Carprofen in veterinary medicine : 1. Plasma disposition, milk excretion and tolerance in milk-producing cows

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CARPROFEN IN VETERINARY MEDICINE. I. PLASMA DISPOSITION, MILK EXCRETION AND TOLERANCE IN MILK-PRODUCING COWS

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SUMMARY

Carprofen, a non-steroidal anti-inflammatory drug (NSAID), was injected intravenously in six cows after calving, either as a single or a daily dose of 0.7 mg/kg for five days.

Carprofen was well tolerated by the cows at this dose rate, the milk production and biochemical variables remaining within the normal ranges.

The plasma elimination half-life of carprofen ranged from 44.5 to 64.6 h after repeated daily injections. These values are longer than those reported for other NSAIDs used in veterinary medicine, e. g. flunixin and phenylbutazone. The volume of distribution and the clearance values calculated after a single intravenous injection amounted to 0.09 l/kg and 9.0 ml/min. The concentration of carprofen in milk collected twice daily (morning and evening) was, in general, below the sensitivity limit of the analytical method (25 ng/ml) up to five days after the last carprofen injection; the concentration of carprofen reached about 30 ng/ml in only a few milk samples collected after the fourth or fifth injection. This indicates that carprofen is poorly excreted in the milk.

KEY WORDS: Pharmacokinetics – non-steroidal anti-inflammatory drug – carprofen – cattle – milk excretion

CARPROFEN IN DER VETERINÄRMEDIZIN. I. VERHALTEN IM PLASMA, AUSSCHEIDUNG IN DER MILCH UND VERTRÄGLICHKEIT BEI MILCHKÜHEN

Carprofen, ein nichtsteroidales, antiinflammatorisches Medikament (NSAID), wurde sechs Kühen nach der Abkalbung intravenös entweder als Einzelgabe oder in täglichen Injektionen in der Dosierung von 0,7 mg/kg KGW während fünf Tagen verabreicht.

In diesen Mengen wurde Carprofen vom Organismus ohne Auswirkungen auf Milchproduktion und biochemische Blutvariablen vertragen.

Die Halbwertszeit von Carprofen im Plasma schwankte nach täglich wiederholten Injektionen zwischen 44,5 und 64,6 Stunden. Dies ist länger als für andere in der Veterinärmedizin gebräuchlichen NSAIDs wie Flunixin und Phenylbutazon angegeben. Das Verteilungsvolumen und die Clearance-Werte nach einmaliger intravenöser Injektion betrugen 0,09 l/kg bzw. 9,0 ml/Min. Die Carprofen-Konzentration in der zweimal täglich (morgens und abends) gewonnenen Milch war bis zu fünf Tagen nach der letzten Carprofen-Injektion im allgemeinen kleiner als die Empfindlichkeitsgrenze der Bestimmungsmethode; nur wenige Milchproben erreichten nach dem 4. oder 5. Behandlungstag Werte von 30 ng/ml. Dies bedeutet, dass Carprofen äusserst gering über die Milch ausgeschieden wird.

SCHLÜSSELWÖRTER: Pharmakokinetik – nichtsteroidales antiinflammatorisches Medikament – Carprofen – Milchkuh – Milchausscheidung

Carprofen [(±)-6-chloro-2-methylcarbazole-2-acetic acid] is a non-steroidal anti-inflammatory drug (NSAID), which has the same analgesic, antipyretic and antiphlogistic activity as indomethacin in rats and mice *(Randall* et al., 1976; *Strub* et al., 1982); in these species it is more potent than phenylbutazone and is better tolerated than other currently used antiphlogistics. Carprofen exhibits a longer plasma elimination half-life ($t_{1/2}$ = 20 h) than phenylbutazone or flunixin (4 to 10 h) in horses (*von Fellenberg* et al., 1986; *Ludwig* et al., 1988). A preliminary trial had been carried out in two cows *(Ludwig* et al., 1987) during which it was found that the half-life of carprofen ranged between 28.5 and 41.1 h. Moreover, carprofen could not be detected in the milk of cows after intravenous injection of 0.7 mg/kg b. w.

The aim of the present study was: i) to investigate the tolerance of carprofen in cows after several daily i. v. injections; ii) to determine the plasma elimination half-life of carprofen in the cow; iii) to measure the residue of carprofen in the milk following the daily intravenous injection of 0.7 mg/kg b. w. for five days; and iv) to evaluate the potency of carprofen to inhibit *in vivo* the biosynthesis of prostaglandin PGF 2-alpha. Results of the prostaglandin PGF 2-alpha inhibition will be reported separately.

