Ezogabine (Potiga) was approved as an add-on drug for the treatment of partial seizures in adults with epilepsy by the US Food and Drug Administration on June 10, 2011, and as retigabine (Trobalt) by the European Medicines Agency on March 28, 2011. Ezogabine has a novel mechanism of action involving activation of the neuronal potassium channels. Its most common adverse effects are shared by other antiseizure medications and consist primarily of central nervous system symptoms, such as somnolence, dizziness, confusion, and fatigue. In addition, a small percentage of patients may have urinary hesitancy; therefore, all patients receiving ezogabine should be monitored carefully for potential urologic symptoms. Overall, the drug appears to be well tolerated and holds promise as a new therapeutic agent for treatment of intractable epilepsy.

Dyspigmentation is the abnormal discoloration of the skin and potentially the mucous membranes. It is usually caused by an increase in either melanin production or in the density of active melanocytes. Dyspigmentation may also be due to the deposition of exogenous substances, such as drugs, drug complexes (eg, with melanin or iron), or heavy metals, within the dermis. The pathogenesis of drug-induced dyspigmentation is often not fully understood and depends on the specific medication. The main drugs implicated are antimalarials, amiodarone hydrochloride, cytotoxic drugs, tetracyclines, heavy metals, and psychotropic drugs. The diagnosis of drug-induced dyspigmentation might be challenging because of the long interval (months to years) from the onset of treatment to its appearance. In some cases, only the fading of the dyschromia after discontinuation of the suspected drug affirms the diagnosis.

We describe 2 patients in whom mucocutaneous dyspigmentation developed several years after starting treatment with a combination of antiepileptic drugs. The sole drug common to the treatment regimens of both patients was ezogabine. To our knowledge, this is the first well-documented report of this unusual adverse effect of ezogabine.

Report of Cases
Case 1
A woman in her 30s with light skin (phototype 2) presented to the dermatology clinic of a tertiary medical center with blue-gray...
discoloration of the skin. She had begun to notice changes in her complexion several years previously. The medical history was remarkable for pharmacoresistant temporal lobe epilepsy with primary generalized tonic-clonic seizures. For the past 6 years, she had received valproic acid, gabapentin, and oxcarbazepine. She had also been taking ezogabine (350 mg 3 times per day) since 2007. There was no known history of drug allergy.

The patient denied having any pulmonary, cardiovascular, or gastrointestinal symptoms. She had no rheumatologic symptoms or signs of Raynaud phenomenon. She had no family history of genetic or metabolic diseases, and she had 2 healthy siblings.

On medical examination, the patient appeared to be relaxed, with no signs of respiratory distress or hypotension. The affected skin appeared blue-gray and slightly hyperpigmented; the discoloration was most pronounced on the sun-exposed areas of the face and lips (Figure 1A and B). Examination of the oral cavity revealed blue pigmentation of the hard palate (Figure 1C). Two blue macules were noted around the knees (Figure 1D). The toenails and fingernails showed transverse blue-colored bands (Figure 1E and F); capillaroscopy was normal. Ophthalmologic examination revealed black pigment deposits on the palpebral conjunctivae and lower fornixes (Figure 1G). The corneas and fundi appeared to be uninvolved. The remainder of the physical examination was normal.

Findings for the complete blood cell count, biochemistry tests, thyroid-stimulating hormone and free thyroxine levels, erythrocyte sedimentation rate, and urinalysis were within the reference ranges (except for a γ-glutamyltransferase level of 75 U/L [for conversion to microkatal/s per liter, multiply by 0.0167]). Serologic testing for rheumatoid factor, antinuclear antibody, and hepatitis B and C was negative. Pulse-oximetry saturation and blood gas levels, including methemoglobin, were within normal limits. Additional tests for blood ferritin, iron, iron saturation, copper, and ceruloplasmin, as well as 24-hour urinary excretion of copper, were within normal limits. No abnormalities were noted on chest radiography or echocardiography. Abdominal sonar scanning showed very mild fatty infiltration of the liver.

