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MONENSIN ENHANCES DIGOXIN-INDUCED ARRHYTHMIAS IN GUINEA-PIGS

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ABSTRACT :

Effects of pretreatment with monensin (150 µg/kg), atenolol (0.3 mg/kg), atenolol plus monensin, verapamil (0.38 mg/kg), verapamil plus monensin,glibenclamide (0.38 mg/kg) and glibenclamide plus monensin on the dose of digoxin required to induce premature ventricular contractions (PVCs) in anaesthetized guinea-pigs were studied. Monensin reduced while atenolol increased the dose of digoxin required to produce PVCs. Atenolol plus monensin increased the dose of digoxin required to produce PVCs in presence of monensin alone. Verapamil reduces the arrhythmogenic effect of monensin on digoxin. Glibenclamide antagonises the effect of monensin on digoxin induced PVCs. From the present data it could be concluded that, monensin enhances digoxin-induced arrhythmias in guinea-pigs. The enhancement of arrhythmias in presence of monensin may be due to catecholamine release by monensin and or may be due to the decrease of action potential duration which in part result from opening of ATP dependent K^+ channels in guinea pig ventricular muscle these channels, which blocked by glibenclamide.

INTRODUCTION

Monensin is a carboxylic ionophore with primary selectivity for transporting Na^+ across biological membranes (1). Pharmacological doses of monensin produce several cardiovascular effects, including increase of myocardial contractility(2). Coronary blood flow and Cardiac output (3).

Cardiac arrhythmias are frequent and serious complications of clinical use of digitalis glycosides (4). These glycosides-induced cardiac arrhythmias are due to both direct actions on the myocardium and indirect effects involving the autonomic nervous system. It is generally

accepted that an inhibition of sarcolemmal Na^+, K^+-ATPase, the membrane sodium pump, is causally related to the direct arrhythmogenic action (5,6). Reports by several investigators showed that in vitro-experiments, the toxicity by cardiac glycosides is enhanced by exposure of the tissue to inotropic concentrations of monensin (7).

The aim of this project was to study the effect of monensin on digoxin induced arrhythmias in guinea pigs. Since the glycosides are the drugs of choice for managing chronic congestive heart failure, and since monensin might find a therapeutic role in managing this diseases we folt justified in selecting this particular interaction for study.

MATERIAL AND METHODS

This work requaired 10 groups of unconsciousness guinea-pigs. Each group included from 4-6 guinea-pigs of either sex weighing 400-700 gm.

Experimental procedure :

All guinea-pigs were anaesthetized with pentobarbital sodium (35 mg/kg), additional doses were administered intraperitoneally when required. The Jugular vein at one side was exposed, canulated and connected to peristaltic pump to adjust digoxin administration.

Digoxin solution (125 µg/ml) was continuously infused at the rate of (1 ml/4 min.). The amount of digoxin required per Kg body weight for the onset of premature ventricular contractions (PVCs), was determined in control and drug-treated animals. The drugs were injected intravenously. Pretreatment for verapamil, monensin or atenolol was 15 min. prior digoxin administration.

Group 1 : This group was used to determine the dose of digoxin which induced PVCs in guinea-pigs under normal conditions.

Group 2 : This group was used to determine the dose of digoxin which induced PVCs in guinea-pigs pretreated with monensin (150 µg/kg b.w.).

Group 3 : This group was used to determine the dose of digoxin which induced PVCs in guinea-pigs pretreated with atenolol (0.3 mg/kg).

Group 4 : This group was used to determine the amount of digoxin which induced PVCs in guinea-pigs pretreated with verapamil (0.38 mg/kg).

Group 5 : In this group, glibenclamide (0.38 mg/kg) was administered orally for 2 days. Then, digoxin was administered as prescribed before and to determine the dose of digoxin which induced PVCs in the presence of glibenclamide.

Group 6 : This group was used to determine the dose of digoxin which induced PVCs in guinea-pigs pretreated with glibenclamide (0.38 mg/kg) and monensin (150 µg/kg).

