Cosmeceutical Critique

Idebenone

Synthesized for the first time a little more than 20 years ago, 2,3-dimethoxy-5-methyl-6-(10'-hydroxydecyl)-1,4-benzoquinone—also known as CV-2619, QSA-10, or idebenone—is similar in structure to the potent antioxidant coenzyme Q10, an integral cell membrane nutrient and contributor to the adenosine triphosphate–producing mitochondrial electron transport chain (Altern. Med. Rev. 2001;6:83-6).

Extensive research has been conducted on this benzoquinone compound for more than 2 decades, mostly to compare it with other drugs for treating patients with Alzheimer's disease, for ameliorating the symptoms of Friedreich's ataxia, and for use in organ transplant solutions.

BY LESLIE S. BAUMANN, M.D.

Studies on rats paved the way to hypotheses regarding the compound's neurologic, cardiologic, and antiaging indications. Those studies ascertained that idebenone inhibits lipid peroxidation, protecting cell membranes and mitochondria from oxidative damage and, in particular, brain mitochondria from swelling (Altern. Med. Rev. 2001;6:83-6; Neurosci. Lett. 1993;163:219-22; Arch. Gerontol. Geriatr. 1989;8:299-305).

Neuronal Activity

In vitro and in vivo studies suggest that idebenone may reduce nerve cell damage induced by ischemia; repair neurotransmitter defects and/or cerebral metabolism; and enhance memory and learning (Altern. Med. Rev. 2001;6:83-6).

In a multicenter, randomized, double-blind, placebo-controlled trial with Alzheimer's patients, idebenone was shown to slow disease progression and to enhance memory, attention, and orientation (Funct. Neurol. 1994;9:161-8).

In another study, repeated oral administration of idebenone, which stimulates the synthesis of nerve growth factor (NGF), partially restored the age-related reduction of NGF in the frontal and parietal cortices. This result is noteworthy because NGF is instrumental in maintaining cholinergic neurons, the degeneration of which is linked to the cognitive impairment displayed by Alzheimer's patients. The authors of the study concluded that idebenone has potential as an oral therapeutic agent in preventing cholinergic dysfunction (Behav. Brain Res. 1997;83:117-22).

The efficacy and safety of idebenone as an Alzheimer's treatment were further established by a prospective, randomized, double-blind, placebo-controlled multicenter study of two doses of the drug (Neuropsychobiology 1997;36:73-82). In a subsequent 2-year prospective, randomized, double-blind, multicenter study of the drug's safety and efficacy in Alzheimer's patients, the compound exerted beneficial therapeutic effects by slowing the course of the disease. The antioxidant also was found to be safe and tolerable (J. Neural Transm. Suppl. 1998;54:301-10).

Clinical trials have shown that patients with mild dementia are more likely to respond than are those with greater functional decline (Drugs Aging 1994;5:133-52).

Oral administration of idebenone also has been shown to improve mitochondrial oxidative metabolism in the brain, suggesting potential as an agent for treating myopathy, encephalopathy, lactic acidosis, and strokelike episodes (Neurol. Sci. 2000;21[suppl. 5]:S981-2; Neurology 1996; 47:583-5). The protection conferred by idebenone to the brain's myelin sheath and energy-producing mitochondria may also position this antioxidant to play a therapeutic role in multiple sclerosis.

Antioxidant Action

As a potent free radical scavenger believed to be much stronger and more efficient than other well-known antioxidants (such as vitamins C and E, coenzyme Q10, kinetin, and α-lipoic acid), idebenone also functions as an electron carrier and is not characterized by occasional prooxidant activity as is the case with coenzyme Q10 under hypoxic conditions. In fact, this potent antioxidant has been shown to be effective under such conditions, preserving adenosine triphosphate formation (Altern. Med. Rev. 2001;6:83-6).

Idebenone is considered to have potential as a therapy to enhance energy and cognition, to protect organs against excitatory amino acid neurotoxicity, and to retard aging. As a coenzyme Q10 analogue, idebenone is thought to work at least as well as its natural counterpart in the electron transport chain to maintain a high energy level. The drug was shown in a rat liver microsomal model to be more effective than coenzyme Q10, though in protecting against lipid peroxidation (Transplantation 1995;60:444-51).

Idebenone also has been shown to improve cardiac function in patients with Friedreich's ataxia, and to be effective in treating mitochondrial cardiomyopathy (J. Inherit. Metab. Dis. 2001;24:28-34).

