Pharmaceutical, chronobiological and clinical aspects of melatonin
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PHARMACEUTICAL ASPECTS OF MELATONIN

- Melatonin: Drugs not for human use
- Melatonin: a survey of suspected drug reactions
- Correlation between concentrations of melatonin in saliva and serum of patients with delayed sleep phase syndrome
2.1 MELATONIN: DRUGS 'NOT FOR HUMAN USE'

Introduction

In the Netherlands the substance melatonin (N-acetyl-5-methoxy-tryptamine) is only available with the qualification 'not for human use'. From September 1995 until April 1996 tablets of melatonin were available on the Dutch market as a food supplement [1]. Merchandise legalisation for food and drugs differs and therefore no pharmaceutical standards have been formulated. Melatonin is not described in the current pharmacopoeias. For some indications, however, clinical use of melatonin is justified. Therefore in this article a survey is given of the production of several formulations with melatonin and the analysis of melatonin.

Chemical aspects

The hormone melatonin is produced by the pineal. The secretion is influenced by the day-night rhythm. Melatonin can be obtained from pineal glands from bovines or be synthesised from various agents e.g. [2]:

1) Starting with 5-hydroxytryptamides, present in the outer layer of the coffee bean. These 5-hydroxytryptamides can be extracted, isolated and derivated leading to melatonin and several other derivatives. In this production process kaliumhydroxide, sodiumhydrogenphosphate, ethanol and methanol are used.

2) Starting with 5-methoxytryptamine which can be treated with acetic anhydride in pyridine at room temperature, forming N,N-bis acetylated derivatives that can be converted to melatonin after washing with base.

3) Starting with 5-methoxyindole. With this agent melatonin can be prepared by adding xylene, hydrogen, platinum oxide and acetic anhydride in pyridine.

Depending on the route of synthesis impurities with organic agents, arsenic and heavy metals can be expected. Before use of melatonin for pharmaceutical properties limits of

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1 JE Nagtegaal, YG van der Meer, MG Smits. This chapter is translated in English from the Dutch article: Melatonin: 'not for human use', published in the Pharmaceutisch Weekblad, 1996; 131 (19): 546-549.
these impurities must be tested for by limit tests for various impurities of the European Pharmacopoeia IX.

Synthesis of endogenous melatonin

Endogenous melatonin is mainly synthesised and secreted by the pineal and the photoreceptors of the retina. One of the precursors of melatonin is tryptophane. Sympathetic nerves that innervate the pineal regulate melatonin production. The process is controlled by the biological clock, which is located in the suprachiasmatic nucleus of the hypothalamus [3]. The endogenous production is about 29 microgram/day for healthy people [4], to 12 microgram/day for patients suffering from livercirrhosis [5]. Several drugs, for example betablockers can suppress the endogenous melatonin secretion [6].

Melatonin binds to melatonin receptors that are located in: the brain, the hypophysis, the hypothalamus, the retina en the genitals. The hormone acts as a neuromodulator and a neurotransmitter [3].

Kinetics of exogenous melatonin

The clearance of melatonin administered intravenously is biphasic [3] with a mean of 631 ml/min in healthy people and a mean of only 127 ml/min in patients with livercirrhosis [4,5]. The half-life times are short: 3 and 45 minutes respectively [3]. The bioavailability of oral formulations varies strongly in the different studies: from 3-6% [7-9] to higher values of 23-76% [4]. Melatonin has a large first-pass effect [3].

Administration of melatonin in circadian rhythm disorders

A low dose of melatonin (1-5 mg) administered at the right time has been effective in several small studies on the treatment of circadian rhythm disorders. Examples of disorders where melatonin appeared to be effective are: jetlag, sleep disruption after shiftwork and the Delayed Sleep Phase Syndrome (DSPS). In this journal articles about the clinical effects of melatonin have been published earlier [10,11]. A higher dose (80 mg) should be effective as a hypnotic [12]. The design and the results of this study, however, do not justify this indication.
In our hospital we have treated DSPS with low doses of melatonin. In the US melatonin is classified as an ‘orphan drug’ for the treatment of circadian rhythm disorders in blind children.

