

A glimpse into the underground market of melanotan

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Abstract

Melanotan-I and melanotan-II are alpha-melanocyte stimulating hormone (α -MSH) analogues that can be purchased illicitly online with relative ease and are injected subcutaneously to stimulate a tan. Little is known about the use of these unregulated substances. An observational survey was posted to an online forum in which participants share their experiences using melanotan-I or melanotan-II. Users were asked to complete this voluntary, anonymous survey, which had questions focusing on motivation and hesitation for and against using melanotan, difficulty in acquiring it, and plans for continuing to use melanotan in the future.

Keywords: melanotan, afamelanotide, alpha-melanocyte stimulating hormone, tanning

Introduction

A large number of people in our society continue to view having tanned or 'bronzed' skin as an attractive trait. Not only do individuals rate others as being more attractive if they have a darker complexion, they also feel better about themselves when they are tan [1-3]. Though the popularity of indoor tanning has been decreasing in the United States, nearly 10 million adults still tan each year [4]. This decline is more likely to be attributed to increased awareness regarding the risks of ultraviolet (UV) radiation as well as legislation restricting access to tanning salons by minors. It is less likely because there has been a shift away from the belief that tanned skin is attractive. This is highlighted by the fact that the self-

tanning industry is still incredibly popular and was rated as one of the top ten fastest-growing industries between 2002 and 2012 [5]. However, rather than utilizing sunless tanners as a substitute for UV radiation, some individuals are turning towards other methods in pursuit of a darker complexion.

Alpha-melanocyte-stimulating hormone (α -MSH) is a peptide hormone of the melanocortin family that is a non-selective agonist of one of several melanocortin receptors including MC1R, MC3R, MC4R, and MC5R. By acting on these receptors, α -MSH plays a role in several processes including appetite regulation, sexual stimulation, and perhaps most notably, regulating pigmentation by stimulating the production of eumelanin. With this in mind, two different α -MSH analogues were developed at the University of Arizona Cancer Center in the 1980s with the goal of using them as a means to prevent skin cancer [6].

The first of these analogues, initially developed under the name 'melanotan-I' ($[\text{Nle}^4\text{-D-Phe}^7]\text{-}\alpha\text{-MSH}$), is a superpotent melanocortin peptide that has increased resistance to enzymatic breakdown, which prolongs its duration of action at the MC1R receptor. The second analogue developed, 'melanotan-II' (Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]- α -MSH), is a shorter cyclic variant that increases pigmentation at a lower cumulative dose than melanotan-I. Additionally, it is not only less specific than melanotan-I, allowing it to interact with a wider range of melanocortin receptors, it is also more lipophilic, which allows it to cross the blood-brain-barrier. For these reasons, melanotan-II has a more

widespread side effect profile including fatigue, loss of appetite, and penile erection dysfunction [6-8].

In what can be a confusing change in nomenclature, the peptide originally known as 'melanotan-I' is now formally known as 'afamelanotide'. Afamelanotide contains the same structure as what was originally developed as melanotan-I ([Nle⁴-D-Phe⁷]- α -MSH), but the two terms are no longer interchangeable and should not be confused. In contrast, 'melanotan-I' and 'melanotan-II' now refer to unregulated compounds which are sold illegally online as a means to stimulate a tan. Sellers of these products make unsubstantiated claims that they are identical to the previously developed melanotan-I ([Nle⁴-D-Phe⁷]- α -MSH, now known as afamelanotide) and melanotan-II (Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]- α -MSH). Conversely, afamelanotide is being developed under the proprietary name Scenesse[®] (Clinuvel Pharmaceuticals Ltd., Melbourne, Australia) and its developers have actively tried to distance themselves from these illicit compounds. For the purposes of this paper, henceforth 'melanotan' will broadly refer to either of these two illicit substances (melanotan-I and melanotan-II) but not afamelanotide, which will be referred to as such.

The α -MSH analogue afamelanotide has been formulated as a rice-sized bioabsorbable subcutaneous implant that has been most extensively studied as a treatment for erythropoietic protoporphyria (EPP). In patients with EPP, afamelanotide has been found to be effective at reducing the number of phototoxic reactions experienced, increasing the duration of pain-free time after exposure to sunlight, and increasing their quality of life [9]. Side effects have been found to be mostly mild and include nausea, headaches, fatigue and reactions at the site of the implant [10, 11]. No serious long-term adverse effects have been reported in volunteers up to 25 years after first exposure or after continuous long-term application of up to 8 years [12]. For these reasons, in December 2014 the European Medicines Agency approved afamelanotide to prevent of phototoxicity in adult patients diagnosed with EPP. Furthermore, afamelanotide has been awarded 'Fast Track Designation' in the United States by the Food and

Drug Administration (FDA) to expedite review. Afamelanotide has also been studied for the treatment of other light-related disorders including polymorphous light eruption and solar urticaria. It has also been studied for the prevention of skin cancer in organ transplant recipients. Additionally, it has been shown to provide some benefit for patients with vitiligo [13, 14].

