Research Article

UV Phototherapy: A New Look at the UV Sources and Doses

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Abstract

Ultraviolet (UV) lamps are widely used in phototherapy, especially for the treatment of skin diseases. Although the positive effect of UV radiation is mainly associated with the synthesis of vitamin D in human skin, nevertheless, to avoid negative consequences, the determination of radiation doses is based on the erythemal activity of UV sources, and, as a rule, the initial doses are 0.5 - 1 MED. Moreover, although broadband UV lamps are known to be more productive for the vitamin D synthesis, narrowband UV sources are preferred to minimize the negative effect of UV radiation on DNA. To find the missing link between the erythemal and 'antirachitic' UV doses we performed direct measurements of the erythemal activity and the vitamin D synthetic capacity of the two most used UV lamps - broadband TL12 and narrowband TL01 (Philips). Erythemal doses were calculated from the spectroradiometer data, and antirachitic activity was measured using an original method based on the *in vitro* model of vitamin D synthesis. As expected, with an erythema dose of 1 SED (100 J/m2), the amount of direct precursor of vitamin D formed under the TL12 lamp was significantly higher than under the TL01 lamp. Thus, if the UV therapeutic effect is associated with the synthesis of vitamin D, then the time of UV irradiation with the TL12 lamp can be significantly reduced. These results show the feasibility of revising the conventional recommendations on UV light sources and doses in order to reduce negative UV effects.

Keywords: UV phototherapy; UV biodose; Erythema; Vitamin D synthesis; Provitamin D photoconversion; UV biodosimeter

Abbreviations

UV: Ultraviolet; SED: Standard Erythemal Dose; MED: Minimal Erythemal Dose; CIE: International Commission on Illumination (Commission International de L'Eclairage); IU: International Unit for Vitamin D3 (1 IU = 40 mcg); 7-DHC: 7-Dehydrocholesterol; Provitamin D3; Pre: Pre-vitamin D; T: Tachysterol; L: Lumisterol; 25(OH)D: 25-hydroxyvitamin D (calcidiol)

Introduction

Phototherapy, literally - "light therapy", has been known since ancient times and implies the use of Ultraviolet (UV) radiation of a certain spectrum for medicinal purposes. Modern studies on physiological and pathological changes in humans have led to the conclusion that UV radiation has both beneficial and harmful effects, while their dependence on the UV dose has a U- shape with a pronounced minimum that corresponds to the maximum positive effect when negative consequences are minimal (that is fully consistent with the famous Paracelsus opinion "medicine or poison is a matter of dosage"). Therefore, the search for such an optimum UV dose in both solar and artificial UV irradiation is an urgent task.

Skin burn and DNA damage are the most known negative consequences of UV overdose, but the synthesis of vitamin D3 from 7-dehydrocholesterol (7-DHC) in skin via a two-step (photo- and thermo-induced) monomolecular transformations is the best studied positive UV effect.

It has long been known that vitamin D3 is necessary for the normal calcium absorption and metabolism in the body, and recent data indicate its important role in reducing the risk of a number of serious diseases (cancer, multiple sclerosis, etc.) [1].

Nonetheless, a dosage regimen for UV phototherapy is established on the basis of Minimal Erythema Dose (MED). The threshold MEDs are different depending on skin types: from 200 J/m² for the fairest skins up to 2000 J/m² for the darkest skins [2]. In view of this, a new unit, the standard erythema dose 1 SED was introduced (1 SED is equivalent to 100 J/m²) [3]. It is important to note that unlike the MED, which provides a physiological measure of skin damage, the SED is purely a physical unit [4].

As for the dosage unit of vitamin D synthesis *in vivo*, the radiative quantity is not established yet, and a dose unit for vitamin D was defined in terms of the physiological response [3]. The "optimum" daily UV dose is not related to SED, but specified as that which produces the same effect on the vitamin D metabolite in serum as an oral dose of about 1000 IU vitamin D3 per day. Several exposure regimes to provide this end point were suggested for sunlight, but they can only be considered as rules of thumb [4].

