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A BIVARIATE MATHEMATICAL MODEL FOR THE EFFECT OF MELATONIN PRODUCTION ON SAMPLINGS

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Abstract: To provide guidelines for collecting and analyzing urinary, salivary, and plasma melatonin, thereby assisting clinicians and researchers in determining which method of measuring melatonin is most appropriate for their particular needs and facilitating the comparison of data between laboratories. The benefits and disadvantages of current methods of collecting and analyzing melatonin are summarized. Although a single method of analysis would be the most effective way to compare studies, limitations of current methods preclude this possibility. Given that the best analysis method for use under multiple conditions is not established, it is recommended to include, in any published report, one of the established low threshold measures of dim light melatonin onset to facilitate comparison between studies. Administration of melatonin with time of day and midnight are fitted with bivariate normal distribution and the probability density function, marginal distributions and corresponding expectations are obtained using stochastic model. Here we suggest that saliva sampling is a good method to measure.
Keywords: Plasma melatonin, salivary melatonin

I. INTRODUCTION

Melatonin: Melatonin is a hormone made by the Pineal gland, a small gland in the brain. Melatonin helps control our sleep and wake cycles. Very small amount of it are found in foods such as meats, grains, fruits, vegetables. Our body has its own internal clock that controls our natural cycle of waking & sleeping hours.Melatonin levels begin to rise from mid to late evening, remain high for the night and then drop in the early morning hours.

Uses of Melatonin: Melatonin supplements are sometimes used to treat jet lag or sleep problems (insomnia). Scientists are also looking at other good uses for melatonin, such as:

- Treating seasonal affective disorder (SAD).
- Helping to control sleep patterns for people who work night shifts.
- Preventing or reducing problems with sleeping and confusion after surgery.
- Reducing chronic cluster headaches

Synthesis: Melatonin synthesis from the pineal gland is regulated by the circadian pacemaker located in the suprachiasmatic nuclei and by ocular light exposure. Melatonin has a circadian rhythm that peaks

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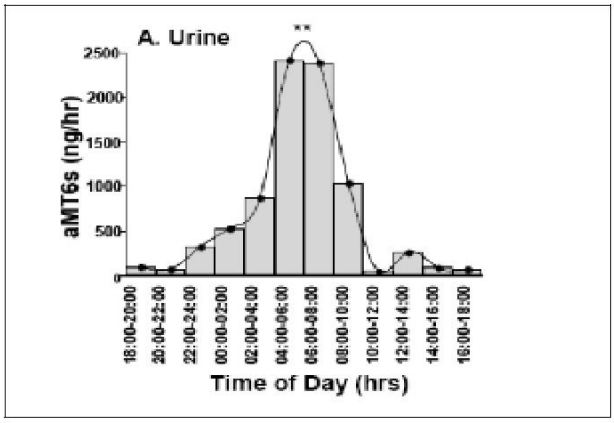
during the night in normally entrained individuals. In the absence of light and other synchronizing signals, the rhythm of melatonin production persists with an elevation that occurs during the subjective, as opposed to the actual, night. There is a relatively direct anatomic pathway between the suprachiasmatic nuclei and the pineal gland, and comparatively few exogenous factors are known to affect melatonin concentrations.

