Journal of Animal and Veterinary Advances 3 (1): 36-38, 2004

Pharmacokinetic Study of Cefixime in the Sheep the and Cattle

[1]A.S. ElDalo, [1]A.S. Ali, [1]S.I. Shaddad and [2]A.H. Mohamed
[1]Department of pharmacology faculty of pharmacy, University of Khartoum. Khartoum, Sudan
[2]Department of pharmacology and toxicology, Medicinal and Aromatic Plant Research Institute, NCR, P.O.Box 2404 Khartoum Sudan

Abstract: In the present work the pharmacokinetic parameters of a new third generation cephalosporin -Cefixime- were evaluated in two species of animals: ovine (the sheep) and bovine (the cattle). One capsule of 400 mg Cefixime was administered to each of six sheep and six cattle in two separate experiments. Plasma concentrations of Cefixime were determined micro-biologically. The pharmacokinetic parameters were computed according to the one-compartment open model of the computer program. The results were statistically analyzed by SPSS program. In the sheep: elimination half-life was 5.96 ± 0.88 hours, clearance 62.48 ± 7.8 L/hour, volume of distribution 4.67 ± 0.61 ml kg^{-1}, area under the plasma concentration curve $6.88 \pm 0.78 \mu g$ hr ml^{-1}, maximum plasma concentration $0.63 \pm 0.06 \mu g$ ml^{-1} and the time to achieve maximum plasma concentration was 4.8 ± 0.22 hours. In the bovine group: elimination half-life was 13.09 ± 0.81 hours, clearance 47.48 ± 5.03 L/hour, volume of distribution 5.02 ± 1.77 ml kg^{-1}, area under the plasma concentration curve $8.98 \pm 1.07 \mu g$ hr ml^{-1}, maximum plasma concentration $0.50 \pm 0.03 \mu g$ ml^{-1} and the time to reach maximum plasma concentration was 2.34 ± 0.51 hours. These finding suggest the rational application of cefixime in veterinary medicine.

Key words: Pharmacokinetic, cefixime, sheep, cattle

Introduction

β-lactam antibiotics constitute more than 60% of the world's antibiotic usage and cephalosporins are the fastest-growing group within the â-lactamase. (Durckheimer *et al.*, 1982). In deed cephalosporins are now the most prescribed of all antimicrobial agents which fact due to their remarkable therapeutic efficacy inasmuch as most are very recent addition to the antimicrobial armamentarium. (Mandell, 1985) Cephalosporins have low frequency of adverse effects in relation to antimicrobials in general. (Ernest Jawetz, 1995)

Cephalosporins have been classified into groups or "generations" depending mainly on the spectrum of antimicrobial activity: First-generation, second-generation, third-genereation, and fourth generation cephalosporins. (Ernest Jawetz, 1995).

The third generation, orally active cephalosporin Cefixime was shown to be effective against various human ailments including drug resistant enteric fever (Farinati *et al.*, 1993; Adam, 1995; Hausen *et al.*, 1995 and Memon *et al.*, 1997). Despite the exellent bioavailability of cefixime in human subject (Brittain *et al.*, 1985 and Faulkner *et al.*, 1988) but dose not yet- receive any pharmacokinetic studies in big animals. The present study is an attempt to persuade its pharmaceuticals parameters in sheep and cattle, the most economically important livestock in Sudan.

Materials and Methods

Materials

Cefixime trihydrate (micronized)	Fujisawa pharmaceutical Co.Ltd. Japan Hikma pharmaceutical, Jordan.
Cefixime Trihydrate (Capsule)Heparin sodium	Koch-Light Laboratories Ltd. England

Six healthy sheep (30-37 kg) and six healthy cattle (250-300 kg) of local bread were selected and subjected to physical examination. All of them were healthy and normal. The animals were kept for 7 days with free access to balanced food and water. At the day of the experiment a sample of 5 ml of blood was withdrawn from each animal (control) and then each animal was dosed orally with 1 capsule cefixime (400 mg). Following drug administration blood samples 5 ml each was drawn for 24 hours. The blood samples were centrifuged immediately and the plasma obtained was stored rapidly at -20°C until assayed.

A suspension containing about 10^8-10^9 colony-forming units per ml was prepared. (Monica, 1991) This solution was used.

The cup-plat agar diffusion method was adopted to assess the anti microbial activity of the standard antibiotic in the plasma using the previous solution. (B.P. 1993) The resultant growth inhibition zone were measured, averaged, and tabulated. These results were drawn as a curve of concentration versus zone diameter to be linear over the range (0.018-40μg ml^{-1}) to give a reference curve for the obtained plasma from animals.

