Taking the Pulse of Hydroquinone Therapy: A Plea for Caution

Pulse therapy under physician supervision can reduce long-term exposure and help reduce the risk of untoward effects of hydroquinone therapy.

BY ZEIN E. OBAGI, MD

For many consumers, hydroquinone is like an old friend who inexplicably turns on you. They may have used it for years, trusting that their dermatologist—or, frequently, some Internet pharmacy—would never recommend a product that could harm them.

But over time, some of these consumers develop new pigment problems in the areas where they have faithfully applied hydroquinone. The product they bought to lighten sunspots, melasma, or other hyperpigmentation paradoxically leaves them with tough-to-treat issues such as severe rebound hyperpigmentation and ochronosis.

Avoiding such side effects requires a shift in our approach to hydroquinone. Specifically, my research and clinical experience have convinced me that our patients should use hydroquinone for no more than four or five months at a time. Then we must give the skin a break and allow it to stabilize before deciding if another course of hydroquinone is warranted. I call this approach Pulsed Hydroquinone Therapy.

MEDICAL PRODUCTS NEED MEDICAL SUPERVISION

I have always been a strong proponent of hydroquinone. Used in reasonable concentrations, under physician supervision, it is safe and effective for pigment problems ranging from chloasma, melasma and postinflammatory hyperpigmentation (PIH) and to prepare skin for treatment of less common concerns such as nevi of Ota and Huri which require pigment laser.

But over the last several years, the Internet has become inundated with discounted, medical-grade products that companies sell directly to consumers without proper medical supervision or sun protection.

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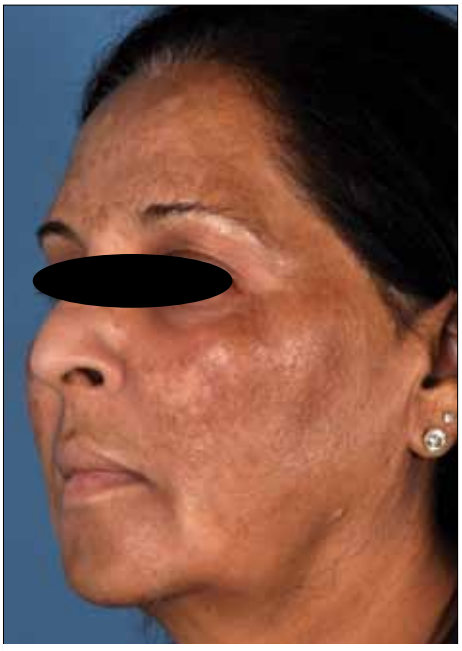
Consumers want to save themselves a consultation fee or doctor visit. I see no problem with buying a simple moisturizer or broad-spectrum sunscreen online. But to continue treatment with hydroquinone (or other medical-grade skin formulations, for that matter) indefinitely, without the oversight and expertise of the dermatologist who originally prescribed it, often creates dermatologic disasters.

Following are the patterns I see increasingly in my clinical practice, and the reasons behind them.

Resistance. Some people who have been using hydroquinone in proper concentration of 4% (alone or in compounded formulations) find that their skin improves for a few months, and then the improvement stops. In my experience, this is particularly common after four to five months of satisfactory response in patients using hydroquinone for melasma.

In such cases, the bleaching effects of hydroquinone appear more pronounced in the areas not affected by melasma. Meanwhile, the dark spots of melasma show no further improvement. In fact, as the active melanocytes in the affected areas develop resistance to hydroquinone, the patient's hyperpigmentation in these areas worsens.



Patient 1.

Patient 2.

That is what happened to a 58-year-old female patient from India who was diagnosed with melasma at our clinic in 2001 (see above, Patient 1). At that time, she was treated successfully with hydroquinone 4%, and hydroquinone mixed with retinoic acid, followed by a chemical peel to the papillary dermis. A decade later, after having obtained branded hydroquinone 4% and retinoic acid products from the web and the black market, she returned and was diagnosed with rebound severe melasma (epidermal and dermal) that did not respond but worsened by her continuous hydroquinone use.

To avoid such problems, I recommend that after no more than five months of hydroquinone application, all patients should cease using this drug for two to three months. This allows melanocytes to stabilize (so they can withstand external and internal factors that might otherwise increase their activity) and restore the skin's natural melanin. During this phase, patients can use other lightening agents, then resume hydroquinone if necessary afterward.

Some dermatologists may choose to treat resistant melasma by increasing the hydroquinone concentration. Instead, I have found that patients respond well to aggressive application of hydroquinone (4%) plus retinoic acid, combined in equal parts. This combination tends not to bleach the skin, but to accelerate attainment of a more natural and even color tone. Once the skin's color has evened out after up to five months of treatment, I have my patients discontinue use of this mixture and switch to retinoic acid alone for two to three months; then patients resume hydroquinone application if needed.

Photosensitivity, phototoxicity. We know that certain topical agents, such as retinoids, aminolevulinic acid, and some systemic medications (such as tobramycin/TCN and hydrochlorothiazide). can increase skin sensitivity to sun exposure. Surprisingly, no one, to my knowledge, has ever considered hydroquinone to be a photosensitizer.

