Khat chewing and arterial blood pressure

A randomized controlled clinical trial of alpha-1 and selective beta-1 adrenoceptor blockade

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ABSTRACT

Objective: The aim of this work was to study prospectively the effect of alpha-1 and selective beta-1 adrenoceptor blockade on cardiovascular effects of khat chewing in healthy volunteers.

Methods: Sixty-three male volunteers chewed khat for 3 hours on 3 separate occasions, 1 or 2 weeks apart. Fifty age and weight matched male controls did not chew. The khat chewers received in a double blind 3-arm crossover design either indoramin 25mg, atenolol 50mg or placebo one hour before starting to chew. The non-chewing controls received atenolol 50mg on a separate occasion. Pulse and blood pressure were measured at regular intervals before, during and after the chewing period. The study was carried out in Sana'a, Yemen between December 2001 and November 2003.

Results: Khat chewers in the atenolol treated group had significantly lower readings for systolic blood pressure (SBP) and pulse rate one, 2 and 3 hours after starting to chew than khat chewers pre-treated with placebo or indoramin and comparable to non-khat chewers. Three hour SPB readings in khat chewers with placebo, with atenolol and with indoramin (mean values [95% confidence interval]) were 123 (120.2-125.7), 115.7 (113.0-118.4), and 119.8 (116.9-122.8) (p<0.0001). Blood pressure and pulse rate were not altered in non-khat chewers taking 50mg atenolol. Diastolic blood pressure during khat chewing rose in the atenolol, indoramin and placebo groups.

Conclusion: The effect of khat chewing on systolic blood pressure and pulse rate is blocked by atenolol but not by indoramin. Beta-1 adrenoreceptors are probably important in mediating the cardiovascular effects of khat in man.

Saudi Med J 2005; Vol. 26 (4): 537-541

The leaves of the khat plant (*Catha edulis Forsk*) are widely chewed in Yemen and East Africa as a mental stimulant. The plant is also legally available in Britain and some other European countries in Yemeni and Somali communities. The leaves contain a number of compounds including cathinone (s(-)-alpha-aminopropiophenone) and norpseudoephedrine (cathine) which have pharmacological actions similar to amphetamine.[1] For example, it is known that khat chewing, like amphetamine use, is associated with a number of sympathomimetic effects, such as tachycardia and an increase in blood pressure.[2-4] The present study examines the effects of α1 (indoramin) and

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Received 27th September 2004. Accepted for publication in final form 16th January 2005.

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selective ß1 (atenolol) adrenoceptor blockade in a prospective randomized double-blind study in healthy khat chewing adults.

Methods. Sixty-three male subjects were recruited with an age range of 20-27 years (mean 23±0.19) and body mass index (BMI) range 15.3kg/m^2 to 28.4kg/m^2 (mean 21.6±0.37). They attended khat chewing sessions in Sana'a, Yemen on 3 separate occasions 1-2 weeks apart at the same time of the day having consumed only a light lunch. Subjects were told to take no caffeine containing drinks during the study. They chewed the same amount of fresh khat obtained that day in the local market for 3 hours and then spat out the leaves.

A control group of 50 (age and weight matched male non-khat chewers) were recruited (age range 20-27 years with a mean age of 23±0.31 and BMI 15.6kg/m^2 to 32.5kg/m^2 mean of 20.5±0.44). Before admission to the study, all subjects underwent medical examination. Subjects were excluded if they had a history of hypertension, cardiac, renal or liver disease or if they were more than occasional (twice per month) khat chewers. None was on any medication and none had chewed khat during the week before the study. Verbal consent was obtained from all participants after full explanation and the project was approved by the Ethical Committee of the Faculty of Medicine, University of Sana'a.

A double-blind 3 arm cross-over placebo controlled study design was used. Three experiments with randomized allocation of α1 (indoramin 25mg) and selective ß1 (atenolol 50mg) adrenoceptor blockade or placebo were performed on each subject 1-2 weeks apart. One hour before starting to chew khat, each subject took either indoramin 25mg or atenolol 50mg or placebo. The 50 non-khat chewing subjects had the same observations as the khat chewers, and 40 of these subjects took atenolol 50mg on a separate occasion. As there was no credible alternative leaf to chew, they were given nothing. Arterial blood pressure and pulse rate were measured at zero time (one hour before khat chewing and just before ingestion of drug or placebo) and at one hour, 2 hours and 3 hours during khat chewing and one hour after spitting out the khat. Further readings were taken at 18 hours and 24 hours after starting khat chewing (namely 15 and 21 hours after stopping khat). Similar measurements were taken for non-khat chewers. The blood pressure was measured using a mercury-based cuffed sphygmomanometer with a bared arm in the sitting position 3 times at 5 minute intervals. The mean reading was taken of systolic (SBP) and diastolic blood pressure (DBP) and pulse rate (PR).

