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STUDY ON THIAMPHENICOL – INDUCED SIDE EFFECTS IN HAMSTERS

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Abstract

The present study investigated the possible adverse effects of thiamphenicol in hamsters following the administration of therapeutic doses. Thiamphenicol was administered by intramuscular injection at a dose rate of 35 mg/kg body weight once daily for 7 days. Functional changes of bone marrow, liver and kidney were monitored; bone marrow cytology and histopathology of the liver, kidneys and heart were performed. Enzymatic markers of hepatic cell damage were slightly increased in the treatment groups. Urea and creatinine concentrations were higher in thiamphenicol-treated hamsters than in the control group, suggesting an alteration in renal function. Haematology parameters were altered in thiamphenicol-treated hamsters and bone marrow smears showed slight bone marrow depression affecting all haematopoietic cell lines. Following histopathological investigations, no changes in liver morphology could be observed. Isolated degenerative changes were observed in the proximal convoluted tubule epithelium, without loss of integrity or changes in renal architecture. Myocardial arteriole and capillary stasis and incipient haemolysis were observed as well as alterations in longitudinally sectioned myocardiocytes.

Rezumat

Prezentul studiu a avut drept scop identificarea unor posibile efecte adverse la hamsteri în urma administrării intramusculare a tiamfenicolului, în doze terapeutice (35 mg/kg corp, o dată pe zi, 7 zile). Au fost urmărite eventualele modificări funcționale ale măduvei osoase hematogene, ficatului și rinichilor; au fost efectuate examene citologice ale măduvei osoase și examene histopatologice ale ficatului și rinichilor. În urma tratamentului, markerii enzimatici ai citolizei hepatice au prezentat creșteri ușoare. Ureea și creatinina au prezentat concentrații serice mai crescute la hamsterii tratați, sugerând o perturbare a funcției renale. Tabloul hematologic a fost modificat, iar frotiurile din măduva osoasă au indicat o ușoară depresie a acesteia, afectând toate liniile celulare. Examenele histopatologice nu au relevat modificări notabile ale morfologiei hepatice. Modificări degenerative izolate au fost observate la nivelul epiteliului tubilor contorți proximali, fără pierderea integrității și fără modificări ale arhitecturii renale. La nivelul cordului au fost observate fenomene de stază în arteriole și capilare, hemoliză incipientă și alterări ale cardiomiocitelor secționate longitudinal.

Keywords: thiamphenicol, hamsters, bone marrow depression, anaemia.

Introduction

The risk of adverse drug reactions has to be considered in establishing dosing regimens for drugs; although the occurrence of side effects is not always predictable, such events can often be reduced or avoided when the toxicological profile of a drug is known.

Thiamphenicol is a broad-spectrum antimicrobial agent used to control infections in humans and animals. It is bacteriostatic, at dosages used therapeutically, in both Gram-positive and Gram-negative aerobes and some anaerobes.

Thiamphenicol is a derivative of chloramphenicol, in which one aromatic nitro group (*p*-nitro) is substituted by a methylsulfonyl group. Some authors consider that thiamphenicol is one to two times less active than chloramphenicol, although it has similar activity against *Haemophilus* spp., *Bacteroides fragilis* and streptococci [6]. Thiamphenicol can be inactivated by bacterial chloramphenicol acetyltransferases, reflecting cross-resistance [1, 14].

Absorption and distribution of thiamphenicol are similar to those of chloramphenicol; thiamphenicol is equally well distributed into tissues and has an oral bioavailability of approximately 60%. Thiamphenicol is excreted unchanged in the urine [6].

Chloramphenicol is known to be hemotoxic in humans. There are two forms of toxicity. The first is a commonly-occurring, dose-related, reversible bone marrow depression, which develops during treatment. The second and rare effect, irreversible and often fatal, is represented by aplastic anaemia, which develops after treatment [14]. The bone marrow suppression caused by chloramphenicol is mainly due to DNA damage, characterized by helix destabilization and strand breakage, following the reduction of the nitro group. Similar phenomena have been observed in dogs and cats treated with high doses of chloramphenicol [7].

