STUDIES ON LOCAL ANAESTHETIC AND ANTIARRHYTHMIC ACTIONS OF 1-ISOPROPYLAMINO-3-(4-INDANOXY)-2-PROPANOL HCl (USVC-6524), A NEW BETA-ADRENOCEPTOR ANTAGONIST

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Summary: 1-isopropylamino-3-(4-indanoxy)-2-propanol (USVC-6524), a new beta-adrenoceptor blocking agent, was found to attenuate both adrenline-and ouabain-induced ventricular arrhythmias in the anaesthetized dog. However, the doses required to combat the latter arrhythmia were far in excess of those used in the former test-procedure. The drug also exhibited local anaesthetic activity as tested by the rabbit corneal (surface anaesthesia), guinea-pig wheal (infiltration anaesthesia) and rat tail-pinch (conduction anaesthesia) methods. Comparison of these results with those obtained with propranolol showed that USVC-6524 was not stronger as local anaesthetic but was stronger in its ability to suppress digitoxic arrhythmia and to induce beta-adrenoceptor blockade. Considering these findings together with the observations made by other workers, it is suggested that : (i) the effectiveness of USVC-6524 in adrenaline-induced arrhythmia is due to its beta-adrenoceptor antagonism; (ii) while local anaesthetic activity may be important for its ability to suppress digitoxic arrhythmias, beta-receptor blockade is relevant to this antiarrhythmic effect.

Key words: USVC-6524 beta-adrenoceptor blocking agent
antiarrhythmic local anaesthesia

INTRODUCTION

All the beta-adrenoceptor antagonists are effective in arrhythmias resulting from excessive cardiac beta-receptor stimulation. However, differences exist in members of this group of drugs in respect of their ability to attenuate arrhythmias arising from digitalis intoxication. For example, propranolol, pronethalol and alprenolol are effective in eliminating ouabain-induced ventricular tachycardia (12, 15), whereas practolol, sotalol and N-isopropyl-1-nitrophenyle ethanolamine (INPEA) are ineffective (7, 9, 24, 26). Local anaesthetic/membrane stabilizing activity, which is the common property of the former group, is not exhibited by the latter (14). 1-isopropylamino-3-(4-indanoxy)-2- propanol (USVC-6524) is a recently described beta-adrenoceptor blocking agent which is approximately ten times more potent than propranolol (11). Since its antiarrhythmic and local anaesthetic properties have not been investigated, the present work has been undertaken. Propranolol was used as a standard drug for comparison

MATERIALS AND METHODS

Antiarrhythmic activity:

Andrenaline-induced arrhythmias: Twelve mongrel dogs of either sex weighing between 10 and 18 *kg* were anaesthetized with pentobarbitone sodium (30 *mg/kg* iv). Arrhythmias

were produced by rapid intravenous injection of adrenaline (100 $\mu g/kg$) at intervals of 15 to 30 min (25). One group of 4 animals served as control while the remaining two groups (4 animals in each group) received USVC-6524 in doses of either 30 or 100 $\mu g/kg$. Electrocardiogram (lead II) was recorded every 30 sec for 4 min following the administration of adrenaline. All beats in each successive 30-sec period were counted and categorized as sinus and ectopic beats and expressed graphically as beats per min.

Ouabain-induced ventricular tachycardia: Seventeen mongrel dogs of both sexes weighing between 10 and 16 *kg* were anacesthetized with choloralose (80 *mg/kg* iv) and pentobarbitone sodium (10 *mg/kg* iv). Lead II of electrocardiogram was recorded. Toxic doses of ouabain were given intravenously in a graded manner (25) till persistent ventricular tachycardia developed. In the control group of 7 animals, the course and duration of arrhythmia was observed. In the ramaining two groups (5 animals in each group), USVC-6524 or propranolol was given intravenously at the rate of 0.5 *mg/kg/min* till restoration to normal sinus rhythm occurred.

Local anaesthtic activity :

Local anaesthetic activity of USVC-6524 in different concentrations was compared with that of propranolol by the following test-procedures: (i) rabbit's corneal reflex for surface anaesthesia (5); (ii) guinea-pig's wheal for infiltration anaesthesia (4); and (iii) rat's tail-pinch method for conduction anaesthesia (2). These techniques have been described in detail in a recent communication (16) The results obtained with different concentrations were plotted on a semilogarithmic scale (simple plots) and EC_{50} values for each drug were determined.