Case 2
A woman in her 30s, phototype 2, was referred to our clinic with signs similar to those of case 1. The dyspigmentation had been present for 2 years. She had received treatment since 2007 for generalized epilepsy, predominantly manifesting as absence seizures, with multiple antiepileptic drugs including carbamazepine, levetiracetam, clobazam, and ezogabine (300 mg 3 times per day). On medical examination, a blue-gray mucocutaneous dyspigmentation was noted localized to the face, including the lips. The fingernails showed transverse blue-colored bands. Further examination disclosed blue pigmentation of the hard palate and black pigmented deposits on the palpebral conjunctivae and lower fornixes, with no involvement of other compartments of the eye.

Follow-up
Because ezogabine was the only common drug in the 2 patients’ treatment regimens, they were advised to discontinue...
the drug. On examination of the first patient 4 months after withdrawal of ezogabine, a significant improvement of her skin, oral mucosa, and nail dyspigmentation was observed (compare Figure 1A vs H, B vs I, C vs J, D vs K, and E vs L). The second patient refused to discontinue the drug.

**Histopathology and Electron Microscopy**

Two punch biopsy samples (each 4 mm in diameter) were obtained from involved skin of the knee and the hard palate in patient 1. The samples were fixed in formalin and embedded in paraffin. For histopathologic examination with light microscopy, the sections were stained with hematoxylin and eosin. In addition, the sections were stained for the presence of melanin (Masson-Fontana stain) and iron (Mallory stain). The biopsy specimen obtained from the blue-colored skin around the knee was characterized by a normal overlying epidermis without pigmentation and a mild perivascular lymphocytic infiltrate in the upper and middle dermis (Figure 2A). Macrophages and other cell types, such as fibroblasts heavily laden with coarse golden-brown pigment granules, were scattered in the middle and deep dermis in a perivascular and perieccrine distribution; some granules were also scattered in the extracellular matrix and inside blood vessel walls (Figure 2A-C). The biopsy specimen of the hard palate showed normal epithelium without pigmentation. There was a coarse golden-brown pigment in the submucosa, both inside macrophages as well as free in the extracellular matrix. The pigment granules in both biopsy specimens were negative for iron (Mallory stain) and positive for melanin (Masson-Fontana stain) (Figure 2D), ruling out lipofuscin.

Additional techniques were used to identify the nature of the deposits. Dark-field microscopy failed to demonstrate brilliantly refractile granules, as typically found in heavy metal deposits. For electron microscopy, skin tissue was fixed in glutaraldehyde, processed according to standard procedures, cut to 0.5-μm-thick slices, and stained with uranyl acetate and lead citrate. Sections from stained and unstained samples were viewed and photographed with an electron microscope (Tecnai T12; FEI) operated at 120 kV and equipped with a charge-coupled device camera (Erlangshen ES500W; Gatan Inc). Electron microscopy revealed primarily intracellular electron-dense granules localized mainly in fibroblasts (Figure 2E and F).
Nuclear Magnetic Resonance and Mass Spectrometry

Given the possibility that the pathogenesis of the dyspigmentation was related to retention of the drug inside dermal cells,8,9,10 we sought to identify its presence by extracting the active molecule from a skin specimen. Nuclear magnetic resonance imaging and mass spectrometry were used to identify the presence of ezogabine in the tissues. For nuclear magnetic resonance analysis, tissue extraction was performed by homogenization with dimethyl sulfoxide. For mass spectrometry, the tissue was crushed with liquid nitrogen, dissolved with isopropanol/formic acid (1:1), and analyzed by a hybrid ion trap quadrupole mass spectrometer (QTRAP-4000; ABSciex). The active drug purified from an ezogabine tablet served as the control sample.

