

SOME ASPECTS OF PHARMACOLOGICAL PROFILE OF SODIUM CURCUMINATE

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Summary : Rapid i.v. injection of sodium curcumin (NaC) produced transient hypotension and bradycardia in anaesthetized dogs and cats which were not blocked by bilateral vagotomy, atropine, mepyramine or propranolol. In open-chest anaesthetized cats, decrease in blood pressure and heart rate was accompanied by simultaneous transient reductions in left ventricular systolic pressure, maximal rate of rise of left ventricular pressure and a concomitant increase in left ventricular end-diastolic pressure. It was concluded that the transient hypotensive effect of NaC is due to its myocardial depressant action. NaC exhibited negative inotropic and chronotropic effect on isolated perfused rabbit heart, an antispasmodic effect on smooth muscle of dog's intestine *in vivo* and of vas deferens of guinea-pig *in vitro* but no effect on the rectus abdominis muscle of frog or its response to cholinergic stimulation.

Key words : sodium curcumin hypotension myocardial depression

INTRODUCTION

The rhizome of *Curcuma longa* Linn. (Zingiberaceae) has been employed since time immemorial by Ayurvedic and Unani practitioners against clinical inflammations (1). Curcumin, the colouring principle of the rhizome of *C. longa* (turmeric), was isolated by Vogel and Pelletier in 1815 (See 7). In recent years the anti-inflammatory activity of curcumin (3, 10) and its natural (9) as well as some semi-synthetic analogues (4) have been investigated. Curcumin (2 to 3 g/kg) was reported to be free from toxicity in rats (3, 10). The clinical utility of curcumin in patients of rheumatoid arthritis is also being evaluated (2, 6, 8). In view of this we have studied some aspects of pharmacodynamic profile of sodium salt of curcumin (NaC) *in vivo* and *in vitro*.

MATERIAL AND METHODS

The blood pressure of chloralose-anaesthetized cats and pentobarbitone-anaesthetized dogs was recorded from left femoral artery using either Statham P 23 AC pressure transducer connected to Grass Model 7 Polygraph or U-Mercury manometer-kymograph assembly.

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The standard limb lead II electrocardiogram was recorded on polygraph. Left ventricular pressure of artificially ventilated and left thoracotomised cats was measured by inserting a metal cannula into the myocardium of left ventricle. The metal cannula was attached by means of a pressure tubing to a Statham P 23AA pressure transducer which in turn was connected to polygraph. The maximal rate of rise of left ventricular pressure (dP/dt) was derived by means of a resistance-capacitance differentiating circuit and it was simultaneously recorded on polygraph. The rate and amplitude of respiration, intestinal motility of dogs and tone of nictitating membrane of cats were recorded on kymograph. The cannulated left femoral vein was used for administration of drugs. The effect of intraduodenally administered NaC on blood pressure and electrocardiogram of cats was also studied.

The standard pharmacological *in vitro* techniques viz., rabbit heart (Langendorff) perfusion, rat hind limb perfusion, guinea-pig vas deferens and frog rectus abdominis muscle were employed to study the effect of NaC on isolated cardiac, smooth and skeletal muscles. Solution of NaC in normal saline or distilled water was used for the study (pH, 9.0). As a solvent control, 1.25×10^{-7} M NaOH solution (pH, 9.0) was used whenever necessary.

RESULTS AND DISCUSSION

NaC (1–10 mg/kg, i.v.) produced a dose-dependent but transient fall in blood pressure and heart rate of anaesthetized dogs and cats. The reductions in blood pressure and heart rate of anaesthetized cats ($n=12$) in response to 1, 3 and 10 mg/kg were 0.4 ± 0.7 , 13.2 ± 1.7 , 25.4 ± 3.0 mm Hg and 0.4 ± 0.6 , 9.8 ± 1.6 , 23.4 ± 3 , 4 beats/min., respectively, and the corresponding changes in anaesthetized dogs ($n=6$) were 1.7 ± 0.9 , 12.0 ± 2.1 , 27.8 ± 4.7 mm Hg and 0.75 ± 1.22 , 8.3 ± 1.8 , 19.2 ± 3.5 beats/min., respectively. The present finding is not in agreement with the earlier reports (5,10). However, the hemodynamic effects of NaC were not seen when it was slowly infused over a period of one min. The rate of i.v. administration is thus an important determinant of responses. No tachyphylaxis was seen, indicating that the effect was direct rather than indirect. The hypotensive and bradycardiac effects of NaC were not antagonised by bilateral vagotomy or after adequate pretreatment with atropine, propranolol or mepyramine ($n=3$, in each case). This excludes the possibility of vagal nerve fibres, muscarinic, β -adrenergic or histaminergic receptors mediating its effects. The role of central nervous system was also ruled out as the drug produced hypotension and bradycardia in spinal cord transected cats ($n=4$). NaC (100 mg/kg) failed to produce hypotension and bradycardia over an observation period of 2 hr when administered intraduodenally into anaesthetized cats ($n=4$). Oral administration of doses of this magnitude as anti-inflammatory medication, would, thus seem to be safe as far as acute cardiovascular effects are concerned.

