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Short Communication

Melatonin Administration to Dogs*

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With 4 Figures

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Summary

Melatonin concentrations in serum and urine were examined following oral administration of melatonin to dogs. Four different doses of melatonin ranging from 10 to 80 mg per kg of body weight were given. Melatonin was rapidly absorbed and reached a maximum serum level after 20—30 min, with a distribution phase of 3.5 hours and elimination half life ($t^1/_2$) of 5 hours. The fraction excreted in the urine was 0.25 % of the administrated dose during the first 5 hours. These results as well as the diurnal rhythm of serum melatonin in the dog are similar to corresponding data reported in the human.

Key words: Melatonin administration, diurnal rhythm, dog, pharmacokinetics.

Introduction

The physiological as well as possible pharmacological psychoactive properties of melatonin in man are presently being explored. Melatonin dissolved in ethanol given orally to humans is rapidly absorbed into the blood (*Wetterberg et al.*, 1978). Less than 0.5 % of

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a given dose of 100 mg is excreted into the urine as immunoreactive melatonin (*Wetterberg et al.*, 1978; *Wetterberg*, 1979).

In the present study we describe the pharmacokinetics of melatonin following its oral administration to dogs, and the canine diurnal rhythm of melatonin in serum.

Materials and Methods

Five female beagle dogs weighing 10.4—11.7 kg were given different doses of melatonin orally. The dogs were fasted overnight prior to the experiment and were given water ad libitum. Melatonin was administered in capsules which were easily swallowed by the dogs. The first dose of melatonin was given at 11 a.m. in all experiments. The dogs were observed and their behaviour recorded. Rectal temperature, heart rate, blood pressure and ECG pattern were recorded continously during the experiments. Venous blood samples were collected into vacutainer tubes at the different time points. Urine was collected continously from the bladder using an indwelling catheter.

In one experiment, performed during the month of August, endogenous levels of melatonin in serum were studied. Eleven venous blood samples were taken over a 24-hour period.

Results

Diurnal Rhythm

The pattern of serum melatonin in the dog over a 24-hour cycle displayed a circadian rhythm with low concentrations during the day and highest levels during the night at 2 a.m. (Fig. 1).

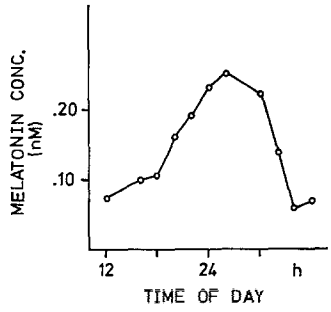

Fig. 1. Diurnal variation of serum melatonin in one dog observed over a 24-hour cycle with light period 6 a.m.—6 p.m. The concentration of serum melatonin is expressed as nanomoles per liter (nM)

Oral Administration of Melatonin

Oral administration of melatonin was studied in two dogs. Each dog received 10, 20, 40 and 80 mg/kg body weight of melatonin given at 2-hour intervals. Melatonin concentrations in serum increased proportionally with increasing dose (Fig. 2).

Four dogs were given a single dose of 40 mg melatonin per kg body weight. Melatonin was rapidly absorbed and reached a peak

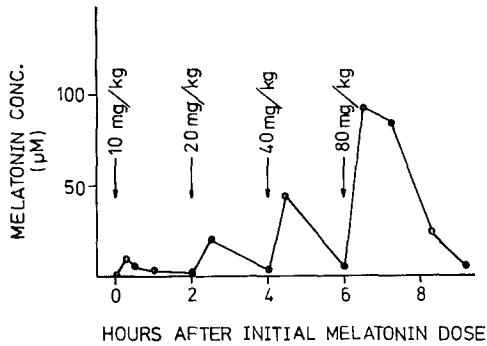

Fig. 2. Serum melatonin concentrations in two dogs following oral administration of four increasing doses at 2-hour intervals. Values shown are means of duplicate assays from the two dogs. Serum melatonin concentrations are expressed as micromoles per liter (μM)