Although the active drug sample contained fluoride, nuclear magnetic resonance analysis failed to demonstrate a

<table>
<thead>
<tr>
<th>Condition</th>
<th>Exposure</th>
<th>Description</th>
<th>Distribution</th>
<th>Histopathologic Findings and Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic disease</td>
<td>AR inheritance</td>
<td>Bronze hyperpigmentation</td>
<td>Generalized</td>
<td>Iron deposition and melanin, diabetes mellitus, and cirrhosis; genetic testing is available for HFE gene mutations</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>AR inheritance</td>
<td>Blue-gray metallic pigmentation</td>
<td>Generalized</td>
<td>Low serum ceruloplasmin level, increased urinary copper excretion, increased hepatic copper content, and/or genetic testing</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Acquired</td>
<td>Slatelike hyperpigmentation</td>
<td>Skin and mucosa with accentuation on main folds, areolas and scars, and nails</td>
<td>ACTH stimulation test with demonstration of increased plasma ACTH levels</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Acquired</td>
<td>Slatelike hyperpigmentation</td>
<td>Localized or generalized</td>
<td>Suppressed TSH</td>
</tr>
<tr>
<td>Heavy metal</td>
<td>Occupational exposure, alternative medications, systemic absorption from topical ocular preparations or wound dressings</td>
<td>Diffuse slate-gray discoloration</td>
<td>Sun-exposed areas, nail unit, sclerae, oral mucosa, sites of topical application</td>
<td>Silver granules in the basement membrane and the membrane propria of eccrine glands, elastic fibers; highlighted by dark-field illumination</td>
</tr>
<tr>
<td>Gold (chryiasis)</td>
<td>Prolonged parenteral use</td>
<td>Permanent blue-gray discoloration</td>
<td>Sun-exposed areas, mostly around the eyes, sparing mucous membrane</td>
<td>Gold particles within lysosomes in dermal macrophages, in perivascular and perieccrine areas; orange-red birefringence</td>
</tr>
<tr>
<td>Iron</td>
<td>Parenteral use</td>
<td>Permanent brown hyperpigmentation</td>
<td>At injection sites or application of ferric sulfate, dermal hemosiderin deposits in venous hypertension, as an adverse effect of sclerotherapy and in pigmented purpuric dermatoses</td>
<td>Pigment coats collagen fibers and in dermal macrophages</td>
</tr>
<tr>
<td>Drug</td>
<td>Oral intake</td>
<td>Gray to blue-black discoloration, rarely resolves completely</td>
<td>Face, hard palate, sclerae, shins, and subungual areas</td>
<td>Dermal deposition of melanin-drug complexes; hemosiderin around capillaries</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Oral intake</td>
<td>Slate-gray discoloration</td>
<td>Sun-exposed areas, especially the face</td>
<td>Golden-brown granules in dermal macrophages around blood vessels; electron-dense inclusion bodies in lysosomes</td>
</tr>
<tr>
<td>Amiodarone hydrochloride</td>
<td>Oral intake</td>
<td>Blue-black discoloration</td>
<td>Sites of inflammation and scars, may also involve nails, sclerae, oral mucosa, bones, thyroid, and teeth</td>
<td>Granules within the dermis containing iron</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Oral intake</td>
<td>Blue-gray macules/patches</td>
<td>Shins</td>
<td>Granules within the dermis containing a minocycline derivative plus chelated iron</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
<td>Oral intake</td>
<td>Variable according to the drug</td>
<td>Variable according to the drug</td>
<td>Increased melanin within the basal epidermis and/or dermal melanophages</td>
</tr>
<tr>
<td>Psychotropic drugs (chlorpromazine, thiouracil, imipramine, desipramine hydrochloride, amitriptyline hydrochloride)</td>
<td>Oral intake</td>
<td>Slate-gray discoloration</td>
<td>Sun-exposed areas, mucous membranes and nail unit</td>
<td>Golden-brown granules in the upper dermis containing melanin, electron-dense inclusion bodies</td>
</tr>
</tbody>
</table>