Other applications

In the Netherlands a clinical trial with a contraceptive containing 500 microgram norethindrone and 75 mg melatonin has been carried out. Melatonin suppresses the release of Luteinizing Hormone causing inhibition of the ovulation. Since in animal experiments melatonin in high doses appeared effective in preventing breast cancer, a melatonin-containing contraceptive seemed interesting.

There are other indications described in literature as well, however, based on studies with only a few subjects and without a double-blind design. Several claims of melatonin are: immunomodulation, stress reduction and antineoplastic properties. Melatonin is considered to be effective in the treatment of depression, mania and schizophrenia [3].

Side effects and contraindications.

Despite the claim of some researchers that melatonin does not have any side effects, various side effects have been described in literature. In our patients gastrointestinal disorders, heart burning, nausea and feeling hungry were observed.

No systematic search for side effects of melatonin is described unto now. It is advised not to take melatonin during pregnancy or during breastfeeding. In rats high dosages administered during pregnancy resulted in a lower birth weight and lower weight of the ovarian of the female offspring.

Production of melatonin containing drugs

Tablets

Tablets containing melatonin have been on the Dutch market as a food supplement (Ultra Snooze®, Kernpharm, Veghel, the Netherlands). These tablets contained 2.5 mg melatonin, lactose, starch, magnesiumstearate and siliciumdioxide. The storage conditions were 3 years at a temperature of 15-25 degrees Celsius at a dry place. This contrasts with
the storage conditions of melatonin by some suppliers of raw materials (for example Acros and Sigma), who advise to store melatonin in the freezer.

**Capsules**

Capsules can be made easily in the (hospital) pharmacy. Variable amounts of melatonin in the range from 1 mg - 5 mg can be processed. As filler either microcrystalline cellulose (own experience) or lactose [13,14] can be used.

**Preparations with slow release**

Aldhous et al have described a capsule where 2 mg of melatonin was manufactured in a mixture of arachide-oil and beeswax in a ratio of 80:20, with a total weight of 200 mg [13]. The inconsistency of the reabsorption by the intestine is a disadvantage of the preparation [3].

A tablet with slow release is used in a clinical trial in the elderly. However, the additives and the pattern of release of this tablet have not been published yet [15].

**Mixture**

A solution of 0.04% w/v of melatonin in vegetable oil and 2% v/v ethanol has been described by Aldhous et al [13]. A volume of 5 ml of this mixture contains 2 mg melatonin and was added to a glass with 50 ml of milk just before administration [13].

**Nasal spray**

To bypass the first-pass effect of melatonin, Volrath et al have prepared a nasal spray containing 0.85% w/v of melatonin in ethanol [16]. Nebulizing two times resulted in a spray dose of 1.7 mg. More information about pattern of release and blood levels has not been published.

**Intravenous fluid**

Strassman et al [17] described an aseptically prepared solution, containing 2 mg of melatonin, dissolved in 1.0 ml of ethanol 96% and adjusted with aqua ad injectabilia till 5.0 ml. Of this solution 0.3 ml is added to 1 litre of NaCl 0.9%. The infusion bag had to be
packed up in dark plastic to avoid photo-oxidation. This solution was infused at a rate of 25 ml/h (0.05 microgram/min melatonin) [17].

Analysis

To our knowledge no qualifications for identification reactions and content of melatonin containing products have been published in international papers until now. Hereby we show the methods of analysis that are performed in our laboratory (Hospital Gelderse Vallei, Ede, The Netherlands).

Control of raw material

Qualitative analysis

Melatonin is a slightly off-white crystalline, homogeneous powder, without foreign particles with a melting point of 116-118 degrees Celsius. The identity can be analysed by Thin Layer Chromatography with a mobile phase of dichloormethane (90) and methanol (10) (saturated during 1 hour). The melatonin is diluted to 5 mg/ml in ethanol 96%. Of this solution 1 microlitre is dropped on the silica gel (254 nm). The solid phase has to be in the mobile phase for 30 minutes. One major spot is seen at 254 nm with a Rf= 0.4. After some hours in daylight the melatonin spots turns yellow.

