A CLINICAL EVALUATION OF THE STIMULANT KHAT AND OF THE KHAT ALKALOID CATHINONE

P Kalix[1], K Mathys[2], R Brenneisen[2], P Widler[3], HU Fisch[3]

Department of Pharmacology[1],[2]University of Geneva, Switzerland; Department of Pharmacy[2] and Department of Psychiatry[3] University of Berne, Switzerland.

The leaves of the khat bush have a stimulating effect which is thought to be due to the phenylpropylamine alkaloid cathinone. The habit of chewing khat is prevalent in East Africa and southwestern Arabia where this plant is cultivated widely, its consumption is estimated at some five million portions per day.

In order to evaluate the effects of khat in humans, we prepared a batch of chopped khat leaves of which the cathinone content had been determined, as well as a batch from which the alkaloid had been removed by extraction. Both types of material were masticated for 60 min by six healthy volunteers in individual tests using a balanced experimental design. In an analogous experiment, we administered pure cathinone and placebo in gelatine capsules.

Cathinone-containing khat as well as pure cathinone enhanced systolic and diastolic blood pressure, and they increased the ratings for stimulation/euphoria and amphetamine effects as determined through standardized questions from the Addiction Research Center Inventory. In both experiments, these changes were concomitant with the presence of cathinone in blood plasma.

Our observations provide strong support for the contention that the sympathomimetic and psychostimulant effects observed after the chewing of khat leaves are due to their constituent cathinone.

Bradycardia-dependent electrophysiological effects of ketanserine analogs in conscious hypokalemic dogs with chronic AV block.

L. Kamoun, T. Atallah, M. Dubar*, C. Ressayre*, F. Chézalviel-Guilbert, J. Weissenburger.

Laboratoire de Pharmacologie, UFR St-Antoine, 75012-Paris, * IRI. Servier 92415-Courbevoie, FRANCE

Potentially arrhythmogenic effects of ketanserine (KT) were related to early-afterdepolarizations (EAD). As a1 adrenoceptor antagonists may inhibit EAD, we compared KT and S14280, two equipotent 5-HT2(-) drugs, but the latter only exhibiting strong a1(-) effects, in a dog model of acquired long QT syndrome using a blind cross-over Latin-square protocol.

Diuretic-induced hypokalemic (K+≤ 3.3mM) dogs with chemically-induced chronic AV-block, instrumented with ventricular epicardial electrodes and femoral-artery pressure telemetry transmitters were selected for that study if they exhibited ventricular tachyarrhythmias (VT) during sotalol infusion (4.5 mg/kg). Six of them were submitted at 6 different study-days to 3 i.v. doses of KT (0.01; 0.1 & 1 mg/kg) and S14280 (0.003; 0.03 & 0.3 mg/kg) and 3 hr's EKG monitoring.

Results:

KT reduced systolic arterial pressure (SAP) at dose 2 (-24±8 mmHg: mean of time 30, 90 & 150min) and dose 3 (-28±10 mmHg). Only dose 3 increased QT interval (+54±10ms) and VERP (+19±4ms) both measured at 60 bpm, and provoked VT or 'torsades de pointes' (TdP) in 3 dogs. S14280 produced almost identical effects than KT on SAP (-19±6 mmHg at dose 2), QT (+51±10ms at dose 3) and VERP (+19±3ms at dose 3) and induced VT or TdP in 2 dogs.

Conclusion: Reduction in arterial pressure can be observed with both 5-HT2(-) without any effect on repolarization. Equiactive doses of KT and S14280 on SAP do not demonstrate different effects on ventricular repolarization despite a1(-) properties of S14280.

ANTIDYSRYTHMIC EFFECT OF GALLIUM CHLORIDE ON PAPILLARY MUSCLE ISOLATED FROM THE GUINEA PIG HEARTS.

JP Kantelip, F Mougin, A Leperre*, R Gautheron, H Millart*, N Platonoff

Lab Pharmacologie Médicale, Faculté de Médecine-25030 Besançon Cedex, France

*Lab Pharmacologie Médicale, Faculté de Médecine- 51092 Reims Cedex, France.

