Zagazig J. Pharm. Sci., June 1996,
Vol. 5, No. 1, pp. 115-119

ISSN 1110-5089

HAEMATOLOGICAL AND BIOCHEMICAL STUDIES OF CEFOPERAZONE, TYLOSIN AND THEIR COMBINATION IN RABBITS

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ABSTRACT

Intramuscular administration of cefoperazone, tylosin or their combination for 5 successive days in their subtherapeutic doses did not produce any harmful effects on blood, liver and kidney of rabbits. Therapeutic or double therapeutic doses of the drugs and their combination produced a significant decrease in erythrocytes, leucocytes counts, Hb% and P.C.V.% with a significant prolonged prothrombin time. It also elicited a significant elevation of SGOT, SGPT and total bilirubin without effect on alkaline phosphatase level. Moreover, the drugs induced a significant elevation of blood urea nitrogen and creatinine without any effect on uric acid level.

INTORUDCITON

Antibacterial drugs are extremely useful group of compounds and represent an important and benificial achievement for vetrinary medicine, as well. Comments on dynamic, kinetics and side effects should be viewed with utmost concern to maintain a proper perspective. Many are extremely safe and free of untoward effects.

There is no doubt that benifits resulting from use of antibacterial drugs are much greater than the expected risks. Like other classes of drugs, antibiotics might interact with each other or with other medication being given to the patient, with possible adverse results.

Antibiotic combinations were used commonly in clinical practice, often with good justification. Although, the evidence for synergism was not clear in many cases, there was a good evidence for clinical benifits for some combinations. On the other hand, the frequent use of antibiotic combinations that had not been validated by clinical trials- or at least by in-vitro or animal testing- should be avoided.

Cephalosporin antibiotics are widely used antibiotics, which are useful in human and animal medicine of which cefoperazone is one of the third generation of cephalosporins. It is more broader in spectrum against most of gram-positive and negative organisms, more soluble and completely absorbed crossing all the body barrier[1].

Also, tylosin is a macrolide antibiotic, used as a vetrinary antimicrobial agent, elaborated by strains of *Streptomyces fradiae* initially isolated from soil collected in Thailand[2].

The present study was conducted to assess the effects of cefoperazone, tylosin and their interaction on the blood picture, liver and kidney functions of rabbits, that eventually could explain and control the adverse effects, if any that could be issued from possible interactions with each other.

MATERIAL AND METHODS

Haematological, liver and kidney function studies:

The effects of different doses of cefoperazone, tylosin and their combination were studied on healthy rabbits. One hundered twenty rabbits were divided into 12 groups, 10 rabbits each. They received the drugs in a daily doses by intramuscular injection for 5 successive days.

Three groups of rabbits were given cefoperazone (70 mg/kg. b. wt), tylosin (1.0 mg/kg. b. wt) and combination of both drugs (cefoperazone, 70 mg/kg. b.wt. and tylosin, 1.0 mg/kg/b.wt). Another three groups of rabbits were given cefoperazone (140 mg/kg.b.wt.), tylosin (10 mg/kg b.wt.) and combination of both drugs (cefoperazone, 140 mg/kg b.wt. and tylosin, 10 mg/kg.b.wt.).

Last three groups received cefoperazone (280 mg/kg.b.wt), tylosin (20 mg/kg.b.wt) and combination of both drugs (cefoperazone, 280 mg/kg.b.wt. and tylosin, 20 mg/kg.b.wt). Three control groups, of 10 rabbits each received saline solution intramuscular for 5 successive days.

The effects of the drugs were studied on the blood, liver function and kidney function of all groups of rabbits. The results were reported before injection and at the fifth day of treatment.

In preparation for drawing blood samples, sterilized, smooth and sharp 12 guage needles and sterilized, 5 ml syringes were used. The rabbit's ear was cleaned by rubbing with 70% alcohol, and dried with absorbent cotton.

Immediately, after drawing three samples of blood

(5 ml, each), from each rabbit's vein; first part of the blood was gently forced into a tube containing dry pot. oxalate (1 mg/ml blood), and shaken to aid dissolving the oxalate, this sample was used for haematological studies. Meanwhile, second sample of blood was mixed with sodium citrate 3.8% (9:1), for prothrombin time determination. The third sample of blood was allowed to stand in vials for separation of cells and plasma. Moreover, the last sample supernatant was centrifuged at 3000 RPM for 20 min to obtain serum for liver and kidney functions studies.

