Br. J. clin. Pharmac. (1990), **30**, 825–828

Amphetamine-like effects in humans of the khat alkaloid cathinone

R. BRENNEISEN[1], H.-U. FISCH[2], U. KOELBING[2], S. GEISSHÜSLER[1] & P. KALIX[3]
[1]Department of Phytochemistry, Institute of Pharmacy; [2]Department of Psychiatry, Faculty of Medicine, University of Berne, Switzerland and [3]Department of Pharmacology, Faculty of Medicine, University of Geneva, Switzerland

1 The chewing of khat leaves as a stimulant is common in certain countries, and the effects of this material are supposed to be due to the phenylalkylamine alkaloid cathinone. In order to determine the effects of this substance in humans, a single oral dose of cathinone or placebo was administered to six healthy male volunteers in a double-blind, random order crossover study.

2 Cathinone produced increases in blood pressure and in heart rate, and these changes were concomitant with the presence of cathinone in blood plasma.

3 The physical and mental changes that the subjects reported during the experiment indicated that cathinone has in humans euphorigenic and psychostimulant effects.

4 These observations support the assumption that cathinone is the constituent mainly responsible for the effects of khat, and they show that this alkaloid has also in humans amphetamine-like effects.

Keywords khat cathinone amphetamine-like

Introduction

In certain regions of East Africa and of the Arab Peninsula, leaves of the khat bush (*Catha edulis*, Celastraceae) are widely used as a stimulant, and the medical and socio-economic problems related with the use of this drug have attracted the attention of international organisations repeatedly (League of Nations, 1936; UN Commission, 1956; WHO Expert Committee, 1964). So far, the habit of chewing khat has remained more or less confined to the areas where the plant grows, since only fresh leaves are active. Nevertheless, in recent years the khat habit has made its appearance in regions far from the areas of cultivation of the plant, and this is mainly due to the possibility of air-transporting the leaves. Thus, fresh khat is now marketed in Great Britain (Mayberry *et al.*, 1984; McLaren, 1987), which is of concern because the consumption of this drug may result in toxic psychosis (Carothers, 1945; Dhadphale *et al.*, 1981), and because its habitual use is characterized by moderate but often persistent psychic dependence (Eddy *et al.*, 1965). Indeed, cases of khat-induced psychosis have now also been observed in Great Britain (Critchlow & Seifert, 1987; Gough & Cookson, 1984; McLaren, 1987; Pantelis *et al.*, 1989) as well as in the United States (Giannini & Castellani, 1982).

Some 12 years ago, the alkaloid cathinone, i.e. S(−)α-aminopropiophenone, was isolated from khat leaves (Szendrei, 1980), and since that time experiments in animals and in isolated tissues have revealed that this substance is a potent amphetamine-like compound (Kalix & Braenden,

Correspondence: Dr Peter Kalix, Département de Pharmacologie, Centre Médical Universitaire, 1211 Genève 4, Switzerland

1985). In view of these findings, and in view of the developments outlined above, we decided to determine the effects of cathinone in humans under controlled conditions, and thus to assess the relevance of this alkaloid to the symptoms that are observed after consumption of khat leaves.

Methods

The subjects were six healthy male volunteers aged 32 ± 4.1 years; before admission to the experiment they underwent medical and psychiatric examination together with an evaluation of their propensity for drug abuse. They had agreed to refrain from psychotropic drugs for the 3 weeks preceding the experiment and to avoid alcoholic and stimulating beverages during the preceding evening and night. Moreover, urine samples were taken before the beginning of the experiment and screened for psychotropic drugs. Before the experimental session each subject chose its preferred position in order to ensure optimal comfort during the experiment, the position was the same in both sessions. All experiments began at 08.00 h after an overnight fast followed by a standardized light breakfast and a light lunch at noon.

Cathinone was obtained through stereospecific synthesis (Wolf & Pfander, 1986) including a verification of its identity with the natural alkaloid; it was administered in individual tests using a placebo-controlled balanced experimental design. The drug was given orally in gelatine capsules as the hydrochloride in an amount corresponding to 0.5 mg base kg^{-1} body weight; for the control experiment, which took place a week earlier or later, lactose was given at the same dosage. Blood pressure and heart rate were automatically recorded with a monitor; blood samples were drawn periodically through indwelling catheters, mixed with sodium citrate buffer, centrifuged and stored at −20° C. The concentrations of cathinone and of its metabolite norephedrine or R,S(−)phenylpropanolamine (Brenneisen *et al.*, 1986) were determined by high-performance liquid chromatography; over the concentration range studied, the inter-day variance of the values for cathinone and norephedrine extended between 6.1 and 14.3% (Brenneisen *et al.*, manuscript in preparation). The chemical stability of cathinone in plasma samples had been ascertained in a control experiment. For determining the subjective and psychological effects of cathinone, the subjects were required to self-report physical and mental changes that they felt to occur by completing a questionnaire of the true/false type, i.e. by answering sets of questions from the Addiction Research Center Inventory that had been developed for recognizing amphetamine effects in humans (Martin *et al.*, 1971).

Results

The administration of cathinone produced clear-cut increases in blood pressure (Figure 1a) and in heart rate (Figure 1b), effects that can be considered as reflecting the sympathomimetic syndrome that may appear after khat consumption and that is characterized by transient hypertension and tachycardia (Gendron *et al.*, 1977; Halbach, 1972); the observed changes were concomitant with the presence of cathinone in blood plasma (Figure 1c). Cathinone was rapidly transformed to norephedrine, however, this metabolite did not sustain the cardiovascular effects of cathinone (Figure 1c *vs* Figure 1 a/b). The subjective effects reported during the experiment (Figure 2) indicate that cathinone is a substance that has in humans marked psychostimulant and euphorigenic effects, effects which can be expected to reinforce the habit of chewing khat.

