

ORIGINAL CONTRIBUTION

Khat: A Plant With Amphetamine Effects

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Abstract—*The chewing of leaves of the khat shrub is common in certain countries of East Africa and the Arabian peninsula, and some khat users are subject to psychic dependence on this stimulant. Recently, important progress has been made in understanding the pharmacological basis for the effects of khat. It is now known that the CNS stimulation is mainly due to the presence of the alkaloid cathinone in the leaves, and the results of various in vitro and in vivo experiments indicate that this substance must be considered a "natural amphetamine." In recent years, several cases of khat intoxication observed in the USA and in Great Britain have been described in the literature. In view of these developments, the khat habit and its health effects are described, and the possibilities for the treatment of acute khat intoxication are discussed.*

Keywords—Khat, abuse, treatment, amphetamine.

INTRODUCTION

THE LEAVES of the khat shrub have a stimulating effect, and the chewing of this material has been practised for many centuries in certain areas of East Africa and of the Arab Peninsula. The effects of khat chewing were mentioned in the early Arab literature (see LeBras & Frétilière, 1965); the habit was described by early foreign visitors to these regions (see Krikorian, 1984), and it has also attracted the interest of writers such as Theodore Dreiser and Evelyn Waugh. Nevertheless, khat has remained almost unknown beyond the areas of cultivation of the plant, which is due to the fact that only fresh leaves are active. In recent times, however, the increased efficiency of regional transportation has led to a strong increase in khat consumption, and the availability of air transport now allows forwarding of the drug to distant countries.

The use of khat may cause health problems for the individual; it is potentially addictive, and it has important social and economic consequences for the countries concerned. Therefore, the problems related to this drug have repeatedly attracted the attention of international organizations and were discussed as early as 1935 by the League of Nations at the level of an Advisory Committee on the Traffic of Dangerous

Drugs (League of Nations, 1936). About twelve years ago, the United Nations Narcotics Laboratory succeeded in isolating a new alkaloid from khat (UN Document, 1975) and this substance, cathinone, is now known to be mainly responsible for the CNS-stimulating properties of the leaf. Due to this discovery, substantial progress has been made in understanding the pharmacology of khat (Kalix & Braenden, 1985).

In 1964, an Expert Committee of the World Health Organization expressed the opinion that, in view of the similarity of their medical effects, the problems connected with khat should be considered in the same light as those connected with the amphetamines, even though there are quantitative differences in the effects of the two drugs (World Health Organization, 1964). In the meantime, several cases of khat intoxication observed in the USA and in Great Britain have been described in the literature (Critchlow & Seifert, 1987; Giannini & Castellani, 1982; Gough & Cookson, 1984; McLaren, 1987). Therefore, the present article intends to inform about the khat habit and its medical consequences, to provide some background information, and to discuss the possibilities for the treatment of acute khat intoxication.

THE KHAT HABIT

The khat plant (*Catha edulis*, Celastraceae) is cultivated as a bush or small tree; its leaves are somewhat leathery with a serrated edge, they are of brownish-

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green colour, and they have a glossy upper surface. Unfortunately, they lack a distinctive morphological or anatomical feature that would allow identification of the leaves by persons who are unfamiliar with them. For consumption, freshly harvested twigs are rapidly transported to the markets where they are sold in bundles that are wrapped in order to preserve freshness. Habitual khat users prefer the leaves from the tips of the branches and those of young shoots since these are the most potent ones; the leaves are taken one by one and thoroughly chewed, the juice is swallowed, whereas the macerated material is kept for a while in the cheek and later expectorated. The size of a portion of khat varies within wide limits; with material of average quality, it is about 100 to 200 grams.