Our work is aimed at elucidating this missing relationship between SED and the amount of photosynthesized vitamin D precursor which can be considered as the so-called "anti-rachitic" UV dose. Two UV lamps most commonly used in UV phototherapy were used as a UV source, a narrowband TL01 and a broadband TL12 (Philips). Notice, that the narrowband TL01 lamp, with a wavelength of 311 nm became widespread for the treatment of a number of skin diseases.

To determine the vitamin D-synthesizing dose, we used the same photoreaction *in vitro* that underlies the natural synthesis of vitamin D in skin, since a linear correlation has been revealed earlier between

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the pre-vitamin D accumulation *in vitro* with the *in vivo* increase of 25-hydroxyvitamin D (25(OH)D) in human blood [5].

Materials and Methods

7-dehydrocholesterol (7-DHC, Provitamin D3) and spectroscopic grade ethanol were purchased from Sigma-Aldrich. 1 mg of 7-DHC was dissolved in 100 ml of ethanol. Samples containing 3.5 ml of the Provitamin D3 solution in ethanol were irradiated in rectangular quartz cuvettes of 1 cm thickness. In other words, each sample contained 35 mcg of Provitamin D3.

The solution concentration (C = 1×10^{-3} wt.%) was chosen in order to satisfy the conditions of an optically thin layer under UV light irradiation. The cuvette was positioned horizontally at a distance of 10 cm under the UV lamp in such a manner to provide just the direct irradiation. The possible effects of reflected and scattered UV light were excluded by using the cuvettes with frosted side walls.

The UV radiation spectra of the narrowband TL 20W/01 and broadband TL 20W/12 lamps were measured at the same 10 cm distance using a portable calibrated Avantes AvaSpec-2048 × 14 Fiber Optic Spectrometer.

The UV absorption spectra of the Provitamin D3 solutions were recorded before and after certain UV exposures with a Perkin-Elmer Lambda 40 UV/VIS spectrophotometer. Further for the concentration analysis these spectra were processed by a computer using original specially designed PC software [6,7].

Results

The measured UV spectral irradiances of both lamps are shown in one figure for clarity of their significant differences (Figure 1).

The measured total irradiances in the range of 280 nm to 400 nm for each lamp, UVB and UVA irradiances separately are presented in Table 1 where the calculated ratios UVB/UVA are also shown. In addition, the erythema effective irradiances and the times to achieve a dose of 1 SED were calculated for each lamp using the standard procedure of "weighing" measured emission spectrum with the erythema action spectrum (AS) [8].

The photoreaction course of pre-vitamin D synthesis was monitored by measuring the absorption spectra of the cells with 7-DHC solution before UV irradiation and at several time intervals after the irradiation start. These spectral transformations are shown in (Figure 2).
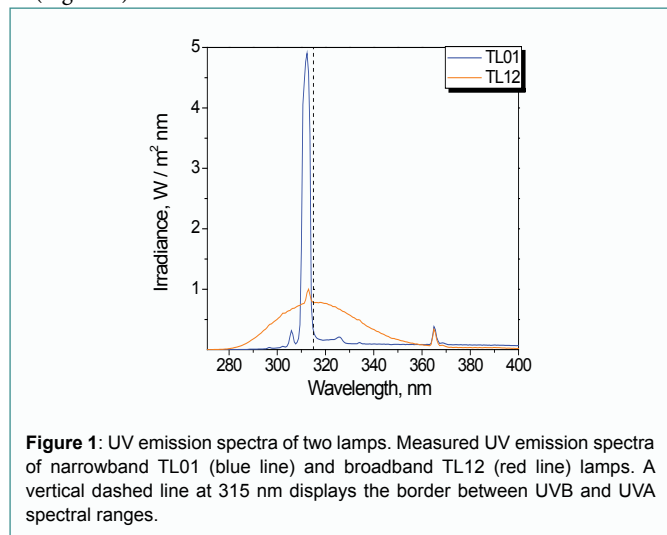

Figure 1: UV emission spectra of two lamps. Measured UV emission spectra of narrowband TL01 (blue line) and broadband TL12 (red line) lamps. A vertical dashed line at 315 nm displays the border between UVB and UVA spectral ranges.