Group 7 : This group was used to determine the dose of digoxin which induced PVCs in guinea-pigs pretreated with atenolol (0.3 mg/kg) and monensin (150 µg/kg).

Group 8 : This group was used to determine the dose of digxin which induced PVCs in guinea-pigs pretreated with verapamil (0.38 mg/kg) and monensin (150 µg/kg).

Group 9 : In this group, ethanol 50% monensin solvent was injected in jugular vein followed by I.V. infusion of digoxin. The dose of digoxin which induced PVCs was then determined.

Group 10: In this group, ethanol 50% was injected in jugular vein, followed by I.V. infusion of digoxin solvent (ethanol + polyethanol glycol + water) at rate 1 ml/4 min. for 30 min.

Recording of electrocardiographic pattern :

Electrocardiographic (ECG) patterns were recorded before and after administration of each drug (at different time intervals) by means of an electrocardiograph (The FUKUDA M.E. Cardiosuny 501) using standard Lead II. The negative (-ve) electrode was connected to the right limb of guinea pig, the positive (+ve) electrode was connected to the left hind limb, while the grounding lead was connected to the right hind limb. The apparatus was adjusted at a speed of 25 mm/sec.

Drugs used :

Digoxin (Lanoxin, wellcome), verapamil (Isoptin, Knoll), atenolol (Sigma, Germany), glibenclamide (Daonil, Hoechst Germany).

Statistical calculation :

Student's "t" test were used for statistical calculation. The data were expressed as mean ± SEM.

RESULTS

1. Arrhythmogenic activity of digoxin on guinea-pigs in the absence and the presence of monensin :

In these experiments, it was found that intravenous infusion of 0.85 ± 0.02 mg/kg b.w. digoxin, at a rate of 125 µg/1 ml/min., was the dysrhythmic dose; the dose that induced premature ventricular contraction (PVCs) and multiple ventricular ectopics as shown in table (1).

Furthermore, another group of guinea pigs were pretreated by intravenous injection of monensin in a dose of 150 µg/kg.b.w. This treatment with monensin caused a significant reduction of the dose of digoxin required to induce arrhythmias as presented in Table (1) and

Table (1) : Effect of pretreatment with monensin (150 µg/kg) on the dose of digoxin required to induce premature ventricular contractions (PVCs) in anaesthetized guinea-pigs

Treatment	No. of experiments	Dose of digoxin induced PVCs
Digoxin alone	6	0.858±0.02 mg/kg
Monensin (150 µg/kg) + Digoxin	5	0.47*±0.01 mg/kg

Values are expressed as mean ± S.E. of mean
* Significant difference from digoxin alone treated group at P<0.05

Table (2) : Influence of pretreatment with atenolol or atenolol plus monensin on the dose of digoxin required to induce premature ventricular contractions (PVCs) in anaesthetized guinea-pigs

Treatment	No. of experiments	Dose of digoxin induced PVCs
Digoxin alone	6	0.858±0.02 mg/kg
Monensin (150 µg/kg) + Digoxin	5	0.47*±0.01 mg/kg
Atenolol (0.3 mg/kg) + Digoxin	6	1.023**±0.08mg/kg
Atenolol (0.3 mg/kg) + Monensin (150 µg/kg) + Digoxin	5	0.603***±0.043mg/kg

Values are expressed as mean ± S.E. of mean
* Significant difference from digoxin alone treated group at P<0.05
** Significant difference from digoxin alone treated group at P<0.05
*** Significant difference from monensin + Digoxin treated group at P<0.05

shown in table (2).

2. Effect of atenolol or atenolol plus monensin on digoxin induced arrhythmias :

In six pentobarbital anaesthetized guinea-pigs, the effect of intravenous injection of 0.3 mg/kg atenolol on both ECG pattern and the dose of digoxin required to induce arrhythmias was studied. Atenolol in a dose of 0.3 mg/kg induced a significant decrease in the heart rate from 238±8 to 190±6 beats/min. Moreover, the dose of digoxin required to induce arrhythmias in guinea-pigs, was significantly increased from 0.85±0.02 to 1.02 ± 0.06 mg/kg in animals pretreated with atenolol as summarized in Table (2).

