International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 2 (1): 24-27, 2005
ISSN 1811-7775

The Tissue Kinetics and Residues of Chloramphenicol in Sokoto Red Goats

[1]E.U. Etuk and [2]P.A. Onyeyili
[1]Department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto
[2]Department of Veterinary Physiology and Pharmacology, University of Maiduguri,
P.O. Box 2298, Sokoto, Nigeria

Abstract: The kinetics and residue of chloramphenicol in the various tissues of the Sokoto red goats has been studied using colorimetric assay method. The results indicate that, Variable concentrations of chloramphenicol were detected 5 min after a single intravenous dose of the drug (25 mg kg^{-1}) in various tissues of the animal. The drug persisted up to 240 h (10 days) in the skeletal muscle of the goats. The kinetics of the drug also show variation among the various tissues considered. These findings are of public health significance.

Key words: Chloramphenicol, concentrations in tissues of Sokoto red goats

INTRODUCTION

Over the years since its discovery in 1947, chloramphenicol has continued to generate a lot of interests and controversies among scientists the world over, hence a significant amount of studies has been done and reported on the drug[1-3].

Comparative plasma, tissue and excretory studies of any drug do have a significant public health implication[2]. The fact that large volumes of drugs are used in food producing animals is well documented[4]. It has been estimated that eighty percent of the animal protein consumed in the United States originate from animals fed medicated feeds for part or for their entire period[5,6]. Presently, it is anticipated that nearly one hundred percent of the animals have been exposed to some form of medication in the control, prevention and treatment of diseases to enable ample quantities of protein in the human diet.

Consequently, the justification for the use of drugs in animal production is also a well-documented fact[7]. Problems associated with use of drugs in food producing animals not only revolves about the detection of drug residues in tissues but also involves the detection of metabolites which may be of greater significance from a public health standpoint than the parent or unmetabolised drug. For this reason, pharmacokinetic studies need to be conducted in a number of animal species to fully comprehend the differences that exist in the metabolic transformation of drugs. It is well known that marked differences exist among the various animal species in the metabolism of drugs and chemicals[3].

The conventional methods used to establish and characterize the residual nature of a drug in food animals involve several time-consuming and costly procedures. Many of the disadvantages and problems associated with conventional residue studies have been discussed[8].

The potential use of pharmacokinetics to better define the residual nature of a drug in tissues of food animals has been discussed in detail in past literature report. The pharmacokinetic approach to the development of a drug residue profile may offer significant advantages from the standpoint of subsequent residue surveillance[8]. The proper understanding and adequate data base about the duration of certain antibiotics used in food animals will lead to the observation of appropriate withdrawal time. Also if a relationship could be established between tissue concentrations and plasma and/or urine concentrations of the drug, it would be possible to predict when the tissue concentrations in an animal had reached preset tolerance limits[8].

Despite the unrestricted use of chloramphenicol in the treatment of both human and animals infections in this environment there is no available data on the residue profile of the drug especially in the animal tissues which is often use as food for humans. Thus appropriate withdrawal time after the use of the drug is not being observed to avoid food contamination by the antibiotic. The present study was intended to provide information about this problem.

MATERIALS AND METHODS

Twenty four adult red Sokoto goats of mixed sexes, weighing between 15.0 to 25 kg with a mean of 18.3 kg

Corresponding Author: Dr. E.U. Etuk, Department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria Tel: 2348036149880

were used for this study. All the animals were certified clinically healthy at the onset of the study. They were housed together in goat pens, fed with hay and concentrates and water provided *ad libitum*.

Two goats were sacrificed for the preparation of control tissues and tissues standards before the drug administration. Chloramphenicol was then administered intravenously at the dose of 25 mg kg^{-1} to the goats and two animals were randomly selected and sacrificed at 0.08, 0.5, 1, 6, 12, 24, 48, 72, 120, 240 and 288 h post drug administration.

Ten grams of tissue samples (liver, skeletal muscle, brain, lungs, kidney, spleen and bone marrow) were taken post-mortem from the animals at each time of sample collection.