Khat is predominantly consumed in a social setting. This is particularly true for Yemen, where the habit is socially sanctioned and even prestigious, and where many houses have a special room devoted to regular sessions of khat chewing. Such khat parties in Yemen are a form of social interaction and status competition, they are governed by subtle rules while being, under certain circumstances, of almost ritual importance. It has been suggested that the function of khat in this context is to provide a pretext for a gathering of high social significance rather than to provide pleasurable effects to the individual (Weir, 1985). Indeed, because of its stimulating and euphorogenic properties, khat is certainly an appropriate tool for enhancing social interaction. In countries other than Yemen, that is, those of East Africa, khat is consumed in a much less rigidly defined context, frequently by individuals who are alone. Therefore, it can be assumed that in East Africa the psychosocial benefits of khat consumption are of secondary importance and that, rather, it is the pharmacological action that induces the use of this drug. This is also borne out by the fact that khat use tends to be compulsive—for certain individuals the cost of the euphorogenic effect of the leaf is addiction.

THE KHAT SYNDROME

The syndrome induced by khat use is characterized by a certain degree of CNS stimulation together with a variety of sympathomimetic effects. Subjectively, the action on the central nervous system is perceived as an increase in the level of energy, of alertness, and of self-esteem together with an improved ability to communicate, the latter factor probably explaining the tendency to group interaction and social contact that is often observed during khat consumption. Further, the euphorogenic effect of khat is felt as an increase in the depth of perception and as enhanced imaginative ability and capacity to associate ideas, leading in turn to grandiose schemes and projects lacking realism.

Objectively, khat use induces a state of mild euphoria and excitement characterized by loquacity and, sometimes, hyperactivity. The associated behavioral syndrome can be described as hypomania (Laurent, 1962b; Margetts, 1967). In exceptional cases, khat consumption may result in toxic psychosis; a number of such cases have been mentioned in the literature (Ardouin & Gendron, 1976; Carothers, 1945; Critchlow & Seifert, 1987; Dhadphale, Mengech & Chege, 1981; Giannini & Castellani, 1982; Gough & Cookson, 1984; Heisch, 1945; McLaren, 1987). Three of these have come to light in recent years in Great Britain, a country where khat use among East African and Yemeni immigrants is substantial (Gough & Cookson, 1987; Mayberry, Morgan, & Perkin, 1984); three further cases of khat-induced psychosis have recently been diagnosed at the Royal Free Hospital in London (Prof. A. Wakeling, personal communication). The published case reports describe the observed symptoms as manic-like (Giannini & Castellani, 1982), schizophreniform (Dhadphale, Mengech, & Chege, 1981; Gough & Cookson, 1984), and paranoid (Critchlow & Seifert, 1987; Dhadphale, Mengech, & Chege, 1981). Incidentally, in the khat-growing areas of eastern Ethiopia, khat-induced psychotic behavior is common enough to be designated by a specific term, "jezba." A further consequence of khat consumption is insomnia with ensuing disruption of the day-night cycle. Other CNS effects of the drug are hyperthermia and anorexia (Halbach, 1972; Laurent, 1962a; LeBras & Frétilière, 1965; Nencini, Amiconi, Befani, Ahmed, & Anania, 1984).

It has been recognized early that, because of their similarity, the effects of khat should be considered in the same light as those of amphetamine (Eddy, Halbach, Isbell, & Seevers, 1965; Hodgkinson, 1962; World Health Organization, 1964). This has been confirmed by Hughes (1973), who reported after personal experience that the effect of a portion of khat is very similar to that of 5 mg amphetamine. Indeed, the difference between the two drugs must be seen as quantitative rather than qualitative, the lower activity of khat being mainly due to differences in dosage and mode of application. In this context, it is important to remember that the ingestion and absorption of the active constituents of khat are limited by the bulkiness of the supporting plant material. This renders an increase of the dose difficult, and it probably explains why tolerance to the CNS effects of this drug does not seem to occur. Although khat consumption does not engender physical dependence, and although there seems to be no craving for the drug, the habit may give rise to moderate but often persistent psychic dependence (Eddy et al., 1965). Indeed, the pleasurable effects afforded by khat are for the habitué a strong inducement to try to obtain by any means at least once a day the necessary supplies, or to repeat or to

prolong the periods of chewing, frequently at the expense of vital needs such as food. The withdrawal symptoms that may occur after prolonged khat use are, however, minor. They consist of lethargy, mild depression, slight trembling, and recurrent bad dreams (Halbach, 1972; Kennedy, Teague, & Fairbanks, 1980).

