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The Interaction of Anthralin, Salicylic Acid and Zinc Oxide in Pastes

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Abstract. When anthralin is applied with a zinc oxide paste as vehicle its antipsoriatic activity decreases in less than 3 weeks.

Laboratory experiments make it probable that this deterioration is due to an interaction between anthralin and hydrolized zinc oxide molecules and simultaneous oxidation of anthralin into inactive 1,8-dihydroxyanthraquinone and other still unknown substances.

The addition of salicylic acid partially inhibits these inactivation processes.

The soft zinc oxide paste used in the clinical trials gave results that were as good as those of a stiffer zinc oxide paste and is easier to prepare and to apply.

Key Words
Interaction of anthralin
Anthralin
Salicylic acid
Zinc oxide
Psoriasis therapy
Pastes

Introduction

Although local treatment of psoriasis vulgaris with corticosteroid creams under plastic occlusion has recently been widely accepted, the treatment of psoriasis with anthralin pastes (dithranol, Cignolin®) is still in current use, as indicated by several publications [1–4]. Not long ago, FARBER and HARRIS [5] recommended a slightly-modified Ingram paste for psoriasis treatment. This led us to compare their anthralin paste ('Stanford paste') with the anthralin paste we use in Leiden.

The Stanford paste differed in two respects from the anthralin in pasta zinci oleosa (PZO) we were using (table 1). First, the Stanford paste is stiffer because it contains hard paraffin instead of oleum sesami, and there are small differences in the amounts of amylum and zinc oxide. Secondly, the Stanford

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paste contains a small quantity of salicylic acid. Initially, we thought this addition to be unimportant, because YOUNG and WEIFFENBACH [6] and DE VRIES [7] had demonstrated that salicylic acid is inactivated by zinc oxide. According to YOUNG and WEIFFENBACH, this is due to the formation of zinc salicylate, a compound lacking any specific therapeutic value.

The purpose of our investigation was to make a clinical comparison of the two pastes shown in table I and to analyse the cause of any difference in therapeutic activity we might find.

Table I. Composition of the pastes

Stanford paste	%	Anthralin in PZO	%
Anthralin	0.1–0.4	Anthralin	0.1–0.4
Acidum salicylicum	0.2–0.4		
Paraffine solidum	5	Oleum sesami	10
Zinci oxidum	25	Zinci oxidum	22.5
Amylum	25	Amylum	22.5
Vaselinum flavum	ad 100	Vaselinum flavum	ad 100

Clinical Trial

Methods. The method of paired comparisons was used. Two pastes containing equal quantities of anthralin were applied with cotton dressings to psoriatic lesions on opposite parts of the body. The skin condition was assessed at the start and after 14 days of treatment. During this interval the anthralin concentration could be increased on both sides simultaneously from 0.1 to 0.2%, 0.3 or 0.4%. In pastes containing salicylic acid, the salicylic acid concentration was 0.2% when 0.1% anthralin was present, and 0.4% when higher percentages of anthralin were added, as proposed by FARBER and HARRIS [5]. The pastes were not used earlier than 3 days after preparation [8] and they were discarded after 3 weeks to avoid the effects of possible long-term conversion processes.

Results

First we compared the stiff Stanford paste with anthralin in the soft PZO. The former gave the best results (table II). In a second series of trials next to the anthralin, salicylic acid was added to the PZO, the difference in consistency now being the only variable in the comparison. These pastes proved to have equal effect in the majority of the patients (table II). From these ob-

servations we concluded that the presence of salicylic acid was the cause of the initial superiority of the Stanford paste. This was confirmed by the third trial, in which salicylic acid was the only variable; in all patients the paste containing salicylic acid gave better results (table II).

Table II. Results of the clinical trial

I	II	I > II	I = II	I < II
Stanford paste	Anthralin in PZO	5	1	0
Stanford paste	Anthralin and salicylic acid in PZO	0	12	2
Anthralin and salicylic acid in PZO	Anthralin in PZO	6	0	0
Anthralin and zinc salicylate in PZO	Anthralin in PZO	5	9	0

Since YOUNG and WEIFFENBACH claim that salicylic acid and zinc oxide react immediately in a paste, resulting in the formation of zinc salicylate, we made a fourth comparison by adding zinc salicylate to the anthralin in PZO in quantities equivalent to the salicylic acid percentages in the earlier trials, and compared this combination with anthralin in PZO. The paste containing zinc salicylate gave slightly better results than the paste without zinc salicylate only in a minority of the patients (table II).

