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THE EFFECT OF ENDOTOXEMIA ON THE PHARMACOKINETICS OF DIGOXIN IN CONSCIOUS MALE RABBITS

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ABSTRACT

Multiple organ failure (MOF) is induced by Escherichia coli lipopolysaccharide (LPS) alters the clearance of several drugs in experimental animals and human being. To give an insight about this phenomenon, the present study aimed to investigate single-dose pharmacokinetics of digoxin in normal healthy male rabbits and LPS pretreated rabbits. Liver and kidney functions as well as their histopathological changes were studied to elucidate the probable mechanism(s) involved in this interaction.

Five groups of healthy male rabbits were used . The first group served as control. The second group received saline(LPS solvent) in marginal ear vein. A third group of rabbits received digoxin (0.02 mg/ ml/kg, p.o).The fourth group received LPS (800 µg/kg) in marginal ear vein. The fifth group received digoxin (0.02 mg/kg, p.o) eight hours after the intravenous injection of LPS(800 µg/kg) .

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN) and creatinine were determined. Serum nitric oxide was estimated by Griess reaction. To study the pharmacokinetic behavior of digoxin, blood was collected 0.25, 0.5, 1, 1.5,2,4,6,8, and12 hours after digoxin administration for determination of its serum level. Administration of digoxin or saline to rabbits had no significant effect on liver functions, kidney functions ,and serum nitric oxide levels. On the other hand, a significant increase in kidney, liver functions and serum nitric oxide were observed in LPS alone or in combination with digoxin treated rabbits. In addition, a significant increase in the area under the serum digoxin concentration-time curve and increase in maximum concentration were observed in rabbits pretreated with lipopolysaccharide.

A brief word caution should be mentioned that in the acute period of Gram-negative bacterial infection, it is necessary to take into account the possibility of significant pharmacokinetic changes of some drugs, especially those having narrow therapeutic range as digoxin. Therefore, digoxin serum level must be monitored carefully in endotoxemic patients, and the doses of digoxin may need readjustment in those patients.

INTRODUCTION

Digoxin is one of the most important drugs in the treatment of congestive heart failure, atirial flutter and fibrillation. Digoxin is an important drug with a narrow therapeutic index and a potentially lethal toxicity. Digoxin is absorbed predominantly from the small bowel[1]. Glomerular filtration is important in the renal handling of digoxin. There is a strong linear correlation between creatinine clearance and digoxin renal clearance[2]. In addition, the liver serves as a minor pathway of digoxin elimination, about 6.5% of a digoxin dose participates in the enterohapatic circulation[3]. Moreover, Kramer and Reuning[4] and Beveridge et al.[5], reported that 50-80% of the administered dose is eliminated unchangoes, via glomerular filtration and not more than 15% undergoing hepatic biotransformation.

Endotoxin, which is an active component of gram-negative bacterial cell wall released during septicemia, is well known to induce damage of numerous organs, including the liver and kidney. The liver and kidney have crucial functions for the elimination of endogenous and exogenous substances, which are converted to more hydrophilic compounds by cytochrome P450 and/or conjugating enzyme and then excreted into bile or urine[6,7,8,9]. Endotoxin reduces the clearance of hepatically metabolized drugs in human[10], as well as in experimental animals[11], and decrease the total cytochrome P450 content and catalytic activity[12].

Therefore, the purpose of the present study was to assess the effect of lipopolysaccharide treatment on the pharmacokinetics of digoxin in male rabbits. Rabbits are more sensitive to LPS than rats[13] and mice[14,15]. Liver, kidney functions, serum nitric oxide as well as histopathological changes in liver and kidney were studied to elucidate the possible mechanism(s) of interaction.

MATERIAL AND METHODS

Material

Lipopolysaccharide (Serotype 055:b5) was obtained from Sigma Chemicals, USA. Digoxin (Glaxo-Wellcome, UK).

Animals

Twenty five male New Zealand rabbits weighing 2.5 – 3 kg were used throughout the study. Rabbits were kept in well-ventilated cages and were fed with dry food and water *ad libitum*. They were housed at a controlled temperature and humidity (22±2° C and 55± 5 % rh). Rabbits were randomly assigned to five groups(5/group) :the first group were served as control, the second group were injected with saline (1 ml /kg) in marginal ear vein, the third group received saline in marginal ear vein (1 ml/kg) and administered intragastrically digoxin (0.02 mg/ ml/kg)[16], the fourth group received LPS (800µg/kg, i.v) and the fifth group

received digoxin (0.02 mg/kg, p.o.) eight hours after administration of LPS (800 µg/kg, i.v.).

