EDITORIAL

AZELAIC ACID

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In the last few years, there have been several reports on the use of azelaic acid (AA) in some skin diseases. There are, however, many aspects of the use of this compound which have remained controversial and uncertain; the foremost being, is it really useful? This doubt is especially relevant when AA is used in a potentially fatal skin malignancy like lentigo maligna (LM). The other question which has often been asked is as to how does AA act. The present article is, therefore, meant to review the position of AA in dermatology.

AA is a naturally occurring, aliphatic, 9-carbon, saturated dicarboxylic acid. It is generated by the disruptive oxidation of ricinoleic acid and occurs when oleic acid turns rancid. It is non-toxic and non-teratogenic even when given in high doses, orally or parenterally.[1]

Interest in the biological activities of AA arose when it was observed that in pityriasis versicolor, the etiologic fungus *Pityrosporum* produced dicarboxylic acids like AA and dodecanedioic acid (DA), both of which act as competitive inhibitors of tyrosinase *in vitro*.[2,3] Earlier ultrastructural studies on the lesions of pityriasis versicolor had revealed damage to the melanocytes ranging from swelling and vacuolation of mitochondria to extensive degeneration of some cells.[4] It was then erroneously concluded that the hypochromia in pityriasis versicolor was due to the anti-tyrosinase and cytotoxic activities of these diacids. From this conclusion arose the possibility that these dicarboxylic acids could be used beneficially for the treatment of hyperpigmented disorders.

AA was used in preference to DA because it was less expensive and it could be more easily incorporated into the creams. A cream containing 20% AA has since been used successfully for the treatment of chloasma, post-inflammatory hyperpigmentation, and hypermelanosis caused by physical and photochemical agents; there is no residual hypochromia.[5] There is, however, no response in patients with freckles, senile lentigines, and pigmented nevi.[6] AA also has no effect on normal skin pigmentation.[7]

There are several reports of the response of lentigo maligna (LM) to AA.[6,8-11] LM is a malignant melanoma in situ. Progression into an invasive LM melanoma occurs in about 30% of the cases. Normally, LM is surgically excised and to many patients this treatment is cosmetically not acceptable. So a lot of excitement has been generated by the reports where AA has been found useful in the management of LM. Nazarro-Porro et al[11] treated 50 patients of LM with topical AA over a period of 10 years. In 27 patients there was complete clinical and histopathological resolution. Ultrastructural examination confirmed the response to treatment. There was no hypochromia or scarring after treatment. Recurrences were observed in 11 patients, but these also resolved on reapplication of AA. Ertle et al[12] also treated LM occurring in patients with xeroderma pigmentosum and found impressive histopathological and ultramicroscopic regression of the neoplastic cells. However, Mclean and Peter,[13]

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found that treatment of LM with AA was not as satisfactory as claimed by Nazarro-Porro et al.[11] Of their 9 patients, only one showed regression and in two patients there was progression to invasive malignant melanoma (MM). Similar dissatisfaction with AA was expressed by Doherty et al.[14] Moreover, there is a subgroup of LM where, though routine histopathological staining does not show dermal invasion, special stains do reveal invasive cells in the dermis. These cases may well be resistant to superficial modalities of treatment like AA and need more active treatment.

AA has also been used for the treatment of MM. Experimental animals inoculated with Harding Passey melanoma showed retardation of tumour growth on oral, subcutaneous and intraperitoneal administration of AA.[2] Based on this observation, Nazarro-Porro et al[15] treated 29 patients with nodular melanoma or superficial spreading MM (without lymph node involvement) with 10-15 gm AA orally and 15% AA topically. All, but 2 of these patients showed a response both clinically and histopathologically. Eight patients had complete regression of the lesions; though further follow-up of these patients is not available. The use of oral AA in the above regime was subsequently found unnecessary.[6] Thus, the use of this drug for the treatment of localised non-metastasized MM needs further evaluation.

