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Extrapyramidal Side Effects of Intramuscular Antipsychotics in Psychosis and Substance Use Disorders, Occurrence and Predictive Factors

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Abstract

This retrospective study aims to determine the occurrence of extrapyramidal symptoms (EPS) after intramuscular (IM) antipsychotic treatment at emergency services and the predictive factors among acute psychotic patients with substance use disorders (SUD). We randomly selected medical records of acute psychotic patients with SUD, free of initial EPS needing IM antipsychotic drugs. The occurrence of EPS and relevant data were collected. The occurrence of EPS was 7.84 %. The proportion of patients with co-morbidities, light smokers who were treated with IM haloperidol and zuclopenthixol were significantly higher in the EPS group (p = 0.009, p = 0.012 and p = 0.011) while the proportion of those with high intensity amphetamine dependence were significantly lower in the EPS group (p = 0.044). However, IM haloperidol with zuclopenthixol was the only predictive factor of EPS (OR = 13.39, p = 0.043). Our results showed a lower risk of EPS in SUD patients compared to 9.8 % in non SUD patients. It was supported by previous findings showing that substance dependence caused persistent high DA concentration after abstinence and probably a decreased risk of EPS in SUD patients. A combination of a typical antipsychotic drug and benzodiazepine is the safer alternative for nonresponsive SUD patients.

Keywords: Extrapyramidal symptoms, substance use disorders, acute psychosis, intramuscular antipsychotic drug

Introduction

Extrapyramidal symptoms (EPS) are the most common side effects of antipsychotic drugs, especially high potency drugs, haloperidol. EPS are abnormal involuntary movements including dystonia, Parkinsonism, akathisia, and dyskinesia resulting from blocking striatal dopamine 2 receptors exceeding 72 % [1,2]. Acute dystonia and acute akathisia were found in up to 50 % of cases with potent antipsychotic drugs and occurred within hours after the initial dose of potent antipsychotics [3].

The prevalence of co-morbidity between mental disorders and substance use disorders (SUD) were 40 - 85 % [4]. The possible reason is that psychoactive substances increase dopamine (DA) concentration in the brain [5,6] by inhibiting DA transporters (DAT), the protein responsible for DA uptake to neurons [5]. In addition, smoking is frequently concomitant with substance dependence. Nicotine can increase as well as decrease DA concentration by stimulating nicotinic acetylcholine receptors in both mesocorticolimbic and nigrostriatal systems and increasing DAT function [7].

Intramuscular (IM) antipsychotic drugs are effective treatment for acute psychotic patients with SUD [8,9] but their adverse effects among SUD patients are less well known. Therefore, this retrospective study aims to determine the occurrence of EPS after IM antipsychotic treatment in an emergency service setting and its predictive factors in acute psychotic patients with SUD.

Materials and methods

This retrospective study was conducted at the Thanyarak Institute, a center for drug addiction treatment, Pathumthani province, Thailand. The study was approved by the local ethics committee (No. 23/2557). In order to determine the occurrence of EPS, the medical chart review is based on 10 cases per variable [10]. The variables were examined to identify as risk factors of EPS consisting of age, sex, high potency antipsychotic drugs, antipsychotic doses, type of substance, route of substance administrations, amount of substance use, Fagerstrom score, the Alcohol Use Disorders Identification Test (AUDIT) score, hardcore score, previous dependence treatment, co-morbidity, medications prior to admission, duration from last treatment and length of dependence [11,12]. Therefore, at least 150 cases are needed.

We recruited SUD patients with acute schizophrenia or other psychotic disorders according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) [13], free of initial EPS and needing IM treatment at emergency services before hospitalization for maintenance therapy. Their inpatient medical records were simply randomly selected, then the predefined case record forms were used to collect patient data as well as EPS occurrence after IM treatment.

Statistical methods

Categorical variables were summarized as frequencies and percentages, and then analyzed using the chi square test or the Fisher's exact test where appropriate. Continuous variables were summarized as mean and standard deviation or median and interquartile range (IQR) values and compared using a t-test or the Mann-Whitney U-test where appropriate. Afterwards, all variables with a statistically significant relationship with EPS were included in the logistic regression model to predict the occurrence of EPS. The variables with statistical significance from this model indicated "the predictive factor". All tests for significance were 2-sided and $p < 0.05$ was considered statistically significant.

Definitions

The Fagerstrom score [14]: the standard instrument for assessing the intensity of physical addiction to nicotine with a total score of 0 - 10. The higher the score, the more intense is nicotine dependence.

AUDIT score [15]: the standard method of screening for excessive alcohol drinking with a total score of 0 - 40. Scores of 8 - 15, 16 - 19 and ≥ 20 indicate: advice on drinking reduction, brief counseling with continued monitoring and further diagnosis for alcohol dependence, respectively.

