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Interference of Khat with Treatment of Paranoid Schizophrenia

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ABSTRACT

Objective: Khat is a habit forming substance widely used in Middle East countries and found to have huge societal and healthcare implications.This study was intended to estimate the possible interference of with antipsychotic medications and to investigate the frequency of relapse associated with concurrent use of anti depressants and khat.

Methods: 69 Patients suffering from paranoid schizophrenia were involved in this study. The participants were classified according to their khat chewing habits into two categories; 1) Controls who did not chew khat during the treatment from acute episodes, and 2) Cases who chewed khat during treatment, during discharged for holidays or when shifted to outpatient facilities.

Results: The results showed that usage the antidepressant fluoxetine in combination with either risperidone or haloperidol increased the tendency of relapse. Khat may interfere with either of the agents alone when used in large quantities, but there was less drug interaction than when fluoxetine was used. The use of depot neuroleptics and haloperidol with the appropriate dose adjustment appeared to reduce the tendency to relapse even though khat was used. Still such a risk of interaction cannot be avoided if khat is abused.

Conclusion: Khat can be described as a substance of potential abuse in psychotic patients and may lead to the aggravation of psychotic conditions due to possible drug interaction with neuroleptics, which may reduce the effectiveness of such drugs and increase the frequency of relapse.

Key words: Khat, Catha edulis, Paranoid Schizophrenia, Neuroleptics.

1. INTRODUCTION

Schizophrenia is a particular type of psychosis which is a mental disorder caused by some inherent dysfunction of the brain characterized mainly by delusions, hallucinations, and thinking or speech disturbances. This mental disorder is a common affliction, occurring among about 1% of the population. The illness often initially affects people during adolescence[1, 2]. The most common type being the paranoid type which is mainly characterized by delusions and hallucination[3,4]. Schizophrenia presents with many symptoms, which are known as positive and negative symptoms. Positive symptoms of schizophrenia are delusions, mood abnormality, auditory hallucination, initial vagueness in speech, awkward social behavior and, lack of insight into the illness[2]; whereas the negative symptoms include a lack of drive, social withdrawal and emotional apathy.

Causes of schizophrenia can be genetic; however, even in monozygotic twins there are

many cases where only one sibling has developed schizophrenia[2]. Another suggestion may be an abnormality of dopamine receptors and, in particular, D_2 receptors. This has largely emerged from research into the effect of antipsychotic drugs.

Other factors implicated in schizophrenia involve: migration, socio-economic factors, perinatal insult, toxins, and family environment.

Although a variety of social and psychological therapies are useful in the treatment of schizophrenia, drugs are the mainstay of treatment. The aim of all therapies is to minimize the level of handicap and achieve the best level of mental functioning. Drugs do not cure schizophrenia. At the same time, benefits have to be balanced against side effects and the need to suppress particular symptoms such as delusions. If, on the other hand, the delusions lead to great distress, violent or dangerous behavior, then a dose increase in antipsychotic drugs may be indicated. It is now accepted that antipsychotic drugs can control or modify symptoms of illness. Antipsychotic drugs increase the length of time between relapse and shorten the length of acute episodes in most patients[2]. Antipsychotic drugs are primarily used to treat schizophrenia. The traditional neuroleptic drugs are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine receptors. These drugs vary in their potency, but no one drug is clinically more effective than other[1].

Khat is a natural stimulant from the (*Catha edulis Forsk*) plant, found in the flowering evergreen tree or large shrub which grows in East Africa and Southern Arabia to tree size[5]. Cathine was the first alkaloid to be isolated, later to be identified as nor-pseudoephedrine (S,S phenylpropanolamine), which was considered to be responsible for the pharmacological (stimulant) effect of khat. Khat contains not only cathine and it's diastereomer; norephedrine (R,S (-) phenylpropanolamine), but also another compound, which was identified as being S (-) α-aminopropiophenone (the keto analoge of cathine), which was named cathinone and its spatial configuration was confirmed through comparison with synthetic cathinone. This allows a conclusion that cathinone is a biosynthetic precursor which accumulates in young leaves. It undergoes enzymatic reduction to the active compound cathine and norephedrine[5,6]. The two isomers of cathinone were found to be approximately equipotent at inducing release at peripheral noradrenergic nerve endings, but the (-) isomer was approximately 3 times more potent than (+) isomer at dopamine terminals in the central nervous system (CNS)[7].