The effect of the drugs and their combination was tested on erythrocyte, leucocyte counts, P.C.V.%, mean corpuscular volume (M.C.V.), mean corpuscular haemoglobin (M.C.H.), mean corpuscular haemoglobin concentration (M.C.H.C)[3], blood haemoglobin[4], and prothrombin time[5]. Serum GOT and GPT[6], total serum bilirubin[7], serum alkaline phosphatase[8], serum creatinine[9], serum urea[10] and uric acid[11] were determined using commercial kits supplied by Sigma Co., St. Louis, Mo., U.S.A.

The results are presented as mean ± SEM and statistical significance was determined by Student's "t" test for paired observation[12].

RESULTS

It has been shown that cefoperazone (70 mg/kg.b.wt., subtherapeutic dose), tylosin (1 mg/kg.b.wt., subtherapeutic dose) or their combination (cefoperazone, 70 mg and tylosin, 1 mg/kg.b.wt.) had no harmful effect on rabbit's blood (Table 1).

Meanwhile, the drugs in their therapeutic doses (cefoperazone, 140 mg or tylosing 10 mg/kg) and their combination (cefoperazone, 140 mg and tylosin, 10 mg/kg.b.wt.) produced a significant decrease in Hb%, erythrocytic count, P.C.V. and leucocytic count and a significant increase in prothrombin time (Table 1). Similar findings were obtained when double therapeutic doses of drugs and their combination were injected intramuscular for 5 successive days (Table 1).

Cefoperazone, tylosin and their combination in the subtherapeutic dose had shown no effects on SGOT, SGPT, serum bilirubin and alkaline phosphatase (Table 2). Meanwhile, the drugs and their combination in therapeutic and double therapeutic doses induced a significant elevation of both SGOT and SGPT but no effects on alkaline phosphatase or serum bilirubin (Table 2).

Cefoperazone, tylosin and their combination in their subtherapeutic doses showed no effect on the kidney function (Table 3). Meanwhile, the drugs in therapeutic and double therapeutic doses and their combination produced a significant increase in both creatinine and blood urea nitrogen levels with no effect on the uric acid level (Table, 3).

DISCUSSION

Results of the persent work are in accord with previous findings[13-15]. These records showed that cefoperazone cause destruction of erythrocytes, leucocytes and blood platelets. Moreover, it had been reported that cefoperazone produced rare instances of bone-marrow depression, characterized by granulocytopenia [16]. Other reports had mentioned that serious bleeding accompanied cefoperazone administration was related either to hypoprothrombinemia, thrombocytopenia and/or platelet dysfunction[17,18]. They suggested that vitamin K was always advisable to be administered in combination with cefoperazone.

It had been reported that tylosin reduced the number of erythrocytes, haematocrit value and haemoglobin level in chicken. They suggested that these changes in blood picture of treated chicken was due to a degenerative changes of liver and spleen[19].

Same results were also obtained[20,21], they reported elevations of SGOT and SGPT during treatment with cefoperazone. They found that this elevation was due to hepatotoxic effects which appear in the form of coagulative necrosis in liver of treated animals.

Also cefoperazone caused no significant increase in total bilirubin[22] and this was in agreement with our findings. It had been stated that hepatitis was a dangerous complication of tylosin therapy[19] and this may explain why SGOT and SGPT were elevated in treated animals.

Nephrotoxicity due to cefoperazone was previously reported[15,20]. They found that cefoperazone in therapeutic and double therapeutic doses increased the level of creatinine and blood urea nitrogen due to degeneration of the renal epithelium.

Also, our results agree with those previously obtained[17]. They found that therapeutic dose of tylosin produced degeneration of the renal epithelium of the treaed chicken.

It could be concluded from our results that combination of both drugs in their subtherapeutic doses did not produce any harmful effects on rabbit's blood, liver or kidney functions. Our study strongly emphasizes that further work should address the clinical implication of any of their effects at least in those patient or animals suffering from renal insufficiency, hepatic dysfunction, and bleeding problems.

Table (1): Effects of intramuscular injection of cefoperazone, tylosin nd their combination for 5 successive days on the blood picture of rabbits (n = 120).