The rabbits were fasted for 18 hours but with free access to water. Fasting was continued for 3 hours after digoxin administration. For pharmacokinetic study, blood was collected 0.25, 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, and 12.0 hours after digoxin administration. For blood biochemistry or nitric oxide determination, blood was collected eight hours after LPS or digoxin administration.

Sample collection and analysis

Blood samples were collected from marginal ear vein. Blood was drawn into serum separation tube and was allowed to clot for 30 min. followed by centrifugation (3000 rpm for 15 min.). Sera was used immediately for blood biochemistry and nitric oxide analysis. For digoxin determination, sera were stored at – 20°C till analysis.

Hepatic dysfunction and failure were assessed by measuring the increase in serum levels of alanine aminotransferase, aspartate aminotransferase and total bilirubin[17]. Renal dysfunction and failure were assessed by measuring the increase in serum levels of blood urea nitrogen (BUN) and creatinine[18].

All previously mentioned indicators were measured by using Synchron® systems, blood biochemical analyzer (Beckman Coulter, UK).

Determination of plasma nitrite

Serum nitrite was determined by using Griess reagent, according to the method of Moshage et al [19].

Determination of serum digoxin levels

Serum concentration of digoxin was determined by enzyme linked fluorescent assay (ELFA) method using Vidas Digoxin kit, (Biomericux, France).

Histopathological study

All animals were autopsied at the end of the study. Kidneys and livers were kept in dilute formalin solution and send for histopathology study.

Statistical analysis

Data from each group are presented as mean ± S.E.M. The significance of differences between groups was analysed using Student's t-test[20]. Differences were regarded significant at $P<0.05$ level of significance.

Pharmacokinetic analysis

Mean maximum serum digoxin concentration (C_{max}) and time (T_{max}) required to reach C max were calculated from individual peak of serum digoxin concentration. The area under the curve (AUC) was calculated using the trapezoidal rule and was extrapolated to affinity. The pharmacokinetic parameters were calculated using NCOMP version 3.1[21].

RESULTS

Laboratory tests

As summarized in table 1, administration of LPS (800µg/kg) induced a significant increase in serum AST from 33.6 ±3.6 to 84.6 ± 9.07 U/L ($P<0.05$), ALT from 26 ± 3.9 to 60.4 ± 6.68 U/L ($P<0.05$); total bilirubin from 5.81 ± 0.9 to 14.86 ± 1.4 µM ($P<0.05$); serum creatinine from 165.1 ± 13.7 to 294.3 ± 24.7 µM ($P<0.05$); serum blood urea nitrogen (BUN) from 6.2 ± 0.9 to 16.06 ±1.8 mmol/L ($P<0.05$); and nitric oxide level from 24.8 ± 2.5 to 81.4 ± 6.74µM ($P<0.05$). In lipopolysaccharide plus digoxin-treated rabbits, the following changes in serum levels were observed: a significant rise of total bilirubin concentration from 5.81 ±0.9 to 16.4 ±1.8 µM ($P<0.05$); AST from 33.6 ± 3.6 to 97.4 ± 7.9 U/L ($P<0.05$); ALT from 26±3.9 to 66.4 ± 4.7 U/L ($P<0.05$); the concentration of serum creatinine from 165.1 ± 13.7 to 324.5 ± 28.3 µM ($P<0.05$); blood urea nitrogen (BUN) from 6.2 ± 0.9 to 16.2 ± 1.2 mmol/L ($P<0.05$); nitric oxide (NO) from 24.8 ± 2.5 to 94 ± 5.9µM ($P<0.05$). On the other hand, Administration of saline or digoxine have no significant effect on the parameters measured.

Table 1. Effect of saline, digoxin, LPS, and LPS+digoxin on liver, kidney functions, and serum nitric oxide level in conscious male rabbits. Data are presented as mean ± SEM (n=5)

Parameters / Groups	AST (µ/L)	ALT (µ/L)	T bil (µM)	Creatin (µM)	BUN mmol /L	NO (µM)
Control	33 ±3.6	26 ±3.9	5.81 ±0.9	165.1 ±13.7	6.2 ±0.9	24.8 ±2.5
Saline-treated	31.4 ±3.0	26.6 ±3.9	6.8 ±0.9	153.8 ±8.4	5.6 ±0.6	29.6 ±3.6
Digoxin-treated	38.0 ±3.5	28.0 ±3.2	5.13 ±0.5	142.5 ±4.5	6.2 ±1.07	33.0 ±3.9
LPS-treated	84.6* ±9.07	60.4* ±6.68	14.86* ±1.4	294.3* ±24.7	16.06 ±1.8	81.4* ±6.74
LPS+Digoxin treated	97.4* ±7.9	66.4* ±4.7	16.4* ±1.08	324.5* ±28.3	16.2* ±1.2	94* ±5.9

* $P<0.05$ Compared with control group.