Hard core drug dependence [16]: Patient who has been addicted to drugs or substances for > 3 years. No abstinence occurs despite several drug rehabilitations with at least one of the following:

- Receiving medical treatment with and without psychotherapy ≥ 3 times/year
- Having intention for abstinence in each rehabilitation
- Be arrested or litigating ≥ 3 times/year

High intensity amphetamine dependence [17]: Patient who abuses amphetamines > 1 tablet daily.

Light smoker [7,18,19]: Patient who smokes ≤ 1 pack daily regarding 0.95 mg of nicotine/cigarette (20 mg of nicotine/pack). Calculation based on maximal reduction of DA concentration at nicotine dose of 0.3 mg/kg in a 60 kg person.

Results and discussion

Socio-demography

After ethic approval was obtained in August 2014, the patient charts were retrospectively reviewed during September - November 2014. A total of 153 patients were enrolled in this study. The occurrence of EPS was 7.84 % with 41.67 and 58.33 % of acute dystonia and acute akathisia. It was lower than non SUD patients (9.8 %) [20]. High DA concentration in SUD patients could be responsible for this difference. The majority of patients were male and similar in both groups (100 vs 84.4 %, $p = 0.217$) (**Table 1**) supporting previous studies [21]. Patients in the EPS group were slightly younger than those in the non EPS group (21.50 vs 26.00 years, $p = 0.564$). Their median age was slightly younger than previous studies (23 - 36 vs 26 - 48 years) [21] while the length of dependence was shorter in this study (4.50 - 10.00 vs 6.00 - 20.00 years) [22]. The proportion of patients with co-morbidity was significantly higher in the EPS group (36.40 vs 6.60 %, $p = 0.009$). After controlling for potential confounders, there was no relationship between co-morbidities and EPS but Alzheimer's disease, Parkinson's disease, diabetes and organic brain diseases showed an increased risk in non SUD patients [12,23,24]. However, underreporting of co-morbidities was possible in SUD patients because they were less likely to seek medical care.

Substance use

Amphetamines were the most common substances in both groups. Proportion of patients with high intensity amphetamine dependence were significantly lower in the EPS group (42.90 vs 80.20 %, $p = 0.044$) while light smokers were significantly higher in EPS group (100.00 vs 58.90 %, $p = 0.012$) (**Table 2**).

The association between substance dependence and EPS is still controversial. The previous study showed that substance dependence was not a predictor of EPS [21] while cocaine and alcohol increased EPS risk [25,26]. Differently, most patients in this study had methamphetamine dependence and none of them was a cocaine user. Unlike other stimulant drugs, methamphetamine causes extremely high DA concentration [27] and persists up to 1.5 years after abstinence [28] since it is a DA reuptake inhibitor, releasing an activator and causing permanent DAT reduction [6,29]. Moreover, substance craving can increase DA in the striatum [29]. Therefore, such a high DA concentration in SUD patients could decrease EPS risk. After controlling for potential confounders, our result showed no association between light smoking and EPS similar to previous studies [30,31] whereas smoking decreased EPS risk in patients susceptible to EPS [32]. This supports that patients with SUD are less likely to be vulnerable to EPS.

Smoking was the route of substance administration in all amphetamine users and most of other substance users. However, this study could not show an association between the route of substance administration and EPS. Furthermore, contaminants such as heavy metals, other chemicals or some plants could be delivered concomitantly and may influence the EPS risk. The exposure of manganese, iron, carbon disulfide and carbon monoxide [33] as well as the abuse of natural psychostimulants such as cathinones from *Catha edulis* (Khat) leaves or ephedrine from various plants of the *Ephedra* genus can provoke movement disorders [34]. The future study is needed to determine their effects on EPS.

Antipsychotic therapy

The most common antipsychotic drug was haloperidol. EPS rates regarding treatment were significantly different ($p = 0.037$). The proportion of patients treated with haloperidol and zuclopenthixol was significantly higher in the EPS group (50.00 vs 16.30 %, $p = 0.011$) (**Table 3**). Co-treatment of haloperidol and zuclopentixol appeared as the single predictor of EPS in SUD patients. Antipsychotic combination, though it is needed in severely ill or unresponsive patients, increases the EPS risk [35,36]. Since experience of acute EPS impacts patient compliance in antipsychotic maintenance therapy [37], a combination of typical antipsychotic drugs and benzodiazepine is recommended as a safer alternative [38].

The predictive factors of EPS

After controlling for potential confounders consisting of having co-morbidity, high intensity methamphetamine dependence and smoking, co-treatment of IM haloperidol and zuclopenthixol appeared as a predictive factor of EPS (OR = 13.39, $p = 0.043$) (**Table 4**).

Table 1 Demographic characteristics of SUD patients with acute psychotic disorders.