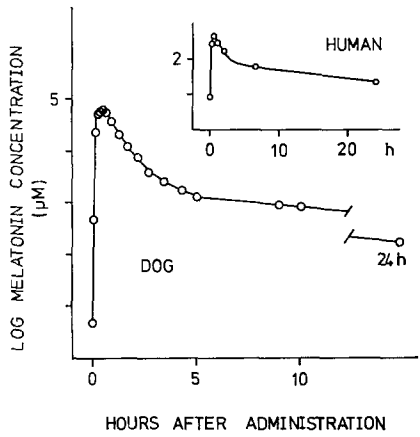

Fig. 3. Serum melatonin concentrations followed for 24 hours in 4 dogs given an oral dose of melatonin (40 mg per kg body weight). The values shown in a logarithmic scale are the means of duplicate assays from 4 dogs. The concentration of melatonin is expressed as micromoles per liter (μM). Inserted at right top corner is shown the serum concentration of melatonin in one man following an oral dose of 100 mg melatonin (cf. *Wetterberg et al.*, 1978)

value in serum between 20 to 30 min following its administration. The distribution phase was 3—4 hours and the elimination half time ($t^1/_2$) was approximately 5 hours (Fig. 3).

Urinary excretion of melatonin was examined after a single dose of melatonin (40 mg per kg of body weight); the amount excreted followed the serum concentration (Fig. 4). The total excreted amount of immunoreactive melatonin during the five hours after its administration was 0.25 % of the dose.

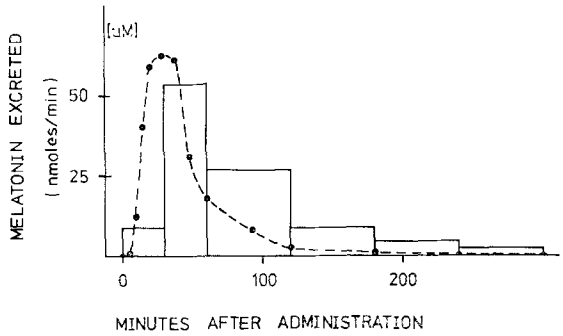

Fig. 4. Urinary melatonin excretion by one dog given an oral dose of melatonin (40 mg per kg body weight). Urine was collected via an indwelling bladder catheter at specified intervals. The values are the means of duplicate assays. Melatonin concentrations are expressed as micromoles of melatonin excreted per minute. The broken line indicates the corresponding serum melatonin concentration expressed as micromoles per liter (μM)

Discussion

The diurnal rhythm of serum melatonin in dogs appears from the present results to be similar to that previously observed in other species including man (*Arendt et al.*, 1977; *Kennaway et al.*, 1977). The endogenous serum levels of melatonin were low as compared to those obtained after oral administration of melatonin, which gave 10^4 to 10^6 times higher levels.

In the experiment where melatonin was given in increasing doses the serum levels increased in a linear fashion, indicating that melatonin is absorbed from the gastro-intestinal tract by a non-saturated transport system (probably mainly passive transport).

The more detailed study of the absorption and elimination of orally-administered melatonin displayed patterns similar to those reported in man (*Wetterberg et al.*, 1978). Thus, as seen in Fig. 3

maximum levels were reached after approximately 20—30 min in both species. Furthermore, the duration of the distribution phase as well as the half time ($t^1/_2$) of elimination were in the same range in both species.

The fractions of the melatonin dose that were excreted unchanged was also of the same magnitude, *i.e.* 0.25 % during the first 5 hours in dogs (Fig. 4) and 0.3 % during the first 6.5 hours in humans (*Wetterberg et al.*, 1978).

The results of this study suggest that the dog may serve as a model species in the further evaluation of the pharmacokinetics of melatonin which is needed before clinical trials in humans.

The behavioural and physiological effects of melatonin administration, including the increase it causes in whole-blood serotonin, will be reported in detail elsewhere.

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