MATERIALS AND METHODS

Test preparations and chemicals

A 5% carprofen injection (Ro 20-5720/656, batch No. G PH 13 027, F. Hoffmann-La Roche & Co. Ltd., Basel, Switzerland) was used for the intravenous injections. The solvents and products utilized for the analysis were purchased either from Merck (Darmstadt/FRG) or Fluka (Buchs/Switzerland).

Animals and sampling

Six pregnant cows of Schweizer Braunvieh breed, between 5 and 11 years old, weighing 530–695 kg, were used for the study. The animals were kept in individual indoor pens and received a commercial standard food (UFA, Sursee/Switzerland), along with hay and water *ad libitum*. Within 1–2 days after calving a single injection of carprofen was given into the right V. jugularis each morning at 8.00 h at a dose rate of 0.7 mg/kg b. w. each day for five days. The injected volume ranged from 6.3 to 10.2 ml, and the injection lasted for 20–30 seconds.

Blood samples (20 ml) were collected into glass tubes (Vacutainer®, Becton Dickson-France SA/France) containing heparine sodium as anticoagulant, from the left jugular vein, before and at various time intervals for about 250 h after the first injection of carprofen. The blood was immediately centrifuged (1300 g, 10 min, 5 °C) after collection, and the plasma was separated and stored at -20 °C in glass tubes until required for analysis.

Milk samples, obtained by hand-milking at normal milking times in the morning and evening, were taken from the whole milk of the four quarters before and until 10 days after the first carprofen injection. Before sampling, the whole milk was well mixed and immediately deep-frozen at -20 °C in polyethylene tubes.

Analytical methods

The plasma and milk samples were assayed for carprofen in duplicate on two different days by means of an HPLC method using a normal phase technique *(Ascalone* and *Dal Bo,* 1983; *Ludwig* and *Jordan,* 1988). The method involves the extraction of the drug and the internal standard Ro 21-0134 [rac. 2-(6-chloro-2-carbazolyl)-propanol] from the plasma buffered at pH 2.8 with butyl acetate. The plasma or milk extracts were directly injected into the chromatographic system. The eluent from the analytical column was monitored by a fluorescence detector HP 1046A, operating at 245 nm for excitation and 375 nm for emission. The limit of quantification of carprofen was 40 ng/ml in plasma and 25 ng/ml in milk, with an accuracy and precision better than 10% when using a 1-ml plasma/milk sample.

Plasma and milk samples spiked with known quantities of carprofen (quality control samples) were analysed along with the unknown samples. These test solutions were prepared by a different person to the one who performed the analysis in order to have an optimum control on the analytical method.

Blood chemistry[1]

The blood characteristics of each cow was examined before and after the first injection of carprofen over a 95-hour period. Especially the activity of two enzymes, known to be indicators of hepatic parenchymal cell damage (aspartate aminotransferase – ASAT – and glutamate dehydrogenase – GLDH) was evaluated in several plasma samples before and after the injection of carprofen. Moreover, the total protein, calcium, bilirubin, urea, cholesterol and potassium concentrations as well as the anorganic phosphate amount were measured in the same plasma according to standard procedures.

Pharmacokinetic analysis

The standardized pharmacokinetic program KINPAK *(Betzien* et al., 1985) was used to determine the pharmacokinetic parameters of carprofen following a single intravenous injection in the cow. In this program, the kinetic parameters are calculated according to the geometric characteristics of the plasma concentration-time curves.

The plasma concentration-time data measured after the multiple dose study were fitted by a one- or two-exponential equation using the superposition technique *(Gibaldi* und *Perrier,* 1982) by means of a non weighted non-linear regression NONLIN program *(Metzler* and *Weiner,* 1986). The Gauss-Newton algorithm with the Hartley's modifica-

[1] The analytics were performed at the laboratory of PD Dr. P. Keller-Rupp, Toxicological Dept. of Roche Basle, according to standard procedures.

tion was used for fitting the mathematical equations.
The terminal plasma elimination half-life $t_{1/2\beta}$ was calculated according to the equation

$$t_{1/2\beta} = \frac{\ln 2}{\beta}$$

where ß/2.303 represents the slope of the terminal phase of the plasma concentration-time curve after the fifth injection of carprofen in a semilogarithmic plot.

tained differed significantly from zero (t-test). The results are shown in table 2. In this study, there is no statistical evidence that the plasma concentrations of the two enzymes ASAT and GLDH as well as total protein, calcium, bilirubin, urea and potassium concentrations changed before and during the experiment ($p > 0.1$). Only the plasma cholesterol concentration was slightly raised, the increase being statistically significant.