Groups	HB (gm %)	R.B.C. (10^6/mm^3)	PCV (%)	M.C.V. (cuu)	M.C.H. (µug)	M.C.H.C. (%)	W.B.C. (102/m)	Prothroumbin time (see)
Subtherapeutic Dose:								
CONTROL	12.7 ± 0.2	5.9 ± 0.5	39.7 ± 0.7	67.3 ± 6.2	21.6 ± 1.3	32.5 ± 2.3	8.1 ± 0.5	10.6 ± 0.6
CEFO.	12.5 ± 0.3	5.7 ± 0.5	39.9 ± 2.5	69.2 ± 0.9	21.7 ± 0.9	31.2 ± 5.1	8.5 ± 0.4	9.9 ± 1.7
TYLO.	12.6 ± 0.2	5.8 ± 0.6	39.8 ± 3.6	68.4 ± 0.8	21.7 ± 1.2	31.5 ± 4.1	8.1 ± 0.1	9.8 ± 0.7
CEFO + TYLO	12.7 ± 0.3	5.8 ± 0.8	39.7 ± 1.7	67.5 ± 0.7	21.6 ± 1.2	32.7 ± 3.2	8.2 ± 0.4	10.9 ± 1.3
Therapeutic Dose:								
CONTROL	12.9 ± 0.2	6.1 ± 0.5	40.7 ± 0.1	57.4 ± 6.2	20.1 ± 0.7	30.7 ± 0.5	10.4 ± 0.5	11.9 ± 0.6
CEFO.	11.1 ± 0.9*	5.1 ± 0.3*	36.9 ± 1.2*	72.7 ± 0.9*	22.9 ± 2.9	33.1 ± 4.2	9.2 ± 1.4	13.9 ± 1.9*
TYLO.	11.0 ± 0.2*	5.2 ±0.4*	35.1 ± 2.7*	67.5 ± 3.9*	22.7 ± 1.2	32.8 ± 4.4	8.9 ± 1.7	14.7 ± 0.9*
CEFO + TYLO*	10.2 ±1.5*	4.1 ± 0.7*	31.1 ± 3.7*	74.5 ± 3.6*	24.4 ± 3.6	36.6 ± 3.1*	7.6 ± 0.4*	15.2 ± 2.4*
Double Therapeutic Dose:								
CONTROL	12.1 ± 0.4	6.9 ± 0.2	40.3 ± 0.1	58.7 ± 5.7	17.6 ± 2.2	29.7 ± 2.7	10.3 ± 0.5	10.7 ± 0.8
CEFO.	10.7 ± 1.7	4.8 ± 0.4*	35.9 ± 2.7*	74.7 ± 3.2*	22.6 ± 1.6*	32.9 ± 2.2	8.1 ± 0.8*	15.3 ± 1.4*
TYLO.	10.6 ± 0.3*	4.9 ± 0.9*	35.0 ± 4.1	74.2 ± 4.3*	22.9 ± 3.1	33.5 ± 3.8	8.3 ± 0.5*	14.9 ± 1.1*
CEFO + TYLO	9.7 ± 0.5*	4.1 ± 0.4*	30.05 ± 4.2*	73.6 ± 2.1*	23.9 ± 3.1	36.6 ± 2.4*	7.0 ± 1.4*	17.3 ± 2.7*

Mean ± SEM
*** P < 0.05**

Table (2): Effects of intramuscular injection of cefoperazone, tylosin and their combination for 5 successive days on liver function of rabbits (n = 120).

