detected the prevalence of tremor that increased with age in males. In another study, Morgan et al. (28) showed tremors that significantly increased with smoking and alcohol consumption. In patients with asthma, there can be a genetic predisposition that increases the prevalence of adverse effects. Pharmacogenetic studies have been conducted on effects and adverse effects of medicine in asthma treatment. There can be specific genes correlated with adverse effects. Palmer et al. (29) showed variations in the frequency of adverse effects that are correlated with specific genes or loci. It was shown that resistance to receptor down regulation developed because of coding of arginine at their 16 and 27 positions in the β2-AR gene. In a study conducted by Wechsler et al. (30), the fact that the presence of arginine/arginine homozygosis instead of glycine/glycine at the B16 amino-acid position of β2 receptors explains the β2-agonist-induced adverse effect frequency. In other words, it should not be ignored that endogenous risk factors such as genes can increase adverse effect predisposition as well as exogenous risk factors.

The possible reason of the fact that adverse effects do not draw adequate attention and are ignored is the difficulty in recognition, identification, and follow-up of conditions such as tremor, cramp, and palpitation and a lack of standardization. Pulmonologists perhaps ignore these adverse effects, but a physiologist, neurologist, or cardiologist cannot ignore the adverse effects. Patients may not be aware of these adverse effects. Some patients on the other hand go to another doctor because of these adverse effects. This phenomenon is very frequently experienced with ACE inhibitors. With the use of ACE inhibitors, which are one of the most effective antihypertensives, coughing at a rate of 20-40% is observed. Patients prefer to have their coughing examined by a different doctor rather than having it examined by the doctor who controlled their blood pressure. Perhaps, they do not consider that the hypertension is correlated with coughing. Maybe doctors who prescribe the drug do not explain this correlation to their patients, and thus, patients who cough because of adverse effects go to pulmonologists.

It is seen that our working method adequately defined tremor, palpitation, and cramp in the first examination and proceeding controls. The patients were not only questioned and examined in the first examination but were also trained on this subject. Therefore, adequate information was obtained from patients who could not come on the 15th, 30th, and 180th days.

Nonetheless, this study was conducted by one person in order to eliminate doctor-dependent differences.

CONCLUSION

In our study, drug-induced tremor, cramp, and palpitation rates were found to be higher that the rates reported in other studies. It was established that drug-induced adverse effects in patients with asthma were more frequently beta-mimetic dependent. The risk of tremor development increased 15.3 times with beta-mimetic use in patients who did not have tremor before. On the other hand, there is float tolerance development to adverse effects. Therefore, patients should be warned in terms of adverse effects, and in case adverse effects develop and the daily life of the patient is affected by them, treatment should be continued with another drug.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of local ethic commitee.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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PATIENT'S QUESTIONNAIRE (FIRST APPLICATION)			
Name-Surname: **Age:** **Sex:**			
1. Do your hands, feet, voice, head, and chin tremble?		yes	no
2. Do you tremble when resting?		yes	no
3. Does your trembling increase when you get excited?		yes	no
4. Do your hands tremble when stretched forward?		yes	no
5. Do you tremble when performing tasks that require attention (while carrying a tray, drinking water, transferring water from one cup to another, using fork and spoon, and writing)?		yes	no
6. For how much time do you tremble?		yes	no
7. Are there any family members, such as your mother, father, their siblings, and your siblings, who tremble?		yes	no
8. Are your mother and father relatives?		yes	no
9. Do you consume alcohol?		yes	no
10. Do you smoke?		yes	no
11. Have you ever taken asthma medication before?		yes	no
12. Did you trembe during the period you received asthma treatment?		yes	no
13. What are the drugs that you are using? Now?	dose	duration	
1-			
2-			
3-			
4-			
5-			
6-			
14. Do you have goiter?		yes	no
15. Do you have palpitation?		yes	no
16. Do you tremble after drinking tea/coffee?		yes	no
17. Do you palpitate after drinking tea/coffee?		yes	no
18. Do you suffer intermittent painful muscle spasms?		yes	no
19. When/where does the cramp appear most frequently?		yes	no
20. FEV_1_____ L/min _____ %	22. DRAW A SPIRAL (_____ handed) score: 1 2 3 4		
FVC: _____ L/min _____ %	RIGHT	LEFT	
FEV_1/FVC: _____			
PEF: _____ L/min_____ %			
21. WRITE A SENTENCE: score: 1 2 3 4			
FEV: Forced expiratory volume; FVC: forced vital capacity; PEF: peak expiratory flow			