Table 1: Amount of milk (kg) secreted in the morning (M) and evening (E) following a daily intravenous injection of 0.7 mg carprofen/kg b. w. for five days.

Days after the first injection*	Falch**		Volga		Malta		Lori		Efrina	
	M	E	M	E	M	E	M	E	M	E
0 (1st inj.)	--	4.2	8.1	6.7	11.2	6.5	8.8	4.8	7.7	3.5
1 (2nd inj.)	7.3	2.1	11.6	7.7	12.6	7.1	9.8	4.6	9.0	4.4
2 (3rd inj.)	2.0	1.0	12.9	7.6	12.5	6.7	10.0	5.1	9.5	5.0
3 (4th inj.)	4.8	2.6	13.2	7.4	12.6	7.1	10.5	5.2	8.8	6.0
4 (5th inj.)	5.0	2.7	13.2	7.2	13.6	7.5	10.6	5.3	10.0	5.4
5	6.3	3.2	13.0	7.1	14.2	7.4	11.2	5.7	9.9	5.8
6	6.0	--	13.5	7.1	13.4	7.4	11.2	5.8	9.8	5.8
7	--	--	12.7	7.5	12.4	6.7	10.7	5.3	10.0	6.1
8	--	--	13.3	7.0	13.0	7.0	7.6	4.2	10.3	6.2
9	--	--	13.2	--	13.2	--	9.9	5.1	10.5	6.5
10	--	--	--	--	--	--	10.3	5.0	11.2	6.7

* Injections were given at 8 a. m. The morning milk of the first day of treatment was measured before the carprofen injection.

** Cow Falch received only a single intravenous injection of carprofen in the morning of the first day of the experiment. Cows Falch and Ani (not shown) suffered from mastitis on the second and fifth day of treatment, respectively.

RESULTS

Tolerance

Carprofen was well tolerated by the cows when administered intravenously at a daily dose of 0.7 mg/kg b. w. for five days. The animals continued to feed normally after the injections, and milk production remained within normal ranges during the experiment (table 1).
Linear regressions were calculated for each biochemical variable measured in the plasma of each cow and the program tested to find out whether the slopes of the curve ob-

Plasma disposition following a single intravenous injection of carprofen

One cow (Falch) was injected intravenously with a single 0.7 mg/kg b. w. dose of carprofen in this trial, similar to a protocol reported earlier *(Ludwig* et al., 1987). The plasma concentrations of carprofen at various times after the intravenous injection of a single 0.7 mg/kg b. w. dose in this cow are listed in table 3 (see also fig. 1).
Carprofen had a low volume of distribution (0.09 l/kg) and a small clearance (9 ml/min) in cow Falch, as was observed in humans *(Crevoisier,* 1982) and dogs *(Rubio* et al., 1980).

Table 2: Slope of the plasma biochemical variables against time curve in each cow.

	Ani	Volga	Malta	Lori	Efrina	Mean	SEM	PRT	n
ASAT	-0.0035	-0.0007	0.0006	0.0016	-0.0004	-0.0005	0.0009	0.619	5
GLDH	-0.0013	0.0050	0.0008	0.0005	0.0004	0.0011	0.0010	0.353	5
Total Protein	-0.0260	0.0161	0.0559	0.0125	-0.0240	0.0069	0.0151	0.671	5
Calcium	0.0015	0.0021	0.0025	0.0060	-0.0008	0.0023	0.0011	0.109	5
Bilirubin	-0.0080	-0.0012	0.0104	0.0098	0.0081	0.0038	0.0036	0.351	5
UREA	-0.0354	-0.0005	-0.0057	0.0057	-0.0145	-0.0101	0.0072	0.232	5
Cholesterol	0.0015	0.0044	0.0044	0.0015	0.0039	0.0031	0.0007	0.010	5
Anorgan. Phosphat	-0.0021	0.0113	-0.0042	0.0111	-0.0073	0.0018	0.0039	0.678	5
NA	0.0056	0.0005	-0.0132	0.0241	-0.0346	-0.0035	0.0098	0.738	5
K	0.0073	0.0054	-0.0062	-0.0032	-0.0117	-0.0017	0.0036	0.662	5

SEM: standard error of mean PRT: P-value of the t-test n: number of animal

Table 3: Mean (±SD) plasma concentration of carprofen (μg/ml) following a single intravenous injection of 0.7 mg/kg b. w. in cow Falch.