The Infra Red spectrum is authentic and has to be in strict accordance with the reference spectrum.

Quantitative analysis

The content can be measured by UV spectrometric analysis. A solution of 0.025 mg melatonin per ml water is to be prepared. The specific extinction at 278 nm was found to be 274 (own results), this is a molar extinction of 6364, which is in accordance with the molar extinction in literature: 6300 [18]. The molar extinction at 223 nm is 27550, which is in agreement with the literature as well [18].

The content which can be measured by High Pressure Liquid Chromatography (HPLC) may not be less than 99.5%. The advantage of HPLC over UV spectrometric analysis is
that the purity can be taken into account. This is important for good analysis of new batches of material and for analysis of storage conditions. This method discriminates between melatonin and its degradation products. A Chromsfer C18 column has been used and a flow of 1 ml/min. The injection volume is 10 microliter. The wavelength of detection is 278 nm, the mobile phase is a mixture of 25 units of methanol and 75 units of water. The internal standard, caffeine (1 mg/100 ml (RT=±2 minutes)) is used and a stockstandard 5 mg/100 ml melatonin (RT=±5 minutes).
Table 3: Demands of purity by three suppliers
(A) Genzyme Pharmaceuticals, Suffolk, England
(B) AMR Pharm Holland
(C) Triple Crown America, inc, USA

<table>
<thead>
<tr>
<th>Test</th>
<th>Demand (A)</th>
<th>Demand (B)</th>
<th>Demand (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphated ash</td>
<td>&lt;0.1%</td>
<td>&lt;0.02%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Lead</td>
<td>-</td>
<td>&lt;0.5 ppm</td>
<td>&lt;1 ppm</td>
</tr>
<tr>
<td>Arsenic</td>
<td>-</td>
<td>&lt;0.2 ppm</td>
<td>&lt;0.5 ppm</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>&lt;20 ppm</td>
<td>&lt;1 ppm</td>
<td>&lt;1 ppm</td>
</tr>
<tr>
<td>Water</td>
<td>&lt;1%</td>
<td>-</td>
<td>&lt;0.3%</td>
</tr>
<tr>
<td>Residue in ethyl acetate</td>
<td>&lt;0.3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Residue in acetic acid</td>
<td>&lt;0.3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melting point</td>
<td>-</td>
<td>116-118 °C</td>
<td>116-118 °C</td>
</tr>
<tr>
<td>IR</td>
<td>In accordance to the reference spectrum</td>
<td>In accordance to the reference spectrum</td>
<td>In accordance to the reference spectrum (The Aldrich Library of Infrared Spectra)</td>
</tr>
<tr>
<td>Purity (HPLC)</td>
<td>&gt;99.0%</td>
<td>&gt;99.5%</td>
<td>&gt;99.5%</td>
</tr>
<tr>
<td>Purity (TLC)</td>
<td>Total impurities not more than 1.0%. No individual impurity more than 0.5%.</td>
<td>Passes test</td>
<td>One major spot</td>
</tr>
</tbody>
</table>
Purity of melatonin

In Table 3 the demands of three suppliers of melatonin is summarised. Our standards were based on these purity claims. Individual impurities must be less than 0.05%, while total impurities may not exceed 0.5%. The water content must be less than 0.3%, the sulphated ash must be less than 0.1%. Heavy metals like lead must be less than 1 ppm and arsenic must be less than 0.5 ppm.

Stability

In the literature only little is described about stability of melatonin. Some manufacturers advise storing melatonin in the freezer (maximum temperature: -20 °C), others state that melatonin has been filled off under nitrogen. From our short and long lasting studies on keeping qualities we have not found a ground for these precautions. We have found melatonin to be a stable substance for temperature and oxygen. The dry agent is stable for 24 hours at 80 °C. Addition of 5 ml sodiumhydroxide 0.1 N or hydrogenperoxide 30% to 50 mg melatonin shows a complete degradation of the melatonin within six hours. Therefore a stable solution with melatonin may not be too alkaline. Based on these results the addition of an anti-oxidant will be useful. We analysed by HPLC that capsules with 5 mg melatonin, with microcristalline cellulose as filling substance, can be kept at 45 °C for at least two years with loss of no more than 5% melatonin.