The electrophysiological effects of gallium chloride (Ga^{+++}) and its activity on the arrhythmias induced by digitalis were investigated in guinea papillary muscle. KCL microelectrodes were used to record transmembrane electrical activity from Purkinje cells from the papillary muscle of guinea pig hearts during superfusion and electrical stimulation in vitro at 37°C. Myocardial contractility was continuously monitored from a strain jauge statham U.C. II. Ga^{+++} was superfused alone in cumulative concentrations ($4.5.10^{-5}$, 9.10^{-5} and $1.8.10^{-4}$ M). Arrhythmias were induced by a superfusion of Digitoxin ($7.5.10^{-7}$ M). A superfusion of Ga^{+++} ($4.5.10^{-5}$ and 9.10^{-5} M) was started 20 mn later and maintained for 45 mn. Ga^{+++} alone produced a dose dependent reduction of action potential duration and contractility (30%). Ga^{+++} potentiated the incidence of decrease in the amplitude and duration of the action potential induced by digitoxin (10%). The incidence of arrhythmias induced by Digitoxin was immediately reduced by the two concentrations of Ga^{+++}. The contractility was reduced by Ga^{+++}(60%) in the digitalized pretreated papillary muscles. It is concluded that Ga^{+++} inhibits calcium movements and has negative inotropic and antidysrythmic effects.

ARRHYTHMIAS IN ISOLATED HUMAN ATRIUM FUNCTIONALLY RELATED TO CYCLIC AMP

A J Kaumann, L Sanders

Clinical Pharmacology Unit, Cambridge University, Addenbrooke's Hospital, Cambridge CB2 2QQ and Human Pharmacology Laboratory, AFRC Babraham Institute, Babraham, Cambridge CB2 4AT, UK

(–)-Noradrenaline (NA), (–)-adrenaline (Adr) and 5-hydroxytryptamine (5-HT) can increase contractile force, cyclic AMP levels and cyclic AMP-dependent protein kinase (PKA) activity in human atrium through β_1-adrenoceptors (β_1AR), β_2-adrenoceptors (β_2AR) and 5-HT_4 receptors respectively (Eur Heart J 10 Suppl B:29–37, 1989; Br J Pharmacol 100: 879–885, 1990). Phosphorylation of sarcolemmal Ca^{2+} channels by PKA can cause myocyte Ca^{2+} overload thereby triggering delayed afterdepolarisations that lead to arrhythmic triggered contractions. We have investigated the arrhythmogenic potential of NA, Adr, 5-HT and dibutyryl cyclic AMP (dBcA) on isolated right atrial appendages obtained from patients chronically treated with βAR blockers who were undergoing coronary artery bypass surgery. Atrial strips were paced to contract isometrically at 37°C. After determination of an interval–force relationship (0.1, 0.2, 0.5, 1, 2 Hz) (staircase) the staircase was run backwards with 2 min rest periods after each pacing rate to detect triggered contractions. This procedure was repeated in the presence of agonists and antagonists. β_1AR were activated by 10 μM NA in the presence of 50 nM erythro-(±)-(α-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol).HCl (ICI 118551) (to block β_2AR). β_2AR were activated by 10 μM Adr in the presence of 300 nM 1-[2((3-carbamoyl-4-hydroxy) phenoxy)-ethylamino]-3-[4-(1-methyl-4-trifluoromethyl-2-imidazolyl)phenoxy]-2-propanol (CGP 20712A) (to block β_1AR). 5-HT_4 receptors were activated by 10 μM 5-HT. NA, Adr, 5-HT and dBcA (1 mM) caused arrhythmias and triggered contractions that were more frequent at low than at high pacing rates. The incidence of arrhythmias (number of patients) was NA 21/21, Adr 21/21, 5-HT 9/10 and dBcA 8/9. The arrhythmias caused by NA, Adr and 5-HT were blocked by CGP 20712A, ICI 118551 and the selective 5-HT_4 receptor antagonist (1-piperidinyl)ethyl 1 H-indole 3-carboxylate (SB 203186) (Br J Pharmacol 108: 68P, 1993) respectively. We conclude that when activated by the relevant agonist coexisting β_1AR, β_2AR and 5-HT_4 receptors can mediate arrhythmias in human atrium, presumably through activation of PKA.