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EFFECTS OF MONENSIN SODIUM ON DIGOXIN KINETICS IN CONSCIOUS MALE RABBITS

Atef S. El-Gharbawy

Deptartment of Pharmacology, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

ABSTRACT

The investigation was performed on male rabbits equally divided into two groups: digoxin treated group and monensin plus digoxin treated group. Digoxin (0.2 mg/kg) was administered orally as a single dose to normal and monensin (6mg/kg for three successive days) pretreated rabbits. Blood samples were obtained at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0,8.0 and 12.0 hr. after digoxin administration. Pharmacokinetic parameters of digoxin were indicated by determination of area under the curve from time 0 to time t (AUC_t), the area under the curve from time zero to infinity(AUC_∞),the half-life of the drug ($t_{1/2}$),time required to reach maximum drug concentration(t_{max}),maximum drug concentration in the blood (C_{max}),drug clearance (Cl) and the area under first moment curve (AUMC) A significant increase in area under the serum concentration –time curve (AUC), increase in maximum concentration (C_{max}), and area under moment curve (AUMC) were observed In addition, Digoxin clearance (Cl) was significantly reduced in rabbits pretreated with monensin. While, half-life ($t_{1/2}$) and time required to reach maximum concentration (t_{max}) was non significantly changed.

The current results suggest that monensin enhance the adverse effects of digoxin in male rabbits. This interaction is played at least in part through an increase of digoxin plasma levels.

INTRODUCTION

Monensin is a selective polyether ionophore widely used in veterinary medicine as a growth-promoting agent for beef, cattle and as a coccidostat in chickens and turkeys[1]. Monensin induced an increase in the force of contraction of atrial and ventricular preparations of guinea pigs[2] and relaxation of contracted aortic strips[3]. Pressman and his co-workers reported that despite of the marked increase in cardiac work, monensin did not produce a corresponding increase of the myocardial O_2 consumption. This seems to be an advantage over the catecholamine related increase in cardiac work[4,5]. So, the cardiovascular effects of the drug might be efficient in certain disease states requiring inotropic support, increase of cardiac output and /or coronary vasodilatation.

Previous investigations by the author and others[6] indicated that there was a significant correlation between the dose of monensin and percentage mortality in digitalized rabbits treated with monensin. In addition, monensin enhanced the arrhythmogenic action of digoxin in guinea pigs pretreated with monensin[7]. The mechanism of interaction has not been completely ascertained. This necessitates further experiments to be carried out to elucidate the possible effect of monensin on pharmacokinetics properties of digoxin.

MATERIAL AND METHODS

Ten New Zealand white rabbits ranging in body weight from two to three kilograms were used. They were divided into two groups (five /group). Rabbits were housed identically at controlled temperature (20-24°C). The first group received a single oral dose of digoxin (0.2 mg /kg). The second group received monensin orally in a dose of 6 mg/kg for three successive days. Digoxin was then administered as single oral dose (0.2 mg/kg). Venous blood samples were obtained at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0 and 12.0 hours by incision of ear marginal vein and blood was collected into EDTA collection tubes. Plasma was separated by centrifugation at 3000 rpm for 10 minutes. Plasma samples were frozen at –20°C until assay. Serum digoxin concentrations were measured using a radioimmunoassay kit (Amerllex-Amersham International), USA.

All data are presented as mean ± standard error of the mean (S.E.M.)

Drugs used

Monensin sodium (Sigma - USA) and Digoxin (Glaxo wellcome, UK).

PHARMACOKINETIC ANALYSIS

Mean maximum serum digoxin concentration (C_{max}) and time (t_{max}) required to reach C_{max} were calculated from the individual peak serum digoxin concentration. The area under the curve (AUC) and the area under the first moment curve (AUMC) were calculated using the trapezoidal rule and was extrapolated to affinity. The pharmacokinetic parameters were calculated using PK Solution 2.0 (Noncompartmental Pharmacokinetics data analysis)(Dr. David S Farrier, Montrose, USA.

STATISTICAL ANALYSIS

Data from each group are presented as mean ± standard error of the mean. The significance of difference between groups was analyzed using Student t-test. $P < 0.05$ was considered as indicative of statistical significance. All statistical procedures were analyzed by a computer assisted program (PC version, University of Georgia, Athens, Georgia, USA)

RESULTS

Pretreatment of rabbits with monensin sodium markedly increased concentration of digoxin in the blood serum as shown in (Table 1 and Figure 1) compared with control group.