Literature


2.2 MELATONIN: A SURVEY OF SUSPECTED ADVERSE DRUG REACTIONS

Introduction

Melatonin, the major hormone produced by the pineal gland, is increasingly described as a drug for certain specific sleep disorders. An important indication for melatonin is the Delayed Sleep Phase Syndrome (DSPS). DSPS is a form of insomnia in which patients prefer to sleep at hours that are much too late to be compatible with a conventional lifestyle. As a result, they usually wake up before sufficient sleep has been achieved. Other indications of melatonin are: prevention of jet lag and treatment of negative effects of shift work.

A lot of studies on melatonin treatment have been published, but only a few adverse reactions have been described. Several authors have even mentioned the absence of adverse reactions during or after melatonin treatment. Arendt reviewed suspected adverse drug reactions (SADRs) in animals treated with melatonin and some case reports about SADRs in humans [1]. Melatonin appears to be relatively non-toxic, but it is a hormone with several physiological functions and therefore the absence of side effects seems unlikely.

In our study 97 patients (32 men, 58 women; 4 boys, 3 girls until 12 years) with circadian rhythm disorders were treated with melatonin 5 mg (until 12 years: 2.5 mg), administered every evening 5 hours before endogenous melatonin starts to be produced: the Dim Light Melatonin Onset (DLMO) [2]. Patients were treated during 2-12 months. The SADRs are spontaneous reports, told by the patient at the consultation; 1 and 3 months after starting the treatment with melatonin. We have never asked for SADRs directly. Twenty-five patients mentioned a total of thirty-five SADRs.

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3 JE Nagtegaal, MG Smits, YG van der Meer, MGJ Fischer-Steenvoorden. This chapter is reprinted from Sleep-wake research in the Netherlands (ISBN 90 73675)1996; 7,115-118.
Chapter 2.2

Results

Table 4: Suspected Adverse Drug Reactions of melatonin (n=97)

1. The co-medication of this patient was: l-thyroxine, metoprolol, nifedipine, flunitrazepam
2. This patient was a stable type 1 diabetic on insulin treatment
   The other patients had no medication that was likely to be suspected for the SADRs, beside the melatonin treatment.

<table>
<thead>
<tr>
<th>Suspected Adverse Drug Reactions</th>
<th>Number</th>
<th>Sex and age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>6</td>
<td>M, 10, 37, 46, 53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F, 37, 47</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>5</td>
<td>M, 12, 37, 47, 68, 70</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>M, 37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F, 48, 60, 74</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>3</td>
<td>M, 10, 53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F, 31</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>M, 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F, 27, 46</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>3</td>
<td>F, 14, 17, 42</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>3</td>
<td>M, 29, 55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F, 37</td>
</tr>
<tr>
<td>Ankle oedema</td>
<td>2</td>
<td>F, 60, 53</td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
<td>F, 19, 46</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1</td>
<td>F, 60</td>
</tr>
<tr>
<td>Hepatic pain</td>
<td>1</td>
<td>F, 46</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>1</td>
<td>M, 53</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1</td>
<td>F, 31</td>
</tr>
</tbody>
</table>
Discussion

It is remarkable that several adverse reactions were mentioned in this study although other publications state that no adverse reactions have been seen. The explanation may be that in earlier studies some clinical events or complaints may not have been recognised as adverse drug reactions in relation to melatonin treatment. We will give a short explanation of some of the SADRs mentioned above based on the pharmacological mechanism of the hormone.

Fever at the first days of melatonin treatment is possibly a reaction on the thermoregulatory function of melatonin [1] or may be related to effects of the agent on humoral and cellular immune responses.