The peripheral actions of khat include cardiovascular effects of the sympathomimetic type, which occasionally lead to acute problems, particularly in older people (Gendron, Ardouin, & Martine, 1977). There are arrhythmias and an increase in blood pressure that depends on the amount and potency of the material absorbed (Halbach, 1972; Nencini, Ahmed, Amiconi, & Elmi, 1984); chronic use of khat may cause persistent hypertension (Halbach, 1972). Moreover, a person who is under the effect of khat usually presents an exaggerated cardiovascular response to physical effort (Galkin & Mironychev, 1964; LeBras & Frétilière, 1965). The changes in pulse rate and blood pressure appear to be less pronounced in chronic users (as compared to subjects unaccustomed to khat chewing), which would indicate that tolerance develops to the sympathomimetic effects of khat (Nencini et al., 1984b). Another sympathomimetic reaction to khat is mydriasis which, along with a staring look and the brownish stain of the teeth, is indicative of the khat habit (Luqman & Danowski, 1976). Furthermore, khat consumption may cause spermatorrhea which is sometimes accompanied by testicular pain, and chronic use may lead to impotence (Halbach, 1972; Laurent, 1962b; LeBras & Frétilière, 1965; Margetts, 1967). The effects of khat on the digestive tract are mainly due to the high tannin content of the leaves. These substances seem to favor the development of periodontal disease (Halbach, 1972; Luqman & Danowski, 1976), and the possibility that they increase the incidence of esophageal cancer has been discussed (LeBras & Frétilière, 1965). The incidence of gastritis among khat users is high (Halbach, 1972; Kennedy, Teague, Rokaw, & Conney, 1983), as is that of constipation, the latter symptom being probably due not only to the tannins, but to the sympathomimetic effect of the khat alkaloids as well (Table 1).

THE ALKALOIDS OF KHAT AND THEIR EFFECTS

The CNS stimulating effect of khat was initially explained by the presence of the alkaloid norpseudoephedrine (sometimes also called cathine) in the leaves. However, later it was pointed out that the amount of this substance contained in a portion of khat was insufficient to account for the symptoms observed (Brücke, 1941). About twelve years ago, the United Nations Narcotics Laboratory succeeded in isolating the alkaloid cathinone from fresh khat leaves, while giving particular attention to the appropriate-

TABLE 1
Common Features in the Effects of Khat in Man
and of Cathinone in Animals

Effects of Khat Chewing in Humans	Effects of Cathinone in Animals
Anorexia Insomnia, lack of fatigue Hyperactivity Excitation	Anorexia (rat, monkey) Restlessness (monkey) Hypermotility (mouse, rat) Stereotyped oral activity (mouse, rat, rabbit)
Euphoria Logorrhoea	
Hyperthermia Increased respiration	Hyperthermia (rabbit) Increased oxygen consumption (rat)
Mydriasis Arrhythmias	Mydriasis (monkey) Positive inotropic and chronotropic effect (guinea pig atrium) Hypertension (cat)
Hypertension Constipation (probably due to tannins)	
Compulsive khat consumption	Cathinone self-administra- tion (monkey)

ness of the extraction procedure. Chemically, cathinone resembles amphetamine; it is a labile substance that is considerably more potent with regard to CNS stimulation than norpseudoephedrine. The concentration of cathinone was found to be highest in young leaves that are fresh, which explains the preference of khat users for this type of material. Subsequent analyses of khat samples from Kenya and Ethiopia have shown that the commercial value of the material correlates with its cathinone content (Geisshüsler & Brenneisen, 1987; Schorno, Brenneisen, & Steinegger, 1982).