In open-chest anaesthetized cats, the hypotensive and bradycardiac effects of NaC were accompanied by simultaneous reduction of maximal rate of rise of left ventricular

TABLE I : Peak hemodynamic changes in open-chest anaesthetized cats induced by sodium curcuminat.^a

Drug	Dose (mg/kg i.v. bolus)	Heart rate (beats/min)	Mean arterial blood pressure (mm Hg)	dP/dt ^b (mm Hg/sec)	Systolic ventricular pressure (mm Hg)	LVEDP ^c (mm Hg)
Control	—	207.5 ± 4.6	130.5 ± 3.6	6048 ± 574	162.2 ± 5.3	6.0 ± 0.8
Sodium curcuminat	1	205.7 ± 4.5	129.4 ± 2.4	5984 ± 564	156.1 ± 3.9	6.1 ± 0.6
	3	198.6 ± 4.7* (12.9 ± 1.8)	113.7 ± 3.1** (12.4 ± 1.8)	5482 ± 518** (10.3 ± 1.5)	145.0 ± 4.3* (10.0 ± 1.5)	7.1 ± 1.1* (9.7 ± 2.0)
	10	186.7 ± 4.8** (27.9 ± 2.9)	93.4 ± 5.1* (29.4 ± 2.8)	4705 ± 450** (26.6 ± 2.4)	123.1 ± 5.5** (29.0 ± 2.5)	8.1 ± 1.2** (27.0 ± 2.3)
1.25x10 ⁻⁷ M Sodium hydroxide solution (pH=9.0)	0.2 ml/kg	207.4 ± 4.3	130.7 ± 4.4	6045 ± 573	162.8 ± 4.7	6.1 ± 0.7

a. Injection volume 0.2 ml/kg. Parentheses indicate the duration of the changes in sec. Values shown are mean ± S.E. (n=7). All changes following injection of 3 and 10 mg/kg dose of sodium curcuminat are significantly different from control values; P values: * < 0.005 ** < 0.001

b. dP/dt = maximal rate of rise of left ventricular pressure.

c. LVEDP = Left ventricular end-diastolic pressure.

TABLE II : Effect of sodium curcuminat on isolated perfused rabbit heart.^a

Drug	Dose (mg)	Heart rate (beats/min)	Amplitude of contraction (mm)	Coronary flow (ml/min)
Nil	—	110.6 ± 2.8	65.2 ± 2.9	11.2 ± 0.3
Sodium curcuminat	1	110.0 ± 2.8	64.4 ± 2.8	11.3 ± 0.3
	3	104.6 ± 2.9*** (15 ± 1.3)	60.8 ± 2.7*** (13.4 ± 1.4)	10.8 ± 0.3*** (206 ± 11)
	10	97.4 ± 2.3*** (26.0 ± 3.4)	53.4 ± 3.0** (29.6 ± 3.8)	10.6 ± 0.3*** (333 ± 26)
	30	81.4 ± 2.9*** (52.0 ± 6.7)	44.6 ± 3.7*** (51.6 ± 5.5)	10.1 ± 0.3* (519 ± 26)
1.25x10 ⁻⁷ M sodium hydroxide solution (pH = 9.0)	0.6 ml	111.2 ± 2.9	65.6 ± 2.9	10.2 ± 0.3** (550 ± 28)

^aDrug was injected in 0.6 ml volume. Parentheses indicate the duration of the changes in sec. Values shown are mean ± S.E. (n=5). All changes following bolus injection of 3, 10 and 30 mg of sodium curcuminat are (t-test) significantly different from control;

P values : * < 0.01 ** < 0.005 *** < 0.001

pressure (dP/dt) and left ventricular systolic pressure. There was a concomitant increase in left ventricular end-diastolic pressure (LVEDP) (Table I). NaC did not modify the pattern of electrocardiogram of cats. The reduction in heart rate, dP/dt and left ventricular systolic pressure and the concomitant increase in LVEDP suggest that NaC is a myocardial depressant. All the hemodynamic changes including heart rate, blood pressure, dP/dt, LVEDP and left ventricular systolic pressure had an approximately equal time of onset (5 to 7 sec at 10 mg/kg dose) and duration (Table I). Moreover the recovery of blood pressure to basal level was temporally well correlated with simultaneous recovery of dP/dt, LVEDP, left ventricular systolic pressure and heart rate to their respective basal values. The existence of good temporal relationship among NaC induced changes in the above hemodynamic variables suggests that its transient hypotensive effect is due to myocardial depressant action. The myocardial depressant action of NaC was further confirmed in *in vitro* rabbit heart perfusion. NaC (1-30 mg) produced dose-dependent transient reduction in rate and amplitude of contraction of rabbit heart (Table II). The effects of drug observed *in vivo* and in Langendorff preparation were not ascribable to pH of drug solution, as equal volume of control pH solution was without such effects (Table I and II).

A relatively prolonged reduction in the coronary flow was also seen with NaC in perfused rabbit heart (n=5). However, control pH solution also produced prolonged constriction of coronary vessels (Table II). The comparable vasoconstrictor effects of NaC and alkaline pH *per se* were also seen in rat hind limb perfusion. The mean per cent reduction in outflow with 30 mg dose of NaC in 0.6 ml volume and 0.6 ml of 1.25×10^{-7} M sodium hydroxide solution were 29 ± 4.4 (n=3) and 31.1 ± 3.4 (n=3) with an average duration of 9 min 40 sec ± 17 sec (n=3) and 10 min 16 sec ± 25 sec (n=3) respectively. This suggests that NaC *per se* is probably devoid of any inherent spasmodic effect on smooth muscle of blood vessels. In fact NaC was spasmolytic on the smooth muscle of guinea-pig vas deferens and intestine of anaesthetized dog. EC 50s of NaC against spasmogenic effects of acetylcholine (1-2 μ g/ml) and histamine (10-20 μ g/ml) on isolated vas deferens of guinea-pig were 132 ± 3.7 (n=3) and 142 ± 10.3 (n=5) μ g/ml respectively, while doses between 1 to 10 mg/kg produced dose-dependent relaxation of intestine in anaesthetized dogs (n=5). The alkaline pH had no demonstrable effect on the intestinal motility of dogs and isolated vas deferens of guinea-pig. NaC did not exhibit any effect on respiration of dogs or nictitating membrane of cats and on isolated rectus abdominis muscle of frog of its response to acetylcholine.

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