The mild effect is due to the delayed plasma peak concentration of cathinone after khat use[8]. The peak plasma cathinone levels were attained at 1.5-3.5 hrs. Maximum levels ranged from 41-141 ng/ml (mean 83 ng/ml), no cathinone was detected at 24 hrs[9]. Following a single oral dose of 0.5 mg/kg of S (-) cathinone, the concentration found in urine ranged from 0.2-3.8 µg/ml of S (-) cathinone, 7.2-46 µg/ml of R,S (-) norephedrine and 0.5-2.5 µg/ml of R,R (-) norpseudoephedrine[10]. d-norpseudoephedrine (cathine) present in khat is excreted unchanged in urine 30-50 minutes after ingestion of synthetic d-nor pseudoephedrine. Approximately 40% of the ingested d-norpseudoephedrine was recovered in urine in the first 6 hr[11]. The main metabolites of S (-) cathinone are R,S (-) norephedrine and d-norpseudoephedrine and the main metabolite of R (+) cathinone is R,R (-) norpseudoephedrine[12]. Both aminoalcohols are formed by a stereo-specific keto reduction[13].

The sympathomimetic effects of khat are mediated through the release of catecholamines from presynaptic storage sites[6]. These amines include dopamine and serotonin[14,15]. Khat may have also MAO-inhibiting action[16]. The psychostimulant activity of khat is mediated through dopamine release; also 5-hydroxytryptamine (5-HT) is

reported to be released. It seems that dopamine release is more important in the effects of khat than 5-HT release[17-19]. After chewing the leaves of khat, chewers become euphoric, loquacious, excited, hyperactive and even maniac[20,21]. High doses of cathinone have evoked seizures comparable to epileptic activity[22].

This study was aimed to estimate the possible interference of khat with antipsychotic medications and to investigate the frequency of relapse associated with concurrent use of anti depressants and khat.

2. MATERIALS AND METHODS

This study was conducted at the mental and psychiatric health hospital in Sana'a, Yemen. Sixty nine patients aged 20-70 years old suffering from paranoid schizophrenia who were treated in the inpatient department were involved in this study. The participants were classified according to their khat chewing habits. Patients who did not chew khat during treatment for acute episodes were taken as controls. The other group included patients who chewed khat during treatment, when they were discharged for holidays or shifted to outpatient services. Age, sex, onset of disease, previous readmission to hospital, past history of mental illness, family history of mental illness, and date of admission were determined and recorded for each patient.

Khat chewing habits were determined as; a) daily, b) 1-2 days a week, or c) rarely. The duration of khat chewing per day was categorized as follows; a) 4 hrs, b) 4-8 hrs, and c) more than 8 hrs. The amount of khat chewed by the patients was classified as follows; a) a lot (abuse), b) moderate, or c) few.

Some patients were granted holidays and some were shifted to the outpatient department. The date of discharge and date of readmission were noted for these patients. The degree of their condition was determined, as well as their khat use at this stage. The date of discontinuation of treatment was also recorded for each patient.

Statistical analysis was performed using SPSS microcomputer system, the scale selected for this study was Positive and Negative Syndrome Scale (PANSS). From a view point of the clinical symptoms of our cases it was found that at least two or more of the following symptoms were always encountered; delusions and hallucinations during which many patients may be extremely anxious. However it confined to the clinical Picture of paranoid schizophrenia.

Case (1): is a 24-year-old male readmitted to mental and psychiatric health hospital in Sana'a on 16-10-02. He had experienced psychosis seven months prior to presentation which manifested itself in different forms including that he thought of being followed everywhere by unknown people who also try to collect information about him, he described his suspects and said that they were trying to take his money. He heard voices and saw pictures facing him. Also, he was unable to concentrate. On the other hand, he had social problems especially with his family, and his home atmosphere wasn't comfortable, since he was not respected in his family. No family history of mental and psychiatric illness. He chews khat, at least 8 hrs a day; he started chewing khat when he was 16 years old, he used to chew moderate amount of khat at the beginning, but now he chews a lot and for longer time.