Histopathological findings

There was no significant change in the liver and kidney of rabbits treated with saline or digoxin alone. On the other hand, the kidney of rabbits treated with LPS alone or in combination with digoxin showed cloudy swelling and collecting tubule hyaline casts. While, the liver of the rabbits showed mild focal necrosis with detected apoptotic bodies as shown in Figure 1.

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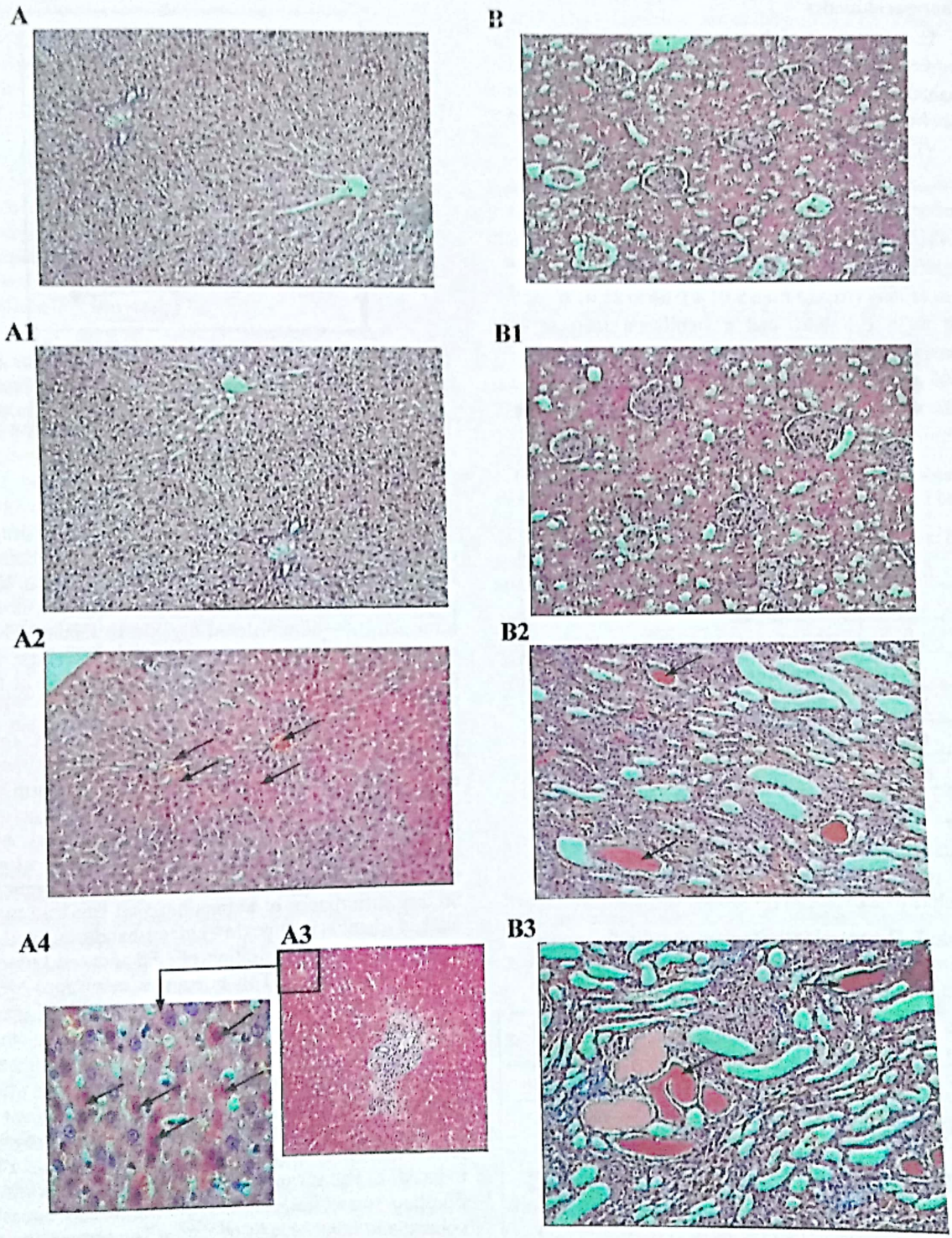