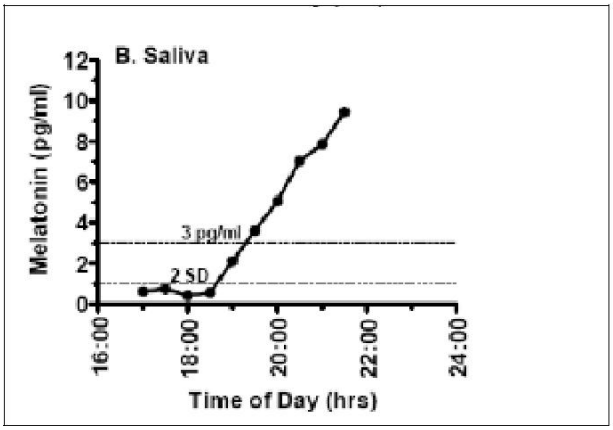
II. METHODS & RESULTS

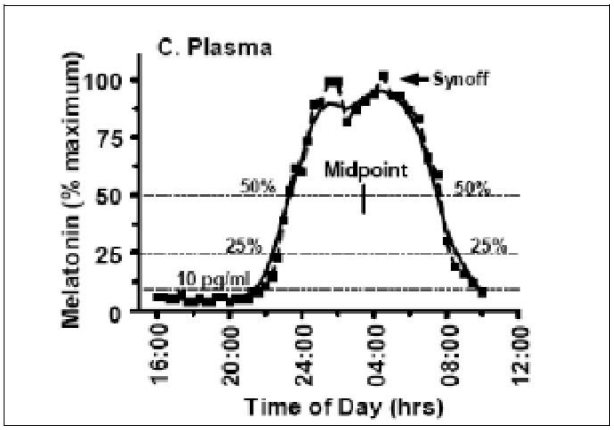
A modified RAND process to determine the level of consensus for each method of collecting or analysing melatonin under specified conditions, which consisted of voting independently to assess the acceptability of each of 54 separate items. The "acceptability" of a particular item was based on reliability, validity, and practical utility. A conference call was then held to assess the level of agreement and disagreement for each item, to discuss reasons for disagreement, and to determine areas of consensus. A consensus-based document was drafted and re circulated for comments and revisions. The draft document was finalized upon approval of all of the workgroup members. [1]

Results: The workgroup's consensus-based summary and recommendations for collection and analysis of urinary, salivary, and plasma melatonin are detailed below. The utility of these methods for studies conducted outside of the clinic or inpatient facility in the natural living environment ("field studies"), studies conducted primarily for phase assessment in a clinical setting ("clinical studies"), and research studies conducted in an inpatient facility under controlled conditions ("research studies") are described.[4]

Figures:







Figures — Illustrations of 3 melatonin sample types and their associated phase estimates.

Figure A Urine : 24-hour rhythm of the primary urinary melatonin metabolite 6-sulphatoxymelatonin (aMT6s) derived from urine samples collected in 2-h bins under dim light. The fitted curve reveals a significant 24-hour rhythm with maximum levels observed between 04:00 and 08:00 (**$p < 0.01$).

Figure B Saliva: Salivary melatonin profile collected under dim-light conditions. The low-threshold dim-light melatonin onset (DLMO) was defined as either the first sample to exceed and remain above a threshold of 3 pg/mL or that was 2 SD above the mean of the first 3 baseline samples (2 SD).

Figure C Plasma: Overnight plasma melatonin profile, plotted as a percentage of maximum (dashed line) and smoothed with a lowest curve fit to the raw data (solid line). Some frequently used phase markers are shown:

DLMO at 10 pg/mL, DLMO or dim-light melatonin offset (DLMOff) at 25% or 50% of maximum levels, the midpoint, and the termination of melatonin synthesis (Synoff)

III. MATHEMATICAL MODEL

Mathematical Model for Bivariate Normal Distribution:

Two r.v.'s(X,Y) have a bivariate normal distribution N($\boldsymbol{\mu}_1$,$\boldsymbol{\mu}_2$,$\boldsymbol{\sigma}_1^2$,$\boldsymbol{\sigma}_2^2$,$\boldsymbol{\rho}$) if their joint p.d.f is Fx,y (x, y) =

$$f_{X,Y}(x,y)=\frac{1}{2\pi\sigma_1\sigma_2\sqrt{(1-\rho^2)}}\,e^{-\frac{1}{2(1-\rho^2)}\left[\left(\frac{x-\mu_1}{\sigma_1}\right)^2-2\rho\left(\frac{x-\mu_1}{\sigma_1}\right)\left(\frac{y-\mu_2}{\sigma_2}\right)+\left(\frac{y-\mu_2}{\sigma_2}\right)^2\right]} \quad (1)$$

for all x, y. The parameters $\boldsymbol{\mu}_1$, $\boldsymbol{\mu}_2$ may be any real numbers, $\boldsymbol{\sigma}_1 > 0$, $\boldsymbol{\sigma}_2 > 0$, and $-1 \le \boldsymbol{\rho} \le 1$.It is convenient to rewrite (1) in the form

$$f_{X,Y(x,y)}=ce^{\frac{-1}{2}Q(x,y)},\ \text{where}\ c=\frac{1}{2\pi\sigma_1\sigma_2\sqrt{(1-\rho^2)}}\quad \text{and}$$

$$Q(x,y)=(1-\rho^2)^{-1}\left[\left(\frac{x-\mu_1}{\sigma_1}\right)^2-2\rho\left(\frac{x-\mu_1}{\sigma_1}\right)\left(\frac{y-\mu_2}{\sigma_2}\right)+\left(\frac{y-\mu_2}{\sigma_2}\right)^2\right] \quad (2)$$

