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Diurnal Rhythm of Melatonin in Bovine Milk: Pharmacokinetics of Exogenous Melatonin in Lactating Cows and Goats

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[1]Department of Basic Veterinary Medicine, Faculty of Veterinary Medicine, Helsinki University, and [2]Department of Applied Zoology and Veterinary Medicine, and [3]Department of Physiology, University of Kuopio, Finland.

Eriksson L, Valtonen M, Laitinen JT, Paananen M, Kaikkonen M: Diurnal rhythm of melatonin in bovine milk: Pharmacokinetics of exogenous melatonin in lactating cows and goats. Acta vet. scand. 1998, 3, 301-310. – We investigated whether the melatonin levels in bovine milk exhibit a similar daily rhythm as serum levels. In 4 Ayrshire cows at the beginning of the lactation period in May the nocturnal rise in milk melatonin was moderate (from 7 ± 2 pg/ml at noon to 15 ± 1 pg/ml at night; mean ± SEM) and did not correlate well with the melatonin level in serum (from 7 ± 2 pg/ml to 27 ± 7 pg/ml, respectively). On the other hand, 6 cows in a later phase of lactation, studied in February, showed a clear long-lasting nocturnal melatonin increase both in serum (from 9 ± 1 pg/ml at noon to 26 ± 3 pg/ml at night) and in milk (from 12 ± 5 pg/ml to 26 ± 7 pg/ml, respectively).
Melatonin kinetics during lactation was studied in more detail in 4 Ayrshire cows and 4 dairy goats by giving an intravenous bolus injection of melatonin. A 3-compartment model with melatonin elimination from the central compartment was used to describe the data. The values (mean ± SD) for the cows and the goats were: elimination half-life 27 ± 4 min and 27 ± 1 min, mean residence time 24 ± 4 min and 18 ± 4 min, steady state distribution volume 1.0 ± 0.3 l/kg and 0.6 ± 0.1 l/kg ($p<0.05$), and plasma clearance 0.044 ± 0.004 l/kg/min and 0.035 ± 0.011 l/kg/min, respectively. Following injection, the melatonin concentration in milk increased rapidly and exceeded the corresponding serum value 15-30 min later, remaining thereafter above the serum level. Our results suggest that milk melatonin levels reflect blood concentrations of melatonin with a short delay.

lactation period; season; ruminant.

Introduction

Melatonin, synthesized by the pineal gland during darkness, is primarily secreted into the circulation and is found in body fluids. As in most mammals, a diurnal rhythm of melatonin secretion has been reported in cattle (*Martin et al.* 1983, *Stanisewski et al.* 1988, *Berthelot et al.* 1990) and small ruminants (See *Lincoln* 1992). Melatonin has also been detected in bovine milk (*Laitinen et al.* 1986), and in human milk it exhibits a diurnal rhythm with maximal excretion at night (*Laitinen & Vakkuri* 1987, *Illnerová et al.* 1993). As no detailed knowledge is available about endogenous levels of melatonin in cow milk, we wished to study whether milk melatonin levels could be used as an index of melatonin production and whether melatonin in milk exhibits a daily rhythm during abundant lactation.

Our preliminary results in lactating goats have shown that during rapid elimination of exogenous melatonin from the circulation, milk levels parallel serum values (*Eriksson et al.* 1993). These results with goats have now been analysed in more detail together with corresponding investigations carried out in lactating cows.

Materials and methods

Animals

The cows used were adult pluriparous Ayrshire cows, weighing 460-600 kg (mean 544 kg). They were housed in a cowshed lit by lamps during working hours, and fed silage, hay, and water *ad libitum*. They were milked at around 0700 and 1700 hours. Concerning the diurnal rhythm 4 cows were studied in May one month postpartum milking about 27 kg/day and 6 cows in February 10 months postpartum. Of the latter cows, 3 were pregnant milking around 9 kg/day and 3 non-pregnant milking around 18 kg/day.

Pharmacokinetic studies were performed in 4 cows in summer at daytime. Three had calved 13-14 months earlier, and milked around 10 l per day. The fourth cow had calved 6 months earlier and its average daily milk yield was 28 l. All cows were non-pregnant.