In contrast, melanotan-I and melanotan-II can be purchased illegally online and are injected subcutaneously to stimulate a tan. Sellers claim they have the same molecular structure as the originally developed peptides. Although they are usually labeled 'for research only' and 'not for human consumption', sellers simultaneously advertise their ability to induce a tan and few would question that they are actually targeting consumers for personal use. A comparison can be drawn between the use of melanotan and anabolic steroids, which are purchased and injected by athletes and bodybuilders. Indeed, there is overlap between users of anabolic steroids and melanotan.

Although afamelanotide has been extensively studied and found to be well-tolerated, risks of melanotan-I and melanotan-II are not as clear. One glaring concern is that they are not regulated and it is therefore impossible to monitor the actual composition of what is being sold. Even if they do consist of an α -MSH analogue as advertised, they may also contain unsafe impurities. For example, one study using liquid chromatography and tandem mass spectrometry to examine what was being sold as melanotan-II from several different vendors found that they contained unknown impurities ranging from 4.1 to 5.9% [15]. They also found that the amount of melanotan-II in vials varied from 4.3 to 8.84mg despite being advertised as containing 10mg. Additional risks are similar to other self-administered injectable substances including the risk of reusing or sharing needles. There have also been a number of case reports describing melanomas arising from existing moles either during or shortly after the use of melanotan [10]. That said, the evidence of a causal association between melanotan and melanoma is lacking and these patients frequently had other risk factors for

melanoma including light skin, frequent use of tanning beds, and family history. In consideration of these facts, these risks have prompted warnings about the use of melanotan by the FDA as well as many international agencies in Australia and across Europe [16].

Given the fact that these substances are not regulated, it is difficult to determine exactly how widespread is the use of melanotan. Although it is far from being a reliable or generalizable barometer, just as one point of reference, one single online vendor selling melanotan-II had 824 followers on Facebook [17]. This may be particularly surprising considering one might not expect users of melanotan to want to broadcast their use publicly. Additionally, an online forum in which users discuss their experiences using melanotan (researchpeptides.com) had over 11,000 discussion threads started as of July 2017 [18]. As there is a paucity of data regarding the use of melanotan, a survey was developed and posted to this particular forum in an effort to ascertain users' motivations for using melanotan as well as their experiences in doing so.

Methods

A recruiting posting was placed on an online forum (<https://researchpeptides.com/forums/34-melanotan-forum>) in which participants reported their own experiences using either melanotan-I or melanotan-II. Participants were asked to complete an online, anonymous survey hosted by surveymonkey.com and a link to the survey was provided. Inclusion criteria were age of 18 years or older, current or past use of melanotan-I or melanotan-II, or individuals who were considering using either of these substances. The questionnaire consisted of 56 questions and was designed to obtain single-answer responses, with some questions allowing the opportunity to provide additional information if the participant desired. The survey covered questions focusing on demographics, motivation and hesitation for and against using melanotan, difficulty in acquiring it, and future plans for continuing to use melanotan.

Results

A total of 21 respondents completed the survey. Of these, 19 participants were either actively using melanotan-I or melanotan-II or had done so in the past, and another 2 were considering using it but had not yet started. Of these, 10 (53%) were currently using melanotan whereas 9 (47%) had used it in the past.

Responses came from around the world with the United States being most commonly represented (5) and the United Kingdom (3) and Canada (2) following. Other countries represented included Belgium, Mexico, Latvia, the Netherlands, Norway, and South Africa. The remaining individuals preferred to leave their location anonymous.

There was a wide distribution of ages, with representatives from all age groups (18-24, 25-34, 35-44, 45-54 and older than 55). The vast majority of respondents were male. Although most respondents reported using melanotan for 2 years or less, one person had been using it for 8 years whereas another three had been using it for at least 6 years. The clear majority of participants (77%) stated that it was 'very easy' or 'easy' to find and purchase melanotan.

Interestingly, although it is commonly implied that melanotan users do so strictly to enhance their appearance, a number of users stated that they did so to prevent getting sunburns. One individual specifically noted that the "primary reason is to enhance my appearance, but, as I work outside in the sun every day in the summer, I take it to prevent burns as I am a skin type 1." Similar to the literature on afamelanotide, the most commonly reported side effects were nausea, flushing, decreased appetite, and drowsiness.