Fig. (1): Effect of LPS plus digoxin on liver and kidney of rabbits . A Section of liver from control rabbit treated with saline. A1 Section of liver treated with saline and 0.02 mg/kg digoxin orally. A2 Section of liver treated with LPS (800 µgm/kg, i.v.). A3 Section of liver from rabbits pretreated with 800 µg/kg (i.v) LPS then with 0.02mg/kg orally digoxin, showing focal necrosis and apoptotic bodies. B Section of kidney from control rabbits treated with saline. B1 section of kidney treated with saline and 0.02 mg/kg digoxin orally. B2 Section of liver treated with LPS (800 µgm/kg, i.v.). B3 Section of kidney from rabbit pre treated with 800 µg/kg (i.v) LPS then with 0.02 mg/kg orally digoxin, showing cloudy swelling and collecting tubule hyaline casts. H & E100 except for A4 which is H & E400.

Pharmacokinetics

Concentrations of digoxin in serum (Table 2 and Figure 2) of LPS+digoxin- treated rabbits were higher than the levels measured for digoxin alone –treated rabbits.

The calculated pharmacokinetic parameters are presented in Table 3. A significant increase in area under the curve from time 0 to time t (AUC_t) from 5.43±0.77 to 11.16 ± 1.09 ng $ml^{-1}h$ ($P<0.5$), a significant increase in area under the curve from time 0 to affinity (AUC_a) from 9.04 ± 0.64 to 25.01 ± 5..89 ng $ml^{-1}h$ ($P<0.5$), and a significant increase of maximum concentration of drug in serum (C_{max}) from 1.03 ± 0.19 to 1.96 ± 0.14 ng/ml ($P<0.5$). On the other hand, there was no significant change in the elimination half-life ($t_{1/2}$) .

Table 2. Serum concentrations of digoxin in control and LPS-treated male conscious rabbits (ng/ml).

Time (hr)	Control group	LPS-Treated group
0.25	0.27±0.04	0.34±0.05
0.5	0.42±0.055	0.77±0.09*
1.0	0.77±0.156	1.57±0.25*
1.5	1.01±0.18	1.89±0.12*
2.0	0.89±0.15	1.57±0.14*
4.0	0.58±0.1	1.23±0.14*
6.0	0.41±0.05	1.0±0.1*
8.0	0.29±0.03	0.7±0.08*
12.0	0.23±0.01	0.44±0.05*

*$P< 0.05$ Compared with control group, values are absolute mean ± S.E.M (n=5)

Table 3. Pharmacokinetics parameters for digoxin in control and LPS- treated rabbits. Data are presented as mean ± S.E.M (n=5).

Parameters (Units)	Control group	LPS-treated group
AUC_t ($ng/ml^{-1}h$)	5.43±0.77	11.16±1.09*
C_{max} (ng/ml)	1.03±0.19	1.96±0.14*
T_{max} (hr)	1.6± 0.1	1.3±0.12
AUC_a ($ng/ml^{-1}h$)	9.04±0.64	25.01±5.89*
$t_{½}$ (hr)	10.31±1.65	14.87±3.24

AUC_t = area under the curve from time 0 to time t; AUC_a = area under the curve from time 0 to infinity; $t_{½}$ = half – life of the drug ; T_{max} = time required to reach maximum drug concentration ; C_{max} = maximum concentration of drug in serum.

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

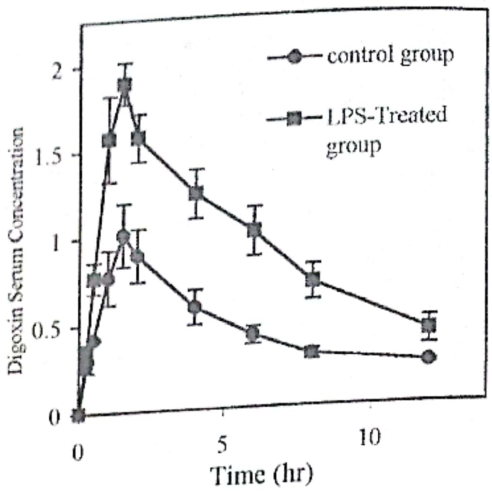

Fig. (2): Mean serum concentration of digoxin in control and LPS-treated rabbits

DISCUSSION

The present study describes a substantial drug-disease interaction of digoxin in endotoxemic patients. Endotoxemia, was induced by LPS administration, has performed effects on the pharmacokinetic behavior of intragastrically administered digoxin in rabbits. This effect was manifested by a significant change in different pharmacokinetic parameters of digoxin as shown by the increase in C max and AUC

