



ACTAS Derma-Sifiliográficas

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OPINION ARTICLE

Melanotan[☆]

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Having a suntan is fashionable in today's society and is associated with an image of health and wellbeing. One only has to look at advertising billboards or popular television series to see the ideal suntanned physique associated with health and fame. This was not always the case, however; a tanned complexion is a fashion trend of the latter two-thirds of the 20th century. In the 19th century, tanned skin was associated with field laborers and the working classes; the middle classes and the nobility had pale skin, in keeping with their socioeconomic status and social activity. In the 20th century, this situation was turned on its head and people without a suntan were those who could not afford holidays. The darker your skin and the longer you had a tan, the better. Gossip magazines showed the influential people of the moment with bronzed complexions enjoying long holidays on idyllic beaches. This was naturally reflected in the general population and there was an increase in tourism to sunny destinations. Over the years, scientific progress has shown how harmful this fashion can be, as it has led to photoaging and an increase in different types of skin cancer. As a result, various sectors of the population who are unwilling to give up the coveted suntan have sought alternative methods of achieving it. In this issue, Dr. Hueso and colleagues report a case of illegal use of a substance to achieve increased melanin production. In this article, I will focus on the drug melanotan.

What is Melanotan?

Melanotan is a synthetic analog of alpha-melanocyte-stimulating hormone (α -MSH), a hormone belonging to the

melanocortin group of peptide hormones, which have different functions in the body.¹ α -MSH binds to different melanocortin receptors to produce different effects, including the following:

1. Increases melanin production by binding to the melanocortin 1 receptor (MC1R), thereby stimulating production of different enzymes, including tyrosinase. It also appears to stimulate melanocyte proliferation.^{1–3}
2. Produces erections and increases libido by binding to MC3R in the central nervous system. Unlike sildenafil, a phosphodiesterase-5 inhibitor that produces erections by means of a peripheral effect, it does not require sexual stimulation and its effect is longer-lasting.⁴
3. Decreased appetite. The anorexigenic effect is caused by the hormone binding centrally to the MC4R and peripherally to the MC2R; it also appears that it may affect lipolysis by binding to the MC5R.⁴
4. Immunomodulating effects. It appears to diminish the body's inflammatory and immune responses.⁴
5. Vasopressor effects on the cardiovascular system that increase blood pressure.⁴
6. Changes in behavior. The effects in this regard are highly variable and may affect learning, attention, and motor coordination, in addition to modifying sexual and eating behaviors.⁴

There are 2 synthetic melanotan molecules^{1–6}:

- Melanotan I ([Nle⁴-D-Phe⁷]- α -MSH) is a 13 amino acid linear peptide in which the fourth amino acid, methionine, is replaced with norleucine and the seventh amino acid, L-phenylalanine, is replaced with D-phenylalanine. This molecule is more resistant to breakdown than its natural

[☆] Please cite this article as: Mahiques-Santos L. Melanotan. Actas Dermosifiliogr. 2012;103:257–259.

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analog, which means that the stimulus received by its receptor (principally MC1R) is more potent.

- Melanotan II (Ac-Nle-[Asp-His-D-Phe-Arg-Trp-Lys]- α -MSH-NH₂) is a shorter variant with a lactam ring. Like melanotan I, this analog is also more potent than natural α -MSH, but it also has more side effects because it is less receptor-specific. In addition to stimulating increased melanin production, this molecule also decreases appetite and increases libido.

What Are the Real or Potential Medical Uses of Melanotan?

The melanotan I and melanotan II molecules were originally developed to investigate their effects on melanin production with a view to achieving an increase in the natural photoprotective effect provided by this hormone. Both molecules proved to effectively increase melanin when injected and, furthermore, the type of melanin produced was eumelanin (which provides greater protection to cells than pheomelanin).¹⁻³ However, as a side effect, melanotan II also produced penile erection. This led to research on Melanotan II as a photoprotector being abandoned and attention was focused on melanotan I, which is more selective of melanin production. Nevertheless, melanotan II did not disappear, but moved to another area of research: erectile dysfunction.¹ Thus, we find that these two molecules have advanced in different areas:

- Melanotan I (SCENESSE, Clinuvel Pharmaceuticals Ltd) is being studied in phase 2 and phase 3 clinical trials as a photoprotective drug for protection against nonmelanoma skin cancer and in other photoinduced skin diseases, such as erythropoietic protoporphyria, solar dermatitis, and polymorphic light eruption. The results of these trials appear to be promising.⁷
- Melanotan II was replaced by a nasally administered molecule (PT-141, Palatin Technologies), which was studied in erectile dysfunction. It was found to produce erections by means of a central mechanism, unlike sildenafil, and to produce a lasting erection independent of sexual stimulation in 80% of patients who did not respond to sildenafil. Although promising, the molecule was never brought to market due to several patients presenting with high blood pressure. The same company is currently studying its use in hemorrhagic shock.²

It should be noted that, while some studies contend that these molecules do not increase the risk of melanoma, their long-term effects are still not fully understood and concerns have been raised about secondary effects, such as the increased proliferation of melanocytes and reduced inflammatory and immune response.

How is Melanotan Being Used in the General Population?

The case reported by Dr. Hueso and colleagues demonstrates the existence of a black market for melanotan. It is sold through websites, which market it under the name

Barbie drug owing to its tanning and anorexigenic effects and the increase in libido it produces; it is also sold through sports gyms, where (along with many other substances) it has apparently become very popular.

Cases have already been reported of the illegal use of these drugs in various countries and of the induction of eruptive nevi,⁸⁻¹⁰ a case of melanoma (although a causal relationship cannot be established), and changes in the appearance of preexisting nevi.⁸⁻¹⁰ To date, no cases had been reported in Spain, but the article published in this issue shows that the drug has reached Spain and that its use is apparently quite common in certain sectors of the population, including those who use sports gyms and esthetic salons.

What Are the Implications of its Use?

This section examines several aspects of the problem:

What is the profile of the person who might want this substance?

Although the idea of a drug that increases tanning, suppresses the appetite, and increases libido could seduce any of us, the fact that it is illegal and has to be injected will quash this desire in most people. However, those who use the substance feel that the benefits outweigh the risks. This attitude is seen particularly in individuals who have a psychiatric disorder called dysmorphophobia, in which patients are never satisfied with their appearance and constantly resort to different ways of changing it, including surgery, hairstyling, different esthetic procedures, and, now, melanotan. The effects are sometimes counterproductive, but these patients do not see it this way. Interestingly, sports gyms are frequented by many people who suffer from this disorder.

What are the risks associated with the use of this substance?

Because this substance is still in the early stages of clinical trials, its long-term effects are not fully understood. Examples of untoward effects include hypertension and the appearance of eruptive nevi. Obviously, the adverse effects of some drugs are discovered through use and subsequently included in the summary of product characteristics; in this case, however, adverse effects are being reported before the substance has been licensed for sale.

Moreover, as this is an injected drug, we cannot ignore the risk of infections due to improper administration or the use of shared needles.

How are these substances acquired?

Drugs can now be acquired through the Internet, in much the same way as other products. Of course, the risk of fraud at different stages of the transaction is evident as no competent medical authority will take responsibility for the possible effects and interactions in each patient (Do we know what we are taking? Who is guaranteeing the product?).

It is a curious fact that many people in Spain do not want to take medication prescribed for them by a physician but will take anything recommended to them on the street because it is "natural". When I see this, I think of Socrates and the very "natural" extract of hemlock that brought him death.

What are the implications for the dermatologist?

Dermatologists should suspect the use of this substance in patients who present with an excessive tan for their skin phototype or the time of year, especially when they report the more or less sudden appearance of dysplastic nevi. If the use of this substance becomes widespread, we should not even expect users to be excessively muscular or present unusual muscle definition (bodybuilding jargon), as it will be used by people of all kinds.

When dealing with a patient of this type, we should also investigate whether there is an underlying psychiatric disorder and make a thorough study of the patient's clinical records in search of any evidence that would support such a diagnosis. If such evidence is found, the patient should be referred to a psychiatrist because dysmorphophobia is a disorder that is complex to treat and requires psychiatric and psychological support.

Because this substance is illegal in Spain, its use should be reported to the authorities as the sale of these products may involve an offence against public-health and must be investigated. Detecting use in a patient may lead to uncovering an illegal supply network.

Conclusions

As dermatologists, we should be alert to the increased use of this substance. Until clinical trials have been completed and conclusions reached, we should advise our patients against its use. However, this new drug should not be stigmatized, as it may have an important future role in dermatology or other fields of medicine. The essential problem, as with the

use of any medical substance for non-medical purposes, is the incorrect use and abuse of a molecule with potential medical indications.

Conflicts of Interest

The author declares that she has no conflicts of interest.

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