Thiamphenicol has been developed as a replacement for chloramphenicol to avoid haemotoxicity. Thiamphenicol does not produce the same effects as chloramphenicol on DNA because it does not contain a *p*-nitro group and is believed not to induce irreversible bone marrow aplasia and aplastic anaemia in humans, due to its different chemical structure [8, 11]. However, several studies have indicated that thiamphenicol is hemotoxic in rats and mice [2, 14, 15]. There is even some evidence that thiamphenicol causes a dose-dependent reversible bone marrow suppression more frequently than chloramphenicol [3, 6]. This reversible myelosuppression appears to be related to the blood concentration of thiamphenicol, the dose

and duration of treatment. Subsequently, reduced elimination may exacerbate haematopoietic changes, especially in patients with renal failure.

Thiamphenicol can also induce haemolysis in subjects with glucose-6-phosphate dehydrogenase deficiency, an enzyme that plays a role in the energy metabolism of red blood cells. Erdogan et al. (2004) reported a decrease of erythrocyte glucose-6-phosphate dehydrogenase activity under the influence of thiamphenicol.

Other side effects of thiamphenicol include testicular toxicity in rats and pruritus in some humans (less than 0.1%) [9, 11].

The aim of this study was to record the possible side effects of thiamphenicol following intramuscular administration to hamsters at a dose of 35 mg/kg b.w. Following treatment, clinical observations, haematological and biochemical parameters as well as bone marrow cytology and histopathology of the liver, kidney and heart are presented.

Materials and Methods

The experimental studies were conducted on European common hamsters (*Cricetus cricetus*). The treatment group consisted of 10 hamsters (5 males and 5 females), aged 4 months and weighing about 150 g. The control group included five hamsters of the same age and weight. The hamsters were kept in separate cages under a light/dark regime of 12/12 hours. Water was provided *ad libitum* and commercial hamster feed supplemented with wheat, corn, grass, cabbage and carrots was provided. All experiments were performed in compliance with European Communities Council Directive 1986 (86/609/EEC) and Ordinance No. 37 of the Romanian Government from February 2nd, 2002.

Thiamphenicol approved for use in pigs and cattle (Thiamphenicol 20% inj, Dutch Farm International BV, The Netherlands) was administered by intramuscular injection at a dose rate of 35 mg/kg b.w. once daily for 7 days. Throughout the study, the hamsters were monitored and any change in their general health status was recorded.

Hamsters were euthanized, by cervical dislocation, after anesthesia with xylazine and ketamine, on day 8. Blood samples were collected for biochemical evaluation (aspartate aminotransferase - AST, alanine aminotransferase - ALT, alkaline phosphatase - ALP, blood urea nitrogen - BUN, creatinine) and haematology evaluation (number of erythrocytes, hematocrit, hemoglobin, leukocyte formula). Bone marrow samples were collected (from the sternum and femur) for cytology. Samples of liver, kidney and heart were taken for histopathological examination [10]. Smears from bone marrow were stained by May-Grunwald Giemsa (MGG) method.

Samples of liver, kidney and heart were fixed in 10% formaldehyde solution. After the inclusion in paraffin, 5 cm sections were stained using the trichromic Masson method.

Statistical evaluation of the measured values was made using One-Way ANOVA.

Results and Discussion

Clinical observations

There was registered a discomfort immediately after the intramuscular administration, manifested as agitation and squeaking for a few minutes after injection. Slight apathy (which increased in time) was reported during the first three days of treatment. Erythema of the hairless regions and moderate pruritus at the injection site were reported. Skin rash was noted in 6 out of 10 hamsters in the treatment group. Four hamsters from the treatment group had diarrhea for the last 2 days of treatment.

Biochemical parameters evaluation

The clinical chemistry results are shown in Table 1.