Most of the earlier studies of the pharmacology of cathinone were initiated by the members of an advisory group to the World Health Organization (WHO Advisory Group, 1980). The effects of cathinone in animals were found to correspond to those observed in khat chewing humans, as can be seen from the pharmacological profiles shown in Table 1 (from Kalix, 1984). Furthermore, the effects listed in the right-hand column of Table 1 describe cathinone as a potent amphetamine-like compound. A series of *in vitro* experiments has shown, in fact, that cathinone has the same mechanism of action as amphetamine, that is, that it induces the release of catecholamines from presynaptic storage sites (Kalix, 1983a). Other findings indicate that cathinone is the dependence-producing constituent of khat leaves. Thus, behavioral studies with rats trained to distinguish between placebo and amphetamine showed that the response of the animals was not modified when amphetamine was replaced by cathinone (Rosecrans, Campbell, Dewey, & Harris, 1979). Self-administration experi-

ments with monkeys also showed that the reinforcing efficacy of cathinone, under certain conditions, was equal to that of cocaine (Woolverton & Johanson, 1984). In experiments of this kind, monkeys will make frequent injections of cathinone for a period of several days; they will then stop because of exhaustion, but will start again after they have recovered (Oinuma, Wakasa, & Yanagita, 1981). This pattern of drug intake is characteristic of amphetamine dependence. In this context, it is important to mention that the aversive properties of cathinone were found to be unexpectedly weak when compared to those of amphetamine (Goudie, 1985).

Among the three main khat alkaloids, cathinone is not only the most potent with regard to induction of release at CNS dopamine terminals, but it is also the most lipophilic, a factor that favors its penetration towards its sites of action in the CNS. It can be assumed, therefore, that the khat-induced CNS stimulation is predominantly due to the cathinone content of the leaves. At peripheral sites, however, cathinone, norpseudoephedrine, and norephedrine are about equipotent with regard to induction of release at noradrenergic nerve terminals (Kalix, 1983b; Kalix, Geisshüsler, & Brenneisen, 1987). Since the concentration of the latter two alkaloids in the leaves is considerably higher than that of cathinone, norpseudoephedrine and norephedrine must be considered as being mainly responsible for the sympathomimetic syndrome induced by the consumption of khat. Another factor to be taken into account is that cathinone is metabolized rapidly (which is in agreement with the rather short duration of the CNS stimulation brought about by a portion of khat), whereas both norpseudoephedrine and norephedrine are slowly absorbed and then excreted mainly in the unchanged form (Brenneisen, Geisshüsler, & Schorno, 1986; Frosch, 1977; Maitai & Muger, 1975).

ACUTE KHAT INTOXICATION AND ITS TREATMENT

Khat induces a euphoric and elated state characterized by joviality, hilarity, and garrulous behavior that may culminate in logorrhoea. During this condition of mild mania, the speech of the patient tends to be rapid and pressured and is at times incoherent; his intellectual and emotional activity is increased while tending to grandiose and unrealistic schemes; the thinking is characterized by an inability to concentrate and by flight of ideas. He is emotionally unstable and irritable and is easily provoked to anger; he may be restless and hyperactive with movements lacking precision. At the stage of advanced intoxication, the behavior of the patient is turbulent and quarrelsome, he displays a suspicious and hostile attitude, while becoming verbally aggressive and violent. He may de-

velop feelings of persecution and report paranoid delusions, but usually he can be made aware of the incongruities of his behavior and thinking. Severe intoxication results in a transient schizophreniform psychosis of the paranoid type, during which the patient shows hypersensitivity to sensory stimulation sometimes accompanied by hyperesthesia.

A person under the effect of khat presents a typically staring look and often mydriasis. He will complain of a dry mouth and of thirst, his respiratory rate is increased, and the body temperature is slightly elevated. Cardiovascular regulation is labile with a tendency to overreact to physical exercise. Heart rate and blood pressure may be increased due to enhanced sympathetic activity, and there may be tachycardia with palpitations. Habitual khat users are often recognized by the brownish stains on their teeth. They suffer from chronic insomnia, anorexia, and obstipation.