Clinical Applications

Idebenone has been used outside the United States for years as an antiaging agent and for improving cognition in patients with Alzheimer's disease and other neurologic disorders.

As a topical agent, idebenone is believed to possess much greater skin penetration potential and higher oxidative stress-protection capacity than does coenzyme Q10. In research reported by Joseph C. DiNardo at the annual meeting of the American Academy of Dermatology in 2004, investigators used various methods to measure the antioxidant capacity of several antioxidants, including idebenone, vitamins C and E, coenzyme Q10, kinetin, and α-lipoic acid. It is important to note that idebenone was not tested against pomegranate and green tea, two agents with strong antioxidant activity.

After extensive in vitro testing of the selected antioxidants in part I of the team's study, the investigators evaluated the same antioxidants in vivo using the human sunburn cell assay. Percent change over baseline, assessed at equivalent concentrations, was found to be 38% for idebenone, 30% for vitamin E, 20% for kinetin, 11% for coenzyme Q10, 9% for α-lipoic acid, and 0% for vitamin C.

After establishing a standardized method of summarizing results, including those of the human sunburn cell assay as well as those of experiments comparing antioxidant performance by photochemiluminescence, inhibition of UVB irradiation of human keratinocytes, and measurement of primary and secondary oxidation products, the researchers reported overall oxidative protection capacity scores as 95 (idebenone), 80 (vitamin E), 68 (kinetin), 55 (coenzyme Q10), 52 (α-lipoic acid), and 41 (vitamin C). They concluded that idebenone exhibits great potential for inclusion in topical skin protection products.

On the Market

Such findings led to a comarketing agreement between Allergan (the manufacturer of Prevage) and Elizabeth Arden to globally distribute a lower-concentration version of Prevage to cosmetic retailers.

The physician-strength product containing 1% idebenone—Prevage—was launched in January 2005. It was reformulated with new vehicle and a lower percentage (0.5%) of idebenone and renamed Prevage MD; this became available to dermatologists in September and will be made available by Elizabeth Arden to leading department stores and so-called prestige outlets in December.

Conclusions

The synthetic coenzyme Q10 analogue, idebenone, has been investigated extensively over the past 2 decades. Its antioxidant and other health benefits are well established, as is its use for various indications outside the United States.

Patients in my practice who used the initial Prevage formulation by Allergan reported acne and contact dermatitis. It is my understanding that the Prevage MD product by Allergan and the Prevage product by Elizabeth Arden have been reformulated, and the new formulations are less likely to result in those side effects.

It is important to remember that this ingredient, like all antioxidants, may prevent signs of aging with consistent use. However, there is no evidence that it will affect wrinkles that already exist beyond increasing skin hydration. ■

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Topical Dapsone Gel Engenders Screening Requirement

Topical dapsone gel, a new option for the treatment of acne vulgaris, requires screening patients for an enzyme deficiency.

Dermatologists are required to test patients for a lack of the glucose 6-phosphate dehydrogenase (G6PD) enzyme before prescribing Aczone (dapsone) gel, 5% (QLT Inc.). Enzyme-deficient patients should be closely monitored for hemolytic anemia.

Males of African descent are the most likely to lack the G6PD enzyme (10%-14% incidence).

"I would check G6PD enzymes in someone I am concerned about," said Jonette E. Keri, M.D., of the University of Miami.

The screening and monitoring may not dissuade dermatologists from use of dapsone gel.

"If this medication will improve my patients' acne, a simple blood test will not affect my decision to prescribe it," said Helen T. Shin, M.D., chief of pediatric dermatology at the Joseph M. Sanzari Children's Hospital of Hackensack (N.J.) University Medical Center.

Efficacy was based on two clinical studies that compared Aczone gel 5% and vehicle in a total of 3,000 patients 12 years and older. After 12 weeks, there was a statistically significant decrease in the number of acne lesions as well as improvements on the Global Acne Assessment Score with treatment vs. vehicle.

Oiliness/peeling, dryness, and erythema were the most common adverse events.

"This approval is important in that it gives us a new medication to treat acne. This is the first time we will have topical dapsone, and it's another option in our armamentarium," Dr. Keri said. Start out slowly with dapsone to monitor response, she advised.

"Although there are numerous treatment options for acne, a novel one is always welcome," Dr. Shin said. "We are finding that there is an increasing incidence of resistance to topical as well as systemic antibiotics currently used to treat acne" (Skin & Allergy News, October 2005, p. 1). Neither Dr. Keri nor Dr. Shin had a financial disclosure regarding Aczone Gel or QLT Inc.

—Damian McNamara