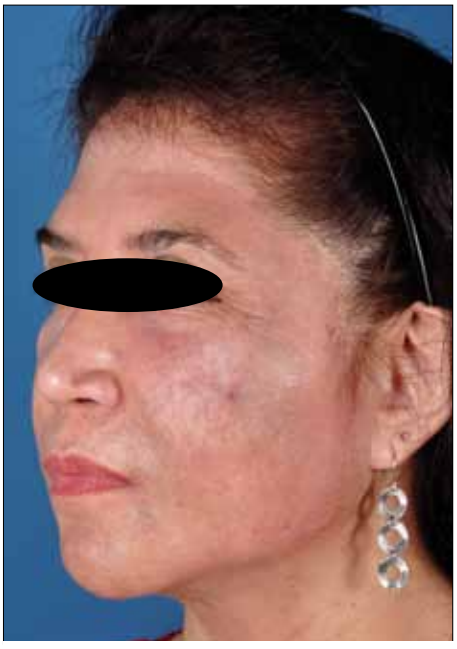
Some patients use hydroquinone indefinitely, thinking it will prevent unwanted pigmentation. But we now know that decreasing the amount of melanin in skin, as hydroquinone does, creates photosensitivity. Without proper sunscreen use (sun protection factor/SPF ≥ 30, frequent reapplication), photosensitivity leads to inflammation, which stimulates melanin production.

The sun can also affect the melanocytes directly, increasing melanin production and possibly leading to rebound pigmentation. Furthermore, phototoxic reactions can trigger a chemically altered bluish melanin compound that's responsible for ochronosis, which is tough to treat because it involves deep pigmentary changes deep in the dermis associated with altered skin texture.

Physicians used to consider ochronosis as a condition that was limited to certain African tribes, and we believed that it stemmed perhaps partially from genetic causes, partially from prolonged hydroquinone use.

However, in the last few years, I have observed a higher incidence of ochronosis not only in African-Americans, but also in Caucasian, Asian, and Hispanic patients who have used various concentrations of hydroquinone, often for years on end. In these patients, ochronosis has occurred in the areas of the face that experience the most sun exposure.

One such patient I saw was a 39-year-old Caucasian female. She had a history of melasma, and underwent the following treatments, prescribed by various dermatologists, in the two years prior to presenting at our clinic with severe ochronosis: three peels consisting of azelaic acid, kojic acid, phytic acid, ascorbic acid, arbutin, and titanium dioxide (Cosmelan, Mesoestetic) in one year; eight intense pulsed light (IPL) treatments; three fractional laser resurfacing (Fraxel, Solta) sessions; six Jessner's peels; and continuous use of hydroquinone 8% throughout the two years.



Patient 3.

Patient 4.

This case also serves as a reminder that when treating hyperpigmentation, we should not use exfoliative procedures, chemical peels, laser resurfacing, or other thermal rejuvenating devices as our first step. Rather, I recommend proper skin conditioning—using hydroquinone, hydroquinone plus retinoic acid, alpha hydroxy acids, antioxidants, and any disease-specific agents necessary—for four to six weeks before and after any procedure (once skin healing is complete). This helps to restore normalcy and functionality to the skin, and it improves the results from procedures.

Excessive HQ concentration. I am used to prescribing hydroquinone concentrations of 4%, and I have treated many patients who used high concentrations on their own or under the supervision of other physicians. Based on my observations and experience, such concentrations deliver no greater or faster results than hydroquinone 4%. On the contrary, concentrations of 6-12% tend to cause more recalcitrant hyperpigmentation, quicker resistance, and a higher rate of ochronosis.

Excessive hydroquinone concentrations may induce toxic or shocking effects on melanocytes, forcing them to regroup and increase their melanin production (resulting in rebound hyperpigmentation). Additionally, high concentrations of hydroquinone may provoke skin inflammation. Used on its own, hydroquinone is an inflammatory agent that can cause redness, itching, and allergic reactions. Inflammation leads to melanocyte hyperactivity, which overpowers hydroquinone's ability to suppress tyrosinase, leading to the rebound hyperpigmentation.

Such was the case with a 66-year-old African-American female with history of melasma who was treated for seven years by other dermatologists (Patient 2). She used hydroquinone 8%, tretinoin (Retin-A, Valeant Dermatology), and desonide cream (Desowen, Galderma) for years. Dissatisfied with the results, she eventually was prescribed hydroquinone 12%, and her dermatologist added topical steroids to her regimen. Ultimately, her worsening condition prompted this dermatologist to refer her to our office, where she was diagnosed with rebound dermal and epidermal hyperpigmentation, ochronosis with severe irritation and sensitivity. We stopped the hydroquinone regimen immediately.

Hydroquinone combination formulations. In this regard, consumers can readily find products that combine hydroquinone with various ingredients such as retinoic acid, glycolic acid, vitamin C, and topical steroids. However, prolonged use of such products can worsen pigmentation and create additional issues. This is especially true of products that combine hydroquinone, retinoic acid, and steroids e.g., Kligman's formula and the combination of hydroquinone, tretinoin, and fluocinolone acetonide (Triluma, Galderma). I have found that long-term use of such products can lead to skin atrophy, the appearance of telangiectasias, skin sensitivity, and, frequently, more stubborn pigmentation than the patient originally had.