Despite the fact that many users expressed concern there may be unknown, long-term side effects of melanotan-I or melanotan-II, 93% of respondents currently using melanotan planned to continue using it for the foreseeable future. This may be because many respondents reported that melanotan increased their self-perceived attractiveness and overall quality of life.

Discussion

In spite of an effort to increase awareness about the risks associated with UV exposure, millions of people a year still choose to go tanning. This is not the only form of risky behavior that people undertake for vanity's sake. For example, of the estimated 2.9 to 4.0 million American men who use anabolic steroids, many actually do so strictly to improve appearance rather than to improve their performance in an athletic competition [19]. Therefore, it is hardly surprising that people are also willing to inject melanotan-I or melanotan-II purchased from unregulated sellers in pursuit of tanned skin.

Although it is easy to assume that users of melanotan do so for its aesthetic appeal, this observational survey demonstrates that there are some users of melanotan who do so in an effort to prevent sunburns. One individual specifically mentioned that he had a 'sun allergy'. In fact, he said that melanotan "really improved my life by allowing me to get out more during the summer months." It is not that farfetched to think that even without having what would be considered a true photosensitive disease, some light skinned individuals are so photosensitive it prevents them from leading what they consider a 'normal' life and they seek out any means necessary to do so.

Regardless of their motivation, many respondents indicated that melanotan increased their ability to tan and reduced the number of sunburns they received. Additionally, a number believed that melanotan increased their self-perceived attractiveness and increased their overall happiness and overall quality of life. Specific responses included that "MT2 [melanotan-II] saved my life!!", and "I think it's very important to raise awareness about the usage of melanotan 2 knowing it can do wonders for someone's self-esteem."

Even though many of these individuals feel that melanotan has improved their quality of life, it remains unclear what risks they are taking by its use. Whereas afamelanotide has proven to be safe and well tolerated in numerous studies, there is a sharp contrast between those side effects and those of unregulated and unstudied melanotan. The most

obvious risk is that users have no idea what they are actually injecting; the preparation may be contaminated with other substances. Furthermore, there is also a concern that users of melanotan may be sharing or reusing needles, which carries the obvious risk of infection. In this regard, no respondents to this small survey reported doing so or having side effects associated with its use.

Furthermore, there have been numerous case reports in which melanotan use has been associated with dysplastic nevi and melanoma. However causal associations are lacking and these patients (and many patients who use melanotan in general) already have additional risk factors such as frequent use of tanning beds, family histories of melanoma, multiple atypical moles, and light skin type [10]. Conversely, though the misconception exists that α -MSH analogues may stimulate development of melanoma, this is not shown to be true and α -MSH analogues are actually believed to protect against melanoma [9]. Although it is reassuring to know that α -MSH analogues have not been implicated in the formation of melanoma, if a patient on melanotan presents to their dermatologist who is unaware of his or her use, it could complicate the physical exam and could potentially lead to unnecessary biopsies being performed.

Having only 21 respondents, this survey is strictly observational, and it is impossible to make any generalizations about the use of melanotan, particularly about the safety or efficacy of melanotan. However, this was not the goal of the survey, which merely sought to provide a glimpse into who is using this product and why they were doing so. Additionally, it aims to explore and stimulate discussion on this topic.

Conclusion

Regardless of the benefits, few would argue in favor of the use of unregulated melanotan-I or melanotan-II purchased online. However, it may only be a matter of time before a systemic α -MSH analogue such as afamelanotide is available commercially. Although the company developing afamelanotide has avoided marketing it as a cosmetic product, there is little

doubt that upon approval for human use and depending on the price, some patients will seek it out as a tanning agent. Although its use would be off-label, it would not be the first instance a systemic medication has been used off-label for cosmetic purposes. Additionally, there is clearly a subset of the population that does not necessarily have a phototoxic disease but is sensitive to the sun to the point it decreases quality of life. This survey has found that this population also may seek out afamelanotide as some have benefited from the use of melanotan.

Whether its use is aesthetic or functional, despite its risks and lack of regulation, some individuals using melanotan-I or melanotan-II believe that it is not only effective but has increased their quality of life. Even if afamelanotide is never used off-label, if it becomes approved by the FDA for EPP it may at the very least lead to increased awareness about melanotan-I and melanotan-II by the general public, which may in turn increase their prevalence of use. It is important for dermatologists to be aware that melanotan-I and melanotan-II are easily accessible online and be ready to educate patients about their potential risks.

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