Drugs:

The following drugs were used: (±) propranolol hydrochloride (I.C.I.); isopropylamino-3-(4-indanoxy)-2-propanol hydrochloride (USVC-6524; US.. Vitamin Corp.); 1-adrenaline (Ward, Blenkinsop and Co.); ouabain (E. Merck). All the drugs were dissolved in isotonic saline and solutions were prepared on the day of the experiment.

RESULTS

Effect on adrenaline-induced arrhythmias : In control animals, adrenaline produced runs of uni-and multi-focal ventricular tachycardia interspersed with ectopic premature contractions. The responses were reproducible when adrenaline injection was repeated at intervals of 15 to 30 min. In animals treated 15 min earlier with 100 $\mu g/kg$ of USVC-6524, adrenaline-induced ectopic beats were reduced by about 50%. More marked antagonism of adrenaline response was observed at 30 min and there were only occasional ectopic beats at 45 and 60 min after drug administration as shown in Fig. 1. Similar but less marked antagonism of adrenaline response was elicited following the administration of 30 $\mu g/kg$ of USVC-6524.

Effect on ouabain-induced ventricular tachycardia: Sequential administration of ouabain resulted in a sustained ventricu lar tachycardia. The average dose required was 57 ± 5.7 $\mu g/kg$. In 6 out of 7 control dogs, the arrhythmias lasted for about 20 min and this was followed by

ventricular fibrillation. In one dog the arrhythmia persisted for 2 hr and then spontaneous reversion to normal sinus rhythm occurred. In the second group, USVC-6524 abolised the

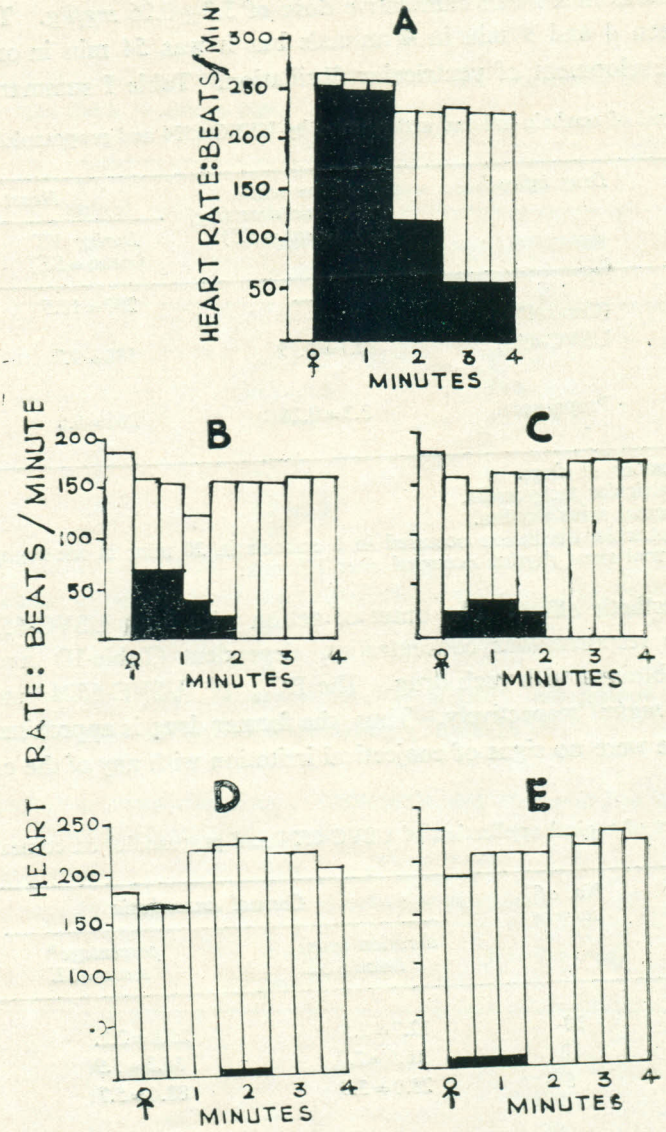

Fig. 1: Antagonism of adrenaline-induced cardiac arrhythmias by USVC-6524 (100 $\mu g/kg$). Data represent the mean of 4 experiments. Each bar represents ectopic (shaded area) and sinus (white portion) beats/min for each successive 30 sec period. Adrenaline was injected at the arrowhead at 0 time. Panel A: Control response to adrenaline prior to USVC-6524. Panels B to E: responses to adrenaline 15, 30, 45 and 60 min after USVC-6524 injection.