The calculated pharmacokinetic parameters are presented in table (2). A significant increase in area under the curve from time 0 to time t (AUC_t) from 4.49 ±0.47 to 8.10 ±0.33 ng/ml h, increase maximum serum concentration of digoxin (C_{max}) from 0.7 ±0.07 to 1.37 ±0.1 ng/ml, increase area under the curve from time 0 to infinity (AUC_a) from 3.96 ±0.56 to 9.40 ±0.53 ng/ml h , and increase area under first moment curve (AUMC) from 24.59 ± 2.96 to 61.06 ± 6.22 ng/h/ml. Drug clearance was significantly decreased from 0.053±0.006 to 0.021±0.001 ml/kg per hour. On the other hand, there was no significant change in other pharmacokinetic parameters ($t_{1/2}$ and t_{max}).

Table 1. Serum concentrations of digoxin in control and monensin pretreated rabbits (ng/ml).

Time (h)	Control group	Monensin pretreated group
0.5	0.38±0.036	0.53±0.054
1.0	0.57±0.064	0.79±0.06
1.5	0.69±0.069	1.34±0.059*
2.0	0.63±0.089	1.33±0.039*
4.0	0.39±0.068	0.95±0.043*
6.0	0.26±0.033	0.68±0.037*
8.0	0.16±0.02	0.47±0.02*
12.0	0.09±0.01	0.23±0.026*

*Significant difference from control group (P<0.05). Values are absolute mean ± S.E.M.

Table 2. Pharmacokinetic parameters for digoxin in control and monensin (6 mg/kg) pretreated rabbits.

Parameters (Units)	Control Group	Monensin treated group
AUC_t (ng /ml . hr)	4.49 ±0.47	8.1 ±0.33*
AUC_a (ng/h . ml)	3.96 ±0.56	9.40 ±0.53*
$t_{1/2}$ (hour)	4.28 ±0.38	3.84 ±0.28
t_{max} (hour)	1.6 ±0.1	1.8 ±0.12
C_{max} (ng/ml)	0.7 ±0.07	1.37 ±0.1*
AUMC (ng/ml . hr)	24.59 ±2.96	61.06 ±6.216*
CL (ml/kg per h)	0.053 ±0.006	0.021 ±0.001*

AUC_t = area under the curve from time 0 to time t ; AUC_a = area under the curve from time 0 to infinity; $t_{1/2}$ = half -life of the drug; t_{max} = time required to reach maximum drug concentration; C_{max} = maximum concentration of drug in serum ; AUMC = area under first moment curve and Cl = drug clearance.

Values are absolute mean ± S.E.M (n=5)

* Significant difference from control group ($P < 0.05$)

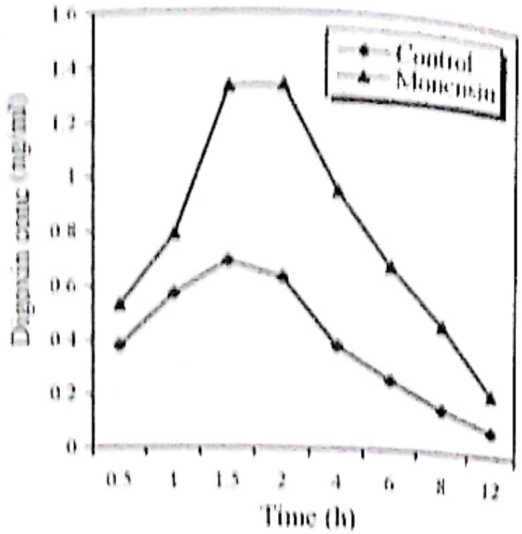

Fig. 1 Mean serum concentrations of digoxin in control and monensin pretreated rabbits.

DISCUSSION

Pharmacokinetics are the mathematical description of the line course of drug absorption, distribution, metabolism and excretion. Clinical pharmacokinetics have proved particularly valuable for those drugs with narrow therapeutic index such as digoxin[8,9].