The response of disseminated MM to parenteral AA has been poor.[6] AA has also been found ineffective in ocular and adnexal melanomas.[16] The problem probably lies in delivering a concentrated amount of AA for sufficiently long periods of time to the neoplastic cells. For instance intralymphatic infusion in one case of disseminated MM did result in clearance of the metastasis in the lymph nodes.[6]

AA acts in disorders of proliferation of the melanocytes because it has anti-tyrosinase activity, due to the inhibition of the mitochondrial respiration,[17,18] and also because it inhibits DNA synthesis.[19]

A number of studies[20-24] have shown that AA has a preferential cytotoxic action against structurally abnormal and hyperproliferating melanocytes. This effect is both dose dependent and time dependent. It has no effect on normal melanocytes. *In vitro* studies on dispersed cultures of epidermal cells revealed no evidence of cytotoxicity on the normal melanocytes even 30 days after the addition of AA. Neither was there any impairment of second generation melanocytes.[20] In contrast, on the human melanoma cell line in tissue culture, AA has a cytotoxic effect.[21,22] This effect does not strictly correlate with the anti-tyrosinase activity of the diacid. This is indicated by the fact that lymphoma and leukemia derived cell lines, which are devoid of tyrosinase, are equally affected.[10,23] Ultrastructural studies have also confirmed that AA is cytotoxic to proliferating structurally abnormal melanocytes and not to normal melanocytes.[10,21,24]

Only abnormal melanocytes are affected by AA, because these cells are three times more permeable to AA than normal cells. So the AA which enters the cells cannot be totally metabolised and the excess which accumulates in the cells is responsible for inhibiting mitochondrial respiratory enzymes and causes cytotoxicity.[6]

Following several studies which showed that AA spares normal melanocytes, a doubt arose as to why does AA cause hypopigmentation in pityriasis versicolor where normal melanocytes are affected. Nazarro-Porro et al[25] have now shown that apart from diacids, *Pityrosporum ovale* also produces a number of highly unstable reactive lipid radicals. These are highly cytotoxic and are responsible for the cellular changes seen in pityriasis versicolor; so AA is no longer thought to be responsible for the hypopigmentation in pityriasis versicolor.

Another condition in which AA has been found effective is acne vulgaris. The observation that acne responded to AA was accidental. During the course of treating chloasma with AA, Nazarro-Porro et al[26] observed that patients with concomittant acne also responded. Since then, a number of workers have found AA effective in acne.

Nazarro-Porro et al,[26] reported benefit in patients with papulo-pustular acne and acne conglobata using a 15% AA cream. There was initially a transient inflammatory reaction followed by a decrease in the lesion count and decreased oiliness of the complexion. Improvement was seen in 4 to 8 weeks. Bladon et al[27] found that oral tetracyclines were only marginally more effective than AA while Norris et al[28] found the response of acne to topical AA comparable to that of oral tetracyclines.

Side effects with topical AA in acne are mild. These include erythema and a mild, temporary inflammatory reaction. The skin may become excessively dry.[26,27] The incidence of side effects, however, is much less than with the other topical modalities available.[28] An added advantage with AA is a lesser tendency to hyperpigmentation following the resolution of the lesions.

The exact mechanism of action of AA in acne still remains unknown. The drug is known to have bacteriostatic effect against aerobic and anaerobic bacteria including *Propionibacterium acnes*.[29] Bladon et al[27] found a 30-fold decrease in the density of micrococci and *Propionibacterium* species after 12 weeks use of AA in acne. AA also has an antikeratinising effect as demonstrated by electron microscopic studies.[24] A comedolytic effect of AA on tetradecane induced comedones of rabbit ears has been shown.[30] It has also been suggested that AA exerts a competitive inhibitory effect on the conversion of testosterone to dihydrotestosterone.[31] It however does not quantitatively or qualitatively alter the sebum production.[27,32] Thus, AA is capable of interfering with several factors which are important in the pathogenesis of acne. But further work is still required on the delivery system of AA. Its use also needs to be evaluated in combination with systemic chemotherapeutic agents and anti-androgens.

The overall studies reviewed above have shown that AA has relevant biological properties which can be exploited for the treatment of skin disorders of different origins. It seems that it operates by interfering with a variety of unrelated mechanisms, but its capability of reversibly inhibiting essential oxido-reductive enzymes suggests a more general mechanism of action.

Its effectiveness as a therapeutic agent has been clearly demonstrated in acne vulgaris. Of additional interest are its effects on abnormal melanocytes which result in highly satisfactory results in the treatment of chloasma. Similarly, though the potential of AA as a treatment modality for LM has been recognised, the results have not been uniformly satisfactory. What is actually essential in this context is the necessity of achieving and maintaining a high intralesional concentration of the diacid for an adequate period of time. So the formulation and the regimen of application become very important factors. Again, though the potential of AA as a drug active against malignant melanocytes *in vitro* has been clearly shown, the drug has not been used to its fullest potential and so the possibility of adapting it for the treatment of MM should be thoroughly investigated.

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