Pharmacological Properties of Azelaic Acid
A Rationale for Clinical Use

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Summary

Azelaic acid is a naturally occurring straight-chained, 9-carbon atom saturated dicarboxylic acid that is nontoxic, nonteratogenic, and nonmutagenic. It can be administered to humans topically (the only approved formulation), orally, by intra-tissue infusion, and systemically (intravenously, intra-arterially, and intralymphatically), all without local or general ill effects. 60% is eliminated in the urine within 12 hours, part is metabolised by β-oxidation in the mitochondria, and part is decarboxylated. In vitro, azelaic acid is a competitive inhibitor of tyrosinase, mitochondrial enzymes of the respiratory chain, thioredoxin reductase, 5-α-reductase, and DNA polymerases. It also inhibits anaerobic glycolysis. It is a scavenger of reactive and cytotoxic hydroxy free radicals, and inhibits the release of reactive oxygen species from neutrophils. In cell culture, it has a time- and dose-dependent antiproliferative and cytotoxic effect, associated with inhibition of DNA synthesis and mitochondrial damage, against human and murine melanoma cell lines, and other tumoural cell lines; normal cells are, in general, not affected. It has a spectrum of antimicrobial activity against a variety of aerobic and anaerobic microorganisms, and a modulating influence on the process of epidermal keratinisation, properties which, together with its anti-inflammatory activity, provide the rationale for its successful use against acne and rosacea. It also has some antimycotic activity. Clinically, azelaic acid is effective in the treatment of postinflammatory hyperpigmentation and melasma, which are due to abnormal hyperactivity of essentially normal cells. The effect can be attributed to the antityrosinase activity, inhibition of the energy-producing and synthetic processes of the cell, and perhaps to the anti-free-radical activity. A beneficial effect on lentigo maligna (melanoma in situ) and individual lesions of primary melanoma is associated with destruction of the hyperactive and frankly abnormal melanocytes by a combination of the same activities, enhanced by the greater permeability of tumoural cells to the diacid.

Webster defines 'rationale' as 'an explanation or exposition of controlling principles', and gives as an example of its usage a quotation from the Journal of the American Medical Association: 'no rationale underlying the new therapeutic approach can be offered at this early stage'. This is by no means an unusual situation in investigative clinical medicine. In the case of azelaic acid, however, a theoretical rationale for its use in the treatment of hyperpigmentary disorders emerged at a very early stage, paradoxically from studies on a hypopigmentary condition, pityriasis versicolor,
a cutaneous yeast infection leading frequently to hypopigmentation of the infected skin.

An interest in the composition of skin surface lipids led Caprilli et al.\(^2\) to investigate the pathogenesis of the hypopigmentation in pityriasis versicolor. The fungus is lipidophilic and lipid-dependent, and in the hypopigmented areas they found that the lipid pattern was affected and that the melanocytes exhibited alterations varying from swelling and disruption of mitochondria to frank degeneration.\(^3\) This suggested that some metabolic product of fungal activity was responsible for damaging the melanocytes. In order to test this proposition, cultures of *Pityrosporum* (*Mallassezia furfur*) supplemented with fatty acids with double bonds in the 6 to 12 positions were prepared, and it was found that dicarboxylic acids of chain lengths C-6 to C-12 were produced. These had an ascending gradient of competitive inhibition of tyrosinase, the key enzyme for melanogenesis.\(^4,5\) This observation, taken with manifest damage to melanocytes in the hypopigmented areas, provided the original rationale for a suggestion that dicarboxylic acids within the stated range of chain lengths might be used to treat hyperpigmentary disorders. A topically applied cream containing 15% of a diacid at the medium range of antityrosinase activity and solubility (azelaic acid, C-9 dicarboxylic acid) was reported to successfully treat hyperpigmentary conditions such as postinflammatory melanosis, melasma and melanoma *in situ* (lentigo maligna).\(^6,7\) There was no clinical depigmenting effect on normal skin, and normal human melanocytes in dispersed culture were unaffected by adding azelaic acid to the medium.\(^8\) Another clinical study established a positive effect of topical and oral azelaic acid in causing regression of lesions of cutaneous malignant melanoma, with histological and ultrastructural evidence of destruction of abnormal melanocytes.\(^9\) A therapeutic approach founded on the rationale appeared to be successful in practice, and it emerged that azelaic acid was selectively active against hyperfunctioning and abnormal melanocytes, with little or no effect on normal cells, a distinct advantage compared with other depigmenting agents currently in use.

These early studies led to further laboratory and clinical investigations that established additional biological activities and properties of azelaic acid and provided additional justification for its therapeutic application, not only to hyperpigmentary disorders, but to other cutaneous diseases as well. Current knowledge on these matters is reviewed in this paper.

1. Chemistry and Biogenesis of Azelaic Acid in Humans

1.1 Chemistry

**Azelaic acid:** 1,7-heptane dicarboxylic acid: nonanedioic acid: HOOC-(CH\(_2\))\(_7\)-COOH; C\(_9\)H\(_{16}\)O\(_4\); C 57.43%, O 34.00%, H 8.57%. Molecular weight 188.22. White monoclinic prismatic needles mp 106.5°C. Solubility in water: 0.1% at 1°C, 0.24% at 20°C, 0.82% at 50°C, 2.2% at 65°C; freely soluble in boiling water and alcohol. K\(_1\) at 25°C C = 2.96 \times 10^{-5}, K\(_2\) = 4.60 \times 10^{-6} (Merck Index).

Azelaic acid is a naturally occurring, saturated 9-carbon atom dicarboxylic acid, originally obtained from the oxidation of oleic acid by nitric acid. It can also be generated *in vitro* by chemical, physical, or biological oxidation of free and esterified fatty acids with the first double bond in position 9 to 10.\(^10\) Its production by *Pityrosporum* (*M. furfur*) is due to the fungus possessing lipoxygenases, enzymes that can oxidise appropriate unsaturated fatty acids in skin surface lipids.\(^5\) It is used in industry for the formation of polymeric materials, and its presence in canvasses as a breakdown product of oil paints helps art historians in estimating the relative proportions of drying oils and egg fats used in the original paint by the Old Masters and, thereby, possibly in determining the provenance and age of paintings.\(^11\)

1.2 Normal Occurrence and Biogenesis in Humans

Azelaic acid occurs in small amounts in the urine of normal individuals, and excessively in the

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