Several mechanisms could contribute to this interaction. First, Digoxin is eliminated almost entirely via the kidney, 60-80% as unchanged form by glomerular filtration and to some extent by active tubular secretion[22,23]. Moreover, Peters and his colleagues[24], reported that a there are a close relationship between digoxin and creatinine clearance. So, any disturbance of kidney function can lead to a marked change in digoxin- kidney handling. In the present study, administration of LPS induced kidney function disturbance. This effect was manifested by a marked increase in serum creatinine, and blood urea nitrogen levels and was confirmed by the abnormalities observed during histopathological examination. The present results are in agreement with others who reported that LPS induced a significant increase in serum creatinine and blood urea nitrogen levels[25,26]. In addition, it is reported that, LPS induced a significant decrease in the glomerular filtration rate (GFR) in rats[27,28,29] and both renal volume and renal blood flow[30,31] . The present study showed an increase in serum NO level in LPS or LPS plus digoxin treated rabbits, such increase in level of NO may be the cause of Kidney dysfunction . This increase in serum No is in accordance with findings of Zhang et al.[25,32] and Hsu and Liu[26] who found that LPS induced a significant increase in serum NO in rats. A role for NO production in renal pathophysiology has been assumed from studies measuring NO production in glomeruli from nephritic

kidneys[33].Moreover, Kabore and his coworkers,[34] reported that NO induced by LPS could induce proximal tubular cell damage. The renal dysfunction caused by endotoxin may be due to overproduction of NO which contributes to the development of renal injury and dysfunction by causing direct cytotoxic effects[35]. Increased generation of NO is capable of inducing intracellular oxidizing reactions and cell death occurred during renal hypoxia and reoxygenation[36]. In addition, histopathological examination of kidney from lipopolysaccharide-treated rabbits showed renal tubular casts and cloudy swelling (Present study)

Other interesting mechanisms could contribute to this interaction. P-glycoprotein (P-gp) is membrane – bound efflux transporter. It is expressed not only in cancer cells, but also in normal tissues, including the intestine, liver, and kidney[37,38], where P-gp contributes to elimination of drug substrates into the gut, bile, and urine , respectively. P glycoprotein (P-gp), acts as an ATP-dependent efflux pump for various drugs, such as *Vinca* alkaloids and anthracycline anticancer drugs, calcium blockers, immunosuppressive agents, and macrolide antibiotics[39,40,41]. Digoxin has been identified in vitro and in animal experiments as a substrate of renal[42,43] and intestinal P-gp[44,45]. Inhibition of P-gp produces an increase in intestinal absorption and decrease in hepatic and renal excretion of its substrates, resulting in elevated plasma and organ drug level[45]. Several studies describe the inhibition of renal P-glycoprotein by co-administration of drugs, resulting in higher plasma concentrations of digoxin[46,47,48]. These studies indicate that P-glycoprotein plays a major role in renal and intestinal excretion[49] and secretion[44] of digoxin. Such interactions are explained by competitive inhibition of P-glycoprotein, resulting in reduced net transport into proximal tubules of kidney. Moreover, Ando and his colleagues[50] reported that endotoxin decreased biliary and renal excretion of rhodamine-123 (p-gp substrate) through suppression of multidrug resistance protein 1a (Mdr1a). Multidrug resistance protein1a is a member of the P-glycoprotein in both liver and kidney of rats.

Liver serves as a minor pathway of digoxin elimination, according to most reports, only 6.5% of digoxin dose participate in enterohepatic circulation[3]. So, disruption of the enterohepatic circulation, which plays, to some extent, a role in the behaviour of digoxin biotransformation, could be a further factor in the elimination of the drug. Moreover, chloestasis is often observed in septic and endotoxemic patients[51]. This observation is supported by Bolder and his coworkers[52], who found that, LPS induced a significant decrease of bile flow in rats. In the present study, LPS induced liver dysfunction as manifested by a significant increase in ALT, AST and total bilirubin. These results are in agreement with others who reported that LPS induced a significant increase in ALT, AST and total bilirubin[32]. Such effect could be attributed to oxidative stress induced by LPS. This is supported by others who mentioned that LPS induced significant increase in plasma lipid peroxidaton[26] and fall of liver GSH content[32]. In the present study, the histopathlogical changes of liver support the previous finding, since, lipopolysaccharide administration induced focal necrosis and detected apoptotic bodies. This may be attributed to excessive production of TNF-α and interferon gamma under the effect of LPS treatment[53]

Therefore, a brief word of caution should be mentioned that in the acute period of Gram-negative bacterial infection, it is necessary to take in consideration the possibility of significant pharmacokinetic changes of some drugs, especially those having narrow therapeutic range as digoxin. Therefore, digoxin serum level must be monitored carefully in endotoxemic patients, and the doses of digoxin may need readjustment in those patients.