During the clinical trial we observed differences in colour between various paste samples. The anthralin pastes without salicylic acid were pink when fresh, but on standing they gradually turned violet. The pastes containing anthralin and salicylic acid were a cream colour when fresh and retained their light colour even after standing for a long time.

Conclusions drawn from the Results of the Clinical Trial

1. Addition of small quantities of salicylic acid to an anthralin zinc oxide paste potentiates the activity against psoriasis vulgaris. Addition of zinc salicylate does not have the same effect. This was contrary to our expectations, since we had assumed that zinc oxide and salicylic acid combine directly to form zinc salicylate.

2. COMAISH [2] and SEVILLE [3] have stressed the importance of using stiff anthralin pastes to obtain optimal therapeutic results in psoriasis. On the basis of our trials, we cannot confirm this opinion. Our soft paste was at

least as effective as a stiffer paste. Because the soft paste is easier to prepare and easier to apply than the stiff paste, the pasta zinci oleosa is in our opinion preferable to the stiff paste as a vehicle for anthralin.

3. In view of the differences in colour and clinical activity between anthralin-zinc oxide pastes with and without salicylic acid, it seems that salicylic acid inhibits a conversion of anthralin into less active substances.

Chemical Analysis

The results of the clinical trial raised two main questions:

(1) What happens to the anthralin in a zinc oxide paste?

(2) How does salicylic acid react in a paste containing zinc oxide when it is not present in a free state, nor can be simply replaced by zinc salicylate, the presumed reaction product of salicylic acid and zinc oxide.

Extensive studies by KREBS and SCHALTEGGER [9] have shown that the antipsoriatic activity of the anthrones, the class to which anthralin belongs, is restricted to anthralin (1,8-dihydroxy-9-anthrone), chrysarobin (1,8-dihydroxy-3-methyl-9-anthrone), 1-hydroxy-9-anthrone, and anthralin triacetate. All other configurations of the anthrone molecule and all oxidized anthrones (anthraquinones), including the oxidation products of these four, are completely inactive. Therefore, it seems essential that anthralin be preserved in its original state in the paste.

COMAISH *et al.* [10] recently published the results of a study on the interaction of anthralin and zinc oxide and the influence of salicylic acid on this reaction. According to them, salicylic acid (a) prevents anthralin from forming a pink complex with zinc oxide, a reaction that is even reversible, and (b) inhibits the auto-oxidation of anthralin. The authors followed spectrophotometrically the formation of a complex by anthralin and zinc oxide in a N-hexane solution and the influence of salicylic acid on this reaction. We repeated this *in vitro* experiment under various conditions in order to collect more information.

Anthralin was dissolved in N-hexane in a concentration of 0.05%. To this solution, increasing amounts of zinc oxide were added. After an hour, the zinc oxide was filtrated from the N-hexane solution. The concentration of anthralin was estimated spectrophotometrically at 350 nm. The amounts of anthralin found in the solution decreased with increasing amounts of zinc oxide (fig. 1). These values agree with those published by COMAISH *et al.* [10]. But when the zinc oxide was filtrated off after 17 h, much less anthralin

