Pharmacokinetics of melatonin in man after intravenous infusion and bolus injection

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Summary. The pharmacokinetics of melatonin during the day-time has been studied in 4 healthy subjects after a bolus i.v. injection of 5 or 10 µg/person and after a 5 h infusion of 20 µg per person in 6 healthy subjects. In addition, a pinealomectomized patient whose nocturnal plasma melatonin had been abolished was investigated after the i.v. infusion – once during the night and once during the day.

The clearance of melatonin from blood showed a biexponential decay. The pharmacokinetic parameters in the two studies were similar, except for the disappearance rate constant β and the apparent volume of distribution at steady-state (Vss). Supplementary peaks or troughs were superimposed on the plateau and the falling part of the profile. They were not due to stimulation of endogenous secretion, because they were also seen in the pinealomectomized patient.

During the melatonin infusion, the plasma hormone level reached a steady-state after 60 and 120 min, and when it was equal to the nocturnal level. The infusion regime may be valuable in replacing blunted hormonal secretion in disease states.

Key words: Melatonin; Pharmacokinetics, replacement therapy

The half-life of melatonin in plasma after a bolus intravenous injection is very short (Iguchi et al. 1982) and its oral pharmacokinetics is influenced by marked first hepatic metabolism (Lane and Moss, 1985). In all the reports describing the serum profile of melatonin, after oral administration to humans (Waldhauser et al. 1984, Vakkuri et al. 1985, Aldhous et al. 1985), the high doses given have led to very supraphysiological levels (several thousand pg/ml) which quickly became undetectable. Under physiological conditions, however, melatonin secretion, which is closely related to the dark period, produces mean plasma levels of ten of pg/ml over several hours, then fall to zero or less than 5 pg/ml during the light period – provided that a specific method of melatonin assay is employed. To gain an insight into the pharmacokinetics of melatonin at somewhere near to a physiological level, its plasma profile in man has now been studied after extended infusion of a low dose. The experiments were performed in 6 healthy subjects during the day period, and in one pinealomectomized patient, so that endogenous hormonal secretion in both cases was negligible. The pharmacokinetic parameters calculated from the data obtained after the infusion were compared with those obtained after a bolus intravenous injection in 4 controls, of whom 3 were also included in the infusion study.

Materials and methods

Melatonin solutions for injection

Two solutions of melatonin suitable for rapid intravenous injection (Solution A) or intravenous infusion (Solution B) were prepared. Crystalline melatonin (Sigma Chemical Co, St. Louis, Mo) was checked by thin-layer chromatography and mass spectrometry (data not shown). To prepare Solution A (melatonin concentration 2 µg/ml) 1 mg melatonin was dissolved in 5 ml absolute ethanol, and then 1 ml of the ethanolic solution was mixed with 99 ml sterile physiological saline. After sterilization by filtration through a Micropore filter 0.22 µm (Millipore, Molsheim, France) the solution was stored in sterile vials in aliquots of 10 ml, under vacuum, until injected. The interval between preparation and injection was less than 24 h.

For Solution B (melatonin concentration 0.4 µg/ml) melatonin 400 µg was dissolved in 10 ml ethanol, and 1 ml of that solution was filtered through a Micropore filter and mixed with 99 ml sterile physiological saline. The vial containing the solution was covered with an aluminium sheet and stored at 4°C until administration of the infusion. Solutions A and B both met the quality criteria of the French Pharmacopoeia.

Study subjects and experimental procedures

Studies were performed on 7 normal volunteers (BPH, RZ, MD, CM, MP, RJF, LM) 23–33 years of age, who had given their written informed consent. They were healthy and had received no medication for at least 15 days prior to the investigation. They were non-smokers and were within 10% of their ideal body weight. The study protocol had previously been approved by the National Ethics Committee.

In a first experiment, after an overnight fast, 3 control subjects (CM, LM, MD) received a bolus i.v. injection of 2.5 ml Solution A (dose 5 µg) and 1 subject (RZ) was given 5 ml Solution A (dose 10 µg). The injection, which lasted up to 2 min, was given at 10.30 h,
through a forearm vein. Blood 3 ml was collected in heparinized tubes from the opposite forearm 2, 5, 8, 12, 16, 20, 30, 40, 50, 60, 90 and 120 min after the injection.

In a second experiment, 6 subjects (BPH, CM, MD, MP, RJF, RZ) were given Solution B as a constant infusion of 10 ml·h⁻¹ (4 µg·h⁻¹) for 5 h, beginning at 11.00 h after an overnight fast. One patient (RP), who had been pinealomectomized 2 years earlier, was also included in the study. Plasma melatonin in him could not be detected during the night (less than 3 pg/ml) between 20.00 h and 08.00 h. He was similarly treated, but received two infusions; the first was 14 months earlier, when the infusion beginning at 20.00 h. Each subject received all a 50 ml infusion given by a volumetric pump (Lepine, Lyon, France) through an indwelling catheter inserted into an antecubital vein; the flow rate of the pump had been previously verified, and so had the lack of adsorption of melatonin on the walls of the catheter. Blood (3 ml) was collected from the opposite forearm every 20 min during the first hour of the infusion period, and then every 30 min until the infusion was completed. Subsequent blood samples were taken at the same times as after the bolus IV injection.

Blood samples were stored at 4°C until the end of each sampling session, and then they were centrifuged, and the plasma was decanted and frozen at −20°C until assayed. Plasma melatonin concentrations were determined by radioimmunoassay (Brun et al. 1985). All plasma samples from each subject were assayed at the same time. The intra-assay coefficient of variation was always less than 9% between 27 and 60 pg·ml⁻¹, and less than 6.5% between 80 and 150 pg·ml⁻¹ melatonin. The inter-assay coefficient of variation was 8.5% and 6.9% (n = 8) at melatonin levels of 55 and 113 pg·ml⁻¹, respectively.

Calculations

The plasma melatonin concentrations over time following the intravenous bolus injection, or lying on the decreasing part of the plasma melatonin curve after the infusion, were analyzed by the program of Cazin and Luyckx (1984), which is a computerized, least squares method for obtaining parameter estimates from polyexponential functions. Experimental plasma concentrations were plotted against time after logarithmic transformation and the graph obtained was broken down into one, two or three phases. The compartmental model or the number of phases was chosen which best fitted the experimental curve.

Pharmacokinetic parameters were calculated by the method of Gibaldi and Perrier (1982) and are given in Tables 1 and 2. Briefly, from a plasma profile obtained after a bolus injection of melatonin, the total area under the plasma concentration versus time curve (AUC) was calculated using the trapezoidal rule. Systemic clearance (CLₕ) was calculated from the relationship CLₕ = dose/AUC. Using the plasma melatonin profile observed during the infusion, the systemic clearance (CLₖ) was obtained as the ratio of infusion rate to