The pharmocokinetic study in goats was performed in 4 adult (>3 years old) Finnish landrace goats, weighing 46-54 kg (mean 50 kg). They were in late lactational stage, milking 0.3-1.4 l per day. The goats were non-pregnant, and more than one year had elapsed since previous parturition. They were kept in pens and moved to metabolism cages before the experiments. They were provided *ad libitum* access to hay, straw, and water. In addition, they were given oats, molasses, and mineral mixture twice daily. The experiments were performed in summer at daytime.

All animals used in these experiments were clinically healthy.

Experimental design

All these experiments were approved by the local ethical committees.

During experiments consecutive samples of blood and milk were taken simultaneously into glass tubes, blood samples via a plastic catheter inserted into a jugular vein and milk samples by hand-milking without milking to dryness. The venous catheter was flushed with sodium citrate solution after samplings. Samples were centrifuged, and serum and fat-free milk fraction were stored at –20 °C until assayed for melatonin.

In the studies of diurnal rhythm, collection of parallel samples of blood and milk was done in May every 3 or 4 h with more frequent sampling at dusk and dawn. In February, the sampling interval was one hour throughout the collection period, starting at noon. The duration of darkness at 63 °N (Kuopio, Finland) was 7 h in May and 14 h in February.

During the pharmacokinetic studies, the cows stood in an examination stand. The experiment started at 1000 h about 3 h after morning milking. Melatonin was given into a jugular vein as a bolus injection of 270 μg/kg. Venous blood samples were collected via a plastic catheter inserted into the opposite jugular vein. Parallel samples of blood and milk were drawn 5 and 2 min before administration of melatonin and 1, 2, 4, 6, 10, 14, 30, 45, 75, 105, 165 and 225 min after.

Since the injection of melatonin in the cows raised their serum melatonin concentration more than expected, the goats were given only 30 μg/kg melatonin into a jugular vein as a bolus injection. The goats were milked in the morning, approximately 3 h before melatonin injection. Parallel samples of blood and milk were drawn 30 and 10 min before the administration of melatonin and 1, 2, 3, 4, 6, 8, 10, 15, 20, 30 min after, and every 30 min until 6 h.

Melatonin radioimmunoassay

Serum concentrations of melatonin were analysed after chloroform extraction using a specific RIA, as previously described (*Fraser et al.* 1983, *Valtonen et al.* 1993).

Briefly, duplicate samples (0.5 ml) of serum and melatonin standards (5 to 200 pg/ml), as well as low- and high-melatonin control samples (8.6 and 53.8 pg/ml, respectively) were extracted with 3.0 ml of chloroform. Defatted milk was used for analysis of milk, as partition studies with ^{3}H-melatonin indicated most of the radioactivity to be associated with the aqueous phase of the milk (*Laitinen & Vakkuri* 1987). Duplicate samples of defatted milk (0.5 ml) were extracted together with melatonin standards and control samples with chloroform. The organic phase was washed once with distilled water and dried under vacuum. The dried residues were reconstituted in phosphate-buffered saline, pH 7.0, containing 1 g of gelatin per liter and assayed for melatonin using the G/S/704-8483 antiserum (Stockgrand Ltd, University of Surrey, Guildford, Surrey, U.K.) and tritiated melatonin tracer (O-methyl-[3H]melatonin, Amersham, specific activity 81 Ci/mmol, 3000 cpm/tube). In our experiment, dilutions of serum and milk gave displacement curves parallel to those obtained using synthetic melatonin standards (not shown). The sensitivity, defined as the value of 2 standard deviations below zero standard binding, was 5 pg/ml. The intra-assay coefficients of variation were 11.7, 9.5, and 4.3% for melatonin concentrations of 21, 69, and 145 pg/ml, respectively. The interassay coefficients of variation were 13.5% and 10.4% for melatonin concentrations of 8.6 and 53.8 pg/ml, respectively.