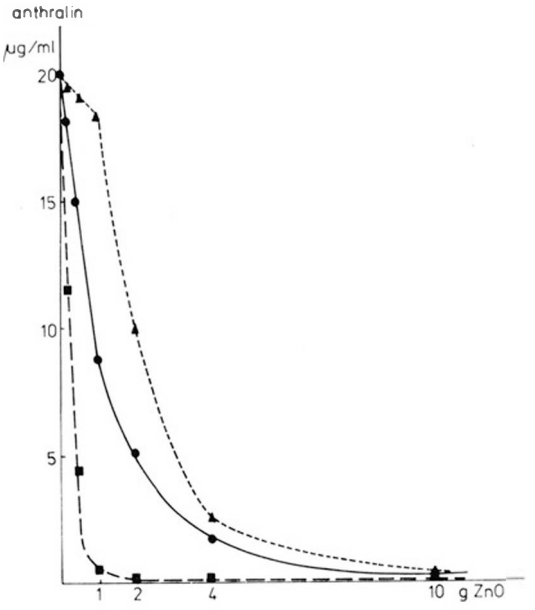

Fig. 1. Interaction of anthralin (● after 1 h; ■ after 17 h; ▲ after 17 h + salicylic acid) and increasing amounts of zinc oxide in a N-hexane solution, and the influence of salicylic acid.

was recovered (fig. 1). Evidently, the conversion of anthralin continues after the first hour. We found that the presence of salicylic acid (0.1 %) gave better preservation of the anthralin in the suspension (fig. 1), but contrary to the results of COMAISH *et al.* [10] complete inhibition of anthralin conversion could not be achieved, even when larger amounts of salicylic acid were added.

The conversion rate of anthralin can be seen from Figure 2. From a mixture of anthralin and zinc oxide in N-hexane, aliquots were taken at certain intervals. The initial concentration of anthralin in N-hexane was 0.05 %; the anthralin-zinc oxide ratio was 1 : 200 as in the paste. A continuous absorption spectrum between 260 and 500 nm was recorded for these samples, and various absorption peaks were found. The amount of anthralin decreased markedly with time, until zero was approached. The addition of salicylic acid (0.1 %) stabilized the anthralin concentration at about 45 % of the original concentration.

Parallel to the disappearance of anthralin, the presence of conversion products was detected (fig. 2), absorption peaks at 390 and 430 nm indicating

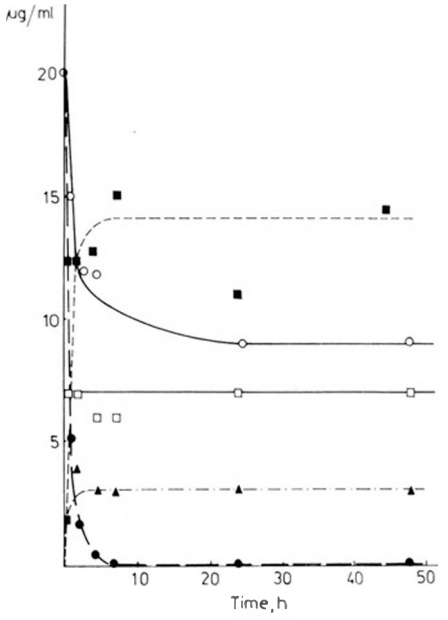

Fig. 2. Conversion rate of anthralin in the presence of zinc oxide in a N-hexane solution with and without salicylic acid, and the conversion products. ● Anthralin; ○ anthralin + salicylic acid; ■ 1,8-dihydroxyanthraquinone; □ 1,8-dihydroxyanthraquinone + salicylic acid; ▲ unknown substance in the solution without salicylic acid.

converted forms of the molecule. The compound responsible for the 430 nm peak proved to be 1,8-dihydroxyanthraquinone. The analysis of the other products is still in progress. In the future, we hope to be able to analyse anthralin conversion products not only in N-hexane solutions, but also in the pastes and other vehicles.

As for the second question, i. e., how salicylic acid reacts in a paste containing zinc oxide, according to POLDERMANN and MELIS[1] zinc oxide powder contains always traces of water resulting in the formation of a small quantity of alkaline zinc hydroxide. They suppose that the rapid deterioration of anthralin in the presence of zinc oxide is induced by the hydroxide ions. When salicylic acid is present it reacts with these ions, thus blocking the anthralin inactivating effect of complex formation between anthralin and

[1] Prof. J. POLDERMAN and R. MELIS, Technological Department of the Pharmaceutic Laboratories, University of Leiden, personal commun.).

the zinc ions. At the same time the binding of the alkaline ions gives less favourable conditions for the oxidation of anthralin since an alkaline environment is known to accelerate the oxidation of the anthrones.

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