Statement: The marginal distributions of N($\boldsymbol{\mu}_1$,$\boldsymbol{\mu}_2$,$\boldsymbol{\sigma}_1^2$,$\boldsymbol{\sigma}_2^2$,$\boldsymbol{\rho}$)are normal with r.v's X and Y havingdensity functions

$$f_X(x)=\frac{1}{\sqrt{2\pi\sigma_1}}e^{\frac{(x-\mu_1)^2}{2\sigma_1^2}},\ f_Y(y)=\frac{1}{\sqrt{2\pi\sigma_2}}e^{\frac{(y-\mu_2)^2}{2\sigma_2^2}}.$$

Proof: The expression (2) for Q(x,y) can be rearranged as follows:

$$Q(x,y)=\frac{1}{1-\rho^2}\left[\left(\frac{x-\mu_1}{\sigma_1}-\rho\frac{y-\mu_2}{\sigma_2}\right)^2+(1-\rho^2)\left(\frac{y-\mu_2}{\sigma_2}\right)^2\right]=\frac{(x-a)^2}{(1-\rho^2)\sigma_1}+\frac{(y-\mu_2)^2}{\sigma_2^2} \quad (3)$$

Where $a=a(y)=\mu_1+\rho\frac{\sigma_1}{\sigma_2}((y-\mu_2))$. Hence $f_Y(y)=\int_{\infty}^{\infty}f_{X,Y}(x,y)dx=\quad ce^{\frac{-(y-\mu)^2}{2\sigma_2^2}}\times\int_{-\infty}^{\infty}e^{\frac{(x-a)^2}{2(1-\rho^2)\sigma_1^2}}$

$dx=\frac{1}{\sqrt{2\pi\sigma_2}}e\frac{-(y-\mu_2)^2}{2\sigma_2^2}$

Where the last step makes use of the formula

$$\int_{-\infty}^{\infty}e\frac{-(x-a)^2}{2\sigma^2}dx=\sqrt{2\pi}\sigma\ \text{with}\ \sigma=\sigma_1\sqrt{1-\rho^2}\,.$$

Smilarly,

$$f_X(x)=\int_{-\infty}^{\infty}f_{X,Y}(x,y)dx=ce^{\frac{-(x-\mu_1)^2}{2\sigma_1^2}}\times\int_{-\infty}^{\infty}e^{\frac{(y-\sigma)^2}{2(1-\rho^2)\sigma_2^2}}dx=1\frac{1}{\sqrt{2\pi}\sigma_1}e^{\frac{-(x-\mu_1)^2}{2\sigma_1^2}}$$

Corollaries

1. Since X ~ N($\boldsymbol{\mu}_1$, $\boldsymbol{\sigma}_1^2$),Y ~ N($\boldsymbol{\mu}_1$,$\boldsymbol{\sigma}_2^2$) we know the meaning of four involved into the definition of

thenormal distribution, namely

$$E(X) = \mu_1, Var(X) = \sigma_1^2, E(Y) = \mu_2, Var(X) = \sigma_2^2.$$

2. X/(Y = y) is a normal r.v. To verify this statement we substitute the necessary ingredients into the formula the relevant conditional density:
In other words

$$X/(Y = y) \sim N(a(y), (1-\rho^2)\sigma_1^2).$$

3. $E(X/Y = y) = a(y)$ or equivalently, $E(X/Y) = \mu_1 + \rho\frac{\sigma_1}{\sigma_2}(Y - \mu_2)$.

In particular, we see that E(X/Y) is a linear function of Y.

4. E(XY) = $\boldsymbol{\sigma_1\sigma_2\rho + \mu_1\mu_2}$ Proof:

$$E(XY) = E[E(XY/Y)] = E[YE(X/Y)] = E[Y(\mu_1 + \rho\frac{\sigma_1}{\sigma_2}(Y-\mu_2))]$$

$$= \mu_1 E(Y) + \rho\frac{\sigma_1}{\sigma_2}\left[E(Y^2) - \mu_2 E(Y)\right] = \mu_1\mu_2 + \rho\frac{\sigma_1}{\sigma_2}\left[E(Y^2) - \mu_2^2\right]$$

$$= \mu_1\mu_2 + \rho\frac{\sigma_1}{\sigma_2}Var(Y) = \sigma_1\sigma_2\rho + \mu_1\mu_2.$$

5. Cov(X ,Y) = $\boldsymbol{\sigma_1\sigma_2\rho}$

This follows from corollary 4 and the formula
Cov(X ,Y) = E(XY) - E(X)E(Y).