Pharmacokinetics and statistical analysis

Values are given as means ± SEM in the study of daily rhythm and as means ± SD in the study of pharmacokinetics. Student's *t* test was used for comparison between the cows and the goats. The nocturnal melatonin values in milk and serum were calculated for each cow as means of the values between 2300 and 0300 hours in May and between 1900 and 0400 hours in February. Previous studies in cattle (*Berthelot et al.* 1990, *Berthelot et al.* 1993) suggest that the elimination of melatonin can be described with a 3-compartment model where the plasma concentration generally follows the tri-exponential equation

$$C = C_1 + C_2 + C_3$$

where

$$C_1 = A_1 \exp(-b_1 t)$$
$$C_2 = A_2 \exp(-b_2 t) \quad (A_n \text{ and } b_n \text{ empirical constants})$$
$$C_3 = A_3 \exp(-b_3 t)$$

The graphical presentation of data indicated that such an equation provided the best fit in the present study as well. Also tests applied using Aikake's information criterion (*Yamaoka et al.* 1978a) favored the use of a tri-exponential function to describe the plasma kinetics of melatonin in each individual animal.

Firstly, the approximate endogenous melatonin level (measured twice prior to melatonin injection) was subtracted from all concentration data:

$$C = C_{total} - C_{endogenous}$$

In plotting ln C against time, the least sum of squares (LSS) method was applied to the right-most straight region on the graph to obtain the parameters A_3 and b_3. It was assumed that at this late stage $C = C_3$, i.e., C_1 and C_2 had a negligible contribution to C ("non-interference").

$$\ln C = \ln A_3 - b_3 t$$

Using these parameters, C_3 was calculated and subtracted from each measurement of C.

$$C' = C_1 + C_2 = C - C_3$$

Having eliminated C_3, LSS method was used again to determine the parameters A_2 and b_2 from the plot ln C' against time (rightmost straight region). C_2 was calculated and subtracted from each C', and parameters A_1 and b_1 were determined by LSS method after plotting ln C_1 against time (remaining points).

$$\ln C' = \ln A_2 - b_2 t$$
$$C_1 = C' - C_2$$
$$\ln C_1 = \ln A_1 - b_1 t$$

Using the calculated parameters, the original assumption of non-interference during the application of LSS method was confirmed by comparing the theoretical values of C_1, C_2 and C_3 to C at each data point in the LSS analysis. Information about the points used for LSS analysis is presented in Table 1.
From the parameters determined and the original dose given (D, in μg/kg), the following parameters were calculated (*Yamaoka et al.* 1978b):

Half-life for each compartment
$$T_{½i} = \ln(2)/b_i$$
Central volume
$$V_c = D/(A_1 + A_2 + A_3)$$
Distribution volume
$$V_d = D/(A_2 + A_3)$$
Area under the curve
$$AUC = (A_1/b_1) + (A_2/b_2) + (A_3/b_3)$$
Area under the moment curve
$$AUMC = (A_1/b_1^2) + (A_2/b_2^2) + (A_3/b_3^2)$$

The model-independent parameters AUC and AUMC were also deduced using the trapezoid method (*Yamaoka et al.* 1978b). The following other model-independent parameters were calculated:

Mean residence time
$$MRT = AUMC/AUC$$
Clearance
$$Cl = D/AUC$$
Steady-state distribution volume
$$Vd_{(ss)} = MRT \times Cl$$

Results

Diurnal rhythm of melatonin in cow milk and serum

Melatonin levels both in milk and in serum exhibited a clear daily rhythm in all cows, although great individual variation in the profile was apparent (Fig. 1A and 1B). The 4 cows in abundant lactation, studied in May, as well as the 6 cows in later lactation stage, studied in February, had almost identical low daytime values of melatonin in milk and serum. The average night-time melatonin concentration in milk during the early lactation period in May was only about half of that present in serum (15 *vs* 27 pg/ml, respectively), whereas during late lactation in February, milk melatonin levels reached those seen in serum (up to 35 pg/ml). In May, the nightly rise in milk concentrations was short and irregular and did not correlate well with that in serum. The night-time melatonin rise in February started already at 17:00 hours and was more pronounced and long-lasting than that in May. Moreover, milk melatonin levels followed those in the serum.

Pharmacokinetics in cows

The solid line in Fig. 2A shows the decreasing serum concentrations of melatonin after a bolus injection of the indole (270 μg/kg) as means + SD of the 4 cows. In the individual curves, using a tri-exponential equation gave a significantly better fit than single- or double-exponential equations. The data were thus described by a 3-compartment open model with melatonin elimination from the central compartment. The kinetic parameters in the cows and their com-

Table 1. Points used for least sum of squares analysis during calculation of serum melatonin kinetics after intravenous bolus injection to 4 cows and 4 goats.

