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Arotinoids

A New Class of Retinoids with Activities in Oncology and Dermatology

Werner Bollag

Pharma Research Department, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basle, Switzerland

Summary. *Arotinoids are a new class of retinoids with particular biological properties. Arotinoid Ro 13-6298 in minute quantities leads to regression of chemically induced papillomas of the skin of mice. The ratio between the antipapilloma effect and the toxic syndrome of hypervitaminosis A is very favorable. Ro 13-6298 also has a therapeutic influence on chemically induced skin carcinomas in mice. As the papilloma model has proved to be suitable for screening for antipsoriatic and antikeratinizing properties as well as for antineoplastic screening, arotinoids might be useful in human clinical dermatology and oncology.*

Introduction

Retinoids are a class of compounds comprising natural forms and synthetic analogs of vitamin A. Evidence that they possess activities useful in the treatment of various dermatological disorders has been found [5]. Furthermore, retinoids exert a positive effect in experimental cancer chemoprevention and chemotherapy [3]. In clinical oncology, however, the results are not yet satisfactory. Aromatic retinoids, e. g., etretinate (Ro 10-9359), have a strong prophylactic and therapeutic influence on certain tumors, such as chemically induced skin papillomas and carcinomas in mice [1, 2]. The experimental skin papilloma, with its high proliferation rate of the basal cell layer and its increased keratinization, proved to be a useful model system for screening antipsoriatic and antikeratinizing in addition to antineoplastic properties of retinoids. Some of the biological effects of a new class of retinoids, the arotinoids [4], are described below. Investigations were carried out with the arotinoid Ro 13-6298.

Materials and Methods

Ro 13-6298, p-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]-benzoic acid ethyl ester (Fig. 1), is a crystalline powder, insoluble in water but soluble in oil.

Skin papillomas and carcinomas were induced by painting the skin of mice with 7,12-dimethylbenz(a)anthracene (DMBA) and croton oil as previously described [1]. The therapeutic experiment consisted of a 14-day trial. Groups of five animals bearing multiple papillomas, or of eight mice with single carcinomas, were formed. The animals received Ro 13-6298 dissolved in arachis oil, either IP or PO, once weekly or daily (five doses/week). In the papilloma experiments the mean sum of papilloma diameters per animal was determined for each group on day 0 and on day 14 of the trial. The increase or decrease of the papilloma diameters, expressed as a percentage, indicates the progression or regression of the papillomas. The therapeutic effect on carcinomas was measured by determining their approximate volume (product of length, width, and height), on day 0 and day 14 and by calculating the percentage of volume change.

Therapeutic Index. As hypervitaminosis A is a limiting factor to the use of retinoids, the therapeutic index, reflecting the ratio between antipapilloma effect and the toxic syndrome of hypervitaminosis A, is an important indicator for the usefulness of a retinoid. The therapeutic index has been defined as the ratio between the lowest daily IP dose causing, in a 14-day study, a defined degree of hypervitaminosis A, and the dose given IP once a week for 2 weeks causing a regression of about 50% (ED_{50}) of papillomas. Details have been described previously [1].

Results

The new arotinoid Ro 13-6298 has a very marked therapeutic effect on chemically induced skin papil-

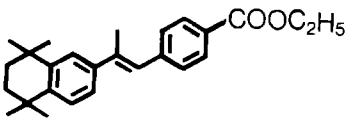

Fig. 1. Chemical structure of the arotinoid Ro 13-6298 (p-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]-benzoic acid ethyl ester)

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Table 1. Results of treatment of skin papillomas with arotinoid Ro 13-6298 for 2 weeks

Ro 13-6298[a] Dose (mg/kg)	Mean sum of papilloma diameters per animal (mm ± SE)		Percentage change in the mean sum of papilloma diameters per animal from day 0 to day 14	*P*-values with respect to untreated controls
	Day 0	Day 14		
Controls[b]	23.3 ± 2.1	29.0 ± 2.0	+ 24.5	
1 × weekly IP				
0.2	25.0 ± 3.5	6.0 ± 1.3	− 76.0	< 0.0005
0.1	28.7 ± 2.3	12.3 ± 1.8	− 57.1	< 0.0005
0.05	28.1 ± 2.7	14.3 ± 1.6	− 49.1	< 0.0005
0.02	25.0 ± 3.0	14.8 ± 2.9	− 40.8	< 0.0005
0.01	30.8 ± 5.0	24.3 ± 3.2	− 21.1	< 0.0005
Daily[c] IP				
0.08	18.0 ± 6.8	5.8 ± 1.2	− 67.8	< 0.0005
0.04	28.0 ± 7.0	12.0 ± 1.7	− 57.1	< 0.0005
0.02	20.5 ± 5.6	13.8 ± 3.8	− 32.7	< 0.0005
0.01	16.0 ± 2.1	12.8 ± 2.2	− 20.0	< 0.0005
1 × weekly PO				
0.2	26.0 ± 5.8	11.1 ± 1.8	− 57.3	< 0.0005
0.1	26.6 ± 3.8	15.6 ± 3.1	− 41.4	< 0.0005
0.05	18.0 ± 4.1	13.8 ± 3.3	− 23.3	< 0.0005
Daily[c] PO				
0.1	19.0 ± 5.3	3.4 ± 0.9	− 82.1	< 0.0005
0.08	28.3 ± 3.4	10.5 ± 1.5	− 62.9	< 0.0005
0.04	24.0 ± 3.3	12.3 ± 1.4	− 48.8	< 0.0005
0.02	25.5 ± 2.6	14.3 ± 2.6	− 43.9	< 0.0005
0.01	21.5 ± 3.8	13.0 ± 1.4	− 39.5	< 0.0005