Table I

Serum biochemical parameters of control and thiamphenicol-treated hamsters

Parameter	Group	Range	Mean $\pm$ Std. Dev.	Std. Err.	Reference interval
ALT (IU/L)	Control	37-45	41.4 $\pm$ 3.4	1.5	28-107 ⁽²⁾
	Treatment	46-65	54.9 $\pm$ 5.5**	1.7	25-70 ⁽³⁾
AST (IU/L)	Control	41-64	53.6 $\pm$ 9.5	4.2	53-202 ⁽²⁾
	Treatment	51-84	68.5 $\pm$ 11.6*	3.6	28-140 ⁽³⁾
ALP (IU/L)	Control	131-162	146.4 $\pm$ 12.8	5.7	8-202 ⁽²⁾
	Treatment	163-198	184.1 $\pm$ 12.5**	3.9	15-160 ⁽³⁾
BUN (mg/dL)	Control	17-26	22.4 $\pm$ 3.6	1.6	12-26 ⁽¹⁾
	Treatment	28-40	35.6 $\pm$ 4.1**	1.3	12-25 ⁽³⁾
Creatinine (mg/dL)	Control	0.3-0.5	0.44 $\pm$ 0.09	0.04	0.4-1.0 ⁽¹⁾
	Treatment	1.1-1.9	1.44 $\pm$ 0.32**	0.10	0.3-1.0 ⁽³⁾

⁽¹⁾Suckow *et al.*, 2012; ⁽²⁾Thrall *et al.*, 2004; ⁽³⁾Research Animal Resources, University of Minnesota - Reference Values for Laboratory Animals, *: indicates the presence of significant differences between thiamphenicol-treated group and control group (* p<0.05; ** p<0.01)

Although hepatic enzymes activity, a marker of liver cell damage, was slightly higher in the treated hamsters (ALT: 54.9 $\pm$ 5.5 IU/L; AST: 68.5 $\pm$ 11.6 IU/L; ALP: 184.1 $\pm$ 12.5 IU/L) than in the control group (ALT:

41.4±3.4 IU/L; AST: 53.6±9.5 IU/L; ALP: 146.4±12.8 IU/L), the values were still within reference interval for this species (Table 1). These findings show that liver function was not strongly impaired by thiamphenicol.

Urea and creatinine concentrations were significantly higher in hamsters treated with thiamphenicol (BUN: 35.6±4.1 mg/dL; creatinine: 1.44±0.32 mg/dL) than in the control hamsters (BUN: 22.4±3.6 mg/dL; creatinine: 0.44±0.09 mg/dL); these values exceeded the upper limit of the reference interval for this species. The obtained results suggest that thiamphenicol in the given dosing regimen affected the renal function.

Haematology

The haematology results are shown in Table II.