Mr. C1 was diagnosed by specialists with paranoid schizophrenia. He received risperidone along with fluoxetine 20mg tab. & akisol. Two days later the patient heard voices that ordered him to discharge himself from the hospital. Five days later, the voices disappeared and treatment was continued till the delusions and other symptoms were resolved completely and discharged in 18.12.02.

Case (2): is a 50-year-old female who developed paranoid schizophrenia with depression three years prior to presentation. Neither prior psychiatric care, nor relapses were reported in patient's file. She was readmitted to mental psychiatric hospital on

26.6.02 and discharged on 26.8.02. She had a negative family history of mental illness and had cardiovascular problems for which captopril (Capoten) 25 mg tab. 1x2 was used simultaneously with antipsychotic drugs. Also ranitidine was prescribed for gastrointestinal problems. Neuroleptics depot and haloperidol were used from 25-6-02 to 22-7-02, without any improvements. On 5-8-02, haloperidol was replaced with risperidone, and one week later, the patient improved and symptoms started to resolve. Then Mrs. C2 continued the usual treatment until recovery and was discharged on reduced dose of risperidone.

Case (3): is a 29-year-old male who had developed Paranoid schizophrenia four years prior to presentation. He was admitted to psychiatric hospital many times due to relapses. His father was receiving treatment for schizophrenia. Mr. C3 readmitted to the hospital in 20-10-02, with delusions, auditory hallucination, disturbed thoughts and was depressed. His self-care was reduced as shown from his dirty clothes and his concentration was also diminished. He is a khat chewer on daily basis for at least 7 hours per day and may chew khat irregularly at night when it is available. He has been chewing khat since he was 18 years old, and had stopped khat chewing when he was admitted to the hospital in his previous relapses, but when he was shifted to outpatient follow up, he used khat and received neuroleptics drugs. Mr. C3 was treated with risperidone, 6 mg a day, akisol and fluoxetine from 26.10.02. Six days later, his thought became better and delusions were reduced slightly, fluoxetine was discontinued. On 13.11.02, the patient improved and was discharged on risperidone and akisol to continue treatment in out patient department. On 21.12.02 patient was readmitted to the hospital and he again had delusion, hallucinations, disturbed thoughts, and bad mood. He received: Flupenthixol 40 mg depot per month and continued risperidone 3 mg tab. 1x2 and akisol 2 mg tab. 1x2. At this stage medications were taken regularly and khat chewing was stopped, patient continued treatment in in-patient department (IPD), till complete improvement.

Case (4): is a 32-year-old male who was diagnosed with paranoid schizophrenia five years prior to presentation by specialists at the hospital and experienced acute episodes a month prior to presentation, there were previous admissions to a psychiatric hospital, and he was also treated in Cairo two years prior to presentation. During his two weeks in Cairo he was able to speak with his family and got better very rapidly. He was also suspicious that national specialists were mistreating him for financial gain. Family history of mental and psychiatrics disorder in this case was negative. He is a regular khat chewer up to 6 hrs daily and has been chewing khat for several years. He consumes moderate to a lot of quantity of khat and has used khat during his previous treatment. Haloperidol was given to the patient on his readmission on 19.11.02. Thirteen days later his symptoms were resolved slightly, hallucination was over, delusion became less severe. His general condition was stable and was temporally discharged on 3.12.02 for Al-Eid holidays. Sixteen days later, he was readmitted to the hospital, his condition was worse than it was before his discharge; hallucination re-appeared thoughts were disturbed as well.

3. RESULTS AND DISCUSSION

Khat is widely used in Yemen by different social classes and it has been found that khat lead to the aggravation of psychotic conditions due to possible drug interaction with neuroleptics, which may reduce the effectiveness of such neuroleptics and increase the frequency of relapse.

