Melanotropic Peptides: What Exactly is Meant by ”Melanotan”?

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Sir,

We read with interest the letter from Thestrup-Pedersen & Søndergaard (1) reporting the augmentation of lentiges and naevi in a young male patient who had been self-injecting with “melanotan”. As in a case we initially reported (2), a clinically suspicious naevus was excised, with histology revealing a benign naevus, with no evidence of malignant transformation. The patient was also noted to be particularly tanned. This report is in keeping with previous case reports, in which the use of “melanotan” has been associated with both changes in the clinical presentation of pre-existing, and the development of new, naevi (2–4). Thus, dermatologists need to be aware of the increasing self-medication by the public of melanotropic peptides, and the presence of an unexpected tan may alert the physician to their use (5). Clinically suspicious naevi must, of course, be excised.

Regarding the recent case report (1), we respectfully draw attention to the fact that “melanotan” is not synonymous with “melatonin.” The latter, a pineal gland hormone synthesized from tryptophan, plays a major role in the regulation of circadian rhythms, and is sometimes utilized for its anti-jet-lag effects (6). Whilst there is evidence that the skin itself may be an important source of melatonin (6), its effects in terms of pigmentation appear to be an inhibition of melanogenesis and melanocyte proliferation, at least in rodent melanoma cell lines (7). Perhaps inadvertently, the authors have highlighted the confusing complexity of nomenclature in the field of melanotropic peptides. The tridecapeptide hormone α-melanocyte stimulating hormone (α-MSH) is known to play a key role in human pigmentation. Produced locally by keratinocytes, and acting via the melanocortin-1 receptor (MC1R) on melanocytes, it stimulates melanogenic enzymes, including tyrosinase. This results in increased eumelanin production, and consequently increased pigmentation (5). In the early 1980s, the synthetic melanocortin, 4-Norleucine, 7-D-phenylalanine-α-MSH ([Nle4-D-Phe7]-α-MSH), was identified and found to have prolonged activity at the MC1R, with subcutaneous administration in humans resulting in increased cutaneous pigmentation (5). [Nle4-D-Phe7]-α-MSH has previously been reported in the literature as melanotan or melanotan-1 (8). Melanotan-2 is a shorter cyclic variant, which increases pigmentation at lower cumulative doses than [Nle4-D-Phe7]-α-MSH, but has the side-effect of penile erections, possibly via an effect on the MC3R in the central nervous system (5). Furthermore, α-MSH analogues in development are also at risk of falling under the popular term “melanotan”, thus adding to the confusion.

Interestingly, [Nle4-D-Phe7]-α-MSH has been shown to have photoprotective effects in clinical trials, including promising effects in the alleviation of photosensitivity disorders (9, 10). These involve the regulated use of regimes and formulations of [Nle4-D-Phe7]-α-MSH that are now formally termed afamelanotide (SCENESSE; Clinuvel Pharmaceuticals Ltd, Melbourne, Australia). Afamelanotide and other regulated drugs require differentiation from the use of a range of unregulated chemicals labelled as “melanotan”, which are often sourced in gyms or via the internet, are of uncertain nature, reportedly used at high dosage, and particularly by people with a sun/sunbed-seeking history. These products incur risks of chemical impurity and of infection in view of potential needle-sharing, and thus are strongly discouraged by the UK and Danish governmental healthcare agencies (5, 11).

Conflict of interest: LER has acted as a consultant for Clinuvel Pharmaceuticals Ltd and has performed clinical trials of α-melanocyte stimulating hormone analogue in photosensitivity disorders funded by Clinuvel Pharmaceuticals Ltd.

Reply to the Letter by Langan & Rhodes

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We thank Langan & Rhodes for their comments and for bringing to our attention their paper in BMJ (2) on a related subject. Langan & Rhodes also correctly point out that melatonin is not melanotan. Melatonin is a pineal hormone that binds to melatonin receptors being G-coupled transmembrane receptors MT1 and MT2 and involved in hair pigmentation and hair follicle function. In lower animals it participates in pigmentation, but less so in humans, where it has other functions associated with neuronal physiology. Melanotans are synthetic peptides

binding to and stimulating melanocortin receptors. In humans alpha-melanocyte stimulating hormone stimulates skin pigmentation, as can the melanotans. Afamelanotide is one of the compounds in melanotan and is currently studied for possible photoprotective effects.

We regret our mix-up of the words melatonin and melanotan. The message in our clinical observation is to remind our colleagues about the existence of internet-available pigmentary compounds. We, too, do not recommend their use, since lentigines and naevi may arise, as demonstrated in our case. Melanotans, including afamelanotide, still need to be studied closely for potential carcinogenic effects, and it is hoped that this will be done in keratinocyte and melanocyte cell lines and in animal experiments, besides clinical observations.

An Erratum to the original paper will be published in this issue and corrections will thereafter be made in the electronic version.

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