Table II

Haematological parameters of control and thiamphenicol-treated hamsters

Parameter	Group	Range	Mean ± Std. Dev.	Std. Err.	Reference interval
RBC (x10 ⁶ /μL)	Control	7.9-9.8	8.82±0.84	0.37	8.1-8.7 ⁽¹⁾ ; 6.8-7.5 ⁽²⁾ , 2.7-12.3 ⁽³⁾
	Treatment	5.9-7.4	6.75±0.49*	0.15	
Ht (%)	Control	36-44	40.0±3.4	1.5	30-50 ⁽²⁾ ; 30-59 ⁽³⁾
	Treatment	23-32	26.8±2.9*	0.9	
Hb (g/dL)	Control	15.3-16.3	15.78±0.43	0.19	15.7-18.0 ⁽²⁾ ; 10.0-19.2 ⁽³⁾
	Treatment	10.2-13.8	12.14±1.06*	0.34	
WBC (x10 ³ /μL)	Control	6.4-8.3	7.46±0.71	0.32	5-10 ⁽²⁾ ; 3-15 ⁽³⁾
	Treatment	4.0-5.9	5.15±0.64*	0.20	
Neutrophils (%)	Control	19-29	24.0±4.1	1.8	26 ⁽¹⁾ ; 22-29 ⁽²⁾ ; 17-35 ⁽³⁾
	Treatment	22-31	26.3±3.3 ^{NS}	1.0	
Lymphocytes (%)	Control	66-77	71.4±4.5	2.0	69 ⁽¹⁾ ; 67.0-73.5 ⁽²⁾ ; 60-80 ⁽³⁾
	Treatment	64-76	70.0±3.9 ^{NS}	1.2	
Monocytes (%)	Control	0-3	1.6±1.1	0.5	0.7-1.2 ⁽¹⁾ ; 2.4-2.5 ⁽²⁾ ; 0-5 ⁽³⁾
	Treatment	0-2	1.3±0.7 ^{NS}	0.2	
Eosinophils (%)	Control	1-3	1.8±0.8	0.4	1-1.8 ⁽¹⁾ ; 0.7-1.1 ⁽²⁾ ; 0-5 ⁽³⁾
	Treatment	1-2	1.3±0.5 ^{NS}	0.2	
Basophils (%)	Control	1-2	1.2±0.4	0.2	0.5-2 ⁽²⁾ ; 0-5 ⁽³⁾
	Treatment	0-2	1.1±0.9 ^{NS}	0.3	

⁽¹⁾Emminger *et al.*, 1975; ⁽²⁾Van Hoosier & McPherson, 1987; ⁽³⁾Suckow *et al.*, 2013; *: indicates the presence of significant differences between thiamphenicol-treated group and control group (* p<0.01); ^{NS}: not significant differences.

In the treated group there were registered slight changes in the haematological parameters assessed: mainly a decrease in the erythrocytes. Count lower levels of haemoglobin and a lowered value of the haematocrit. The leukocytes count was comparable to the reference interval for this species.

Although RBC, Hb and Ht values were lower in the thiamphenicol-treated group (RBC: $6.75 \pm 0.49 \times 10^6/\mu\text{L}$; Hb: $12.14 \pm 1.06 \text{ g/dL}$; Ht: $26.8 \pm 2.9\%$) than in the control group (RBC: $8.82 \pm 0.84 \times 10^6/\mu\text{L}$; Hb: $15.78 \pm 0.43 \text{ g/dL}$; Ht: $40.0 \pm 3.4\%$), they were close to the lower limit of the reference interval for this species (according to various authors). However, the decrease of RBC, Hb and Ht suggests a certain degree of toxicity exerted by thiamphenicol on bone marrow, especially on the erythroid lineage.

Cytology and histopathology

The bone marrow smears showed hypocellularity, with a left shift of the maturation curve and an increased percentage of immature cell forms, as an expression of the inhibition of maturation and division (Fig. 1).

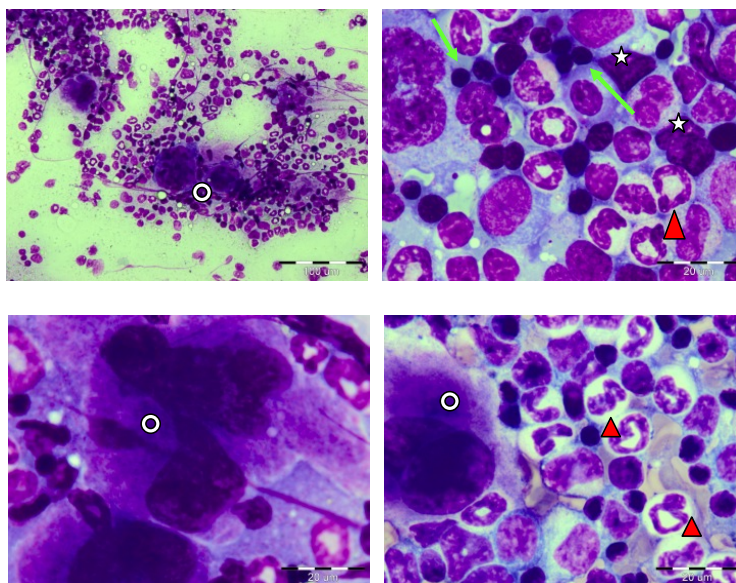


Figure 1.