arrhythmia in 4 out 5 animals in a mean cumulative dose of 2.1±0.19 *mg/kg* restored norm sinus rhythm. However, the sinus rhythm was of short duration (range: 3-14 min.) One do died of cardiac asystole after administration of USVC-6524. In the third group, propranol suppressed arrhyhmias in a mean cumulative dose of 3.3±0.26 *mg/kg*. The duration of sinu rhythm was between 4 and 9 min in 4 animals but it was 54 min in one animal. One do died due to the development of ventricular fibrillation. Table I summarizes the results.

TABLE I: Reversal of ouabain-induced arrhythmias by USVC-6524 and propranolol in anaesthetized dogs.

Control heart rate/min (mean ± SE)	*Drug infused*	*Cumulative anti-arrhythmic dose (mg/kg) (mean ± SE)*	*Heart rate/min*	
			During VT (mean ± SE)	*After drug(NSR) (mean ± SE)*
178 ± 7.9 (n=7)	Nil (Control*)	—	203 ± 10.5	—
160 ± 9.2 (n=4)	USVC-6524	2.1 ± 0.19	188 ± 9.7	93 ± 6.4
214 ± 13.0 (n=4)	Propranolol	3.3 ± 0.26	266 ± 6.0	104 ± 20.8

n — Number of dogs.
VT — Ventricular tachycardia.
NSR — Normal sinus rhythm.
* — Ventricular fibrillation occurred in 6 animals in 20 min; in one dog spontaneous reversion to normal sinus rhythm occurred after 120 mih.

Surface anaesthetic effect: The onset of action with both USVC-6524 and propranolol was 2-3 min. The response was concentration dependent (Table-II) and a linear dose-response curve was obtained with each drug. The EC_{50} of USVC-6524 and propranolol were 8.6 *mg/ml* and 4.2 *mg/ml* respectively. Thus the former drug is approximately half as potent as the latter. There were no signs of conjectival irritation with any of the concentration of the two drugs used.

TABLE II: Effect of topical application of USVC-6524 and propranolol on corneal reflex in rabbits.

Concentration (%)	*No. of corneas*	*Corneal anaesthesia*		EC_{50}
		duration (min) mean ± SE	*percentage* mean ± SE*	
USVC-6524				
0.5	10	12.7 ± 2.5	25.8 ± 2.2.	
1.0	12	16.6 ± 2.0	54.3 ± 5.9	8.6 *mg/ml*
2.0	6	28.0 ± 3.0	88.4 ± 5.7	
Propranolol				
0.125	5	8.3 ± 3.3	22.1 ± 2.9	
0.25	5	13.3 ± 3.6	27.7 ± 2.6	
0.5	8	20.0 ± 2.8	51.3 ± 7.3	4.2 *mg/ml*
1.0	5	28.7 ± 1.2	85.4 ± 5.4	

* Mean precentage of failure of response (blinking) to the application of hair-aesthesiometer.

Infiltration anaesthetic effect: USVC-6524 and propranolol were approximately equiactive, the EC_{50} values being 2.4 and 2.0 *mg/ml* respectively (Table III). The onset of action with both the drugs was 2-3 min.

TABLE III: Effect of intradermal injection of USVC-6524 and propranolol on the response to light pinch in guinea pigs.