Nevertheless, it was observed in this study that all patients were khat chewers prior to hospital readmission with exception to seven cases (10%). One of whom was a male and the other six were females. Of the seven patients, four were reported of being discharged from hospital before the first visit to the hospital, but their files were considered in this study due to the unavailability of non khat chewer cases during the survey. However this defect was

Table 1: The age distribution and drug used

Age (Year)	Haloperidol		Resperidon		Neuroleptics (Total)	
	Case	Control	Case	Control	Case	Control
20-30	12	2	9	1	21	3
30-40	6	5	12	6	18	11
40-50	3	4	3	1	6	5
50-60		1	1	2	1	3
>60				1	0	1
Total	21	12	25	11	46	23

Table 2: Sex distribution and drugs used

Sex	Haloperidol		Resperidon		Neuroleptics (Total)	
	Case	Control	Case	Control	Case	Control
Male	19	8	22	6	41	14
Female	2	4	3	5	5	9
Total	21	12	25	11	46	23

Table 3: Drugs used and adjuvant

Adjuvant	Haloperidol		Resperidon		Neuroleptics (Total)	
	Case	Control	Case	Control	Case	Control
Drug alone	7	3	13	7	20	10
Fluoxetine	6	4	9	3	15	7
Depot Neuroleptics	8	5	3	1	11	6
Total	21	12	25	11	46	23

Table 4: Improvements from acute episodes

Time of symptoms	Haloperidol		Resperidone		Neuroleptics (Total)	
Resolution	Case	Control	Case	Control	Case	Control
1-2 Weeks	0	3	0	0	0	3
2-3 Weeks	0	2	0	1	0	3
3-4 Weeks	0	3	0	3	0	6
4-5 Weeks	6	3	1	6	7	9
5-6 Weeks	4	1	2	1	6	2
6-7 Weeks	7	0	3	0	10	0
7-8 Weeks	1	0	6	0	7	0
> 8 Weeks	3	0	13	0	16	0
Total	21	12	25	11	46	23

Table 5: Drugs and relapse

Adjuvant	Haloperidol			Resperidone			Neuroleptics (Total)		
	Case	Non R.	Relapse	Case	Non R.	Relapse	Case	Non R.	Relapse
Drug alone	7	5	2	13	9	4	20	14	6
Fluoxetine	6	1	5	9	2	7	15	3	12
Depot neuroleptics	8	6	2	3	3	0	11	9	2
Total	21	12	9	25	14	11	46	26	20

compensated by the inclusion of patients who have stopped khat chewing during treatment as control. This study was conducted for six months from Oct 2002-Mar 2003.

The results presented in Table 1 showed that 53 (77%) patients' age ranged between 20-40 years, while 55 (80%) patients were males (Table 2). In this study, it was observed that only 23 (33%) of the total cases had a family history of psychiatric illness. Most of the cases had experienced previous psychiatric care with an uncertain number of readmissions (at least two relapses), with the exception of three patients who experienced their first psychotic episodes.

Of the patients who were khat chewers, the results showed that they took khat on a daily basis and for at least 6 hours a day. Most of these patients started chewing when they were 17 years old. No association between the onset of depression and inception of khat chewing found in the khat chewers. Only three (4%) suspected cases were considered to be khat induced paranoid schizophrenia since a rapid response occurred on discontinuation of khat in the hospital.

With respect to the clinical symptoms of the studied cases, it was found that at least two or more of the following symptoms were always encountered; delusions and hallucinations during which many patients were extremely anxious. However, this was confined to the clinical picture of paranoid schizophrenia. Risperidone was used in 36 (52%) of the total cases. In 12 (17%) of these cases, fluoxetine was prescribed along with risperidone. Flupenthixol and depot neuroleptics were used in 4 (6%) cases only as an adjuvant to risperidone. Anti-Parkinson's that exert their action via acetylcholine pathways were also used in 9 cases.

Haloperidol was received in 33 (48%) of the total 69 cases, depot neuroleptics were used in 13 (19%) cases along with haloperidol, while fluoxetine was only taken in 10 (14%) cases, and tricyclic antidepressants (TCAs) were used in 5 (7%) cases (Table 3).

Antihypertension drugs were used in 3 patients, while drugs for peptic ulcer were used by 2 patients, and antiamoebic drugs were taken by 4 patients. None of these drugs introduced interfered with the treatment drugs because their mechanisms of action do not interfere with the release of dopamine, serotonin or norepinephrine neurotransmitters.