Cytology of the bone marrow of hamsters treated with thiamphenicol for 7 days. Heterogeneous aspect of the bone marrow in femur and sternum.

Presence of precursor elements of both the erythroid lineage (arrow) and myeloid lineage (white star). Mature neutrophils (triangle) and a variable number of basophilic promegakaryocytes and megakaryocytes (white circle) were found in all smears. (MGG stain, ob. 20 and 100)

The results of bone marrow cytology confirmed that there was a haematopoietic disorder that included all haematopoietic cell lineages. The toxic hyporegenerative anaemia, evidenced by the presence of basophilic and polychromatophilic erythroblasts, can lead to blood disorders such as erythropenia and leukocytopenia. Individuals with bone marrow suppression (impaired myeloid and erythroid lines), had microscopic morphological abnormalities, manifested as vacuolation of bone marrow blast cells and depression of erythropoiesis.

The cytology of bone marrow could be correlated with the recorded changes of haematological parameters, the decrease of erythrocytes count, haemoglobin and haematocrit being a natural consequence of the alterations observed in smears made from bone marrow.

There were minor and variable changes in liver structure observed in the treated hamsters that varied between individuals. The observed changes included stasis in centrilobular veins (Figure 2).

In general, the liver architecture remained preserved. Centrilobular hepatocytes exhibited a low degree of granular degeneration, without hepatocyte necrosis. This was considered to be a non-specific, reversible, low severity lesion, because it was observed inconsistently in the animals from the treatment group.

We hypothesize that it is related to individual variability rather than to the action of thiamphenicol. Intravascular haemolysis was registered in two animals and it coexisted with centrilobular vein stasis. Haemolysis was observed only in two hamsters from the treatment group, thus excluding the possibility that it may have been occurred during euthanasia (Figure 2).

In three of the ten hamsters there were isolated islands of hepatic haematopoiesis, which can be interpreted as an adaptive response to bone marrow suppression.

In conclusion, liver morphology was not significantly affected by the administration of thiamphenicol. The hepatocellular changes were of a reversible degenerative nature, and the minor morphological changes reported did not led to functional consequences as altered levels of serum enzymes markers of liver cell damage (AST, ALT, ALP).