The results of the present work showed that the mean concentrations of digoxin in monensin pretreated rabbits were higher than the digoxin concentration in control rabbits. The increased serum digoxin level may be due to an increase in digoxin absorption from gastrointestinal tract. Digoxin is absorbed by a passive, non-saturable transport process[10], predominantly from the small bowel[11]. Alteration of gastrointestinal motility by other drug may lead to change in digoxin absorption. Enhanced absorption of drugs appear to result from medications such as diphenoxylate with atropine which decrease intestinal motility[12]. Monensin may cause a decrease in gastrointestinal motility. This possibility is supported by the finding of other investigators who reported that monensin induced smooth muscle relaxation of guinea pig aorta[13] and guinea pig taenia coli[13,14].

A small fraction of digoxin is metabolized in the liver with the formation of the derivatives 3b-digoxigenin, b-digoxiingenin and mono and bis-digitoxoside[15]. In addition Schmoldt and Absendorf[16] reported that cytochrome P450 is necessary for the metabolism of digoxin. The observed increase in serum digoxin level in the present work may be attributed to inhibition of hepatic metabolism of digoxin. This was supported by Daly[17] who reported that monensin depressed significantly the activity of cytochrome P-450[17]. Moreover, it has been reported that monensin induced hepatic toxicity in many species as goats[18], sheep[19], human[20] and rats[21].

Digoxin is eliminated almost entirely via the kidney, 60 - 80% in unchanged form by glomerular filtration and to some extent by active tubular secretion[22,23]. Glomerular filtration is important in the renal handling of digoxin. There is a strong linear correlation between creatinine clearance and digoxin renal clearance[24,25]. Moreover, it has been reported that , monensin induced slightly manifested degeneration of epithelium of kidney tubuli cantorti[26]. Furthermore, the results of Caldeira and his colleague[20] showed that monensin induced acute renal tubular injury and an increase in creatinine plasma level in human. At the same time, monensin induced a decrease in clearance of digoxin (present work). This may explain the observed increase in serum digoxin level in the present work.

In conclusion, pretreatment with monensin increased digoxin serum level of conscious rabbits. Digoxin elevation is probably through enhancement of absorption, lack or inhibition of liver microsomal enzyme system and /or interference with its elimination through the damage of kidney tubules. A brief word of caution will be mentioned because of the extreme toxicity of monensin, individuals dealing with it especially persons under digoxin treatment, should be advised and protected to avoid exposure to it.

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تاثير مونتسين صوديوم علي حركية الديجوكسين في ذكور الارانب الواعية

عاطف سعد الغرباوى

قسم الفارماكولوجي – كلية الصيدلة- جامعة الزقازيق

تم إجراء هذا البحث علي مجموعتان من ذكور الأرانب. مجموعة ضابطة والأخرى تم معالجتها مسبقا بالمونتسين (٦مج/كجم.لمدة ثلاث أيام متتالية).ولقد تم إعطاء الديجوكسين لكلتا المجموعتين كجرعة واحدة عن طريق الفم (٢و مجم/كجم). تم اخذ عينات الدم بعد.٥و-١-٥و١-٢-٤-٦-٨-١٢ ساعة من إعطاء الديجوكسين لقياس كمية الديجوكسين.

- تم دراسة مؤشرات حركية الديجوكسين في الجسم عن طريق حساب كل من:
  - المساحة تحت المنحنى من الوقت صفر إلى الوقت t
  - المساحة تحت المنحنى من الوقت صفر إلى الوقت ما لانهاية
  - زمن نصف العمر
  - الوقت اللازم للوصول إلى أعلى تركيز في الدم
  - أعلى تركيز للدواء في الدم
  - معدل تخلص الجسم من الدواء

ولقد أظهرت النتائج أن اعطاء الديجوكسين بعد المونتسين يسبب زيادة معنوية في كل من المساحة تحت المنحنى وكذلك أقصى تركيز للديجوكسين في الدم. بالإضافة لحدوث نقصاً معنوياً في معدل التخلص من الديجوكسين وذلك في الأرانب المعالجة مسبقا بالمونتسين. أما المؤشرات الأخرى لحركة الدواء مثل فترة نصف العمر أو الوقت اللازم لحدوث أقصى تركيز للديجوكسين في الدم فإنها لم تظهر تغييراً جوهرياً.

-من خلال نتائج البحث يمكن استنتاج أن مونتسين الصوديوم يزيد من مستوي تركيز الديجوكسين في دم ذكور الارانب الواعية مما قد يكون له آثاراً جانبية ضارة.