Striking is the number SADRs of hyperkinesia in this study. Two men complained of restless legs during the first weeks of treatment, three of them had muscular unrest that remained in two of them during the treatment. There are no publications about a relationship between melatonin treatment and hyperkinesia but it is published as an adverse reaction of tryptophan, which is a precursor in endogenous melatonin synthesis [1,3].

Menorrhagia during treatment with melatonin may be explained by a decrease in plasma concentration of LH and FSH, which is found in earlier studies. Melatonin may act in long day seasonal breeders and humans to modify feedback sensitivity to gonadal level by modification of steroid synthesis and metabolism [1]. The three women mentioned, did not use oral anticonception and had a normal regular menstruation before they started to use melatonin. The eldest woman with these complaints had a sparse loss of blood before she started with melatonin.

Pigmentation on arms and legs after melatonin intake is not mentioned earlier in humans, although it is known that melatonin plays an important role in pigment migration phenomena in amphibians.

Headache and abdominal reactions (nausea, dyspepsia, abdominal pain) are mentioned frequently in drug trials and may be explained by other than pharmacological causes. These SADRs may possibly be due however to a false transmitter effect on serotonergic systems.
Since melatonin or its kynurenamine metabolites can inhibit prostaglandin synthesis, they may influence clotting and this may be an explanation for the thrombosis in the woman in the 8th week of treatment with melatonin. She has had another thrombosis 10 years earlier.

This survey of SADRMs shows the importance of pharmacovigilance of this agent. To complete this list of adverse reactions it is necessary to administer melatonin under controlled medical condition for strict indications. Before melatonin will be permitted on the market again, it should be registered as a drug by the authorities. For this registration adequate information about the balance between effectivity and safety will be necessary. When the drug will actually (again) be available on the market, pharmacovigilance plays an important role to obtain more information about serious or non-expected adverse drug reactions during melatonin use.

Literature
2.3 CORRELATION BETWEEN CONCENTRATIONS OF MELATONIN IN SALIVA AND SERUM IN PATIENTS WITH DELAYED SLEEP PHASE SYNDROME*

Summary

Exogenous melatonin, which can be used to treat certain circadian rhythm disorders, maximally advances delayed rhythms when taken 5 hours before the endogenous melatonin starts to increase. The time of the start of the endogenously release of melatonin is defined as Dim Light Melatonin Onset (DLMO). The DLMO concentration has been defined in serum to be 10 pg/ml. Because of the greater practicability of frequent saliva sampling over blood sampling, we have validated radioimmunoassay (RIA) measurements of melatonin in saliva in patients diagnosed as suffering from a typical circadian rhythm disorder: Delayed Sleep Phase Syndrome (DSPS). Based on these results we have defined the equivalent salivary DLMO concentration to be 4 pg/ml.

Introduction

Melatonin, a hormone produced by the pineal gland during the dark phase of the day-night cycle, is a robust marker for the timing of circadian rhythms [1]. In humans, bright light is capable of suppressing the melatonin production. Thus, under conditions of dim light the melatonin rhythm accurately reflects the phase position of circadian rhythmicity, which is driven by a circadian pacemaker, located in the suprachiasmatic nuclei of the hypothalamus. To serve as an accurate phase marker, melatonin should be sampled at least once every hour. Thus, only sampling of blood and saliva, but not urine is appropriate. When the subject is awake, frequent saliva sampling has obviously greater practicability than blood sampling, e.g. as a diagnostic tool in case of suspected circadian rhythm disorder. Therefore this study sought to validate radioimmunoassay (RIA) measurements

* JE Nagtegaal, ABH Peeters, ACW Swart, MG Smuts, GA Kerkhof, YG van der Meer. This chapter is reprinted from Therapeutic Drug Monitoring 1998; 20: 181-183.
of melatonin in saliva in three patients diagnosed as suffering from Delayed Sleep Phase Syndrome (DSPS).

DSPS is characterised by the inability to fall asleep at a conventional time with a concomitant difficulty awakening at socially acceptable hours in the morning. This is attributed to an abnormally delayed phase of circadian rhythms. A relatively late start of melatonin production is characteristic in these patients [2].