Timpe pi. (h)	Mean*	SD
0.25	13.72	0.55
0.50	11.52	0.08
0.75	11.29	0.05
2.00	9.20	0.20
3.00	7.67	0.36
5.00	7.81	0.11
6.50	7.56	0.07
10.00	7.27	0.21
24.50	5.82	0.04
25.00	5.50	0.11
26.00	5.34	0.16
34.00	5.45	0.12
48.50	4.74	0.07
49.00	5.05	0.18
50.00	5.10	0.07
72.50	4.09	0.38
74.67	3.59	0.08
95.25	2.67	0.02
96.25	2.83	0.19
97.25	2.77	0.08
144.00	1.72	0.03
147.25	1.67	0.03

* Mean of two determinations.

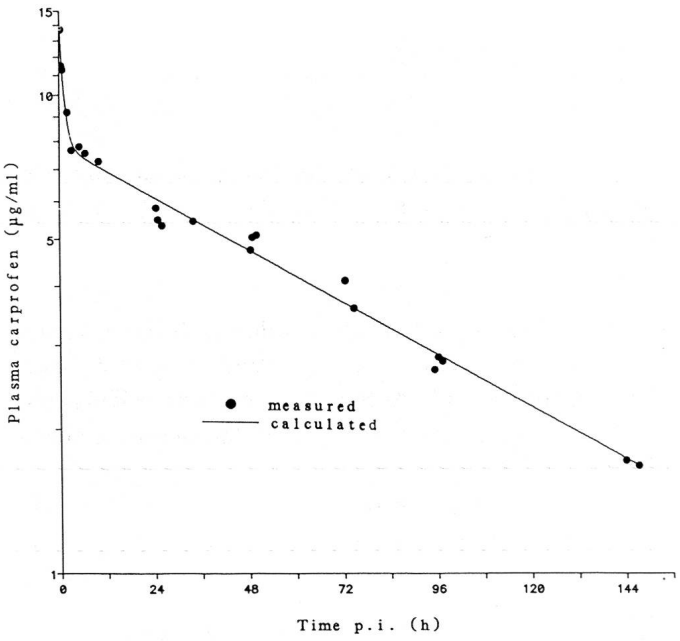

Fig. 1: Plasma concentration-time curve of carprofen following a single intravenous injection of 0.7 mg/kg b. w. in cow Falch.

Plasma disposition of carprofen following daily injections

The plasma concentrations of carprofen in cows at various times following the daily intravenous injection of a 0.7 mg/kg b. w. dose for five days were determined in five dairy

cows. An open two-compartment model was used for the data analysis as shown in fig. 2 for cow Ani.

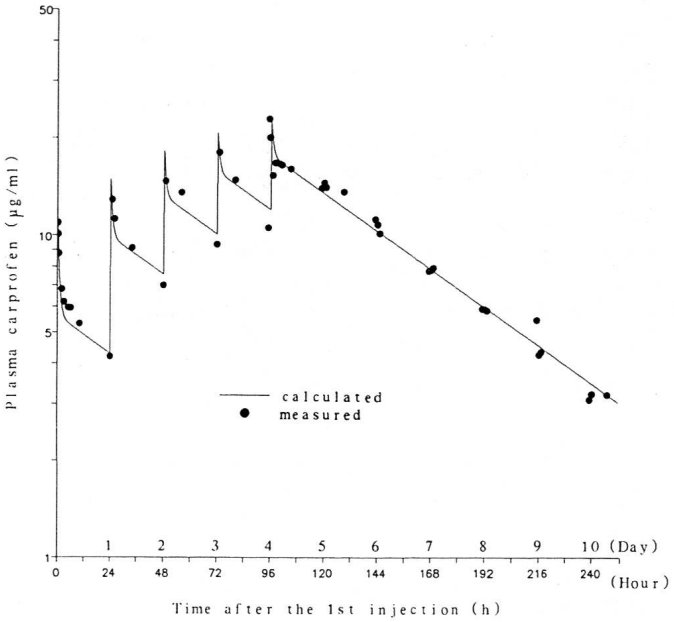

Fig. 2: Plasma concentration-time curve of carprofen following daily intravenous injection of 0.7 mg/kg b. w. for five days in cow Ani.

As expected from the long elimination half-life of carprofen, the steady-state plasma concentrations were not reached after the fifth injection, thus allowing no calculations of either the volume of distribution or the clearance of carprofen.

