SHORT COMMUNICATION

A COMPARATIVE STUDY OF 4(2-HYDROXY-3-ISOPROPYL AMINOPROPOXY) INDOLE (VISKEN) AGAINST OUBAIN-INDUCED CARDIAC ARRHYTHMIAS IN ANAESTHETISED DOGS

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Summary: The effect of 4(2 hydroxy-3-isopropyl aminopropoxy) indole (Visken) was compared with propranolol on oubain-induced cardiac arrhythmias in anaesthetised dogs. Pretreatment with the drugs increased the fatal dose of oubain while administration of the drug after marked ventricular arrhythmias were induced caused prolongation of survival period without restoring stable normal sinus rhythm. This antiarrhythmic effect of the drugs appears to be due to non-adrenergic mechanism.

Key words: oubain cardiac arrhythmias Visken propranolol

INTRODUCTION

4(2-Hydroxy-3-isopropylaminopropoxy) indole (Visken), a recent beta-adrenergic blocking agent (2) is reported to be highly specific and potent in its beta-adrenergic blocking actions. Beta-adrenergic blockers including Visken have been known to possess activity against various types of experimental cardiac arrhythmias (1, 2, 4, 8, 10, 11 ,12). The present investigation was undertaken to assess the anti-arrhythmic activity of Visken in camparison with propranolol against oubain-induced arrhythmias.

MATERIALS AND METHODS

Dogs of either sex weighing 5-7 *kg*. were used. The animals were anaesthetised with phenobarbitone sodium (120-130 *mg/kg* iv) All drugs were administered through cannulated femoral vein. Carotid blood pressure was recorded as usual and electrocardiographs were recorded from lead II. Ventricular arrhythmias were induced by using the technique described by Somani and Lum (12) with some modification. All doses of oubain were administered by slow intravenous infusion lasting for 10 to 15 min as in preliminary experiments rapid injections were found to cause sudden cardiac arrest Initial dose of 40 $\mu g/kg$ was used as a loading dose and the dog was observed for 30 min. If no alteration in cardiac rhythm was seen, an additional dose of 20 $\mu g/kg$. followed by doses of 10 $\mu g/kg$ at 15 min intervals were given till a persistent ventricular arrhythmia was produced.

The effects of beta-blockers were studied in two ways;

1. The dogs were pretreated with 5 *mg/kg* doses of propranolol and Visken to see the

manner in which they modify oubain-induced arrhythmias. The drugs were given by slow infusion over a period of 10 min followed by doses of oubain as described above to determine the fatal dosse. Oubain was in this manner titrated against the blocking drugs.

2. In six dogs ventricular arrhythmias were induced by oubain as in control experiments. Several min after these arrhythmias were persistently observed, propranolol and Visken were administered in doses of 5 *mg/kg*.

RESULTS

Both Visken and propranolol were found to cause increase in the total dose of oubain required for the terminal fatal effect (Table I).

TALBE I: Effect of pretreatment with propranolol (5 *mg/kg*) and Visken (5*mg/kg*) on the fatal doses of oubain in anaesthetised dogs.

Dog	*Control (oubain alone μg/kg)*	*Pretreatment with propranolol (oubain μg/kg.)*	*Pretreatment with Visken (oubain μg/kg)*
1	40	70	70
2	40	70	60
3	60	80	70
4	40	70	70
5	60	70	80
Mean	48	72	70
S.D. ±	10.95	4.472	7.61

Similarly both Visken (5 *mg/kg*) and propranolol (5 *mg/kg*) were found to delay the fatal effect of oubain i.e. instead of control 30 to 45 min the dogs survived for 2 to 3½ hr after the administration of arrhythmic doses of oubain. In all experiments the sinus rhythm was restored only during the terminal few min of the infusion of these beta-blockers, and the arrhythmia returned on completion of the infusion The animals finally developed fatal ventricular arrhythmia like the control animals.

DISCUSSION

The present investigation has shown propranolol and Visken to significantly increase the total dose of oubain and to cause marked prologation in the duration of survival period after the typical ventricular arrhythmias were induced. This finding is discordant with that of Clark and Saameli (2) who also reported effectiveness of Visken against such arrhythmias but found that the heart reverted to sinus rhythm following Visken. In our studies normal sinus rhythm was restored only for a few min and persistent ventricular arrhythmia then returned; the beta-blocker prolonging only the survival period. Somani (13) had similar findings in his studies with another beta-adrenergic blocker, I.C.I. 45763.

The mechanism of action of beta-adrenergic blocking drugs against cardiac arrhythmias caused by cardiotonic glycosides is a subject of controversy. However, the fact that doses required for antagonising these arrhythmias are several times higher than those which are required to block arrhythmias induced by adrenergic mechanism is a strong point in favour of nonadrenergic mechanism being involved (7, 12, 14, 15). This is further borne out by the fact, that drugs like INPEA, MJ 1999 and PMI (paramethylisoprenaline) which are potent beta-adrenergic blocking agents have no significant effect on oubain-induced arrhythmias. Resolution of the beta-adrenergic blocking agents into laevorotatory and dextrorotatory isomers has provided ample evidence to distinguish the beta-adrenergic blocking effects from nonspecific antiarrhythmic action. Thus, Lucchesi (6) found that dextro-propranolol suppressed digitalis-induced arrhythmias in the same dose range as the racemic mixture, although the dextroisomer is about 40 times less potent in producing beta-receptor blockade. Results obtained with dextro and laevo isomers of propranolol and H 56/28 also showed that both isomers are equally effective against digitalis arrhythmias, whereas the laevoisomers were more effective against adrenergically mediated arrhythmias and were more potent in producing beta-receptor blockade (3, 5, 7).

Barret and Cullum (1) are of the view that the beta-blocking activity alone will not reverse oubain arrhythmias, though such a property may be an advantage in compounds which also possess local anaesthetic property. Saameli(9) found beta-adrenergic blocking activity of Visken to be more than 4 times greater than that of propranolol, and in his studies the two drugs showed similar ratio of activity against oubain-induced arrhythmias, though Visken showed a considerably lower quinidine like activity. Saameli (9) therefore, has concluded that beta-sympathetic mechanisms play a greater part in digitalis arrhythmias than has hitherto been assumed. However, in the present investigation Visken and propranolol were found to be equiactive against oubain-induced cardiac arrhythmia, a finding which lends support to the earlier reports attributing this antiarrhythmic property of beta-adrenergic block agents to effects other than beta-adrenergic blackade.

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