[a] Ro 13-6298 dissolved in arachis oil
[b] Control group, ten mice; treated groups, five mice
[c] Daily treatment: 5 days per week

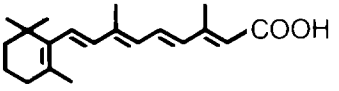
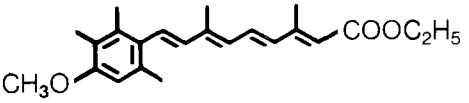
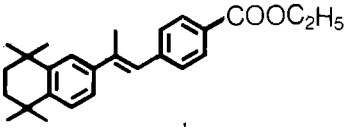
Table 2. Results of treatment of skin carcinomas with the arotinoid Ro 13-6298 for 2 weeks

Ro 13-6298[a] Dose (mg/kg)	Mean carcinoma volumes (mm^3 ± SE)		Percentage change in carcinoma volumes from day 0 to day 14	*P*-values with respect to untreated controls
	Day 0	Day 14		
Controls[b]	1,381.6 ± 412.4	3,106.1 ± 1,010.9	+ 124.8	
0.1 mg/kg[b] PO daily[c]	1,284.4 ± 346.9	1,980.8 ± 861.1	+ 54.2	< 0.05
0.2 mg/kg[b] PO daily[c]	1,680.8 ± 567.9	422.0 ± 309.2	− 74.9	< 0.0025
0.3 mg/kg[b] PO daily[c]	1,478.3 ± 905.0	234.8 ± 116.9	− 84.1	< 0.0005

[a] Ro 13-6298 dissolved in arachis oil
[b] Groups of eight mice
[c] Daily treatment: 5 days per week

lomas (Table 1) and carcinomas (Table 2). The outstanding property of this compound is its antitumor efficacy in minute amounts. A dose of 0.2 mg/kg IP once a week leads, in a 14-day experiment, to a 76.0% regression of papillomas; even with a dose of 0.05 mg/kg IP once a week a 49.1% reduction is achieved. The compound is also active following oral administration. When given daily by the oral route, a dose of 0.02 mg/kg provokes a 43.9% regression. In Table 3, a comparison is made between all-trans-retinoic acid of the first generation, the aromatic retinoid etretinate (Ro 10-9359) of the second generation, and the arotinoid Ro 13-6298 of the third generation of retinoids. Concerning the antipapilloma activity, the arotinoid, with an ED_{50} of 0.05 mg/kg, is 500 times more active than the aromatic retinoid etretinate (Ro 10-9359) with an ED_{50} of 25 mg/kg, and as much as 8,000 times more effective

Table 3. Comparison of three compounds belonging to the first, second, and third generation of retinoids, considering hypervitaminosis A, antipapilloma effect and therapeutic index

	Hypervitaminosis A min dose/day	Antipapilloma effect ED_{50}	Therapeutic index
All-trans-retinoic acid 	80 mg/kg	400 mg/kg	$\frac{80}{400} = 0.2$
Aromatic retinoid etretinate (Ro 10-9359) 	50 mg/kg	25 mg/kg	$\frac{50}{25} = 2$
Arotinoid Ro 13-6298 	0.1 mg/kg	0.05 mg/kg	$\frac{0.1}{0.05} = 2$

than all-trans-retinoic acid (ED_{50} = 400 mg/kg). Concerning the therapeutic index, the arotinoid possesses as favorable an index as that of the aromatic retinoid (2.0), which is ten times superior to that of all-trans-retinoic acid (0.2). The arotinoid Ro 13-6298 also has a dose-dependent therapeutic effect on chemically induced carcinomas. An oral daily administration of 0.2 mg/kg leads to a 74.9% regression; 0.3 mg/kg causes as much as 84.1% regression of these tumors. These doses, however, already induce some hypervitaminosis A symptoms.

Discussion

The new class of retinoids, the arotinoids, are therapeutically active against chemically induced epithelial tumors in mice, at extremely small doses compared with other retinoids. The therapeutic index of the arotinoid is similar to that of aromatic retinoid etretinate (Ro 10-9359), which is clinically useful. The fact that arotinoid Ro 13-6298 has a really new chemical structure and particular biological properties makes this compound a candidate for clinical trials in dermatology as well as in chemoprevention and chemotherapy of cancer. These investigations are currently under way.

References

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