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REFERENCES

1- Bearmann, B.; Hellstrom, K. and Rosen, A.; **Clin. Sci.**, 43:507-518 (1972)
2- Okada, R.D.; Hager, W.D.;, Graves, P.E.; Mayers, O.M.; Perrier, D.G. and Marcus, F.I.; **Circulation**, 58: 1196-1203 (1978).
3- Soldin, S.J.; **Clin. Chem.**, 32:5-12 (1986)
4- Kramer, W.G., and Reuning , R.H.; **J. Pharm. Sci.**, 64:141-142 (1978)
5- Beveridge, T.; Nuesch, E. and Ohnhous, E.E.; **Arzneim. Forsch.**, 28:701-703 (1978).
6- Nadai, M.; Hasegawa, T.; Kato, K.; Wang, L.; Nabeshima, T. and Kato, N.; **Drug Metab. Dispos.**, 21: 611-616 (1993).
7- Nadai, M.; Hasegawa, T.; Wang, L.; Haghgoo, S.; Nabeshima, T.; and Kato, N.; **Biol. Pharm. Bull.**; 18: 1089-1093 (1995)
8- Nadai, M.; Hasegawa, T.; Wang, L.; Haghgoo, S.; Okasaka , T.; Nabeshima, T. and Kato, N.; **J. Pharm. Pharmacol.**, 48: 744-748 (1996)
9- Haghgoo, S.; Hasegawa, T.; Nadai, M.; Wang, L.,T.; Nabeshima, T. and Kato, N.; **Antimicrob. Agents Chemother**. 39 : 2258-2261 (1995).
10- Shedlofsky, S.I.; Israel, B.C.; McClain, C.J.; Hill, D.B. and Blouin , R.A.; **J. Clin. Investig.**, 94: 2209-2214.(1994).
11- Nadai, M., Sekido, T.; Matsuda, I.; Wang, L.; Kitaichi, K.; Itoh, A.; Nabeshima, T. and Hasegawa., T.; **J. Pharm. Pharmacol.**, 50: 871-879 (1998).
12- Morgan, E.T.; **Drug Met. Rev.**, 29: 1129-1188 (1997).
13- Ben-Shaul, V.; Sofer,Y.; Bergman, M.; Zurovsky, Y. and Grossman, S.; **Shock**, 12: 288-93 (1999)

