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Mode of Action of Dithranol, Pharmacokinetics/Dynamics

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INTRODUCTION

Following the elucidation of the chemical structure of the active principle of Goa Powder (1) originally used as an antimycotic agent for the skin and subsequently found to be effective in the treatment of psoriasis, Unna (2) found that a related compound 1,8 dihydroxy-anthrone, DITHRANOL (Anthralin), had remarkable antipsoriatic properties. During the past seventy-five years over 1000 publications have appeared relating to the chemistry, pharmacology, toxicology and clinical efficacy of this drug which is now a mainstay in the clinical management of chronic plaque psoriasis in many centers. In this review the pharmacology, pharmacodynamics and pharmacokinetics will be discussed.

An appreciation of the chemistry of dithranol is needed in order to understand both the risks and benefits of this drug. The keynote of this chemistry is instability with two focal points: phenolic hydroxyl groups at carbon atoms 1 and 8, and two reactive hydrogen atoms on carbon ten. The hydrogen bonding between the phenolic hydrogen atoms and the central carbonyl function account for both the relative stability of dithranol in aprotic media such as Vaseline, but in the presence of protic solvents this bonding is disturbed,the keto-enol tautomerism (Fig. 1) is altered and auto-oxidation centering on C_{10} can occur. It is not surprising that this oxidation is both pH and light dependent. In the presence of light, dithranol is considered as a singlet oxygen sensitizer. In the dark superoxide radical anion (O_2^-) is formed (3). In the skin (4, 5), cell culture (6) and isolated mitochondria (7, 8) dithranol displays distinct chemical behavior involving hydrogen atom abstraction and electron transfer to yield the corresponding anthronyl radical (Fig. 1).

PHARMACOLOGY AND MODE OF ACTION

Psoriasis vulgaris is characterized by four histopathological changes; hyperproliferation, hyper/parakeratosis, epidermal accumulation of polymorphonuclear leukocytes (PMN) and dermal inflammation. These features are resolved following topical therapy with dithranol (9, 10). Dithranol inhibits cell proliferation both in cell culture systems (11) and *in vivo* (12). This is not a direct action on DNA but more likely to be a consequence of a potent effect on cellular respiration and subsequently, energy production. Indeed strong evidence points to the idea that the target organelle for dithranol is the mitochondria (13) and further that the interaction occurs with the electron transport chain on the inner mitochondrial membrane resulting finally in a reduction of ATP synthesis. The mechanism by which this process occurs is contested (7, 8).

Many enzymes associated with cell proliferation are reported to be inhibited by dithranol; Glucose-6-Phosphate-Dehydrogenase; Ornithine Decarboxylase; Lipoxygenase; Pro-