Parameters	Species	Time range[a] (min)	Number of points[a]
A_1, b_1	Cow	1 – 2	2
	Goat	1 – 2,3,3,2	2,3,3,2
A_2, b_2	Cow	4,4,6,6, – 10,15,15,15	3,4,3,3
	Goat	6,6,6,3 – 0,30,30,15	6
A_3, b_3	Cow	45,45,45,30 – 165,165,105,105	4,4,3,4
	Goat	60 – 180	5

[a] Commas separate values for different individuals.

parison with those of the goats are shown in Table 2. The mean terminal elimination half-life ($T_{½_3}$) was the same as in the goats (27 min), but there was greater variation between the animals. The distribution half-life ($T_{½_1}$) varied between 0.3 and 0.9 min, partly due to few points left for calculation. Calculation of the steady-state distribution volume, mean residence time, and plasma clearance by using the 3-compartment model and the trapezoid method gave practically identical results (Table 2). Plasma clearance was 0.044 ± 0.004 l/kg/min, and it did not correlate with daily milk yield. Mean residence time was 24 ± 4 min, being shortest (20 min) in the cow milking most, but it did not correlate with milk yield in the other cows. In the cows, the distribution volume (0.96 ± 0.17 l/kg) and steady state distribution volume (1.0 ± 0.3 l/kg) were significantly higher than in the goats (0.5 ± 0.2 l/kg and 0.6 ± 0.1 l/kg, respectively; $p<0.05$).

After a bolus injection of melatonin, the milk concentration increased rapidly and exceeded the serum level within 30 min. In the cow milking most (28 l/day) this time was 15 min and in the cow milking least (8 l/day) 45 min. The milk melatonin then remained higher than the serum level during the remainder of the experimental period (Fig. 2A).

Pharmacokinetics in goats

The solid line in Fig. 2B shows the decreasing serum concentrations of melatonin after a bolus injection of melatonin (30 μg/kg) as means + SD of the 4 goats. Also in the goats, a 3-compartment model gave the best fit. Table 2 gives the kinetic parameters. The elimination phase was very similar in all goats, yielding a terminal half-life ($T_{½_3}$) of 27 ± 1 min. The calculated distribution half-life ($T_{½_1}$) varied between 0.3 and 0.8 min, partly due to few points left for calculation. Plasma clearance appeared to correlate with daily milk yield, being 0.022 l/kg/min in the goat milking 0.3 l per day and 0.046 l/kg/min in the goat milking 1.4 l per day. Mean residence time was around 20 min. It was longest in the goat milking least (25 min) and shortest in the goat milking most (15 min).

After the bolus injection, the concentration of melatonin in milk increased rapidly reaching the serum level within 15-30 min, and thereafter remaining higher than the serum level (Fig. 2B).

Discussion

A daily rhythm in milk melatonin has been observed in human milk (*Laitinen & Vakkuri* 1987, *Illnerová et al.* 1993). The present study shows a similar reflection of serum melatonin profile in bovine milk. Both in serum and in