Thus, the clinical manifestations of acute khat intoxication consist of a syndrome characterized by psychomotor stimulation and sympathomimetic effects, and this raises the issue of the treatment of such patients. Through the experimental studies summarized above, it has become evident that the main psychoactive constituent of khat, cathinone, must be considered a natural amphetamine. Therefore, with regard to pharmacodynamic effects, the chewing of a portion of khat is equivalent to the intake of a certain amount of amphetamine, and this should determine the therapeutic approach of the psychiatric and somatic problems that may arise from khat consumption.

For the treatment of khat-induced behavioral disturbances, antipsychotic drugs of the phenothiazine type have been used in most of the cases described in the literature, and methoxyphenothiazine is used routinely for such patients in the main hospital of Djibouti (Dr. J. Chuiton, personal communication), a country where khat use is a major medical problem. Dhadphale, Mengech, and Chege (1981) have treated two cases of khat-induced schizophrenia-like psychosis accompanied by paranoid delusions. One patient was given 600 mg thioridazine per day and recovered within one week, whereas the other received initially chlorpromazine followed by a short course of other phenothiazines. A third patient mentioned in this report, who showed khat-induced aggressivity, received an IV injection of diazepam followed by treatment with haloperidol and supportive psychotherapy. McLaren (1987) has treated a case of psychosis due to khat consumption with 200 mg chlorpromazine three times a day, the symptoms disappearing within three days. Similarly, Gough and Cookson (1984) have used 300 mg thioridazine per day for the treatment of a khat-induced schizophreniform psychosis characterized by paranoid delusions and hyperactivity; the patient recovered within one week. In another case of paranoid delusions due to khat, reported by Critchlow

and Seifert (1987), the patient received 5 mg trifluoperazine three times a day for five days and then intermittently; recovery was complete on the twelfth day. Laurent (1962b) describes the treatment of a khat-intoxicated patient with haloperidol (IV, presumably 10 mg/day) and chlorpromazine (100 mg/day IM) resulting in recovery within two days. Finally, mention must be made of the case of manic-like psychosis due to khat that was observed by Giannini and Castellani (1982) in which the patient recovered within five hours without specific treatment. Taken together, these different examples would indicate that it is probably not critical which type of antipsychotic is chosen for alleviating the khat-induced symptoms, and this is borne out by experimental observations indicating that the effect of cathinone on the locomotor activity of mice can be antagonized by antipsychotic compounds both of the phenothiazine and of the butyrophenone type (Valterio & Kalix, 1982).

It is surprising that, among the case reports summarized above, that of Giannini and Castellani (1982) is the only one that mentions increased sympathetic activity as accompanying the behavioral symptoms shown by the khat-intoxicated patient. Indeed, in the publications that recount the general symptomatology resulting from khat use (Halbach, 1972; Laurent, 1962a; LeBras & Frétilière, 1965), the sympathomimetic effects have a prominent place, especially those that occur at the cardiovascular level. These publications are, however, based on observations made in regions where much low-grade khat is consumed, and it can be argued that the sympathomimetic effects occur predominantly after consumption of leaves that have a low content of cathinone, but contain substantial amounts of norpseudoephedrine and norephedrine. Furthermore, all of the case reports summarized above pertain to rather young patients, whereas acute cardiovascular problems after khat use are most likely to occur in older people (Gendron, Ardouin, & Martine, 1977). It is also possible that, in countries where khat is almost unknown, cases of dangerously increased sympathetic tone have been treated without recognizing khat as a cause. Finally, it might be that, as suggested by McLaren (1987), sympathetic arousal accompanies manic-like psychoses that are *caused* by khat intoxication while being much less evident in cases of psychosis that are *exacerbated* by khat. Threatening sympathetic hyperactivity occurring after khat consumption should be treated in the classical fashion, that is, tachycardia (together with the resulting anxiety) by beta-blocking agents, and tachyarrhythmias by lidocaine. Persisting hypertension may require treatment with vasodilating substances such as either diazoxide and hydralazine or nitroprusside.