Chloramphenicol contents of the tissues were determined colorimetrically using the method developed by Kakemi *et al.*[9] modified by Hughes and Diamond[10], Watson[11]. Briefly, two grams of the tissue was taken at a time, crushed into tiny particles and trichloroacetic acid was added to coagulate the proteins. The filtrate was treated with phosphate buffer, amylacetate, sodium hydroxide and isonicotinic acid. The density of the resultant colour change observed was measured with Spectrophotometer at 430 nanometre.

The half-lives and the elimination constants of the drug were determined using standard procedures[12].

RESULTS

The result of this study indicates that chloramphenicol administered intravenously to Sokoto red goats at 25 mg g^{-1} body is readily absorbed. Table 1 indicate that measurable levels of the drug were obtained in the various tissues of the animals 0.08 h after the drug administration.

The peak concentrations of the drug were established in the various tissues at the same 0.08 h (5 min) post drug administration except in the brain of the Sokoto red goats and its skeletal muscles. The highest concentrations of the drug obtained in the liver, bone marrow, kidney, spleen, lungs and heart were 68.96, 56.20, 53.01, 41.33, 39.00 and 34.61 μg g^{-1}, respectively. The concentrations showed continuous decline in these tissues until the minimum levels of 0.38, 0.12, 0.83 and 0.11 μg g^{-1} were measured respectively in the liver, bone marrow, kidney and spleen of the animals at 120 h (5 days) after the drug administration (Table 1). However, the minimum concentrations of the drug in the lungs and heart of the goats (0.14 and 0.1 μg g^{-1}), respectively were obtained after 72 h.

The brain at 0.08 h had a concentration of 0.1 μg g^{-1} and this increased to 0.63 μg g^{-1} at 0.50 h. Thereafter, there was a continuous decrease and at 24 h post drug administration, the concentration came down to 0.18 μg g^{-1}. In the case of skeletal muscle, concentration of 0.93 μg g^{-1} was obtained at 0.08 h in the animals, thereafter the concentration increased and at 1.0 h, a peak concentration of 4.62 μg g^{-1} was obtained in the goats. Least detectable levels of the drug were obtained in the skeletal muscle at 240 h (0.12 μg g^{-1}). The half-lives of the drug in the liver, kidney, brain, heart, lungs, bone marrow, spleen and skeletal muscle were 1.375, 3.554, 21.00, 1.95, 0.785, 1.529, 0.846 and 23.896 h while the elimination constants were 0.504, 0.195, 0.033, 0.355, 0.883, 0.453, 0.819 and 0.029, respectively (Table 2).

DISCUSSION

The distribution of chloramphenicol after intravenous administration of a single bolus (25 mg kg^{-1}) to the various tissues and organs examined was very rapid. The drug was detected in all the tissues examined 5 min (0.08 h) after administration. The distribution of the chloramphenicol to the tissues and organs of the goats was not uniform. The tissues sampled in diminishing order of chloramphenicol concentrations were Liver (68.96 μg g^{-1}), spleen (41.33 μg g^{-1}), lungs (39.0 μg g^{-1}), heart (34.61 μg g^{-1}), skeletal muscle (0.93 μg g^{-1}) and brain (0.21 μg g^{-1}).

This result has shown that, the concentrations of chloramphenicol at 5 min were relatively higher in all the tissues examined (except skeletal muscle and brain tissue) than 25.63±2.01 μg mL^{-1} in plasma of the Sokoto red goats[13].

In the liver, the concentration of chloramphenicol was approximately two and half times that of the plasma. The concentrations in kidney, spleen and bone marrow were about twice that of the plasma. The lungs and heart drug concentration was about one and half times the amount of the drug in plasma[13]. These variable tissue concentrations of chloramphenicol recorded in this study is in agreement with the previous findings[3,14,15]. The concentrations of chloramphenicol in the corresponding tissues were lower in the present study than when Watson and McDonald[2] assayed chloramphenicol chemically in the tissue homogenates of goats at 1.5 h after dosing the animals orally with 50 mg kg^{-1} body weight of the drug.