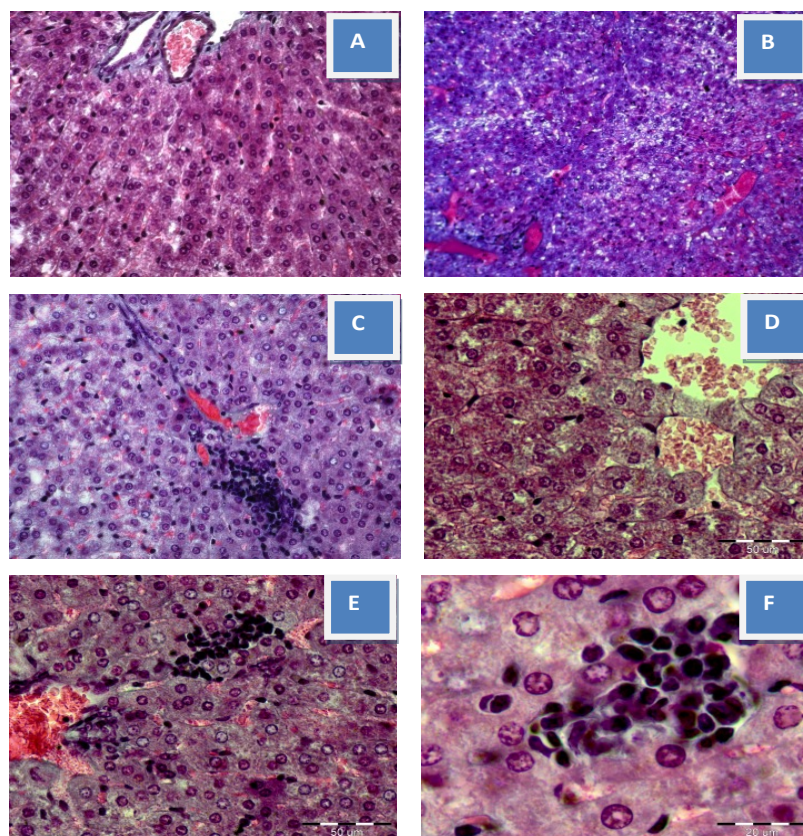


Figure 2.

Histopathology of the liver of hamsters treated with thiamphenicol for 7 days: A – Unchanged general structure; minor vascular reaction – hyperaemia (Trichromic Masson stain, ob. 20). B – Overview: the cytoplasm of hepatocytes of different stains - oxyphil, basophilic, clear with fine granulation. Intravascular hemolysis (bottom left corner) (Trichromic Masson stain, ob. 10). C – Microarea of haematopoiesis, unchanged liver parenchyma (Trichromic Masson stain, ob. 20). D – Hyperaemia - erythrocytes morphologically unchanged (Trichromic Masson stain, ob. 40). E – Stasis and incomplete hemolysis in centrilobular vein; microarea of haematopoiesis (Trichromic Masson stain, ob. 40). F – Extramedullary haematopoiesis microarea (Trichromic Masson stain, ob. 100)

In the kidneys, marked interstitial stasis was noticed, while in the renal glomeruli stasis was observed inconsistently; intravascular hemolysis was present. However, in general, the renal tissue architecture was preserved. Only isolated focal degenerative changes, vacuolar degeneration,

without loss of integrity of renal tubules epithelium, were observed in the proximal convoluted tubule epithelium (Figure 3). Structural changes were considered to be of a reduced intensity and potentially reversible, taking into account the lack of tubular necrosis. The presence of pigment in the renal tubule lumen was also noted. The presence of hemosiderin at this level indicated that stasis had been present for some time in the kidneys and had not developed as a result of euthanasia (Figure 3).

Histopathological changes in the kidneys could be correlated with the recorded functional changes (increased concentrations of blood urea nitrogen and creatinine), but did not differ greatly from control group of hamsters.

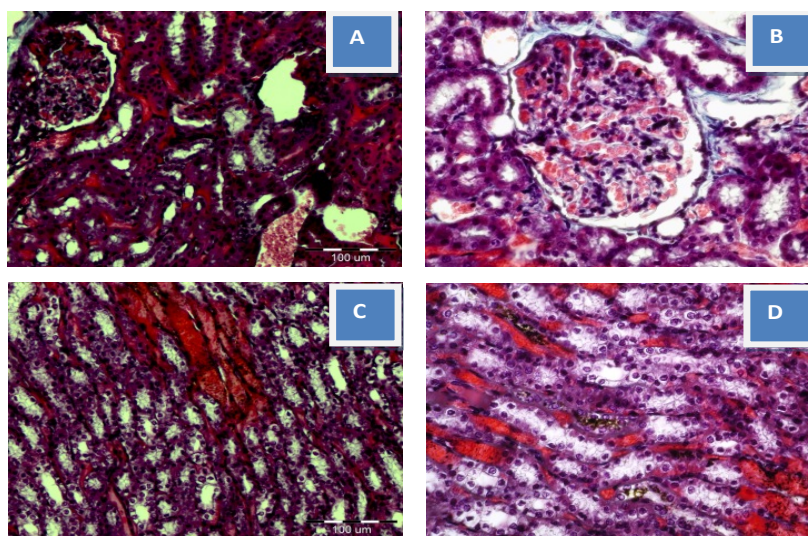


Figure 3.