From a comparison of the spectral patterns in Figure 2, we can conclude that the photoreaction proceeds differently when irradiated with a TL01 lamp or a TL12 lamp, and this difference is even more noticeable when comparing the results of concentration analysis obtained by computer processing of these spectra (Figure 3). As is known, under UV irradiation of the initial 7-DHC, a mixture of photoisomers is formed due to side reversible and non-reversible photoisomerizations of the synthesized pre-vitamin D [9], therefore not only a 7-DHC decay and a pre-vitamin D accumulation, but also the formation of side photoproducts and the irreversible photodegradation of the photoisomer mixture are presented in (Figure 3).
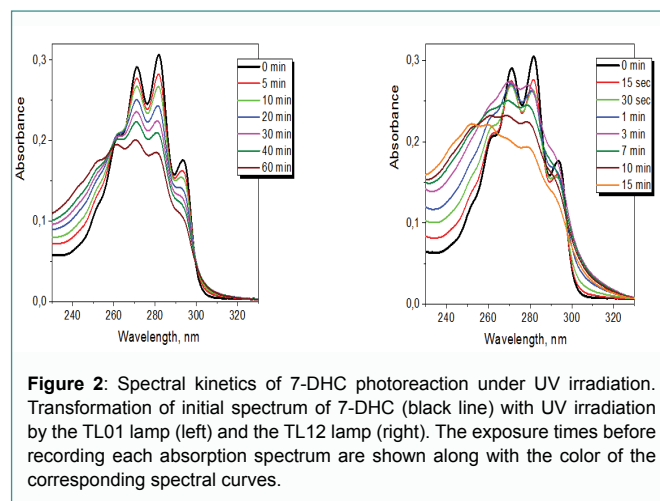
Figure 2: Spectral kinetics of 7-DHC photoreaction under UV irradiation. Transformation of initial spectrum of 7-DHC (black line) with UV irradiation by the TL01 lamp (left) and the TL12 lamp (right). The exposure times before recording each absorption spectrum are shown along with the color of the corresponding spectral curves.
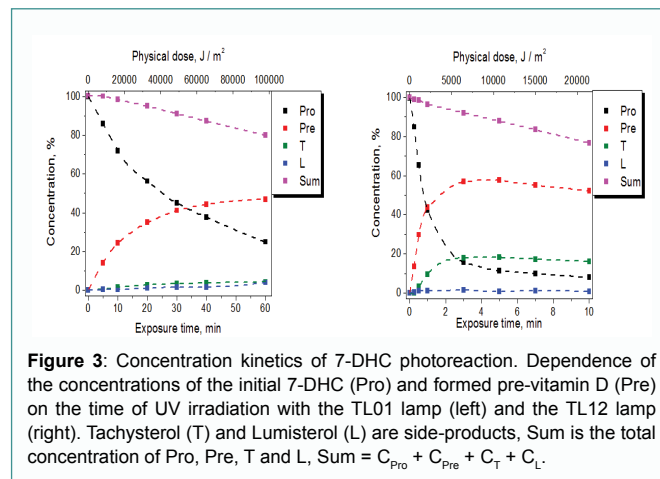
Figure 3: Concentration kinetics of 7-DHC photoreaction. Dependence of the concentrations of the initial 7-DHC (Pro) and formed pre-vitamin D (Pre) on the time of UV irradiation with the TL01 lamp (left) and the TL12 lamp (right). Tachysterol (T) and Lumisterol (L) are side-products, Sum is the total concentration of Pro, Pre, T and L, Sum = $C_{Pro} + C_{Pre} + C_T + C_L$.
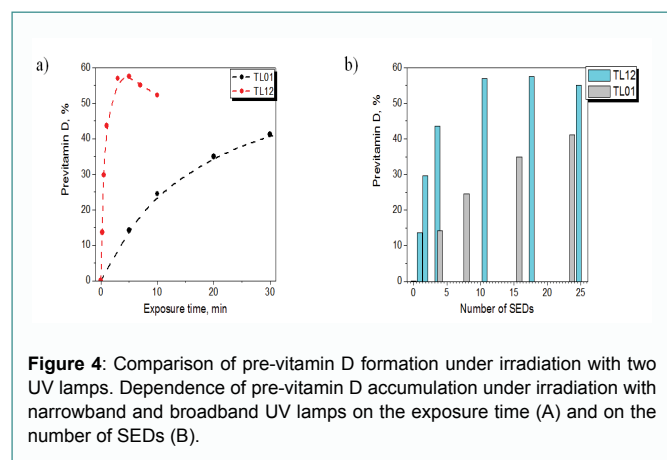
Discussion