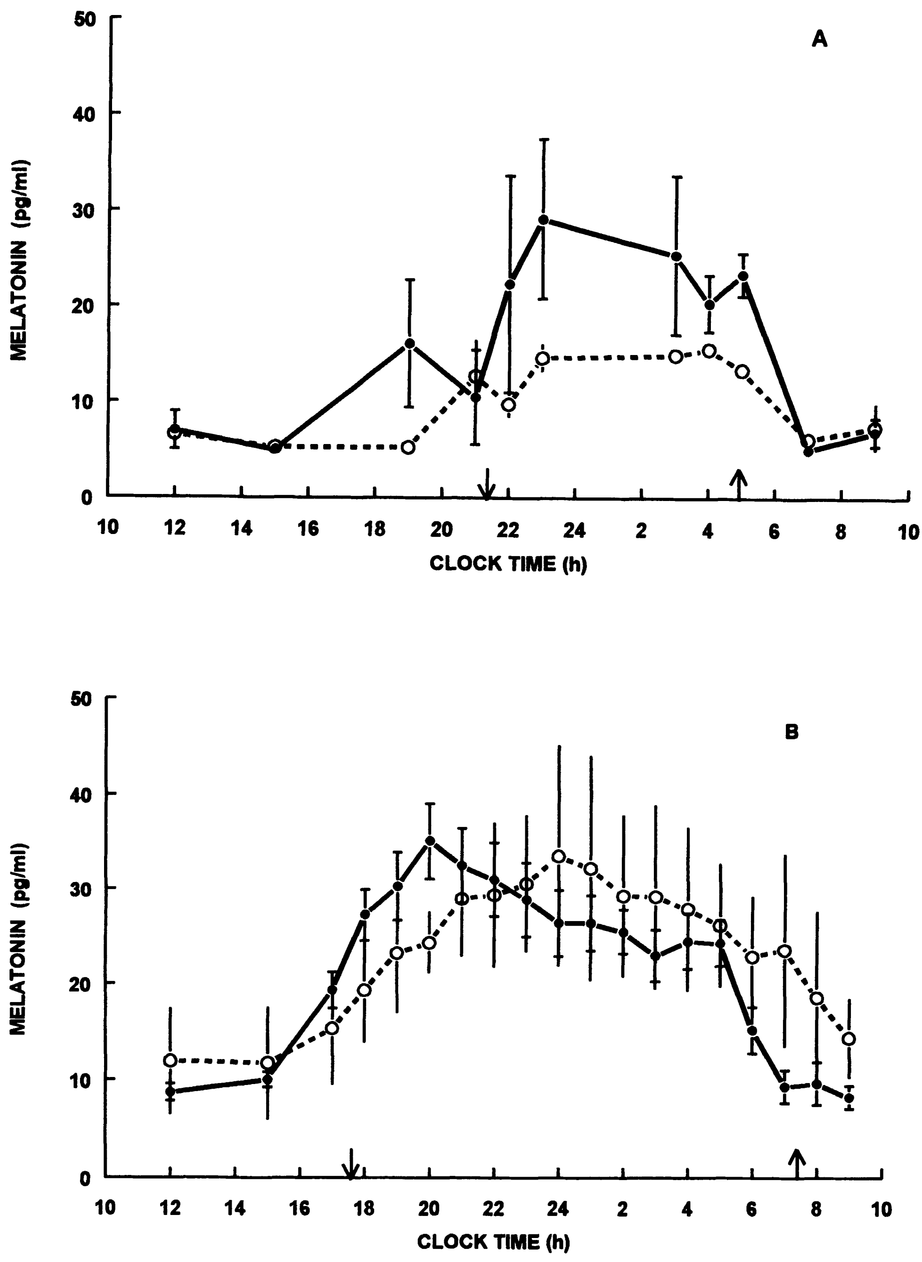

Figure 1A an 1B. Melatonin concentrations in serum (solid line) and milk (broken line) of lactating cows showing a nocturnal rise of melatonin. Fig. 1A shows means ± SEM of 4 Ayrshire cows at the beginning of lactation in May and Fig. 1B means ± SEM of 6 Ayrshire cows in late lactation period in February. The times for sunset and sunrise are indicated by arrows.