Exogenous melatonin, which can be used to treat DSPS, maximally advances circadian rhythms when taken 5 hours before the endogenous melatonin starts to increase: the dim light melatonin onset (DLMO) [3]. The DLMO concentration has been defined in serum to be 10 pg/ml [3]. This report defines the equivalent salivary DLMO concentration.

Methods

Patients

In three patients with DSPS who were diagnosed on the basis of International Classification of Sleep Disorders criteria [4], we have studied the endogenous melatonin production during a 24-h period. Every hour, 5 ml blood was collected through permanent forearm venous cannulas into glass tubes. At the same time the patient had to chew on a cotton plug (Salivetten®, Sarstedt Nümbrecht, Germany) for 1 minute. The patients did not smoke or brush their teeth during the study, and did not drink or eat from 15 minutes before until the end of each sampling. The patients stayed in bed during a 24-hour period, in a dimly lit room (<100 lux) at a constant ambient temperature [5].

Melatonin assays in serum

Blood samples were kept at 4 degrees Celsius until the experiment ended; then they were centrifuged (1000g, 10 minutes) and serum samples were stored at -20 degrees Celsius until the radioimmunoassay started. Melatonin levels in serum were measured by a commercially available RIA kit (Bühlmann Laboratories AG, Basel, Switzerland). Reversed-phase column-extracted samples were used. Aliquots of 400 microliter of the eluate were added directly to the assay tubes. The detection limit of the assay was 1 pg/ml for each sample. The intraassay coefficients of variation on the kit controls 1 and 2 were
9% and 7% respectively (mean 3.3 and 17.6 pg/ml (n=6)). The interassay coefficients of variation were 12% and 14% respectively (mean 2.9 and 20.6 pg/ml (n=30)).

**Melatonin assays in saliva**

Melatonin levels in saliva were measured by a RIA kit (Bühlmann Laboratories) which became available recently. Saliva samples were kept at 4 degrees Celsius until the experiment ended; then they were centrifuged (1000g, 2 minutes) and saliva samples were stored at -20 degrees Celsius until the radioimmunoassay started. Aliquots of 400 microliter of the saliva sample were added directly to the assay tubes. The detection limit of the assay was 0.5 pg/ml sample. The intraassay coefficients of variation on the kit controls 1 and 2 were 10% and 7% respectively (mean 1.6 and 16.4 pg/ml (n=10)) and the interassay coefficients of variation were 14% and 9% respectively (mean 2.0 and 14.5 pg/ml (n=9)).

**Results**

A clear circadian rhythm pattern of melatonin was observed in all patients as is shown in Figure 9.

The orthogonal regression line y = 0.368x-1.0, r=0.886, P<0.001 was obtained for 40 value pairs. The regression and correlation coefficients were almost equal for the peak values of melatonin and during the rising and descending phases of the secretion patterns.

The DLMO in serum is defined as 10 pg/ml [3]. In this concentration range, the melatonin concentration in saliva is lower by a factor 2.5, this justifies the definition of a DLMO of 4 pg/ml in saliva. The values for DLMO observed in our patients were: Patient 1: serum: 22:03 hours, saliva: 22:11 hours; Patient 2: serum: 23:42 hours, saliva: 23:41 hours; Patient 3: serum: 04:40 hours, saliva: 04:38 hours.
Figure 9: Endogenous melatonin measured in serum and saliva. Profiles of three patients.

Discussion

A comparison of melatonin concentrations in saliva and blood has been published earlier [6]. The current study has a methodological advantage, in presenting results of a recently
introduced RIA method, which uses only small amounts of saliva, i.e. 1 ml instead of 10 ml [6]. In addition, even in individuals with an extremely low production of melatonin (patient 3), this assay method appears to produce valid results. From the results of this study we can conclude that very similar values for DLMO can be observed with serum and with saliva RIA measurements. The value for DLMO in saliva is proposed to be 4 pg/ml, a factor 2.5 lower than the DLMO-concentration defined in blood.

Conclusion

The measurement of melatonin in minimal amounts of saliva offers a valid and practical alternative for invasive blood sampling.

Literature