Groups	sGOT (u/ml)	sGPT (μ/ml)	Alkaline phosphatase (μ/ml)	Serumbilirubin (μ/ml)
Subtherapeutic Dose:				
CONTROL	19.8 ± 0.5	20.1 ± 0.8	10.7 ± 0.7	0.55 ± 0.031
CEFO	19.8 ± 0.8	20.1 ± 1.2	10.8 ± 1.1	0.50 ± 0.071
TYLO	19.7 ± 0.7	20.4 ± 1.3	10.9 ± 1.0	0.52 ± 0.110
CEFO + TYLO	19.9 ± 1.2	20.8 ± 0.7	10.3 ± 0.9	0.57 ± 0.012
Therapeutic Dose:				
CONTROL	22.2 ± 0.7	23.0 ± 0.9	11.7 ± 1.3	0.62 ± 0.0711
CEFO	30.8 ± 0.3*	32.6 ± 2.7*	13.8 ± 1.8	0.73 ± 0.052
TYLO	30.9 ± 0.6*	35.8 ± 3.2*	12.7 ± 2.3	0.68 ± 0.010
CEFO + TYLO*	32.7 ± 3.8*	39.1 ± 2.8*	13.9 ± 1.7	0.79 ± 0.110
Double Therapeutic Dose:				
CONTROL	23.4 ± 0.7	24.8 ± 2.7	12.6 ± 0.3	0.78 ± 0.032
CEFO	36.7 ± 1.2*	38.1 ± 2.5*	13.8 ± 1.2	0.89 ± 0.011
TYLO	36.9 ± 2.7*	38.9 ± 1.2*	14.1 ± 2.4	0.79 ± 0.050
CEFO + TYLO	40.1 ± 2.8*	42.0 ± 3.6*	14.1 ± 1.7	0.91 ± 0.040

Mean ± SEM * P < 0.05

Table (3): Effects of intramuscular injection of cefoperazone, tylosin and their combination for 5 successive days on kidney function of rabbits (n = 120).

Groups	Creatinine (mg %)	Blood Urea Nitrogen (mg %)	Uric Acid (mg %)
Subtherapeutic Dose:			
CONTROL	0.99 ± 0.13	25.8 ± 0.8	0.71 ± 0.041
CEFO	0.979 ± 0.12	25.7 ± 0.7	0.72 ± 0.05
TYLO	0.95 ± 0.02	25.4 ± 0.5	0.79 ± 0.07
CEFO + TYLO	0.96 ± 0.07	25.3 ± 1.4	0.73 ± 0.13
Therapeutic Dose:			
CONTROL	0.79 ± 0.01	25.7 ± 0.6	0.78 ± 0.011
CEFO	2.34 ± 0.12*	28.9 ± 0.9*	0.79 ± 0.15
TYLO	2.45 ± 0.28*	28.6 ± 0.5*	0.76 ± 0.02
CEFO + TYLO*	3.76 ± 0.84*	32.0 ± 1.7*	0.78 ± 0.14
Double Therapeutic Dose:			
CONTROL	0.89 ± 0.34	26.1 ± 1.5	0.88 ± 0.034
CEFO	2.67 ± 0.11*	28.7 + 1.1*	0.84 ± 0.02
TYLO	2.55 ± 0.21*	28.9 ± 2.3*	0.85 ± 0.07
CEFO + TYLO	3.11 ± 0.54*	32.0 ± 0.7*	0.89 ± 0.02

Mean ± SEM * P < 0.05

Zagazig J. Pharm. Sci., June 1996,
Vol. 5, No. 1, pp. 115-119

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دراسة تأثير السيفوبيرازون والتيلوزين وخليط منهما على صورة الدم وعلى بعض المكونات الكيميائية الحيوية فى الأرانب

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يعتبر السيفوبيرازون من المضادات الحيوية النصف المخلقة من الجيل الثالث لعائلة السيفالوسبورين والتى تحتوى على البيبرازين وهو يستخدم فى علاج بعض الأمراض المعدية فى الإنسان والحيوان بينما التيلوزين أحد مضادات الميكروبات التى لا تركيب الماكروليدات وهو ذو فائدة فى علاج ميكوبلازما الجهاز التنفسى وكذا أمراض الجهاز التنفسى الأخرى.

لم يؤدى حقن السيفوبيرازون أو التيلوزين أو خليط منهما فى العضل لمدة خمسة أيام متتالية فى الجرعات تحت العلاجية إلى حدوث أى آثار ضارة على الدم أو الكبد أو الكلى بينما أدى حقن الجرعة العلاجية وضعفها إلى نقص معنوى فى عدد كريات الدم الحمراء والبيضاء والهيموجلوبين وحجم الكريات المضغوطة وكذا زيادة ملحوظة فى زمن البروثروبين كما أدى الحقن إلى حدوث زيادة معنوية فى مستوى أنزيمات الترانس أمينازس والصفراء ولم يكن هناك أى تأثير على نشاط إنزيم الفوسفاتيز القاعدى هذا علاوة على ارتفاع معنوى فى مستوى بولينا الدم والكرياتينين بدون أى تأثير على مستوى حامض البوليك.