During the study, three patients received anti hypertensive medications, two received anti secretary drugs and four patients were on anti-amoebic medications. However, none of these drugs could have interfered with the treatment as their mechanism of action does not involve the release of dopamine, serotonin and norepinephrine neurotransmitters.

In terms of improvement from acute episodes using time symptoms resolution, specific neuroleptics received and khat chewing as parameters, it was shown that, in

patients receiving risperidone from the control group 11 (16%) cases, the symptoms were resolved for six cases within 4-5 weeks, three cases within 3-4 weeks, one case within 2-3 weeks, while one patient's symptoms showed improvement within 5-6 weeks (Table 4). Flupenthixol was used in addition to risperidone for this patient. However, it was noted that when khat was taken during risperidone therapy, the time taken for symptoms to improve from acute episodes was significantly increased (Table 4). The results showed that 13 out of 25 patients receiving risperidone from the group who chewed khat took more than 8 weeks for symptoms to improve (as in Case 3 and 4 described previously).Eight of the patients received a combination of fluoxetine and risperidone and other five patients received only risperidone. . On the other hand, 6 (8%) of the former 8 cases were shown to relapse very rapidly within approximately 2 weeks with reinstatement of khat chewing when patients were on Al-Eid holidays (Table 5). Of these 13 (19%) patients, there was only 1 patient who took medications irregularly which accounted for the relapse, rather than khat use. Only 3 (4%) cases from patients who received risperidone were reported to have had relapses. Accordingly, 10 (14%) patients out of the 13 cases were relapsed, while the remaining 3 (4%) cases although no apparent relapse occurred, very little improvement was observed with an exception of one case, where there was significant improvement despite khat use and this case was shifted as an outpatient follow up.

Upon readmission of the relapsed 10 cases, flupenthixol depot 40 mg per month was prescribed for 4 patients and dosage was readjusted for the other cases including those cases that had not relapsed. In 6 (8%) out of 25 patients receiving risperidone, there was generally improvement within 7-8 weeks, in the marginal region of the maximum taken for the control subjects. Fluoxetine was taken in only 1 of these 6 patients, and it was interestingly observed that this patient was the one that had relapsed in comparison to the other 5 patients who had shown delayed response and a slight worsening of the condition. The symptoms for 3 (4%) out of the 25 patients receiving risperidone were resolved within 6-7 weeks. However, these patients had also received flupenthixol depot before they were discharged temporarily for Al-Eid holidays. No relapse occurred in any of these patients in spite of khat use, similar to the other cases. Moreover these three cases were improved significantly during treatment in outpatients department. The symptoms for 2 (3%) patients receiving risperidone alone were improved within 5-6 weeks, in 1 patient, symptoms improved within 4-5 weeks, although khat was used but it had no impact on the success of the therapy.

Haloperidol was taken by 33 (48%) patients out of the total study population of 69 patients. Twelve out of the 33 patients were controls, 3 of them experienced relief of symptoms within 2 weeks.Two (3%) patients showed marked improvement within 2-3 weeks, while the other patients was improved within 4-5 weeks; this is consistent with the range of 8 weeks for controls as expressed in literature. Twenty one (30%) patients received haloperidol and chewed khat during treatment. Symptoms were resolved within more than 8 weeks in 3 (4%) patients, 2 of whom used fluoxetine along with haloperidol, and relapse was observed in all 3 patients. One patient's symptoms improved within 7-8 weeks. While in 7 (10%) patients, symptoms improved within 6-7 weeks, and in only 4 patients was relapse observed. In terms of the drugs used in these 4 patients, the results showed that 3 of the patients used fluoxetine. On the other hand, 2 of the 7 patients used depot neuroleptics along with haloperidol and 1 patient received haloperidol alone, no relapse was noted in any of these patients. Ten (14%) patients improved within 4-6 weeks with no tendency to relapse. Fluoxetine was used in

1 of the ten 10 cases while depot neuroleptics were used by five 5 patients.