Statistical analysis. Repeated measures of variance (Multiple analysis of variance, Statistical Package for Social Sciences [SPSS]) were used to assess the null hypothesis that the arterial blood pressure parameters on the α1 and selective ß1 adrenoceptor blockade treatment study days would not differ from those on the day of placebo treatment and in the non-khat chewing subjects. Confidence intervals were calculated using SPSS.

Results. Analysis of variance (ANOVA) detected no evidence of persistence of drug effect across the washout period on the 3 study days for khat chewers (**Tables 1-3**). The mean baseline arterial blood pressure values and pulse rate at zero time in the 5 studies did not differ significantly ($p>0.05$). In the placebo controlled experiment khat chewers showed a significant and progressive elevation of systolic and diastolic blood pressure and PR at hourly intervals after starting to chew khat compared with baseline values ($p<0.05$). The means and 95% confidence intervals are all recorded in **Tables 1-3**. One hour after stopping khat and at 15 and 21 hours after stopping khat all mean parameters were significantly lower ($p<0.05$) than the peak value observed at 3 hours (**Tables 1-3**). The non-khat chewers with no tablet showed no significant change in any values during the study.

Analysis of variance of SBP and PR at one, 2 and 3 hours from starting to chew khat showed there was a significant difference between the atenolol and placebo arms ($p<0.05$) but no difference between the placebo and indoramin arms (**Tables 1 and 3**). However, 15 and 21 hours after stopping khat there was no significant difference between either of the 2 drug groups and the placebo groups ($p>0.05$).

The mean values of SBP and PR at one, 2 and 3 hours in the khat chewers on atenolol were not significantly different from the readings in the non-khat chewing controls whether or not taking atenolol and significantly lower than the values in the khat chewers on placebo and indoramin ($p<0.05$). In contrast ANOVA of DBP readings at one, 2 and 3 hours after starting to chew khat did not show significant differences between the mean values in the atenolol, indoramin and placebo groups (**Table 2**). Moreover, these values were significantly higher than the mean values for non-khat chewers with or without atenolol at the corresponding times ($p<0.05$). The readings in the latter 2 groups did not differ significantly. At the 24 hour point the mean values of all readings in the 5 groups did not differ significantly (**Tables 1-3**).

Discussion. Khat chewing has been associated with a transient rise in blood pressure and pulse rise for some years.[1-4] Similar results were obtained when pure cathinone in gelatin capsules was ingested and the rise in blood pressure and pulse

Table 1 - The comparison of mean values (95% CI) of systolic blood pressure (mm Hg) for khat chewers (+ placebo or atenolol or indoramin) (n=63), non-khat chewers (n=50) and atenolol intake only (n=40).

Time	Non-Khat chewers	Khat placebo	Khat Atenolol	Khat Indoramin	Atenolol intake only	ANOVA *p* value
0 hour (0 time)						0.519
Mean	115.50	113.39	114.10	116.16	113.54	
(95% CI)	(111.94-119.06)	(111.22-115.55)	(112.06-116.14)	(113.14-119.19)	(110.30-116.79)	
1 hour during chewing khat						0.002
Mean	115.05†	120.08	112.96*	117.62	112.59*	
(95% CI)	(111.13-118.97)	(117.28-122.88)	(110.51-115.42)	(114.71-120.53)	(109.07-116.11)	
2 hour during chewing khat						0.000
Mean	114.10*	122.78	115.69*	119.95	113.04*	
(95% CI)	(110.32-117.88)	(120.03-125.53)	(113.17-118.21)	(116.98-122.92)	(110.41-115.67)	
3 hour during chewing khat						0.000
Mean	114.50*	122.99	115.71*	119.84	112.92*	
(95% CI)	(111.00-118.00)	(120.24-125.74)	(113.02-118.41)	(116.86-122.83)	(110.46-115.37)	
1 hour after spitting out khat						0.000
Mean	115.10	118.70	112.83*	118.44	110.42*	
(95% CI)	(111.36-118.84)	(116.09-121.31)	(110.31-115.35)	(115.71-121.17)	(108.25-112.59)	
18 hour after starting chewing khat						0.006
Mean	113.10	110.93	108.28‡	112.67	107.63‡	
(95% CI)	(109.59-116.61)	(108.70-113.15)	(105.97-110.60)	(110.57-114.78)	(105.45-109.80)	
24 hour after starting chewing khat						0.249
Mean	114.10	113.44	110.90	112.67	110.63	
(95% CI)	(110.64-117.56)	(111.23-115.64)	(108.91-112.89)	(110.49-114.86)	(107.42-113.83)	
ANOVA p-value	0.977	0.000	0.000	0.000	0.036	

*$p<0.05$ compared with Khat + placebo and khat + indoramin, †$p<0.05$ compared with khat + placebo, ‡$p<0.05$ compared with non-khat chewers and khat + indoramin, ANOVA - analysis of variance, CI - confidence interval.

