Plasma concentrations of melatonin in man following oral absorption of different preparations

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The plasma concentrations of melatonin in man, fasting and fed, were determined after ingestion of three different oral preparations. A dose of 2 mg was given as either a gelatine capsule, a solution in corn oil or as a slow-release pill. Gelatine capsules and the corn oil preparation gave reproducibly timed peak plasma concentrations, 30 to 60 min after ingestion regardless of nutritional status, and plasma melatonin remained at or above endogenous night-time levels for 3–4 h with mean elimination half-lives of 0.54 to 0.67 h. The slow-release preparation usefully extended high plasma melatonin concentrations for 5–7 h after ingestion but the timing of peak concentrations was very dependent on nutritional status. These preparations should be of use in the study of timed melatonin administration in man.

Keywords melatonin oral clinical preparation

Introduction

The pineal neurohormone melatonin in physiological quantities is known to have potent effects on reproductive (Reiter, 1980; Bittman, et al., 1983) and other functions (Hoffman, 1981) in photoperiodic seasonal breeders. Its effectiveness is highly dependent on the time of its administration (Tamarkin, et al., 1976) and the duration of high plasma concentrations (Carter & Goldman, 1983; Arendt et al., 1983). It appears to act in a manner analogous to that of the light-dark cycle.

In rodents pharmacological doses of melatonin will entrain the rest-activity cycle (Redman et al., 1983) thus acting on the circadian system as a time-cue or zeitgeber. In pharmacological quantities it is known to have hypnotic properties in man and other species (Cramer et al., 1974) and to have very low toxicity (Sugden, 1980; Lerner & Nordlund, 1978). So far, however, no other consistent observation of possible therapeutic benefit has emerged. An agent such as melatonin capable of entraining, or speeding up the resynchronisation (Murakami et al., 1983) of circadian rhythms in man would be potentially useful in the treatment of disordered biological rhythms. In order to pursue this possibility we have investigated the plasma concentrations of melatonin after oral ingestion of different preparations.

Methods

Preparations of melatonin

Melatonin was obtained from Sigma Chemical Company Ltd, and made up in three formulations: (a) gelatine-coated capsules containing 2 mg melatonin dispersed in 250 mg lactose, (b) slow-release pills consisting of 2 mg melatonin in arachis oil: beeswax, 80:20, total weight 200
mg, kindly provided by Eli Lilly & Co. Ltd, (c) 0.04% w/v solution of melatonin in corn oil containing 2% v/v ethanol. 5 ml of this preparation thus provided 2 mg melatonin, and for ingestion was dispersed in 50 ml milk.

Protocol

The trial was divided into three phases, one for each melatonin preparation. Twelve normal healthy volunteers, six men and six women, aged 21 to 39 years weight range 50 to 85 kg, were assigned in groups of five to the gelatine capsule and slow-release pill and a group of four to the corn oil preparation. Two subjects had two melatonin preparations. Ethical approval for this study was obtained from St Luke’s Hospital, Guildford Ethics Committee.

Each phase of the trial was carried out on 2 separate days with at least 2 days interval in between (median 17 days, range 2–21 days). On the first day, the subjects had a standard breakfast of a small bowl of cereal, two slices of toast and tea before 08.00 h. On the second day the subjects fasted from 21.00 h the previous day until after the first 2 h of blood sampling.

A basal blood sample was taken at 09.00 h and the melatonin preparation was taken immediately after a second basal sample at 10.0 h. Gelatine capsules and slow-release pills were taken with a little water (approx 50 ml). Blood samples were taken from an indwelling venous cannula into heparinised tubes at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6 and 7 h after dosing, and immediately centrifuged. Plasma was separated and stored at −20°C until analysed for melatonin by radio-immunoassay using the method of Fraser et al. (1982). The interassay coefficients of variation for four quality control samples during this study were 8% (25 pg/ml), 7.1% (108 pg/ml), 12% (141 pg/ml) and 4.9% (526 pg/ml) and the limit of detection was 10 pg/ml.

Analysis of results

Areas under the plasma concentration curve (AUC), calculated to the limit of detectability above basal melatonin concentrations were derived using a computer programme, ‘Stripe’ (Johnston & Woollard, 1982), as were the timing of peak plasma melatonin (tmax) and the elimination half-life. Basal melatonin concentrations (at 10.00 h) were subtracted from post-ingestion plasma concentrations prior to analysis.