The effect of intravenous infusion of digoxin at a rate of 125 µg/ml/4 min. in guinea-pigs pretreated with atenolol (0.3 mg/kg) and monensin (150 µg/kg) was studied. Atenolol induced a significant decrease of heart rate from 231 ± 9 to 179 ± 11 beats/min. While, monensin had no significant effect on the heart rate when administered to animals pretreated with atenolol. Moreover, in previously mentioned pretreated animals premature ventricular contractions (PVCs) were observed after intravenous infusion of 0.6 ± mg/kg digoxin as summarized in Table (2).

3- Effect of verapamil or verapamil plus monensin on digoxin induced arrhythmias :

To emphasize the effect of verapamil on the enhanced effects of monensin on digoxin induced arrhythmias, the following series of experiments were done.

In the first series of experiments, the effect of intravenous administration of verapamil in a dose of 0.38 mg/kg on both ECG pattern

and the dose of digoxin required to induce arrhythmias were studied. Verapamil induced a significant decrease in the heart rate from 255 ± 19 to 225 ± 16 beats/min. In addition, the dose of digoxin required to induce arrhythmias was significantly decreased from 0.85 ± 0.02 to 0.6 ± 0.06 mg/kg as summarized in Table (3).

4- Effect of glibenclamide or glibenclamide plus monensin on digoxin induced arrhythmias :

As shown in table (4) oral administration of glibenclamide (38 mg/kg) to guinea-pigs, had no effect on heart rate. Premature ventricular contractions (PVCs) were observed at a dose of 0.65 ± 0.06 mg/kg b.w. digoxin as summarized in Table 4.

Furthermore, the effect of intravenous infusion of digoxin to guinea-pigs pretreated with 0.38 mg/kg glibenclamide and 150 µg/kg monensin was studied. Premature ventricular contractions (PVCs) were observed after administration of 0.52 ± 0.04 mg/kg digoxin as summarized in Table (4).

DISCUSSION

The results of this study show that monensin significantly decreased the dose of digoxin required to induce arrhythmias in guinea-pigs. Monensin, a carboxylic ionophore with selectivity for Na^+ increases sodium influx by transporting the ion down its concentration gradient acros the cardiac membrane (1). In addition, it was reported that monensin increase Na^+ influx and in turn reduce the reserve capacity of sodium pump. This inhibition of sodium pump reserve capacity would sensitize the myocardium to digitalis induced arrhythmias (8). Several investigators have suggested that the mechanism of digitalis-induced arrhythmias involve calcium overload resulting from sodium pump

Table (3) : Influence of pretreatment with verapamil alone or verapamil plus monensin on the dose of digoxin required to induce premature ventricular contractions (PVCs) in anaesthetized guinea-pigs

Treatment	No. of experiments	Dose of digoxin induced PVCs
Digoxin alone	6	0.858±0.02 mg/kg
Monensin (150 µg/kg) + Digoxin	5	0.47*±0.01 mg/kg
Verapamil (0.38 mg/kg) + Digoxin	4	0.60**±0.06 mg/kg
Verapamil (0.38 mg/kg) + Monensin (150 µg/kg) + Digoxin	5	0.56±0.06 mg/kg

Values are expressed as mean ± S.E. of mean
* Significant difference from digoxin alone treated group at P<0.05
** Significant difference from digoxin alone treated group at P<0.05

Table (4) : Influence of pretreatment with glibenclamide alone or glibenclamide plus monensin on the dose of digoxin required to induce premature ventricular contractions (PVCs) in anaesthetized guinea-pigs