However, the NONLIN program computed the plasma elimination half-life of carprofen after the fifth dose. The value of the half-life in this case ranged from 44.5 to 64.6 h, with a mean value of 57.8 h (table 4).

Excretion of carprofen in the milk of healthy cows

In 3 animals, the concentrations of carprofen in milk of healthy cows were below the limit of quantification of the analytical method (25 ng/ml), even after five daily intravenous injections of 0.7 mg carprofen/kg b. w.

In 2 cows (Volga and Malta), the milk concentration of carprofen reached about 30 ng/ml after the fourth and fifth injection, respectively (table 5).

Table 4: Terminal plasma-elimination half-life of carprofen measured after the fifth intravenous injection of a 0.7 mg/kg b. w. daily dose for five days in different cows.

Cows	$t_{1/2}$ (h)
Ani	61.3
Volga	55.9
Malta	44.5
Lori	64.6
Efrina	62.5
MEAN	57.8
SD	8.1
MINIMUM	44.5
MAXIMUM	64.6

Excretion of carprofen in the milk of cows suffering from mastitis

Two cows (Falch and Ani) suffered from an acute mastitis in one quarter of the udder on the second (Falch) and fifth day (Ani) of the experiment. The milk from the infected quarter was collected separately. Nevertheless, the concentration of carprofen in milk samples from the three healthy quarters showed high values between 165 and 218 ng/ml (table 5).

The mastitis in both cows was cured by giving:

Vetoprim[2] intravenously for three days and
Neo-Remusin[3] intramammary into the infected quarters on the first day of infection.

The concentration of carprofen in the milk fell below 25 ng/ml immediately after the udder inflammation had disappeared.

DISCUSSION

Tolerance

In all cows the activities of aspartate aminotransferase (ASAT) and glutamate dehydrogenase (GLDH) were in

[2] Coopers Ltd. (UK), batch No. 03 641B; combination of 40 mg trimethoprim/100 mg sulfadimidine/100 mg sulfathiazole per ml.

[3] Veterinaria AG (Switzerland), batch 70207; combination of benzylpenicillin, procain and neomycin sulfate.

Table 5: Concentration of carprofen (ng/ml) in milk secreted in the morning (M) and evening (E) following a daily intravenous injection of 0.7 mg carprofen/kg b. w. for five days.

Days after the first injection*	Falch**		Ani**		Volga		Malta		Lori	
	M	E	M	E	M	E	M	E	M	E
0 (1st inj.)	--	49.8	<25	<25	<25	<25	<25	<25	<25	<25
1 (2nd inj.)	72.2	218	<25	<25	<25	<25	<25	<25	<25	<25
2 (3rd inj.)	28.7	<25	<25	<25	<25	<25	<25	<25	<25	<25
3 (4th inj.)	<25	<25	<25	<25	<25	32	--	--	<25	<25
4 (5th inj.)	<25	<25	165.5	31.2	<25	<25	28	33.2	<25	<25
5	<25	<25	30.9	<25	<25	<25	27.2	<25	<25	<25
6	<25	<25	<25	<25	<25	<25	<25	<25	<25	<25
7	--	--	<25	<25	<25	<25	<25	<25	<25	<25
8	--	--	<25	<25	<25	<25	<25	<25	<25	<25
9	--	--	<25	<25	<25	<25	<25	<25	<25	<25

* Injections were given at 8 a. m. The morning milk of the first day of treatment was measured before the carprofen injection.

** Cow Falch received only a single intravenous injection of carprofen in the morning of the first day of the experiment. Cows Falch and Ani suffered from mastitis on the second and fifth day of treatment, respectively.

the normal range during the whole treatment period indicating that there was no negative influence of the drug on hepatic function. Although the plasma cholesterol concentrations showed slight increases during the trial, they remained within the normal range of 1.6 to 5 mmol/l *(Fraser* and *Mays,* 1986). In general, no obvious deviations in blood chemistry were observed after carprofen given in a daily dose of 0.7 mg/kg b. w. for five days.

Plasma disposition following a single intravenous injection of carprofen

The kinetic parameters (half-life, volume of distribution and clearance) reported for cow Falch are somewhat different from those found in a previous study *(Ludwig* et al., 1987). As blood samples were collected only over a 48-hour period in our eralier report, the pharmacokinetic parameters evaluated in this experiment with samples obtained up to 147 h after the carprofen injections are more reliable for future investigations.