Abbreviations: ACTH, corticotropin; AR, autosomal recessive; TSH, thyroid-stimulating hormone.
accentuation of the lesions in sun-exposed areas. Other mechanisms are often exacerbated by sun exposure, leading to melanin clearance in the dermal macrophages. This represents a nonspecific cutaneous inflammatory reaction to the drug, which may be due to its hyperproduction by epidermal melanocytes specifically stimulated by the medication or it may represent a nonspecific cutaneous inflammatory reaction to the drug. Alternatively, a stable drug-melanin complex may prevent melanin clearance in the dermal macrophages. This mechanism is often exacerbated by sun exposure, leading to accentuation of the lesions in sun-exposed areas. Other reported mechanisms are accumulation of the triggering drug without melanin; synthesis of special pigments, such as lipofuscin, under the direct influence of the drug; or deposition of iron owing to drug-induced damage to dermal vessels.

In the present report, the discoloration appeared in both women 4 months after the discontinuation of the suspect drug, ezogabine, a significant improvement was observed, further supporting the diagnosis of ezogabine-induced dyspigmentation.

The incidence of drug-induced dyspigmentation depends on the specific medication. It varies from isolated cases to up to 25% of patients. The pathogenesis also varies by the causative medication. Generally, it results from the accumulation of melanin, either free in the dermis or contained within cells, particularly the dermal macrophages, rather than in the basal layer of the epidermis. The accumulation of melanin may be due to its hyperproduction by epidermal melanocytes specifically stimulated by the medication or it may represent a nonspecific cutaneous inflammatory reaction to the drug. Alternatively, a stable drug-melanin complex may prevent melanin clearance in the dermal macrophages. This mechanism is often exacerbated by sun exposure, leading to accentuation of the lesions in sun-exposed areas. Other reported mechanisms are accumulation of the triggering drug without melanin; synthesis of special pigments, such as lipofuscin, under the direct influence of the drug; or deposition of iron owing to drug-induced damage to dermal vessels.

In the present report, the discoloration appeared in both women after onset of ezogabine treatment. This is in line with chronology studies of dyspigmentation-inducing drugs. Histopathologically, the main finding was dermal cells heavily laden with coarse melanin granules. The granules were located mainly around blood vessels and adnexa. and appeared ultrastructurally mostly inside cells, as reported in cases of dyspigmentation induced by psychotropic drugs and amiodarone. The peculiar skin pigmentation in our patients could be explained by the Tyndall effect, ie, the perception of dermal melanin as blue, gray, or blue-gray because of the selective scatter of shorter wavelengths. It remains unknown whether ezogabine induces melanin synthesis or, alternatively, hampers the degradation of melanin. The nuclear magnetic resonance imaging and mass spectrometry results provided no evidence of drug deposition in the tissue. Nevertheless, we cannot rule out the presence of drug derivatives or metabolites that could not be detected by our analysis. Following our report of these 2 cases to the drug company (GlaxoSmithKline), the US Food and Drug Administration began to work with the manufacturer to gather and evaluate all available information. On April 26, 2013, the US Food and Drug Administration published a statement announcing that ezogabine can cause blue skin discoloration and pigment changes in the retina. As of April 23, 2013, a total of 38 of the 605 ezogabine-treated patients tested (6.3%) were found to have skin discoloration. However, not all patients have been examined to date; therefore, this rate might be an underestimation.

In addition, approximately one-third of patients given eye examinations had retinal pigment changes. It is not known whether the pigment is deposited in other organs as well or whether the changes are reversible. Subsequently, on October 10, 2013, the US Food and Drug Administration approved changes to the drug label of ezogabine that underscore its risks to the retina and skin dyspigmentation, all of which may become permanent. The revised label includes a new boxed warning—the most serious type of warning—because of the potential risk of irreversible vision loss.

The mainstay of treatment of drug-induced dyspigmentation is sun avoidance with application of sunscreen and, if possible, interruption of the implicated drug. In most cases, these measures lead to improvement, albeit very slowly. The significant improvement in the mucocutaneous dyspigmentation following discontinuation of ezogabine, as observed in our patients, suggests that ezogabine-induced dyspigmentation might be reversible.