Results

The mean plasma melatonin concentrations (±

![Figure 1](image-url)  
**Figure 1** a) Plasma concentrations of melatonin (mean ± s.e. mean, n = 5) after 2 mg melatonin taken orally as a gelatine capsule at time 0 h. ▲——▲: after overnight fasting; ▼——▼: after a standard breakfast and b) Plasma concentrations of melatonin (mean ± s.e. mean, n = 4) after 2 mg melatonin taken orally in 5 ml corn oil at time 0 h. ▲——▲ after overnight fasting: ▼——▼: after a standard breakfast.
s.e. mean) following gelatine and corn oil preparations are shown in Figures 1a and 1b. Both preparations gave similar plasma concentration profiles, with melatonin levels maintained above the daytime range (< 10–23 pg/ml in this study) for 3–4 h. Mean melatonin concentrations were higher in the fed than in the fasted state with both preparations, as shown in a comparison of AUCs (Table 1). No significant differences were found in the timing of peak plasma melatonin levels between these preparations in either the fasted or the fed state, $t_{\text{max}}$ varied from 0.46 ± 0.07 h (gelatine capsule fed), to 0.95 ± 0.42 h (corn oil, fasting, mean ± s.e. mean). Very large interindividual differences were evident in the maximum plasma melatonin concentrations achieved, these being 35-fold in the case of the gelatine capsule and 16-fold for the corn-oil preparation. The elimination half-life varied from 0.54 ± 0.03 h (gelatine capsule, fasting) to 0.67 ± 0.03 h (corn-oil preparation, fed mean ± s.e. mean).

In view of their great variability, individual concentration-time profiles of melatonin following ingestion of the slow-release preparation are shown in Figure 2. Clearly, when subjects had eaten, high plasma concentrations of melatonin were maintained for 5–7 h in four out of five individuals with values above the physiological daytime range (< 10–23 pg/ml in this study) and within or above the night-time range (< 10–250 pg/ml, as observed in our laboratory). Secondary peaks were evident in the majority of individuals and were particularly marked in the fasted state. Comparison of areas under the curve indicated that no significant differences were present between fasting and fed plasma profiles. The peak plasma concentrations obtained with this preparation were considerably lower than those given by the gelatine and corn oil preparations (Figures 1 and 2) and the timing of peak concentrations was inconsistent particularly in the fasting state.

**Discussion**

Very few human studies of the plasma pharmacokinetics of melatonin have been undertaken. Wetterberg (1978) reported the plasma concentrations of melatonin as up to

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**Figure 2** Plasma concentrations of melatonin after 2 mg taken orally as a slow-release preparation (arachis oil: beeswax, 80:20, weight 200 mg, Eli Lilly & Co. Ltd) at time •. Each individual profile is plotted separately. (a) after a standard breakfast and (b) after overnight fasting.
Table 1  Areas under the plasma concentration curve (AUC, mean ± s.e. mean), calculated to the limit of detectability above basal melatonin concentrations following ingestion of 2 mg melatonin as gelatine capsules or corn oil preparation.

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<th>Gelatine capsule</th>
<th>Corn-oil preparation</th>
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<td></td>
<td>Fed</td>
<td>Fasting</td>
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<td>AUC (pg ml⁻¹ h)</td>
<td>8036 ± 2455*</td>
<td>3712 ± 703</td>
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*P < 0.05, fed compared to fasting. Significance level assessed by paired Student's t-test.

1000 fold physiological levels after ingestion of 100 mg by a single volunteer. Wurtman et al. (1983) found 20-fold variations in absorption following a dose of 80 mg crystalline melatonin in three volunteers and reported an elimination half-life of 45–60 min. All three preparations listed here showed very large variations in plasma concentrations in agreement with Wurtman et al. (1983). Gelatine capsules and the corn-oil preparation were virtually equivalent in the timing of peak melatonin concentrations, the duration of high plasma concentrations and AUCs. The increased AUC in the fed state is unlikely to be of clinical significance, particularly in view of the large inter-individual variations. The elimination half-lives were within the range previously reported (Wurtman et al., 1983). However, the absolute values are of questionable significance in view of the variability in the data.

Although the order of treatments was not randomised, the results were consistent over the wide range of time elapsed between studies. Moreover, basal 09.00 h and 10.00 h melatonin concentrations were always within the normal daytime range (Fraser et al., 1983) and thus any hangover effect from previous treatment is very unlikely.

The slow-release preparation is of interest in that it is able to maintain high, near physiological, plasma levels in most individuals for 5–7 h. Unfortunately, the nutritional state of the individual greatly influences the timing of peak concentrations and the pattern of release into the blood.

Any investigation of the physiological functions of melatonin in man will require it to be administered in as near a physiological manner as possible. Thus, with careful control of nutritional status the slow-release preparation is likely to be useful. On the other hand, the reproducible timing of high blood concentrations achieved by both corn oil and gelatine capsule preparations, independent of nutritional status, provides a pharmacological tool for investigating the effects of timed melatonin administration in man.

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References


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