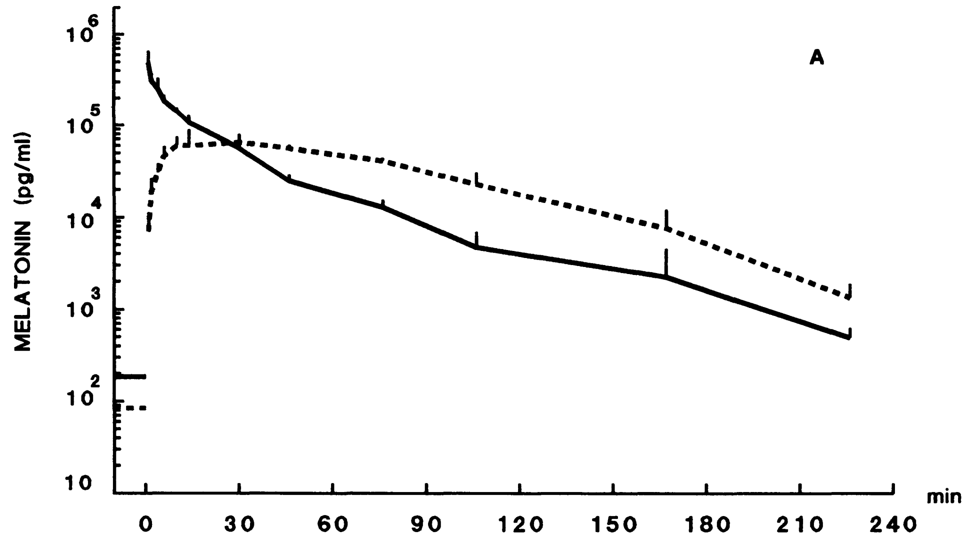

Figure 2A. Melatonin concentrations in serum (solid line) and milk (broken line) after an intravenous bolus injection (270 μg/kg). Means + SD of 4 cows.

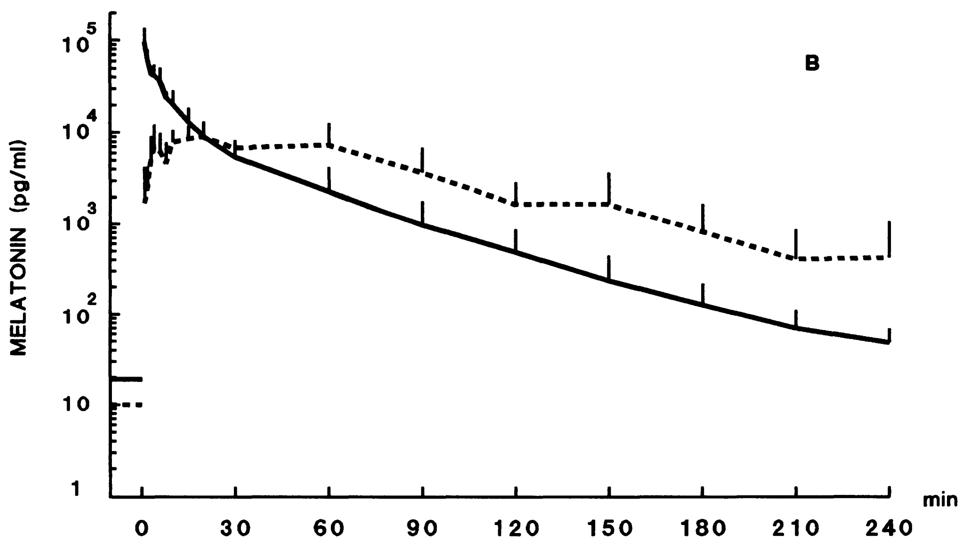

Figure 2B. Melatonin concentrations in serum (solid line) and in milk (broken line) after an intravenous bolus injection (30 μg/kg). Means + SD of 4 goats.

Table 2. Pharmacokinetic parameters (Means ± SD) describing the disposition of melatonin in serum after an intravenous bolus injection of melatonin to 4 cows (270 μg/kg) and 4 goats (30 μg/kg).

		Cow		Goat	
		Mean	SD	Mean	SD
$T_{1/2}$ (min)	1	0.5	0.2	0.5	0.3
	2	7.3	2.3	5.3	1.3
	3	26.6	3.6	27.0	1.1
Distribution volume (1/kg)		0.96	0.17	0.50[a]	0.16
Steady state distribution volume		1.04[c]	0.25	0.61[a,c]	0.11
(l/kg)		0.95[d]	0.25	0.59[a,d]	0.10
Mean residence time		23.7[c]	4.2	18.0[c]	4.3
(min)		22.9[d]	3.9	18.0[d]	4.1
Clearance		0.044[c]	0.004	0.035[c]	0.011
(l/kg/min)		0.043[d]	0.004	0.034[d]	0.010

Harmonic means were used, except for clearance.
[a] The values in cows differed significantly from those in goats ($p<0.05$).
[c] Calculated from equation.
[d] Calculated by the trapezoid method.

milk, the duration of night-time melatonin rise was longer in winter than in spring, indicating the effect of season.

At midnight, serum melatonin concentrations were reasonably similar in May and in February, whereas milk melatonin concentrations mimicked serum levels in winter but were clearly below serum levels in spring. The cows studied in winter were in late lactation period and this may be one reason for the more effective accumulation of melatonin in milk. Melatonin may play a role in the control of mammary gland involution, since melatonin appears also to retard the growth of mammary glands during puberty and pregnancy in heifers and mice (*Sánchez-Barceló et al.* 1991, *Recio et al.* 1994, *San Martín et al.* 1995). However, hormonal regulation of mammary development and involution are not yet fully understood.