Histopathology of the kidneys of hamsters treated with thiamphenicol for 7 days.

A – Cortical area - interstitial and glomerular stasis and haemolysis; oxyphyl cytoplasm of the convoluted tubules epithelium (Trichromic Masson stain, ob. 20). B – Cortical area - glomerular stasis and tubular degeneration (Trichromic Masson stain, ob. 40). C – Medullary area - stasis and interstitial hemolysis (Trichromic Masson stain, ob. 20). D – Medullary area - interstitial renal stasis and hemosiderin deposits in the renal tubules lumen (Trichromic Masson stain, ob. 40)

In the myocardium, stasis in arterioles and capillaries and incipient haemolysis were observed. Variable and segmental homogenization of longitudinally sectioned oxyphyl myocardiocytes was also noticed (Figure 4).

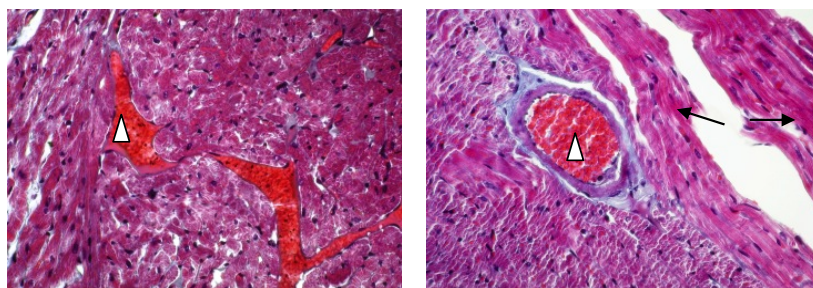


Figure 4.

Histopathology of the heart of hamsters treated with thiamphenicol for 7 days: stasis and weakly expressed haemolysis in the arterioles and capillaries (white triangle), homogenization and oxyphil segmentation of myocardiocytes (arrow) (Trichromic Masson stain, ob. 20)

In relation to bone marrow injuries, following this research, the administration of thiamphenicol in hamsters in the specified dose-rates and period is considered to be safe, taking into account that bone marrow depression is thought to be reversible, as reported by several studies [6, 14, 15]. Related to injuries caused by thiamphenicol in kidneys and liver tissue, although they were low as intensity and inconsistent, we recommend that the treatment with thiamphenicol to be accompanied by the administration of hepatoprotective products and sufficient water supply.

Special precautions are considered to be necessary in elderly patients and in those with kidney disorders: increased dosage intervals and/or decreased dose-rates, depending on the creatinine clearance; moreover, thiamphenicol should be avoided in individuals with anaemia or immunosuppression.

Conclusions

The administration of thiamphenicol to hamsters by intramuscular injection at a dose rate of 35 mg/kg b.w. once daily for 7 days resulted in minor changes in hepatic enzymes activity and significant increases of serum urea and creatinine levels. Haematologically, the most significant changes were the decrease of erythrocyte counts, haemoglobin and haematocrit values. Cytological examination of bone marrow smears showed hypocellularity and bone marrow suppression, with impaired myeloid and erythroid lineages. Histopathology examination did not reveal significant changes of liver and myocardium, only isolated focal degenerative changes were observed in kidneys.