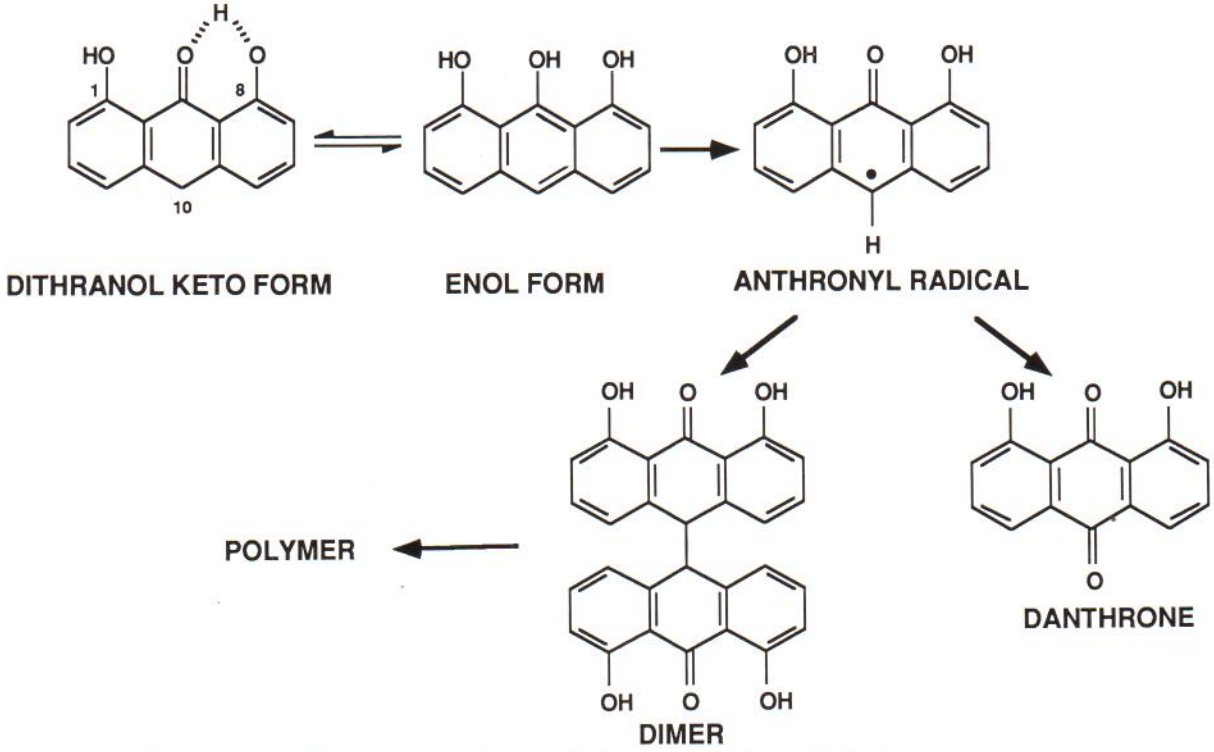

Fig. 1. Dithranol keto-enol tautomerism, dimerisation and polymerization via the Anthron-yl radical.

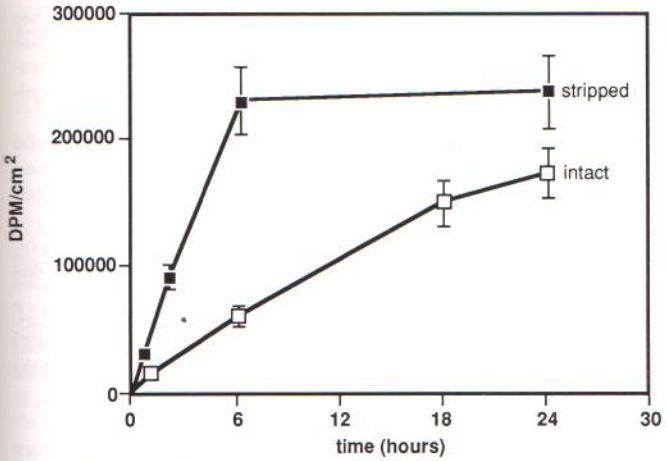

Fig. 2. Time course of accumulation of ^{14}C-dithranol and its metabolites in rat skin with and without stratum corneum.

tein Kinase C. In a recent comprehensive review (14) these and other targets such as Calmodulin and cyclic Nucleotides are discussed. However, as these reviewers point out, dithranol at certain concentrations stimulates epidermal DNA synthesis and hyperplasia thus the antiproliferative effect may not be primordial.

Attractive alternatives propose that the initial target cells are not the keratinocyte but either PMN leukocytes located deep in the stratum corneum, or the Langerhans cell implying immune modulation. Anti-chemotactic activity of dithranol has been described in psoriatic skin (15).

Most likely the target is not restricted to one cell type, and it is the redox chemistry of dithranol interfering with cellular metabolism that accounts for the ubiquitous pharmacology of the drug. There are two questions arising from this general statement. First, what happens to dithranol itself in the cell and in the skin? Secondly, if these effects are not specific to sub-populations of cells in the skin, what side-effects will be manifest in normally appearing skin following treatment with dithranol? In essence study of the latter question brought forth answers to the first. During the auto-oxidative process dithranol dimerizes and oxidizes to danthrone or a dimer (Fig. 1) which in turn further oxidises to "dithranol brown", an insoluble pigment devoid of biological activity and possessing a free radical structure (16). En route to this material of unknown structure, many colored substances are produced depending on pH, the presence or absence of light and metal ions. Thus staining of skin and clothes is not surprising (17). Perilesional inflammation is the major adverse reaction to dithranol. The biochemical mediators of this process include the oxygen radical species generated *in situ* by dithranol auto-oxidation as well as released histamine, prostaglandins, and platelet activator factor. Once again, review of the extensive studies carried out (14) leads to the conclusion that no single mechanism is predominantly operative and that selectivity and therapeutic improvements could be found by development of new chemical analogues or changes in clinical modalities. Only the latter question will be dealt with here.