In this study, the pattern of chloramphenicol distribution in skeletal muscle and brain tissues were observed to differ from others. There was an initial period

Table 1: Chloramphenicol concentrations in the various tissues (μg g^{-1}) of the Sokoto red goats treated with a single dose of the drug

Time after injection (h)	Liver	Bone-marrow	Kidney	Spleen	Lungs	Heart	Skeletal muscle	Brain
0.08	68.96	56.20	53.01	41.33	39.00	34.61	0.93	0.10
0.50	35.08	26.11	26.22	23.11	19.31	18.03	1.26	0.36
0.50	18.34	14.03	13.18	11.03	8.78	8.94	2.98	0.63
1.00	14.30	11.33	10.23	9.61	7.01	6.82	4.62	0.41
6.00	10.98	8.12	7.03	6.22	5.21	4.03	3.98	0.32
12.00	8.42	6.01	5.16	4.08	3.04	3.22	3.90	0.28
24.00	7.06	3.98	4.33	2.63	1.33	1.04	3.64	0.18
48.00	6.32	1.32	4.02	0.86	0.98	0.46	2.98	0.00
72.00	2.09	0.89	3.61	0.52	0.14	0.10	1.07	0.00
120.00	0.38	0.12	0.83	0.11	0.00	0.00	0.54	0.00
240.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.00
288.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Average values based on two observations

Table 2: The half-lives and elimination rate constants in various tissues of the goats treated with 25 mg g^{-1} of chloramphenicol intravenously

Plasma/Tissues	Half-lives (h)	Elimination constant (h^{-1})
Plasma	2.450±1.23	0.350±0.18
Liver	1.375	0.504
Kidney	3.554	0.195
Brain	21.000	0.033
Heart	1.950	0.355
Lungs	0.785	0.883
Bone marrow	1.529	0.453
Spleen	0.846	0.819
Skeletal muscle	23.896	0.029

of gradual build up in the concentration of the drug within the said tissues until a peak concentration of 0.63 and 4.42 μg g^{-1} were reached in the brain and skeletal muscles at 0.5 and 1 h, respectively. This was then followed by another phase of gradual decline. In an earlier study the concentration of the drug present in the brain at the first sampling time was lower, than that of the blood, however, the concentration in the brain later increased and at 12 h post drug administration it was 9.2 μg g^{-1} which was much higher than that of the blood (0. 8 μg mL^{-1}) at the same time period[2].

The significantly high concentrations of chloramphenicol in the kidney obtained in this study may be attributable to the fact that, the kidney is the major excretory organ for this drug. Chloramphenicol succinate is known to be rapidly cleared from plasma by the kidneys[16,17]. The high concentrations present in the liver and lungs could be due to the fact that these organs serve as the possible sites for the metabolism of this drug. Although it is unclear where the hydrolysis of chloramphenicol occurs *in vivo*; the esterases of the liver and lungs all may be involved[18].

The above reason may not be able to explain the high concentrations of chloramphenicol in the bone marrow and spleen (approximately two times that of plasma). However, there could exist a special affinity between chloramphenicol and the red blood cells or immature/regenerative tissues. Slue *et al.*[19] reported that, mammalian erythropoietic cells seem to be particularly sensitive to chloramphenicol. The most important adverse effect of chloramphenicol is on the bone marrow; it is hoped that the development of other forms of chloramphenicol with less tendency to accumulate in the bone marrow may reduce the risk of the adverse effect. Previous experiments did not study the concentration of chloramphenicol in the bone marrow despite the adverse effect of the drug on this tissue. In the present study chloramphenicol occurred in the bone marrow of goats treated with a single intravenous dose of the drug (25 μg kg^{-1}) for upto 120 h (5 days) and this could be a factor in the toxicity of the drug. However, further studies need to be undertaken to determine correlation between chloramphenicol concentration in the bone marrow and the known adverse effects of the drug.

Due to the different rates at which chloramphenicol is distributed to various tissues, it might be beneficiary if the dosage and frequency of administration of the drug be selected based on the site of the infection. Similar suggestion had previously been made by Watson and McDonald[2]. These selective dosages may result in the reduction of the amount of the drug introduced into the system and thereby minimising the risk of toxicity.

The findings that, a single intravenous dose of chloramphenicol at 25 mg kg^{-1} can persist in the edible tissues of the goats up to 240 h (10 days) after administration is of public health significance. It might be possible to predict when the tissue concentrations of the drug in goats has reached a pre-set tolerance limit and thus suitable for human consumption without antibiotics contamination. While the half-life of chloramphenicol in plasma was longer than that in the lungs, spleen, heart, bone marrow and liver it was shorter than those of kidney, brain and skeletal muscle of the goats.