Finally, other antiepileptic agents, such as hydantoins and barbiturates, have rarely been reported to induce skin pigmentation but with patterns and pathomechanisms different from those of ezogabine. Hydantoins may induce melasma and barbiturates are associated with diffuse brown postexanthematous discoloration.

Conclusions

Ezogabine should be added to the list of drugs that can induce mucocutaneous discoloration. All patients need to be monitored carefully for the potential development of skin, nail, oral mucous membrane, conjunctival, and retinal discoloration.

Discussion

The differential diagnosis of the mucocutaneous dyspigmentation in our 2 patients includes a wide range of genetic, metabolic, and endocrine diseases, as well as deposits of metal ions (Table). All of these were excluded in the first patient by both medical history and extensive laboratory investigations, including dark-field microscopy and electron microscopy. That left the possibility of drug-induced dyspigmentation (Table). Indeed, 4 months after the discontinuation of the suspect drug, ezogabine, a significant improvement was observed, further supporting the diagnosis of ezogabine-induced dyspigmentation.

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Additional Contributions: Talmon Arad and Smadar Zaidman, PhD, Irving and Cherna Moskowitz Center for Nano and Bio-Nano Imaging, Weizmann Institute of Science, conducted the electron microscopy studies. Ana Tovar, MD, Institute of Pathology, Bellin Hospital, assisted with electron microscopy data analysis. There was no financial compensation for these contributions.

REFERENCES

NOTABLE NOTES

Saving Their Skins
How Animals Protect From the Sun

Sowmya Varada, BS, Dana Alessa, MD

A distinctive evolutionary change experienced by our ancestors as they branched away from their fellow apes was the loss of body hair. While this may have had certain benefits, our species has also suffered drawbacks; for one, without thick fur or hair to scatter sunlight, our skin is more susceptible to burning in the sun. Indeed, sunburns have been observed in other relatively hairless members of the animal kingdom, including whales, dolphins, fish, elephants, and rhinoceroses. But just as humans have evolved physiologic and behavioral adaptations to protect from the sun, other creatures too have developed their own.

Whales have hairless, streamlined bodies and frequently travel to the sea surface for air, making them particularly vulnerable to UV-induced skin damage. The sperm whale, which spends up to 6 hours at a time at the surface, is known to activate genotoxic stress pathways in response to persistent UV exposure.1 While the fin whale possesses constitutively high levels of melanin, the blue whale modulates its skin melanin throughout the year, becoming darker when UV levels are highest from February to May.1 This adaptive pigmentation has also been observed in hammerhead sharks and some fish.

Equatorial Africa, which receives abundant daily sunlight year round, is home to the world’s 3 largest pachyderms: the elephant, rhinoceros, and hippopotamus, for whom learned behaviors are essential for sun protection. The African elephant uses its prehensile trunk to throw dust onto its back, the rhinoceros wallows in and coats itself with mud, and the hippopotamus submerges itself in water.2 The hippopotamus also possesses a curious adaptation found in no other animal—it manufactures its own sunscreen. The hippopotamus’s “blood sweat” is a thick, reddish fluid that is neither blood nor true sweat, as the animal’s skin contains no sebaceous glands. It is secreted by subdermal glands through large skin pores and contains 2 pigments, hippusosudoric acid and norhippusosudoric acid, whose polymerization gives the fluid a reddish orange color and whose absorption of UV light makes this substance a highly effective sunscreen.3 Some animals are well covered with fur but may need to protect other body parts from the sun. A giraffe’s long tongue, frequently outstretched to forage the treetops for leaves, is colored blackish purple from the circumvallate papillae to the tip, believed to protect it from sunburn.2 The meerkat’s eyes are surrounded by dark bands to reduce sun glare, and the nictitating membrane covering a polar bear’s eye filters bright sunlight reflected by the snow.

Increasing UV exposure from a depleted ozone layer will certainly exert a selective pressure on animals to evolve more sophisticated skin defenses. Studying these creatures may provide greater insight into skin physiology and how our own species will adapt to a changing solar environment.

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