Concentration (%)	*No. of animals*	*Infiltration anaesthesia*		EC_{50}
		duration (min) mean ± SE	*percentage * mean ± SE*	
USVC-6524				
0.125	5	13.0 ± 1.2	17.0 ± 3.5	
0.25	5	19.5 ± 3.5	53.4 ± 8.6	2.4 *mg/ml*
0.5	7	36.0 ± 4.4	84.0 ± 8.0	
Propranolol				
0.125	8	10.0 ± 0.9	24.9 ± 3.3	
0.25	8	26.2 ± 5.9	51.8 ± 11.9	2.0 *mg/ml*
0.5	8	50.0 ± 5.9	96.5 ± 2.6	

* Mean percentage of failure of response (contraction of the surrounding skin) to the application of prick.

Conduction anaesthetic effect: USVC-6524 was slightly less potent than propranolol, the EC_{50} values being 7.4 and 6.0 *mg/ml* respectively (Table IV).

TABLE IV: Conduction anaesthetic effect of USVC-6524 and propranolol as determined by rat's tail-pinch technique.

Concentration (%)	*No. of aninals used*	*Conduction anaesthesia*		EC_{50}
		No. of animals showing anaesthesia	*duration (min)*	
USVC-6524				
0.5	10	3	60	
1.0	10	7	>120	7.4 *mg/ml*
2.0	10	10	>120	
Propranolol				
0.25	10	2	< 30	
0.5	10	3	< 30	6.0 *mg/ml*
1.0	10	7	>120	

DISCUSSION

USVC-6524 suppressed both adrenaline-and ouabain-induced arrhythmias. Howe the latter arrhythmia was attenuated in doses which were more than 20 times of those requ in the former test-procedure. Further, the antagonism of adrenaline-induced arrhythmia observed for about 1 hr, whereas digitalis-induced ventricular tachycardia was eliminated o for a few min. These findings suggest that mechanisms involved in adrenaline and ouab arrhythmias are not the same.

Somani and Lum (25) postulated that adrenergically-induced ventricular arrhythm were due to activation of beta receptors in the heart. Davis and Temte (6) studied the effe of adrenaline on transmembrane potentials of purkinje fibers of the dog's heart and observ that adrenaline increased both the rate and magnitude of diastolic depolarization and this w completely blocked by propranolol. Suppression of adrenaline-induced arrhythmias by USV 6524 in dose-range which is reported by Levy and Wasserman (11) to be just adequate to i duce cardiac beta-receptor blockade, provides support to the concept that specific beta-adr noceptor blockade is responsible for antiarrhythmic effect in this test procedure.

It has been demonstrated that only those beta-adrenoceptor blocking agents are effecti in ouabain-induced ventricular tachycardia which exhibit local anaesthetic/membrane stabiliz activity (14, 17). Hence the efficacy of these drugs in arrhythmias following digitalis intoxic tion is attributed to their potent local anaesthetic activity (10, 13) and to their ability to al the rate of depolarization of action potential of cardiac muscle (27). However, evidence accumulating to indicate that beta-adrenoceptor blockade may contribute to the effectiveness of drug in arrhythmias due to digitalis intoxication. It has been repeatedly recognized that re duction of adrenergic influences on the heart either by cardiac denervation or by drugs such a reserpine and TM-10 inhibits digitalis arrhythmias (3, 8, 18, 21, 23). On the other hand administration of adrenergic drugs aggravates digitoxic arrhythmias (20, 22). Further, of th isomers of propranolol having equial local aneesthetic activity, the laevo variety, which is mor potent beta-adrenoceptor antagonist, exhibits activity stronger than of dextro isomer in com bating digitalis arrhythmia (1). Raper and Wale (19) reported that beta-adrenoceptor blcking doses of propranolol and sotalol were effective in converting digitalis arrhythmias in 20 per cen of experiments. Although propranolol and USVC-6524 were not effective in beta-recepto blocking doses in any experiment in this study, relevance of beta-receptor blockade in attenuatin ouabain-induced arrhythmia cannot be precluded. USVC-6524 is stronger than propranolo inducing beta-receptor blackade (11) and it is also about one and a half times more potent than propranolol in converting digitalis arrhythmia into normal sinus rhythm (Table I). However, its local anaesthetic activity as determined in various tests is not greater that of propranolol. It is thus possible that the greater efficacy of USVC-6524 than that of propranolol in counteract- ing digitoxic arrhythmia is the consequence of the difference in beta-adrenoceptor blocking potencies.

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