Amphetamine intoxication can be treated causally by urine acidification resulting in an accelerated excretion of the drug. This is possible because of its high

ionization constant ($pK_a = 9.90$), and it is of particular interest because amphetamine is long-acting and is excreted to a large extent as the unchanged molecule. The three main khat alkaloids are structurally closely related to amphetamine; it seemed worthwhile, therefore, to consider the possibility of hastening their excretion by acid diuresis. Although cathinone is rather short-acting and metabolized almost completely (Brenneisen, Geisshüsler, & Schorno, 1986), its ionization constant was determined for the purpose of the present review and it was found to be, in three titrations, between 10.03 and 10.37 (P. Kalix, unpublished experiments¹). According to the literature, the ionization constants of the long-acting khat alkaloids norpseudoephedrine and norephedrine (the latter being also the main metabolite of cathinone) are, respectively, 9.40 (Vree, Muskens, & van Rossum, 1969) and 9.55 (Kisbye, 1958). Thus, all three khat alkaloids have quite a high ionization constant, and it should be possible to reduce the consequences of khat intoxication, especially the sympathomimetic effects, by administering ammonium chloride for urine acidification. With regard to the psychiatric symptoms, however, this approach is only useful if the presence of khat alkaloids in the body is not only the triggering, but also the sustaining, factor. Unfortunately, there is so far no published method for measuring the serum concentrations of the khat alkaloids, and the temporal correlation between khat-induced symptoms and blood levels of the different khat alkaloids remains to be determined.

Discontinuation of the khat habit does not seem to create any major problem for the individual. Indeed, there seems to be no craving sensation, and only occasionally there is a mild degree of reactive depression upon abstinence which requires, if any, psychological rather than medical support. Accordingly, habitual users report that they have no serious difficulties when moving to an area where khat cannot be obtained. However, most of them resume the use of khat upon returning to their previous environment, which can be taken as indicating the contributing role of the psychosocial factors involved in the habit.

CONCLUSIONS

For a patient who presents a schizophreniform syndrome and who is known to have ingested leafy plant material, the clinician should consider the possibility of khat intoxication, in particular if there are signs

¹A 0.01 M aqueous solution of S(-) cathinone hydrochloride was titrated at 24°C by adding 0.1 N KOH from a microburette. The stepwise increase in pH of the solution as indicated by a pH-potentiometer was plotted against the amount of base added; the maximum of the resulting curve indicates the apparent ionization constant.

of increased sympathetic activity. As far as the therapeutic approach is concerned, khat intoxication must be seen in the same light as amphetamine intoxication; indeed, with the exception of certain symptoms at the gastrointestinal level, the syndrome due to khat is more or less the same as that brought about by amphetamine. There is, however, a quantitative difference: the amount of cathinone—the main psychoactive constituent of khat—that can be extracted by chewing from a portion of leaves is quite limited, and its absorption is delayed by the mastication process. On the other hand, as cathinone seems to be metabolized rather quickly, there is probably a limit to the cathinone blood levels that can be attained by khat chewing. In comparison to amphetamine, which is usually consumed in pure form, this would represent a safety factor.

Especially in countries where khat use is widespread, the indirect health effects of the habit are important as well. These are mainly due to malnutrition that is often a consequence of khat use, partly because khat induces anorexia, and partly because the user prefers to spend money on khat rather than on food. With regard to the resulting susceptibility to infectious diseases, tuberculosis is a particular threat (Laurent, 1962b) since the participants of a khat session usually eject the chewed residues of the leaves by spitting.

Besides its negative effects on health, the khat habit engenders socio-economic problems detrimental to the individual and to the community, such as diversion of income and loss of productivity. These aspects have been an important factor in the decision of governments that have restricted or prohibited khat use. On the other hand, the khat habit has, especially in Yemen, a deep-rooted social and cultural function (Weir, 1985), which makes it difficult and precarious to put any such restriction into effect. At present, khat begins to be introduced to certain developed countries, and substantial amounts of the drug are air-transported to, for example, Great Britain (Gough & Cookson, 1987; Mayberry, Morgan, & Perkin, 1984). Therefore, the clinician should be familiar with the khat syndrome. In this context, the possibility of a preventive prohibition of this drug should be considered before an increase in the habit, particularly in immigrant circles, leads to increased problems for substance abuse treatment centers.

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