Variables	n	EPS				*p*-value
		n	yes	n	no	
Male sex; n (%)	153	12	12 (100)	141	119 (84.4)	0.217
Age (year); median (IQR[a])	153	12	21.50 (20.00 - 36.00)	141	26.00 (21.00 - 31.00)	0.564
Married; n (%)	150	12	2 (16.70)	138	24 (17.40)	1.000
Senior high school and lower; n (%)	144	12	10 (83.30)	132	116 (87.2)	0.658
Co-morbidity; n (%)	148	11	4 (36.40)	137	9 (6.60)	0.009
Allergic disorders			1 (9.1)		4 (2.9)	
Asthma			1 (9.1)		1 (0.7)	
Diabetes			1 (9.1)		0	
Peptic ulcer			1 (9.1)		0	
HIV infection			0		1 (0.7)	
Thalassemia			0		1 (0.7)	
CVS diseases			0		1 (0.7)	
Hemorrhoids			0		1 (0.7)	
Occupation s; n (%)	146	12	3 (25.00)	134	31 (23.10)	1.000
Mechanics			2 (66.70)		1 (3.20)	
Government employee			1 (33.30)		3 (9.70)	
Labour			0		11 (35.50)	
Merchant			0		9 (29.00)	
Farmer			0		3 (9.70)	
Fisher			0		1 (3.20)	
Private employee			0		2 (6.50)	
Business owner			0		1 (3.20)	
Household; n (%)	145	12	12 (100.00)	133	130 (97.70)	1.000
Parents			8 (66.70)		82 (63.10)	
Spouse			2 (16.65)		18 (13.90)	
Children			2 (16.65)		3 (2.30)	
Non family members			0		27 (20.70)	

[a]interquartile range

Table 2 Substance use patterns among SUD patients with acute psychotic disorders.

Variables	n	EPS				*p*-value
		n	yes	n	no	
Type of substance; n (%)	153	141		12		0.974
Amphetamine			6 (50.00)		66 (46.80)	
Cannabis			4 (33.30)		31 (22.00)	
Methamphetamine			1 (8.30)		22 (15.60)	
Alcohol			1 (8.30)		9 (6.40)	
Inhalants			0		6 (4.30)	
Mitragyna speciose Korth (Kratom)			0		3 (2.10)	
Heroin			0		2 (1.40)	
Ketamine			0		1 (0.70)	
The cocktail called 4x100			0		1 (0.70)	
Length of dependence (years); median (IQR[a])	148	12	4.50 (2.00 - 6.75)	136	5.00 (2.00 - 10.00)	0.709
History of SUD[b] treatment; n (%)	141	12	6 (50.0)	129	47 (36.4)	0.367
Duration from last treatment (month); median (IQR[a])	37	4	20.32 (4.20 - 52.63)	33	14.60 (8.64 - 27.32)	0.807
High intensity methamphetamine dependence; n (%)	88	7	3 (42.90)	81	65 (80.20)	0.044
Alcohol; n (%)	153	12	1 (8.30)	141	20 (14.20)	1.000
Smoker; n (%)	105	10		95		0.012
Light			10 (100.00)		56 (58.90)	
Heavy			0		39 (41.10)	
Fargerstrom score; median (IQR[a])	94	9	4.00 (3.50 - 5.00)	85	5.00 (3.00 - 6.00)	0.730
Hardcore drug dependence; n (%)	138	11	5 (45.50)	127	43 (33.90)	0.514

[a]interquartile range, [b]substance use disorders

Table 3 IM antipsychotic treatment at emergency service setting.

Antipsychotic drug	n	EPS				*p*-value
		n	Yes	n	No	
IM antipsychotic drug; n (%)	153	12		141		0.037
Haloperidol			3 (25.00)		63 (44.70)	0.186
Zuclopenthixol			3 (25.00)		48 (34.00)	0.768
Olanzapine			0		7 (5.00)	1.000
Haloperidol + Zuclopenthixol			6 (50.00)		23 (16.30)	0.011

Table 4 The predictive factor of EPS after IM antipsychotic treatment.

Variables	Adjusted OR	95 % CI	*p*-value
Co-morbidity	15.98	0.78 - 326.50	0.072
High intensity methamphetamine dependence	0.56	0.08 - 3.92	0.559
Light smoker	0.16	0.01 - 1.81	0.139
IM Haloperidol + Zuclopenthixol	13.39	1.09 - 164.51	0.043

Limitations of the study

There was some potential bias in this study due to incomplete entries in the medical records and patients omitting information.

Conclusions

SUD did not increase the risk of EPS while co-treatment of IM typical antipsychotic drugs was a predictor of EPS. A combination of a typical antipsychotic drug and benzodiazepine is recommended for nonresponsive patients to achieve rapid tranquilization with low risk of EPS.

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