Table 2 - Comparison of mean values (95% CI) of diastolic blood pressure (mm Hg) for khat chewers (+ placebo or atenolol or indoramin) (n=63), non-khat chewers (n=50) and atenolol intake only (n=40).

Time	Non-Khat chewers	Khat placebo	Khat Atenolol	Khat Indoramin	Atenolol intake only	ANOVA *p* value
0 hour (0 time)						0.287
Mean	72.70	75.24	74.26	76.14	75.25	
(95% CI)	(70.29-75.11)	(73.04-77.44)	(72.12-76.40)	(73.74-78.53)	(73.02-77.48)	
1 hour during chewing khat						0.001
Mean	71.66‡	77.51	77.91	75.42	72.13‡	
(95% CI)	(69.02-74.30)	(74.83-80.20)	(75.69-80.13)	(72.76-78.08)	(70.28-73.97)	
2 hour during chewing khat						0.000
Mean	70.80*	80.74	80.00	78.39	70.85*	
(95% CI)	(68.10-73.50)	(78.31-83.17)	(77.58-82.42)	(75.74-81.03)	(69.41-72.29)	
3 hour during chewing khat						0.000
Mean	69.90*	81.80	80.90	79.79	74.35*	
(95% CI)	(67.23-72.57)	(79.30-84.30)	(78.52-83.28)	(77.40-82.17)	(72.78-75.92)	
1 hour after spitting out khat						0.000
Mean	71.30*	78.62	77.80	80.19	73.47*	
(95% CI)	(68.55-74.05)	(76.26-80.99)	(75.36-80.25)	(77.94-82.43)	(71.92 to 75.03)	
18 hour after starting chewing khat						0.000
Mean	69.40†	74.21	73.39	76.27	73.29	
(95% CI)	(66.85-71.95)	(72.02-76.39)	(71.30-75.47)	(74.33-78.21)	(71.62-74.96)	
24 hour after starting chewing khat						0.239
Mean	71.90	74.26	73.33	75.05	72.25	
(95% CI)	(69.70-74.10)	(72.17-76.35)	(71.39-75.28)	(72.83-77.27)	(71.17-74.33)	
ANOVA *p*-value	0.558	0.000	0.000	0.005	0.010	

* $p<0.05$ compared with khat + Placebo; khat + Atenolol and khat + Indoramin, †$p<0.05$ compared with khat + Placebo; khat + Atenolol; khat + Indoramin and non-khat chewers, ‡$p<0.05$ compared with khat + Placebo and khat + Atenolol, ANOVA - analysis of variance, CI - confidence interval.

rate ran parallel to blood cathinone levels suggesting that of the numerous constituent of khat leaves the cathinone is probably important in this context,[5-7] although cathine may also play a role. The relative amounts of these alkaloids in the khat leaves depends on their freshness. The mechanism by which khat chewing produces these cardiovascular effects is probably complex involving both the heart and arterial tree. Intravenous injections of cathinone into anesthetized rats[8] and dogs[9] raised the heart rate, arterial blood pressure and contractile force. In vitro experiments demonstrated that cathinone had a positive inotropic and chronotropic effect on isolated guinea pig atria,[8,10] and in these experiments cathinone was found to have a potency comparable to [+] amphetamine. Knoll[11] also demonstrated contraction of the rabbit ear artery and pulmonary arterial strip. It was postulated that analogous to amphetamine, these effects were mediated by release of noradrenaline from presynaptic storage sites and this was confirmed by Kalix[12] who demonstrated this in a dose dependent manner using 3H noradrenaline pre-labeled rabbit heart tissue. It was found that both cathinone and cathine were about equipotent. This effect of cathinone and cathine was abolished by pre-perfusing the tissue with cocaine and desipramine, leading to the conclusion that these alkaloids are indirectly sympathomimetic.[1] More recent studies[13,14] using isolated guinea pig hearts showed that cathinone produced dose dependent vasoconstriction in the coronary artery bed, and as this effect was not inhibited in the presence of cocaine or prazosin, it was concluded that this was a direct effect of the drug not acting via noradrenaline release. Such coronary artery vasoconstriction was suggested as the cause of the observed negative inotropic in this preparation. Cathinone also caused vasoconstriction in an aortic ring preparation,[13,14] which was abolished in the presence of cocaine and prazosin. This suggests that in this preparation, cathinone works peripherally by releasing noradrenaline onto α1 receptors.