Treatment	No. of experiments	Dose of digoxin induced PVCs
Digoxin alone	6	0.858±0.02 mg/kg
Monensin (150 µg/kg) + Digoxin	5	0.47*±0.01 mg/kg
Glibenclamide (0.38 mg/kg) + Digoxin	3	0.65**±0.06 mg/kg
Glibenclamide (0.38 mg/kg) + Monensin (150 µg/kg) + Digoxin	4	0.522±0.04 mg/kg

Values are expressed as mean ± S.E. of mean
* Significant difference from digoxin alone treated group at P<0.05
** Significant difference from digoxin alone treated group at P<0.05

inhibition, an elevation of intracellular Na+ and ensuring changes in Na^+/Ca^{2+} exchange reaction (9,10). This calcium overload may produce release of Ca^{2+} into the myoplasm from intracellular storage sites, deciting oscillatory changes in ionic conductance of the sarcolemma, transient inward currents and oscillatory after potential. Oscillatory after potential, then trigger arrhythmogenic contraction.

Pretreatment of guinea-pigs with intravenous injection of 0.3 mg/kg atenolol 15 min. before administration of digoxin induced a significant increase in the dose of digoxin required to cause arrhythmias. This effect may be attributed to reduction of sympathetic tone as a result of atenolol administration. This proposal was in agreement with the observation of (11) who noted that the cardiotoxic action of digitalis is mediated, at least in part by an action on adrenergic innervation of the heart. Furthermore, it was reported that the reduction of adrenergic nervous influences on the heart reduced the capacity of digitalis to produce arrhythmias (12).

In addition, guinea-pigs pretreated with 0.3 mg/kg atenolol followed by monensin required a more amount of digoxin to induce arrhythmias than in animals pretreated with monensin alone. This effect may be due in part to the blockade of B-adrenergic activity of catecholamines released under the effect of monensin. Consequently, the capacity of digoxin to produce arrhythmias was decreased as a result of reduction of adrenergic nervous influences on the heart (12). Several investigators noted that monensin causes the release of catecholamines in myocardial tissue (2,3,13,14).

Pretreatment of guinea-pigs with intravenous injection of 0.38 mg/kg verapamil 15 min. before administration of digoxin induced a significant decrease in the dose of digoxin required to cause arrhythmias. This effect may be due to an increase of digoxin plasma level under the effect of verapamil. Previous studies reported that in patients receiving verapamil

and digoxin, they show a higher level of digoxin plasma level (15).

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المونتسين يعزز الإضطرابات المستحدثة بالديجيتالا فى ضربات قلب خنازيرغينيا

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فى هذا البحث تم دراسة تأثير المعالجة الأولية بكل من المونتسين منفردا ومع الأتينولول - والمونتسين والجليبنكلاميد منفردا ومع الفيرابااميل والجيبنكلاميد منفردا ومع المونتسين على كمية الديجيتالا اللازمة لإستحداث خفقات البطين الغير كاملة فى خنازير غينيا المخدرة.

وقد اظهرت نتائج البحث أن المونتسين يعزز حدوث الإضطرابات المستحدثة فى ضربات القلب بتخفيض الجرعة اللازمة مع الديجيتالا بينما يحدث العكس فى حالة الأتينولول منفردا ، ويقل هذا التأثير فى حالة الأتينولول مع المونتسين ، وقد خفض الفيرابااميل تأثير المونتسين المعزز للإضطراب الحادث بالديجيتالا ، وكذلك فإن الجليبنكلاميد يقلل من تأثير المونتسين المعجل بحدوث الخفقات بالبطين الغير ناضجة.

من خلال نتائج البحث يمكن إستخلاص أن المونتسين يعجل من حدوث الإضطراب المستحدث بالديجيتالا فى ضربات قلب خنزير غينيا وقد يعزى هذا التأثير الى زيادة إفراز أمينات الكاتيكول بالمونتسين - أو الى نقص فترة فاعلية الجهد الناتجة من فتح قنوات البوتاسيوم الحساسة للأدينوزين ثلاثى الفوسفات فى خلايا البطين ، وهذه القنوات تغلق بالجليبنكلاميد.