The low volume of distribution of carprofen in the cow is probably related to a poor tissue distribution.

Plasma disposition of carprofen following daily injections

The half-lives measured during the multiple dose experiment ranging from 44.5 to 64.6 h are within the estimated limits following a single intravenous injection. Therefore, the pharmacokinetic characteristics of carprofen in cows are not altered to any significant extent when injected daily at 0.7 mg/kg b. w.

Hardee et al. (1985) determined a plasma elimination half-life for flunixin in dairy cows of 8.1 h, i. e. carprofen has a longer plasma elimination half-life in cows than flunixin.

Excretion of carprofen in the milk of healthy cows

In healthy cows, carprofen is excreted in milk to a very low extent, thus allowing a short withholding period (≦ half a day) for the milk when treated with this drug. Furthermore, cows under treatment could continue to suckle calves as there is no risk of a large transfer of carprofen to the calf through the milk of the mother.

Excretion of carprofen in the milk of cows suffering from mastitis

The transfer of carprofen from the blood into the milk of cows suffering from mastitis is greatly enhanced by the inflammatory process; such a phenomenon is not surprising, it has already been proved that the concentrations of nonsteroidal anti-inflammatory drugs are significantly higher in the inflamed tissues than in healthy ones *(Higgins* et al., 1986; *Heintz* et al., 1981). Nevertheless, the concentrations of carprofen fell below 25 ng/ml milk immediately after the mastitis was cured. At this time, the milk could be used for human consumption, provided there are no residues from co-administered drugs utilized to cure the mastitis (in our case: trimethoprim/sulfadimidine/sulfathiazole and benzylpenicillin/procain/neomycin sulfate).

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Carprofen en médecine vétérinaire. I. Disposition plasmatique, excrétion dans le lait et tolérance chez la vache laitière

Une dose intravineuse de 0,7 mg/kg de carprofen, un nouvel anti-inflammatoire non stéroidien (AINS), a été injectée à six vaches ayant vêlé, soit sous forme d'une dose unique, soit quotidiennement pendant cinq jours.

Le carprofen a été bien toléré à la dose administrée, et tant les paramètres biochimiques que la production de lait ont été maintenus dans des marges de variations normales tout au long du traitement.

La demi-vie d'élimination plasmatique calculée à partir de la dernière injection de carprofen, varie entre 44,5 et 64,6 h selon les animaux. Ces valeurs, qui ne diffèrent pas de manière significative de celles trouvées après injection intravineuse unique, sont supérieures aux demi-vies d'élimination rapportées par différents auteurs pour la phénylbutazone et la flunixine. Par ailleurs, le volume de distribution et la clairance du carprofen ne dépassent guère 0.09 l/kg et 9 ml/min respectivement. Enfin, la concentration du carprofen dans le lait reste, en général, inférieure à la limite de détection de la méthode d'analyse (25 ng/ml), même après administration répétée. Ceci indique que le carprofen n'est que faiblement excrété dans le lait.

Carprofen nella medicina veterinaria. I. Comportamento nel plasma, secrezione attraverso la mammella e tolleranza nella vacche da latte

Carprofen, un medicamento antiflogistico non facente parte del gruppo dei steroidi (NSAID), è stato somministrato per via endovenosa a 6 vacche dopo il parto. L'iniezione è stata fatta una volta sola, o in dosi giornaliere di 0.7 mg/kg di peso corporeo, per 5 giorni.
In queste quantità il Carprofen è stato tollerato molto bene dall'organismo, senza effetti sulla produzione di latte o i parametri sanguinei. Il tempo di dimezzamento della concentrazione (T/2) nel plasma per le dosi ripetute giornalmente, varia tra 44,5 e 64,6 ore. Se confrontiamo i tempi con altri medicamenti del gruppo NSAID impiegati in medicina veterinaria (per es. il Flunixin o il Phenylbutazon), l'effetto di questi ultimi è meno duraturo.
I volumi di distribuzione e i valori della Clearance dopo una somministrazione endovenosa corrispondono a 0.09 l/kg e rispettivamente 9.0 ml/min.
La concentrazione di Carprofen nel latte munto giornalmente (mattino e sera), non raggiunge mai, nei 5 giorni successivi all'ultima somministrazione, valori abbastanza alti da poter esser individuati dai nostri metodi di determinazione. Solo pochi campioni di latte dopo 4 o 5 giorni di iniezione raggiunsero valori di 30 μg/ml. Questo significa che il Caprofen viene eliminato in quantità molto esigue attraverso il latte.

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