Accordingly, fluoxetine was used in 6 (9%) patients out of the 21 patients, 5 of whom had relapsed when khat was used during treatment. Eight (11%) patients out of the 21 cases used depot; relapse was observed only in 2 cases (Table 5). When haloperidol was used alone in 7 cases, relapse was observed in only 2 patients. When fluoxetine was used with haloperidol in 6 patients, relapse was observed in 5 patients. But when depot neuroleptics were used in 8 cases, only 2 patients experienced relapse of symptoms. Whereas, when risperidone was used alone in 13 (19%) patients, relapse was observed in 4 patients, thus when risperidone was used with fluoxetine in 9 cases, 7 patients experienced relapse of symptoms, but when depot neuroleptics were used along with risperidone for 3 cases, relapse was not observed in any of the patients.

Khat may cause a functional psychosis following consumption of exceptionally potent material, when taken in excess or in a predisposed individual[23]. In the literature reviewed, Cathinone and Cathine are considered as the most important psychoactive ingredients of khat. Cathinone [(–)-alpha-aminopropiophenone] is a stimulant of sympathomimetic and central nervous system similar to amphetamine; wheres cathine being a less potent psychostimulant than cathinone[24]. Cathinone and Cathine act via two important neurochemical pathways of dopamine and noradrenalin. They induces release of dopamine from central nervous system and augment the activity of the dopaminergic pathways[25,26]. Further it was proposed that cathinone and cathine cause increase in the level of synaptic noradrenaline levels by inhibiting noradrenalin uptake[27]. It is further proved that cathinone releases serotonin in the central nervous system, like amphetamine.

Cathinone is reported to be a reinforcer and hence dependence-producing component of khat. This fact is further reinforced by animal studies[18,28]. Some authors describe dependence caused by khat as being more psychological than physical one[29]. Yousef *et al*[30] and Pantelis *et al*[31] have reported that the main psychiatric manifestations related to the use of khat are short-lived schizophreni-form psychotic illness and rarely depression. We realized the same fact during the course of our experiment. Dhadphale and Omolo[32] studied psychiatric morbidity among khat users and reported that with moderate quantities of khat there was no excess morbidity, but when the amount was greater than two bundles, morbidity was significantly increased[32]. Other research and our clinical experience confirm the dose related adverse effects of Khat[33,34]. Intoxication with chronic consumption of khat can lead to impairment of mental health and 'mental deterioration[35]. In contrast, Dhadphale and Omolo[32] reported that there is no evidence for increased long-term psychiatric morbidity associated with chronic khat chewers.

Khat can interact with a number of therapeutic agents. The concurrent use of monoamine oxidase inhibitors (MAOI) can lead to hypertensive crisis due to abnormal surge of monoamines. Surgical anaesthetics have the potential to leave the khat user agitated and over aroused during the postoperative period. Phenylpropanolamine, a common ingredient in anti-cold OTC preparations can exert synergism with Khat[24]. In terms of relapse cases and the drug used, there may have been an interaction with active constituents of khat. It appears that when the antidepressant fluoxetine was used with either risperidone or haloperidol, the tendency to relapse increased. Khat may have interfered with either of the agents alone when used in large quantities, but there was less drug interaction than when fluoxetine was used.

The use of depot neuroleptics and haloperidol with the appropriate dose adjustment appeared to reduce the tendency

of relapse, even when khat was used; nevertheless there is still a risk of expected drug interaction if khat is abused. From literature review and the findings from this study, khat can be described as a substance of potential abuse in psychotic patients and may lead to the aggravation of psychotic condition and the possible drug interaction with neuroleptics, leading to decreased efficiency of neuroleptics and an increased frequency of relapse.

Therefore, it is recommended that khat use should be totally stopped in psychotic patients due to its potential interference with therapy and associated health problems. The difficulty in treatment of psychotic patients in Yemen, in comparison to successful treatment of refractory cases outside Yemen, is not as a result of a lack experienced and qualified specialists but rather khat chewing during treatment which introduces many difficulties.

4. CONCLUSION

Khat can be described as a substance of potential abuse in psychotic patients and may lead to the aggravation of psychotic conditions due to possible drug interaction with neuroleptics, which may reduce the effectiveness of such drugs and increase the frequency of relapse.

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