Studies on melatonin pharmacokinetics have been conducted in several species (*Gibbs & Vriend* 1981, *Brown et al.* 1985, *Vakkuri et al.* 1985, *English et al.* 1987, *Berthelot et al.* 1990, *Guillaume et al.* 1995, *Cavallo & Ritschel* 1996) but, so far, no information has been available on melatonin kinetics in lactating animals. Melatonin is also excreted in milk, and the present study showed that the pharmacokinetic parameters in lactating cows and goats were very similar in spite of different doses. Also studies in sheep (*English et al.* 1987) and cattle (*Berthelot et al.* 1990) support the concept of dose-independence in melatonin kinetics. The only difference between cows and goats was in the distribution volume and steady state distribution volume, both of which were higher in cows. The elimination half-life of around 30 min in lactating cows was about half of that reported by *Berthelot et al.* (1990, 1993) in dry cows. The higher metabolic rate and elimination of melatonin via milk may well explain this difference between lactating and non-lactating animals.

Clearance is the other pharmacokinetic parameter which reflects the capacity to metabolize and eliminate a substrate from the body. In the goats, which had relatively greater individual differences in their daily milk yields, the clearance appeared to be higher in goats milking more. In cows, no such tendency was seen, apparently due to the more equal daily milk yields.

In non-lactating cows, *Berthelot et al.* (1990, 1993) found melatonin clearance to be of the same magnitude although the mean value in their dry cows was somewhat lower than in our lactating cows. They considered that the melatonin clearance value was similar to the hepatic blood flow. This agrees with our results and suggests the existence of a first-pass hepatic effect for melatonin also in lactating animals.

The physiological role of melatonin in milk remains to be elucidated. It has been suggested that it is one of the means of communication between mother and suckling (*Koldovsky et al.* 1995). Human studies (*Laitinen & Vakkuri* 1987, *Illnerová et al.* 1993) as well as our observations of the daily rhythm of melatonin in milk of cows indicate that suckling provides a rhythmic source of melatonin to the newborn.

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Sammanfattning

Melatonins dygnsrytm i komjölk: Farmakokinetik av exogent melatonin i lakterande kor och getter.

Vi undersökte om det förekommer en likartad dygnsrytm i melatoninhalt i komjölk som i blodserum. Fyra Ayrshire kor i början av deras laktationsperiod (maj månad) hade en måttlig stegring av melatoninhalten i mjölk under natten (från 7 ± 2 pg/ml mitt på dagen till 15 ± 1 pg/ml på natten; medelvärde ± SEM). Denna skillnad var mindre väl korrelerad med melatoninhalten i serum (från 7 ± 2 pg/ml till 27 ± 7 pg/ml). Å andra sidan visade 6 kor i sen laktationsfas (februari månad) klar långvarig parallell nattlig stegring av melatonin både i serum (från 9 ± 1 pg/ml mitt på dagen till 26 ± 3 pg/ml på natten) och i mjölk (från 12 ± 5 pg/ml till 26 ± 7 pg/ml).

Melatonins kinetik undersöktes i 4 lakterande Ayrshire kor och likaså i 4 lakterande getter genom att ge en intravenös engångsdos av melatonin. En 3-kompartmentmodell, med melatonin-eliminering som central kompartment, användes för att beskriva värdena. Följande värden (medelvärde ± standardavvikelse) erhölls för korna och getterna: eliminationshalveringstid 27 ± 4 min respektive 27 ± 1 min, "mean residence time" 24 ± 4 resp. 18 ± 4 min, distributionsvolym vid "steady state" 1,0 ± 0,3 resp. 0,6 ± 0,1 l/kg ($p<0{,}05$) samt plasmaclearance 0,044 ± 0,004 resp. 0,035 ± 0,011 l/kg/min. Efter injektionen steg melatoninhalten i mjölk snabbt och överskred halten i serum 15-30 min senare och blev sedan högre än i serum både hos kor och getter. Våra resultat tyder på att melatoninnivån i mjölken följer halten i blodet med viss fördröjning.

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