6. $\boldsymbol{\rho}$(X, Y) = $\boldsymbol{\rho}$. In words, $\boldsymbol{\rho}$ is the correlation coefficient of X, Y. This is now obvious from the definition

$$\rho(X,Y) = \frac{Cov(X,Y)}{\sqrt{Var(X)Var(Y)}}.$$

IV. MATHEMATICAL RESULTS

For different values of shape & scale parameters we have following figures for the application part.

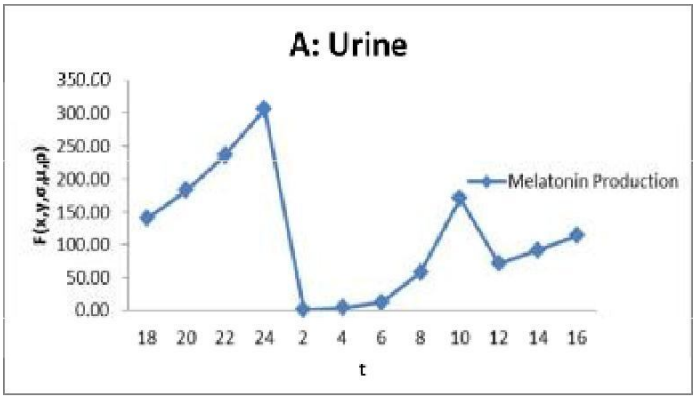


Figure A. Level of Melatonin produced depending upon Time of day (hrs) for Urine sample

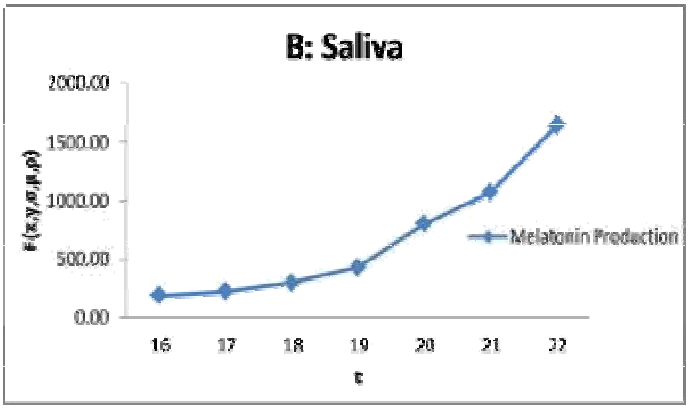


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Figure B. Level of Melatonin produced depending upon Time of day (hrs) for Saliva sample

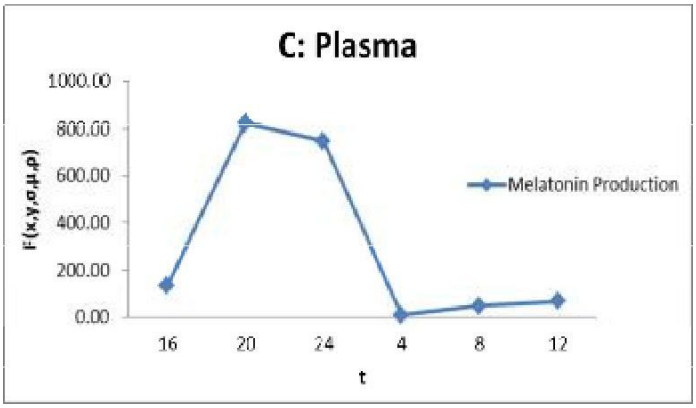

Figure C. Level of Melatonin produced depending upon Time of day (hrs) for Plasma sample

V. CONCLUSION

We have shown the Melatonin production depending upon the time factor for the 24 hr clock rhythm. Inthis respect we have concluded with the following observations. Figure A shows the 24 hr rhythm of the Urine samples fitted by the Bivariate Mathematical model giving a curve (both rising & declining) which reveals with maximum levels observed in the midnight. It shows also a decline at 2AM with again a short rise overnight. Figure B shows a visual estimate of the point of change from baseline to rising levels.It depends on the level of Melatonin produced. In this direction we have developed a Bivariate Mathematical model and it gives us a monotonically increasing curve (rising curve) for various Saliva sampling. Figure C shows an overnight Melatonin profile. Here the model helps us to determine the rising or declining phase and also the midpoint between the rising & declining phase which fits the data into a curve. The curve is fixed with low baseline levels during the day and improves gradually to the rising phase overnight.The mid of the curve represents the transition from the maximum nocturnal Melatonin production to the morning decline of the curve. These give a clear picture if we compare with the medical curves. Here we suggest that saliva sampling is a good method to measure but in the medical dataset 2- to 8- hour saliva samples are not tested.

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