Discussion

Our observations support the assumption that cathinone is the constituent that is mainly responsible for the effects of khat, and they implicate cathinone as the dependence-producing constituent of this drug. In fact, the dose of 0.5 mg kg^{-1} that we used in our experiments would correspond to the consumption by a person of medium body weight of 100 g khat having average cathinone content (Geisshüsler & Brenneisen, 1987). With regard to the other two phenylpropylamines present in the leaves, it can be assumed that they do not contribute significantly to the stimulatory effect since wilted khat, in which their concentration remains elevated while that of cathinone is strongly reduced (Schornò *et al.*, 1982), is ineffective. Indeed, in the experiments that we report, cathinone alone produced clear sympathomimetic and subjective effects of the amphetamine type at a dose that corresponds to the content of a portion of khat of current quality. Even so, the effects of a given batch of the drug depend not only on the alkaloid concentration, but also on the efficiency of the mastication process, and with regard to the dose it must be kept in mind that it is difficult to increase the intake of khat beyond a certain limit because of the bulkiness of the plant material.

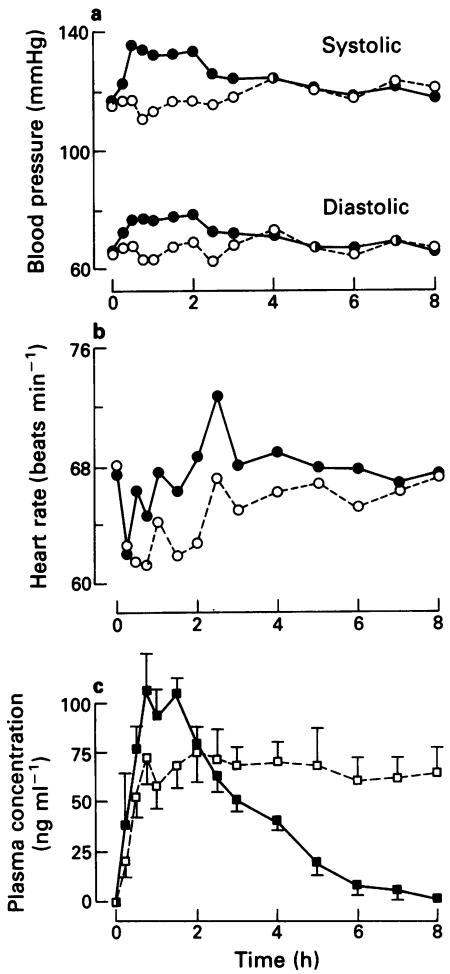


Figure 1 Time course of the averages of systolic and diastolic blood pressure (a) and of heart rate (b) in six healthy subjects after administration of 0.5 mg kg^{-1} cathinone (●) and of placebo (○), and time course of the average plasma concentrations of cathinone (■) and of its metabolite norephedrine (□) (c). The bars in Figure 1c represent standard error; two factorial (subject × drug) analysis of variance for repeated measures with time square as covariate (Winer, 1971) indicates a highly significant main effect of cathinone for both systolic [$F(1,5) = 61.7$, $P < 0.0001$] and diastolic [$F(1,5) = 79.4$, $P < 0.0001$] blood pressure as well as for heart rate [$F(1,5) = 73.1$, $P < 0.0001$].

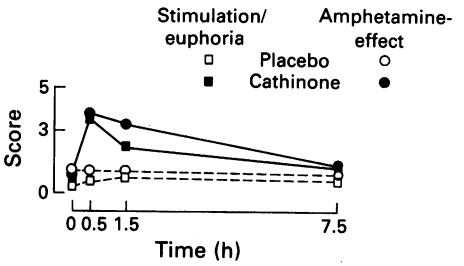


Figure 2 Time course of the average subjective effects of cathinone (●, ■) in comparison with those of placebo (○, □) as reported by six volunteers. Drug and placebo were administered orally under double-blind conditions in individual sessions at a dose of 0.5 mg kg^{-1} body weight, and the subjects were asked to complete periodically a questionnaire of the true/false type. The evaluation of amphetamine-like effect (●, ○) was made by submitting the eleven amphetamine-specific questions proposed by Martin *et al.* (1971), that for stimulation/euphoria (■, □) by submitting the fifteen questions selected to this end by Cole *et al.* (1982) from the Addiction Research Center Inventory; the questions were used in German translation. The scores were assessed with a three-factorial (subject × drug × time) analysis of variance for repeated measurements, the levels of significance for main effect of cathinone were found to be for stimulation/euphoria $F(1,5) = 19.41$, $P < 0.01$, and for amphetamine effect $F(1,5) = 7.99$, $P < 0.05$.

Presently, the worldwide consumption of khat can be estimated at some 5 million portions per day, although it is virtually completely limited to East Africa and southwestern Arabia. However, there are indications that the drug is at the point of spreading beyond the ethnic groups who traditionally use it. To date, khat is not an illegal drug in Great Britain or in the United States, but it is in France. The objective and subjective effects of cathinone that we report here may lead, together with epidemiological data, to a reconsideration of the use of khat as a stimulant and social drug.

We are grateful to the participating volunteers for giving their informed consent to the study; the experimental protocol had been approved by the Commission on Clinical Ethics of the University of Berne. We thank K. Michel, M.D., M.R.C.Psych., for preliminary examination of the test subjects, and P. Ballinari for statistical analysis of the data. Our work was supported by the Swiss Federal Health Office and by the Swiss National Science Foundation.

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(Received 1 May 1990, accepted 3 August 1990)