As can be seen from the Table 1, the UVB irradiances from both lamps differ slightly in favor of TL01, while the UVA irradiance of TL01 lamp is more than 2 times less than from TL12. This difference is even more pronounced for erythemal effective irradiance, and therefore the times required to reach a dose of 1 SED are significantly different for the two lamps. (It is appropriate to note here that the quantitative data in Table 1 are critically dependent on the adequacy of the spectrometer readings when measuring UV lamp radiation).

From a comparison of the graphs in Figure 3, a significant difference between the two lamps is also clearly visible both in the rate of formation of pre-vitamin D and in its maximum achievable

Table 1: Radiation characteristics of two UV lamps.

UV lamp	Total irradiance, W/m²	UVB, W/m²	UVA, W/m²	UVB/UVA	Erythema-weighted irradiance, W/m²	Time for 1 SED
TL01	27,239	18.24	8.996	2.028	1.313	~76 s
TL12	35,734	14.89	20.85	0.714	5.93	~17 s

Figure 4: Comparison of pre-vitamin D formation under irradiation with two UV lamps. Dependence of pre-vitamin D accumulation under irradiation with narrowband and broadband UV lamps on the exposure time (A) and on the number of SEDs (B).

concentration in favor of the broadband lamp TL12 (the reason for this is detailed in [10]).

This difference is even more clearly seen in Figure 4A, which shows the accumulation of photosynthesized pre-vitamin D upon irradiation with each lamp on a common time scale, and by recalculating this scale, the desired relationship between the amount of accumulated pre-vitamin D and the amount of SEDs was obtained (Figure 4B).

The graphs in Figure 4 show that both the rate of formation of pre-vitamin D and its dependence on erythemal doses differ significantly for the two lamps. The fact that with an almost equal UVB irradiance in two lamps (Table 1), the formation of pre-vitamin D occurs less actively when irradiated with the narrow-band TL01 lamp is explained in [10]. And the significant difference between the erythema AS and the absorption spectrum of 7-DHC [11,12] in the UVA region is an important contribution to the lack of a clear correspondence between the concentration of pre-vitamin D ('anti-rachitic' dose) and the erythema dose (MED or SED).

Besides, the graphs in Figure 4 clearly show the non-linear nature of the accumulation of pre-vitamin D both from the time of irradiation and from the number of erythema doses, which is also consistent with the accumulation of 25-hydroxyvitamin D in the blood [13]. Therefore, an increase in the number of SEDs during a phototherapy session does not lead to a proportional accumulation of pre-vitamin D, and in some cases it can even lead to a decrease in its concentration due to photodegradation (Figure 4A).

And finally, as can be seen in Figure 4, the amount of pre-vitamin D, for which 4 SEDs are required under the TL01 lamp, is formed in a much shorter time under the TL12 lamp and, accordingly, requires a much smaller number of SEDs. Thus, the use of a TL12 broadband lamp is preferable not only to overcome vitamin D deficiency in sub-erythema doses, but when choosing radiation doses based on the pre-vitamin D synthesis, it can be safer for the treatment of skin diseases, contrary to the prevailing view of the preference for a narrow-band lamp TL01.

Conclusions

1. The metrology of UV lamps used for medical (and cosmetic) purposes should include an assessment of its vitamin D synthetic activity because the amount of accumulated pre-vitamin D during the time corresponding to 1 SED is variable being critically dependent on the UVB/UVA ratio in the emission spectrum of an UV lamp [14].

2. The personal UV D-biodosimeter would be useful when taking a course of phototherapy because an increase in the number of SEDs does not lead to a proportional accumulation of pre-vitamin D [15].

3. Our work opens up new possibilities for elucidating the role of vitamin D in the treatment of psoriasis, since there are conflicting opinions on this issue and the complex relationship between vitamin D and psoriasis is not fully understood [16,17].

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