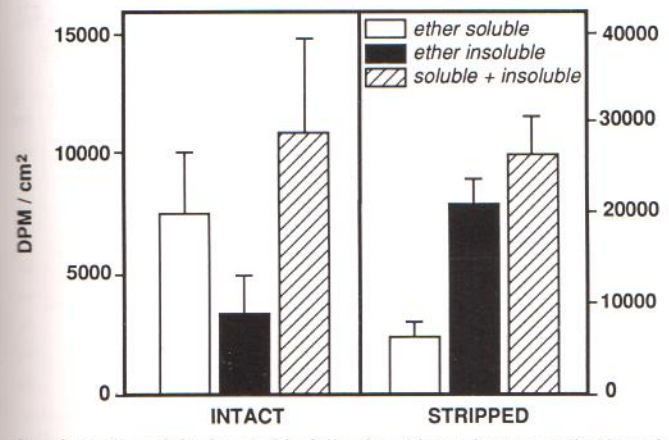

Fig. 3. Radioactivity in rat skin following thirty minutes application of ^{14}C-dithranol: ether soluble fraction mainly dithranol, ether insoluble mainly dithranol brown, total skin content.

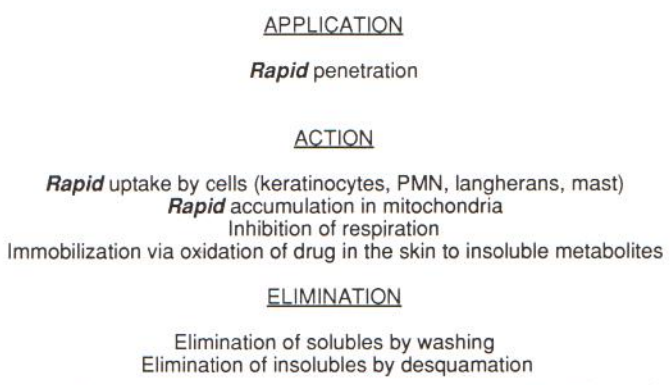

Fig. 4. A schematic representation of dithranol, delivery action and elimination in skin.

Early pharmacokinetic studies with tritium labelled dithranol revealed that the molecule penetrated faster and in greater amounts into artificially damaged skin than into normal skin. Even after a contact time of thirty minutes significant radioactivity was detected and, more importantly, the difference in concentration between normal and tape-stripped skin *in vitro* was more pronounced thirty minutes following application than after 1000 minutes (16). In the hairless rat *in vivo* it was confirmed that significant amount of drug had penetrated into the skin after thirty minutes contact time. Unchanged dithranol was found to reside in the stratum corneum but in tape stripped skin mainly dithranol dimer and insoluble material were present (Figs 2, 3) (4). Following topical application of dithranol in chloroform to pig skin in organ culture, free

Table I. *Summary of the distribution of dithranol and its breakdown products in isolated cells and skin.*

SOURCE	DITHRANOL AND METABOLITES			
	DITHRANOL	DANTHRONE	DIMER	POLYMER
Mitochondria in vitro	+	-	+	+
Keratinocytes in vitro	+	-	+	+
Intact skin (rat)	+	-	+	+
Stripped skin (rat)	+	+	+	+

radical concentrations rose steadily with time. The identity of the radical is unknown but it is clearly not the simple anthron-10-yl radical (5) (Fig. 1), thus confirming that extensive oxidation is occurring *in vivo*.

Finally in cultured human keratinocytes fast uptake and conversion of ^{14}C-labelled dithranol into insoluble and unidentifiable materials was observed. This material accumulated in the particulate fraction consisting mainly of the mitochondria (6). The foregoing observations on dithranol distribution in cell culture and in skin are summarized in Table I. The scheme of events illustrated in Fig. 4 can be encompassed into a modality called Short Contact Therapy (19). Application of dithranol at concentrations as low as 0.5% for ten minutes to the skin, followed by washing with acidic soap permitted sufficient dithranol to be delivered to the lesion to exercise its therapeutic effect and removing most of the drug from the intact stratum corneum in the surrounding skin reduced perilesional irritation.

Earlier investigators had shown that application for a period of minutes with relatively high concentrations (1%) of dithranol were effective (20).

Several variants of this modality now exist based in the main on modified vehicles to facilitate washout, or modified washing procedures to block dithranol action by rapid chemical degradation. Such a technique was described by Ramsay et al (20) using a triethanolamine containing cream, and although they report a reduction of irritation and maintenance of efficacy, increased staining in the skin would be predictable.

In conclusion the chemistry of dithranol is related to aspects of therapy, mechanism of action and side effects of this useful drug.

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