References

1. Adams P.E., Varma K.J., Pomers T.E., Lamendola J.F. Tissue concentrations and pharmacokinetics of florfenicol in male veal calves given repeated doses. *Am. J. Vet. Res.*, 1987; 48(12): 1725-1733.
2. Ando J., Ishihara R., Imai S., Takano S., Kitamura T., Takahashi M., Yoshida M., Maekawa A., Thirteen-week subchronic toxicity study of thiamphenicol in F344 rats. *Toxicol. Lett.*, 1997; 91(2): 137-146.
3. Duck P.D., Dillon J.R., Eidus L., Effects of thiamphenicol and chloramphenicol in inhibiting *Neisseria gonorrhoeae* isolates. *Antimicrob. Agents Chemother.*, 1978; 14(5): 788-790.
4. Emminger A., Reznik G., Reznik-Schuller H., Mohr U., Differences in blood values depending on age in laboratory-bred european hamsters (*Cricetus cricetus* L.). *Lab. Anim.*, 1975; 9: 33-42.
5. Erdogan O., Ciftci M., Ciltas A., Hisar O., Inhibition effects of some antibiotics on the activity of glucose 6-phosphate dehydrogenase enzyme from rainbow trout (*Oncorhynchus mykiss* Walbaum, 1792) erythrocytes. *Turk. J. Vet. Anim. Sci.*, 2004; 28: 675-681.
6. Giguere S., Prescott J.F., Baggot J.D., Walker R.D., Dowling P.M. (Eds.), Antimicrobial Therapy in Veterinary Medicine. 4th ed., Blackwell Publishing, Ames, Iowa, U.S.A., 2006; 245.
7. Harvey J.W., Atlas of veterinary hematology – blood and bone marrow of domestic animals. Saunders Company, Elsevier, Philadelphia, U.S.A., 2001.
8. Lashev L., Haritova A., Comparative allometric analysis of pharmacokinetics of florfenicol and thiamphenicol. *Bulg. J. Vet. Med.*, 2006; 9(2): 115-122.
9. Maita K., Kuwahara M., Kosaka T., Inui K., Sugimoto K., Takeuchi Y., Hatakenaka N., Harada T., Yasuhara K., Mitsumori K., Testicular toxicity of thiamphenicol in Sprague-Dawley rats. *J. Toxicol. Pathol.*, 1999; 12: 27-34.
10. Păunescu A., Dima R., Ponopal M.C., Brinzea G., Iosub I., Soare L.C., Drăgănescu D., Dinu-Pirvu C., The protective role of malvidin on the hematological, biochemical and histopathological parameters of marsh frog (*Pelophylax ridibundus*) exposed to sublethal doses of Roundup®. *Farmacia*, 2013; 61(3): 439-447.
11. Reich A., Ständer S., Szepletowski J.C., Drug-induced pruritus: a review. *Acta Derm. Venereol.*, 2009; 89: 236-244.
12. Skolimowski I., Knight R.C., Edwards D.I., Molecular basis of chloramphenicol and thiamphenicol toxicity to DNA *in vitro*. *J. Antimicrob. Chemother.*, 1983; 12(6): 535-542.
13. Suckow M.A., Stevens K.A., Wilson R.P., The laboratory rabbit, guinea pig, hamster, and other rodents. Academic Press, Elsevier, San Diego, U.S.A., 2012.
14. Șerban C., Mitrea N., Ordeanu V., Research on bacterial resistance to antibiotics, in suspicion of nosocomial infections, in major hospitals in Bucharest. *Farmacia*, 2012; 60(3): 350-357.
15. Thrall M.A., Baker D.C., Campbell T.W., DeNicola D.B., Fettman M.J., Lassen E.D., Rebar A., Weiser G., Veterinary hematology and clinical chemistry. Wiley-Blackwell, Ames, Iowa, U.S.A., 2004.
16. Turton J.A., Andrews C.M., Havard A.C., Robinson S., York M., Williams T.C., Gibson F.M., Haemotoxicity of thiamphenicol in the BALB/c mouse and Wistar Hanover rat. *Food Chem. Toxicol.*, 2002; 40(12): 1849-1861.
17. Turton J.A., Havard A.C., Robinson S., Holt D.E., Andrews C.M., Fagg R., Williams T.C., An assessment of chloramphenicol and thiamphenicol in the induction of aplastic anaemia in the BALB/c mouse. *Food Chem. Toxicol.*, 2000; 38(10): 925-938.
18. Van Hoosier G.L.Jr., McPherson C.W., (Eds.). - Laboratory hamsters. Academic Press, Inc. Orlando, U.S.A., 1987.

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