14- Redl, H., Bahrami, S.; Schlag, G. and Traber, D.L.; **Immunobiology**. 187:330-345 (1993).
15- Dinges, M.M. and Schlievert, P.M.; **Infection and Immunity**. 69:7169-7172 (2001)
16- Wojcicki, M., Drozdzik, M.; Sulikowski, T.; Gawronska-Szklarz, B., Wojcicki, J.; Romenwicka, L., Skowron, J., Zielinski, S., Musial, H. and Zarkrzewski, J; **J. Pharm. Pharmcol.**, 49:1082-1085 (1997)
17- Hewett, J.A. and Roth, R.A.; **J.Pharmacol.Exp.**, Ther. 272:53 (1995)
18- Thiemermann, C.; Rutten, H.; Wu, C.C.; and Vane, J.R. Br.; **J. Pharmacol.** 116: 2845 (1995)
19- Moshage, H., Hok, B.; Huizenga, J.R. and Jansen., P.L.M.; **Clin Chem**. 41:892 (1995)
20- Snedecor, G.W., and Cochran, W.G., Statistical methods. The Lowa state university press. Ames. Lowa, USA.Pp.393 (1967).
21- Laub, P.B., and Gallo, J.M.; **J.Pharm Sci.**, 85:393-395 (1996).
22- Sumner, D.J., and Ressel, A.J. Br. **J. Clin. Pharmacol.**, 3: 221-229 (1979).
23- Mooradian, A.D.; **Clin. Pharmcokin.**, 15:165-179 (1988).
24- Peters, U., Falk, L.C.,and Kakman, S.H. **Arch. Intern. Med.** 138: 1074-1076 (1978).
25- Zhang, C., Walker,L.M., and Mayeux, R.; **Biochem. Pharmacol.**, 59:203-209 (2000a)
26- Hsu, D.Z., and Liu, M.Y.; **Crit. Care Med.**, 30: 1859-1862 (2002)
27- Lugon, J.R.; Boim, M.A., Ramos, O.L.; Ajzen, H. and .Schor, N.; **Kidney Int.**, 36:570-575 (1989).
28- Hasegawa, T.; Nadai, M.; Wang, L.; Takayama, Y.; Kato, K.; Nabeshima, T. and Kato, N.; **Drug Metab. Dispos.**, 22: 3-13 (1994).
29- Wang, W.; Falk, S.A.; Jittikanont, S.; Gengaro, P.F.; Edelstein, G.L. and Schrier, R.W.; **Am. J. Physiol. Renal Physiol.**, 283:F583-F587 (2002).
30- Mitaka, C.; Hirata, Y.; Yokyama, K.; Nagura, T.; Tsunoda, Y. and Amaha, K.; **Crit. Care Med.** 27:146-153 (1999).
31- Yao, K.; Ina, Y.; Nagashima, K.; Ohno, T. and Karasawa, A.; **Jpn. J. Pharmacol.**; 84: 310-315 (2000)
32- Zhang, C.; Walker, L.M.; Hinson, J. and Mayeux, R. J.; **Pharmacol. Exp. Ther.** 293:968-972 (2000b).
33- Cook, H.T., and Sullivan R.; **Am. J. Pathol.** 139: 1047-1052 (1991).
34- Kabore, A.F.; Denis, M. and Bergeron, M.G.; **Antimicrob. Agents Chemother.**, 41:557-562 (1997).
35- Millar, C.G. and Thiemermann., C.; **Br. J. Pharmacol.**, 121:1824-1830 (1997).
36- Paller, M.S., Weber, K., and Patten, M.; **Ren. Fail.** 20:459-469 (1998).
37- Thiebaut, F., Tsuruo, T., Hamada, H., Gottesman, M.M., Pastan, I., and Willingham, M.C.; **J. Histochem. Cytochem**. 37: 159-164 (1989).
38- Pastan, I. and Gottesman, M.M..; **Ann Rev. Med.**, 42: 277-286 (1991).
39- Tsuruo, T.; Iida, H.; Tsukagoshi, S. and Sakurai, Y.; **Cancer Res.** 42: 4730-4733 (1982).
40- Twentyman, P.R., Fox, P.R. and White, D.J.; **Br. J. Cancer**, 56: 55-57 (1987)
41- Wang, L.; Kitaichi, K.; Cai, S.H.; Takagi, K.; Takagi, K.; Sakai, M.; Yokogawa, K.; Miyamoto, K.I. and Hasegawa, T.; **Clin. Exp. Pharmacol. Physiol.**, 27: 587- 593 (2000).
42- Ito, S.; Koren, G., and Harper, P.A.; **Can. J. Physiol. Pharmacol.**, 71: 40-47 (1992).
43- Ito, S.; Woodland, C.; Harper, P.A. and Koren, G.; **Life Sci.**, 53: PL 25-PL31 (1993).
44- De Lannoy, I.A.M. and Silverman, M.; **Biochem.Biophys. Res. Commun.**, 189: 551-557 (1992).
45- Schinkel, A.H.; Wagenaar, E.; Van Deemter, L;, Mol, C.A.A.M. and Bores, P.; **J. Clin. Invest.**, 96: 1698-1705 (1995).
46- De Lannoy, I.A.M.; Koren, G.; Klein, J.; Charuk, J. and Silverman, M.; **Am. J. Physiol.**, 263: F613-F622 (1992).
47- Okamura, N.; Hirai, M.; Tanigawara, Y.; Tanaka, K.; Yasuhara, M.; Ueda, K.; Komano, T. and Hari, R.; **J. Pharmacol. Exp. Ther.**, 266:1614-1619 (1993)
48- Su, S.F. and Huang, J.D.; **Drug Metab. Dispos.**, 24: 142-147 (1995).
49- Hori, R., Okamura, N., Aiba,T. and Tanigawara, Y.; **J. Pharmacol. Exp. Ther.**, 266:1620-1625 (1993).
50- Ando, H., Nishio,Y., Ito,K., Nakao, A., Wang, L., Zhao, Y.L., Kitaichi, K., Takagi, K. and Hasegawa, T.; **Antimicrob. Agents Chemother.**, 45:3462-3467 (2001).
51- Zimmerman, H.J.; **Arch. Intrn. Med.**, 139:1038-1045 (1979).
52- Bolder, U.; Schmidt, A.; Landmann, L.,Kidder, V.; Tange ,S. and Jauch, K.W.; **Gastroenterology** 122:963-973. (2002).
53- Leist, M.; Gantnez, F.; Bohlinger, I.; Tiegs, G.; Germann, P.G. and Wendel, A.; **Am. J. Pathol.** 146:1220-1234 (1995)