This study therefore concludes that, the withdrawal time after the use of chloramphenicol in the Sokoto red goats should be more than ten days to avoid the antibiotic food contamination.

REFERENCES

1. English, P.B., 1961. Plasma and tissue concentrations of chloramphenicol in the pig. Australian Vet. J., pp: 9-11.
2. Watson, A.D.J. and P.J. McDonald, 1976. Distribution of chloramphenicol in some tissues and extravascular fluids of dogs after oral administration. J. Vet. Pharmacol. Ther., 5: 557-559.
3. Mercer, H.D., E.H. George, E. Patricia, D. H. Long and T. Powers, 1978. Drugs residues in food animals. 1. Plasma and tissue kinetics of chloramphenicol in young cross-breed swine. J. Vet. Pharmacol. Ther., 1: 19-36.
4. Mercer, H.D., 1975. Antimicrobial drugs in food producing animals; control mechanisms of government agencies. Vet. Clinics of North America, 5: 3-34.
5. Van Houweling, C.D., 1971. Antibiotic Residues in Animal Food Products. Annals of the New York Academy of the United States of America, 182: 441.
6. Lehmann, R.P., 1972. Implementation of the recommendations contained in the report to the commissioner concerning the use of antibiotics in animal feeds. J. Anim. Sci., 35: 1340-1341.
7. Morrison and Munro, 1969. National Academy of Science Publication. No. 1679. Washington, D.C.
8. Mercer, H.D., J.D. Baggot and R.A. Sams, 1977. Application of pharmacokinetics methods to the drug residue profile. J. Toxicol. Environ. Health, 2: 787-801.
9. Kakemi, K., T. Arita and S. Ohashi, 1962. Absorption and excretion of drugs IV. Determination of chloramphenicol in blood. J. Pharm. Soc. Japan, 82: 342-347.
10. Hughes, D.W. and L.K. Diamond, 1964. Chloramphenicol in blood, simple chemical estimations in patients receiving multiple antibiotics. Antibiot. Sci., 114: 296-297.
11. Watson, A.D.J., 1979. Plasma chloramphenicol concentration in cats after parental administration of chloramphenicol sodium succinate. J. Vet. Pharmacol. Ther., 2: 123-127.
12. Baggot, J.D., 1977. Principles of Drug Disposition in Domestic Animals: The Basis of Veterinary Clinical Pharmacology. 1st Edn., W.B. Saunders Company. Philadelphia.
13. Babale, B.K., 1985. Effects of fever on plasma levels and pharmacokinetics of chloramphenicol in goats. In: Desertification Submitted to Tuskegee Institute, Alabama, USA.
14. Davis, E.L., J.D. Baggot and T.E. Powers, 1972. Pharmacokinetics of chloramphenicol in domesticated animals. Am. J. Vet. Res., 33: 2259-2265.
15. Davis, L.E. and C.N. Davis, 1974. Dosage regimens of chloramphenicol in domesticated animals. J. South African Vet. Assoc., 45: 77-79, 142.
16. Slaughter, R.L., J.A. Pieper, F.B. Cerra, B. Brodsky and J.R. Koup, 1980. Chloramphenicol sodium succinate kinetics in critically ill patients. Clin. Pharmacol. Ther., 28: 69-77.
17. Mulhall, A., J. Louvois and R. Hurley, 1983. The pharmacokinetics of chloramphenicol in the neonate and young infant. J. Antimicrob. Chemother., 12: 629-639.
18. Shann, F., V. Linnemann, A. Mackenzie, J. Barker, M. Gratten and N. Crinis, 1985. Absorption of chloramphenicol sodium succinate after intramuscular administration in children. New Engl. J. Med., 313: 410-414.
19. Shu, X.O., Y.T. Gao, M.S. Linet, L.A. Brinton, R.N. Gao, F. Jin and J.F. Fraumeni (Jr.), 1987. Chloramphenicol use and childhood leukaemia in Shanghai. Lancet, 2: 934-937.