The same method was adopted to assess the ant microbial activity of the antibiotic in the animal plasma. The concentration of the unknown samples was read from the standard curve. The concentration was tabulated versus time. (B.P., 1993)

The pharmacokinetic parameters (half life, peak height, maximum time to peak, volume of distribution, and clearance) were calculated referring to the concentration of cefixime in plasma using MEDUSA program (Version 1.6 model po 1 pl (c) Varkonyi 1990). The results were analyzed using SPSS program (SPSS for windows, release 7.5.1, Dec. 20 1996) by using descriptive statistics. The significance of change of plasma concentrations with time was obtained by the Student paired T- test.

Results and Discussion

The plasma concentration of the orally administered cefixime (400 mg) in both the sheep and the cattle (Table 1 and 2, Fig. 1 and 2) and the values thus obtained were utilized to calculate the other most important pharmacokinetic parameters of the drug (Table 3).

The peak plasma concentrations (0.63 ± 0.06 μg ml^{-1} and 0.5 ± 0.03 μg ml^{-1}) were found to be achieved in 4.80 ± 0.22 and 2.34 ± 0.51 hours in the sheep and the cattle respectively. The absorption of cefixime in the cattle was more rapid compared with that in the sheep, which probably attributed to the variable surface area at the site of absorption (Maclom and Thomas, 1980). Further follow up of the plasma concentration of the drug show that for at least 14 hours in the sheep and 6 hours in the cattle cefixime attained concentration above the minimum inhibitory concentration (MIC) of most pathogenic microorganisms such as *Branhamella sp., E. colli, Salmonella sp., and Shigella sp.* (Dornbusch *et al.*,1987 and Neu, 1984). The elimination half life in the sheep was found to be 5.96 ± 0.88 hours comparable with that in human 5.08 hours as reported by Nix and his co-worker 1997 but very short related to that in the cattle 13.09 ± 0.81 hours. That mean with the specified oral dose cefixime (400 mg) to maintain the plasma concentration of cefixime above the MIC of the most infectious microorganism for 24 hours, the drug should be administered 12 hourly in the sheep and 6 hourly in the cattle, or may increase the dose in the cattle to ensure convenient dose interval.

The clearance in the sheep (62.48 ± 7.81 L hr^{-1}) was faster than that in the cattle (47.48 ± 5.04 L hr^{-1}) and accordingly the mean resident time varied in the tow animals. When we compared this result with the clearance reported for the human, which was 161 ± 74 ml min^{-1}, and 190 ± 76 ml min^{-1} after 200 mg and 400 mg oral capsule respectively. (Faulkner *et al.*, 1987 and Klepser *et al.*, 1995)., the sheep and the cattle showed a very high

Table 1: The levels of plasma concentration (Cp) of cefixime (μg ml^{-1}) from the sheep for 24 hours after oral administration of 400 mg

Time (hr)	Mean Cp* (μg ml^{-1})
0	0
0.5	0.1 ± 0.01
1	0.16 ± 0.01
1.5	0.26 ± 0.03
2	0.26 ± 0.03
3	0.37 ± 0.05
4	0.39 ± 0.06
6	0.63 ± 0.06
10	0.25 ± 0.02
14	0.17 ± 0.04
20	0.09 ± 0.01
24	0.08 ± 0.02

* Plasma concentration

Table 2: The levels of plasma concentration (Cp) of cefixime (μg ml^{-1}) from the cattle for 24 hours after oral administration of 400 mg

Time (hr)	Mean Cp* (μg ml^{-1})
0	0
0.25	0.18 ± 0.01
1	0.23 ± 0.01
2	0.31 ± 0.02
3	0.50 ± 0.03
4	0.28 ± 0.03
6	0.22 ± 0.02
10	0.15 ± 0.02
13.25	0.17 ± 0.01
22.25	0.14 ± 0.01

* Plasma concentration

Table 3: Pharmacokinetic parameters in the sheep and the cattle

Pharmacokinetic parameters	The sheep	The cattle
$T_{1/2}$ (hr)	5.96 ± 0.88	13.09 ± 0.81
CL (L hr^{-1})	62.48 ± 7.81	47.48 ± 5.04
Vd (ml kg^{-1})	4.67 ± 0.61	5.03 ± 1.77
AUC ($\mu g.hr$ ml^{-1})	6.88 ± 0.78	8.98 ± 1.08
MRT (hr)	13.22 ± 1.98	32.14 ± 6.29
T_{max} (hr)	4.80 ± 0.22	2.34 ± 0.51

values which explained species variation effect on drug pharmacokinetic reported by Davis and his co-worker, 1972.