The topical steroids in these formulations aim to suppress inflammation. This is critical because inflammation excites melanocytes, which stimulate melanin production. However, topical steroids only work on pigmentation induced by trauma or disease (PIH). In contrast, we must avoid prescribing topical steroids for patients with pigment problems not caused by inflammation, such as melasma.

Moreover, to avoid disrupting cellular function, these triple-combination products should not be used for longer than five to seven days, in accordance with their instructions. As an alternative, I prefer the combination of hydroquinone and retinoic acid without a steroid. It is safer, yet quite effective when used properly for three to five months with strict sun protection.

RETINOIDS REQUIRE CAUTION

As with hydroquinone, however, many medical-grade ingredients, such as retinoic acid and other retinoids, if used indefinitely, prove helpful for two or three months but can then cause continuous irritation. This irritation can lead to inflammation and create more damage as the skin builds resistance to the treatment.

The following patients' experiences are typical in this regard.

Patient 3 (photo previous page), a 59-year-old Hispanic female with a history of melasma, acne, and scarring, was successfully treated in 1990 with topical creams, isotretinoin, and trichloroacetic acid peels. Her maintenance program included hydroquinone 4%and a hydroquinone-retinoic acid combination, as described above. About five years ago, she returned to the clinic with ochronosis, primarily on the left side of her face (because she drives long distances). She is currently being treated for her ochronosis.

Patient 4 (photo previous page) is a 57-year-old African-American female, seen 25 years ago for PIH and melasma. She responded well to a topical medication that included hydroquinone 4%, used daily, and hydroquinone mixed with retinoic acid in the evening. She also had a trichloroacetic acid peel down to the papillary dermis. Subsequently, she did not follow-up with her treatments, but eventually returned many years later. She had been using the hydroquinone medications continuously, and presented with ochronosis. I had her immediately stop the hydroquinone treatment; she did not desire to treat the ochronosis, saying it did not bother her.

Based on such cases, I now view retinoic acid as a tool for general skin repair; beyond that, it is not always an ideal agent. Patients generally find retinoic acid hard to tolerate long-term because the portion of the drug that is not absorbed for skin repair remains on the skin's surface, which can provoke continuous reactions. Along with irritation, these reactions can include redness, dryness, and exfoliation. For some patients, these continuous reactions can even break down the skin's barrier function, creating skin sensitivity. These side effects explain why many patients abandon treatment with retinoic acid.

To avoid these problems, I now recommend that patients use retinoic acid for no longer than five months. That is sufficient time to accomplish general skin repair, without risking long-term skin reactions. After five months, I switch my patients to an agent with specific skin repair functions, such as retinol. For normal to dry skin, it improves barrier function while also stimulating and stabilizing the skin. Because retinol is converted intracellularly to retinoic acid, it leaves no free, unused retinoic acid on the skin's surface to provoke reactions.

All the cases outlined above share key similarities. Although each patient began treatment under a doctor's care, they later purchased medical-grade hydroquinone, and other medical-grade ingredients, through online and other unauthorized sources selling at deep discounts. The ready availability of these products, often from websites owned by physicians, pharmacies or other retailers, enabled consumers to use these products without physician oversight for more than five years continuously. Accordingly, I oppose selling medical-grade products on the Internet if they are being offered for the purpose of treating skin conditions without medical supervision. I believe the FDA should intervene to halt such practices.

Conversely, I believe that formulations combining hydroquinone with botanical anti-inflammatory agents and antioxidants that can suppress skin inflammation induced by factors such as sun exposure, hormones, and diet are very helpful in treating hyperpigmentation. Even systemic inflammatory agents such as ibuprofen can accelerate a patient's response to hydroquinone. They do this by arresting or suppressing chronic skin inflammation.

However, in my view, adding vitamin C or glycolic acid to hydroquinone offers no scientifically documented extra benefits. In fact, vitamin C and glycolic acid can irritate the skin, which leads to inflammation and worsening of existing hyperpigmentation (rebound hyperpigmentation).

PULSED REGIMEN REDUCES RISKS

In conclusion, hydroquinone is safe and effective when used as directed by a physician for a wide variety of pigmentation problems. To increase its efficacy and avoid unwanted side effects, dermatologists should consider the following protocol:

- Prescribe hydroquinone concentrations no higher than 4%.
- Require patients using hydroquinone to use proper sun protection.
- Continue prescribing hydroquinone for no more than four to five months.
- Allow the skin to rest and restore itself for two to three months after hydroquinone therapy.
- Resume hydroquinone therapy, if needed, only after such a break.

Adopting the pulsed approach will spare our patients from the disfiguring and needless side effects of extended, self-directed use of hydroquinone. ■

Dr. Obagi is medical director of ZO Skin Health, Inc. He has no affiliation with Obagi Medical Products, Inc.

He is a board-certified dermatologist based in Beverly Hills, California.