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تأثير الذيفان الداخلي علي حركيه الديجوكسين في ذكور الأرانب الواعية.

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قسم الفارماكولوجى - كليه الصيدلة - جامعه الزقازيق – الزقازيق - مصر.

الفشل العضوي المتعدد المستحدث بواسطة السكريات المتعددة الدهنية الناتجة من بكتريا اشريشيا كولاي تؤثر علي تخلص الجسم من معظم الأدوية في حيوانات التجارب والإنسان. ولمزيد من البحث في هذه الظاهرة تمت مقارنه حركيه الجرعة الواحدة من الديجوكسين في ذكور الأرانب العادية وكذلك الأرانب المعالجة مسبقا بالسكريات المتعددة الدهنية وتمت دراسة وظائف الكبد والكلية وكذلك الفحص الهيستولوجي لهما لتوضيح الآلية المحتملة لهذا التداخل.

فى هذا البحث تم استخدام خمسة مجموعات من ذكور الأرانب حيث تم استخدام المجموعة الأولي كمجموعه ضابطة وتمت معالجه المجموعة الثانية من الأرانب بمحلول الملح (١ ملليتر/كجم) بالوريد فيما عولجت المجموعة الثالثة بالديجوكسين (٠,٠٢مجم/مليليتر/كجم) عن طريق الفم وأعطيت المجموعة الرابعة السكريات المتعددة الدهنية (٨٠٠ميكروجرام/مليليتر/كجم) بالحقن في وريد الأذن أما المجموعة الأخيرة فقد تم إعطائها الديجوكسين (٠,٠٢مجم/مليليتر/كجم) عن طريق الفم بعد ثمان ساعات من حقن السكريات المتعددة الدهنية(٨٠٠ميكروجرام/كجم).

هذا وقد تم قياس إنزيمات ناقلات الألانين ، إنزيمات ناقلات الأسبرتات ، البيلوروبين الكلي ، النيتروجين الازوتي والكرياتينين في مصل الدم. وكذلك تم تقدير مستوي أكسيد النيتريك في مصل الدم باستخدام تفاعل جريس. ولدراسة حركيه الديجوكسين فقد تم اخذ عينات من الدم بعد ٠,٢٥، ٠,٥، ١، ١,٥، ٢، ٤، ٦، ٨، ١٢ساعه من إعطاء الديجوكسين وذلك لتقدير كميه الديجوكسين في الدم. و أيضا تم اخذ عينات من الكليه والكبد في نهاية الدراسة للفحص الهستولوجي.

وقد أظهرت النتائج أن إعطاء محلول الملح أو الديجوكسين منفردين أو متحدين ليس لهم أي تأثير جوهري علي وظائف الكبد أو الكلي أو مستوي أكسيد النيتريك في الدم. ومن ناحية أخري فقد لوحظ أن هناك زيادة جوهرية في وظائف الكبد و الكلي ومستوي أكسيد النيتريك في الدم في الأرانب المعالجة بالسكريات المتعددة الدهنية منفردا او السكريات المتعددة الدهنية و الديجوكسين معا. بالاضافة انه وجد أن هناك زيادة ملحوظة في المساحة تحت المنحني و كذلك في الزيادة القصوي للديجوكسين في دم الأرانب المعالجة مسبقا بالسكريات المتعددة الدهنية.

كلمة تحذيرية مختصرة لابد أن تذكر انه في الإصابات الحادة بالميكروبات سالبه الجرام لابد من أن نأخذ في الحسبان امكانية حدوث تغيير ملحوظ في حركيه بعض الأدوية و بخاصة تلك الأدوية ذات حدود الأمان الضيقة مثل الديجوكسين. وبالتالي لابد من متابعة مستوي الديجوكسين في دم مرضي الذيفان الداخلي حيث أن جرعه الديجوكسين في تلك الحالات ربما تحتاج إلي تعديل.