In conclusion, this study showed that, the oral dose (400 mg) of cefixime exhibited an excellent bioavailability in both the sheep and the cattle. Therefore it seems to be useful in treating many pathogenic microorganism invading animals. However further studies need to look for its economical feasibility in veterinary medicine.

References

Adam, D., 1995. Cefixime study group, U. Hostalek, K. Tröster: 5- day cefixime therapy for bacterial pharyngitis and/or tonsillitis: Comparison with 10-day penicillin V therapy: Infection 23 suppl. 2 ©MMV Medizin Verlag GmbH München, München.

British pharmacopoeia, B.P., 1993. Her majesty's stationary office. University Press, Cambridge, Vol. II. Appendix XIV, pp: A164-A169.

Brittain, D.C., B.E. Scully and T. Hirose, 1985. The pharmacokinetic and bactericidal characteristics of the oral cefixime. Clin. Pharmacol. Ther., 38:590-594.

Davis, L.E., C.A. Neff, J.D. Baggot and T.E. Powers, 1972. Pharmacokinetic of chloramphenicol in domesticated animals. Am. J. Vet. Res. 33: 2259 In: William G. Huber Veterinary pharmacology and therapeutics. L. Mayer Jones. Ed. By Nicholas H. Bocth and Leslie E. McDonald. Fourth edition. Ames: The Iowa state University Press, PP: 947.

Dornbusch, K., G. Kronvall and E. Goransson, 1987. Comparative in vitro ant microbial activity and â-lactamase stability of cefixime. Advanced in Exper. and clin. Chemo. Workshop, 15th International Congress of Chemother. Istanbul, Turkey.

Durckheimer, W., J. Blumbach and R. Heymes, 1982. Chemistry and structure activity relationships in the aminothiazole cephalosporin series, in Neu HC (ed): New Beta-lactam Antibiotics. Areview from chemistry to clinical efficacy of the new cephalosporins. Symposia on Froniers of pharmacology, Vol. 1 Francis Clark Wood Inst. For the history of Medicine. College of Physicians and Philadelphia, Philadelphia.

Ernest Jawetz, 1995. Penicillins and cephalosporins, In: Basic and clinical pharmacology Bertram G. Katzung.International edition, Six edition. Copyright © 1995 by Appleton and Lange PP: 686-688.

Farinati, A.E., G.M. Casellas, I.R. Exeni, I. Grimoldi, Pereira T. Silva, M. Golberg, M. Dugo, I.Bernaldo and de Quiros, 1993. Cefixime therapy for pediatric urinary tract infections, J. Drug Dev. 6 (suppl.1); 45-47.

Faulkner, R.D., P. Fernandez and G. Laurence, 1988. Absolute Bioavail-ability of cefixime in man. J., Clin. Pharmacol., 28: 700-706.

Faulkner, R.D., A. Yacobi and J.S. Barone, 1987. Pharmacokinetic profile of cefixime in man. Pediatr. Infect. Dis. J., 6:963-970.

Hausen, Th., G. Weidlich and J. Schmitt, 1995. Safety and efficacy of cefixime in treatment of respiratory tract infections in Germany. Infection 23, Suppl.2 © MMV Medizin Verlag GmbH, München.

Klepser, M.E., M.N. Marangos, K.B. Patel, D.P. Nicolau, R. Quintiliani and C.H. Nightingale, 1995. Clinical pharmacokinetics of newer cephalosporins. Clin. Pharmacokinetic 28: 361-384.

Malcolm Rowland and Thomas N. Tozer, 1980. Basic consideration; In: Clinical pharmacokinetics Concepts and applications. Copyright © by Lea and Febiger. Philadelphia, PP:9-15.

Mandell, G.L., 1985. Cephalosporins, In: Mandell GL., Douglas RG., Bennett JE. (eds): Principle and practice of infectious disease. New York, Wiley Medical Publication, John Wiley and Sons. pp: 180-182.

Memon, Iqbal Ahmad, Abdul Gaffar Billoo and Hamida Iqbal, 1997. Cefixime for enteric fever in children, Southern medical J., 90:1204-1207.

Monica, C., 1991. Medical laboratory manual for tropical countries, Vol. II. Microbiology. Butterworth-Heineman (pub), pp: 196-205.

Neu, H.C., N-X Chin and P. Labthavikul, 1984. Comparative in vitro activity and â-lactamase stability of FR 17027, a new orally active cephalosporin. J. Antimicrob. Agents Chemother., 26:174-180.

Nix, D.E., W.T. Symonds, J.M. Hyatt, J.H. Wilton, M.A. Teal, P. Reidenberg and M.B. Affrime, 1997. Comparative pharmacokinetics of oral ceftibuten, cefixime, cefaclor, and cefuroxime axetil in healthy volunteers. Pharmacther, 17:121-125.