In preliminary experiments using isolated rats myocytes (data from Dr Sian Harding not shown) there was no significant change in the amplitude of myocyte contraction with cathinone either in the absence or presence of isoprenaline and there was little or no effect on the speed of contraction or relaxation. This suggests cathinone acts as a modulator of noradrenaline levels rather than a compound with direct cardiac effects. How these in vivo and in vitro animal experiments relate to man is unknown.

The effect of selective ß1 blockade with atenolol in attenuating the effects of khat on SBP and PR points to the importance of this receptor in the

Table 3 - Comparison of mean values (95% CI) of pulse rate (beats per minute) for khat chewers (+ placebo or atenolol or indoramin) (n=63), non-khat chewers (n=50) and atenolol intake only (n=40).

Time	Non-Khat chewers	Khat placebo	Khat Atenolol	Khat Indoramin	Atenolol intake only	ANOVA *p* value
0 hour (0 time)						0.266
Mean	79.38	83.20	82.35	82.49	81.55	
(95% CI)	(76.95-81.81)	(80.77-85.62)	(79.71 to 84.99)	(80.06-84.91)	(79.13-83.97)	
1 hour during chewing khat						0.000
Mean	78.44*	89.01	75.66*	92.13	77.47*	
(95% CI)	(75.67-81.21)	(85.76-92.25)	(72.77 to 78.55)	(88.31-95.94)	(74.66-80.29)	
2 hour during chewing khat						0.000
Mean	77.34*	90.15	73.10*	92.69	74.03*	
(95% CI)	(74.44-80.24)	(86.79-93.51)	(70.25 to 75.95)	(88.90-96.47)	(70.20-77.86)	
3 hour during chewing khat						0.000
Mean	76.46*	89.99	70.98*	90.48	71.83*	
(95% CI)	(73.58-79.34)	(87.34-92.64)	(68.53-73.44)	(87.31-93.64)	(68.33-75.34)	
1 hour after spitting out khat						0.000
Mean	75.40*	83.49	70.71*	85.19	71.75*	
(95% CI)	(72.75-78.05)	(80.45-86.52)	(68.11-73.31)	(82.26-88.11)	(69.04-74.46)	
18 hour after starting chewing khat						0.000
Mean	72.44*	77.79	71.76*	77.47	72.93*	
(95% CI)	(69.45-75.43)	(75.44-80.15)	(69.44-74.08)	(75.37-79.57)	(69.77-76.09)	
24 hour after starting chewing khat						0.075
Mean	77.08	80.60	77.12	80.31	78.00	
(95% CI)	(74.89-79.27)	(78.01-83.18)	(74.63-79.62)	(78.04-82.58)	(75.92-80.08)	
ANOVA *p*-value	0.011	0.000	0.000	0.000	0.000	

*$p<0.05$ compared with khat + Placebo and khat + Indoramin, ANOVA - analysis of variance, CI - confidence interval.

mechanism of action of khat. Atenolol alone at the dosage given without khat chewing had no effect on blood pressure or pulse measurements. It is possible that the rise in SBP is attributable at least in part to an increase in cardiac output, as the beta blocker which was effective had no vasodilator activity. Alpha 1 adrenoceptor blockade with indoramin had no effect in blocking the blood pressure or pulse rate changes induced by khat. Previous studies by our group, however, have shown that this drug at this dosage totally blocked the effects of khat chewing on the smooth muscle of the bladder neck.[15] However, the α1 receptor subtypes at the bladder neck and on vascular smooth muscle are not the same and it is therefore impossible to exclude an alpha adrenergic effect as suggested by the experimental data above. It would be worth exploring alpha blockers further.

The current studies were performed on healthy young adults and the changes in the blood pressure and pulse rate induced by khat chewing, whilst significant, were small. Unpublished observations in older people and individuals known to be hypertensive have indicated a greater effect and occasionally a substantial and potentially dangerous rise in blood pressure can occur. Indeed there are reports of cerebrovascular events apparently being precipitated by khat chewing,[16] and a recent case control study in Yemen has implicated khat chewing as an independent risk factor for myocardial infarction which often occurs in the hours following khat use.[17]

We advise that middle aged or older individuals should have their blood pressure monitored when chewing khat and consideration should be given to the protective effect of beta blockers in chewers.

Acknowledgment. We are most grateful to all the volunteers who took part in the studies for attending throughout this period without complaint. We are indebted to Mr. Mohammed Al-Qubati for his statistical advice and to Dr Sian Harding for the data on isolated myocytes.

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