

Photosensitizers and Radiosensitizers in Dermatology and Oncology

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SUMMARY

Two therapeutic modalities are currently of great interest, namely photo- and radiosensitization. Whereas photosensitizers only function in combination with ultraviolet (UV) light, radiosensitizers act only in combination with ionizing radiation. Because of the small UV penetration, up to a maximum of 0,5 mm, photosensitization can take place only at the surface of the body, i.e. the skin. Photosensitizers are applied in dermatology in order to optimize and improve the UV therapy of certain diseases (mainly psoriasis, mycosis fungoides and vitiligo). Radiosensitizers lead to an increase in sensitivity of the hypoxic and therefore radioresistant parts of tumours against X- and gamma-radiation. With sufficient concentration within the tumour, they can act where the radiation can reach, even in the deeper parts of the body. They represent a modern and useful aid to radiation oncology. Because of neurotoxic effects, however, their practical use is limited. A short review of the history, mechanisms of action, application and side-effects of these photo- and radiosensitizers is presented.

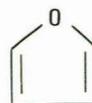
S. Afr. med. J., 56, 528 (1979).

Two therapeutic modalities have currently gained increased importance, namely photosensitization (better known as photochemotherapy or PUVA therapy (psoralen plus ultraviolet A)) and radiosensitization. Both are accomplished with chemical compounds, the so-called sensitizers, which ideally have no effects themselves, but act only in combination with radiation, thereby increasing its effect. Compounds which sensitize the body against UV light are called photosensitizers, whereas those with the appropriate property against ionizing radiation are known as radiosensitizers.

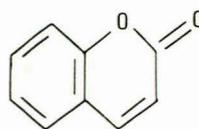
PHOTOSENSITIZATION

The phenomenon of photosensitization has been recognized for a long time. For example, there is the treatment of vitiligo with certain plants in combination with sunlight, the occurrence of a phytophotodermatitis after sunbathing in meadows, and berlock dermatitis after the use of certain perfumes. The basic requirement for these reactions is always the simultaneous presence of photosensitizing plant substances, the furocoumarins

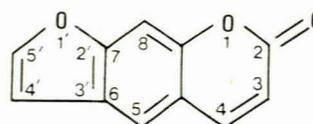
(psoralens) (Fig. 1) and long-wave UV light of 320 - 380 nm (UV-A).¹²



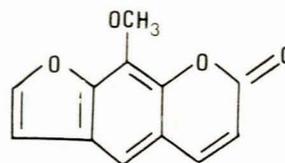
Furan



Coumarin



Furocoumarin
(Psoralen)



8-Methoxypsoralen
(8-MOP)

Fig. 1. Structure of the photosensitizers.

As the total penetration depth of UV radiation in the human body does not exceed 0,5 mm, photosensitizers can act only at the surface of the body, i.e. in the outer layers of the skin. Nowadays this is exploited therapeutically to a greater extent, since high-intensity UV-A irradiation facilities permit short exposure times.

Biochemical Mechanism

The most probable explanation of the biochemical mechanism is as follows: under the influence of long-wave UV light (365 nm) the furocoumarins, for example 8-methoxypsoralen (8-MOP), react with the pyrimidine bases of DNA, for example thymine (Fig. 2). By breaking open the 5,6 double bond of the thymine on the one hand, and the 3,4 and/or 4,5 double bond of 8-MOP on the other hand, a new bond between the photosensitizer and the DNA is established, with the formation of a typical

C₄ ring. A one-sided or a double-sided photo-addition is possible, through which the two adjacent DNA strands can be cross-linked. As a result of this interaction between the psoralen and the DNA of dermal and especially epidermal cells, DNA synthesis and therefore mitosis is inhibited, a process which is, of course, PUVA dose-dependent.¹⁴

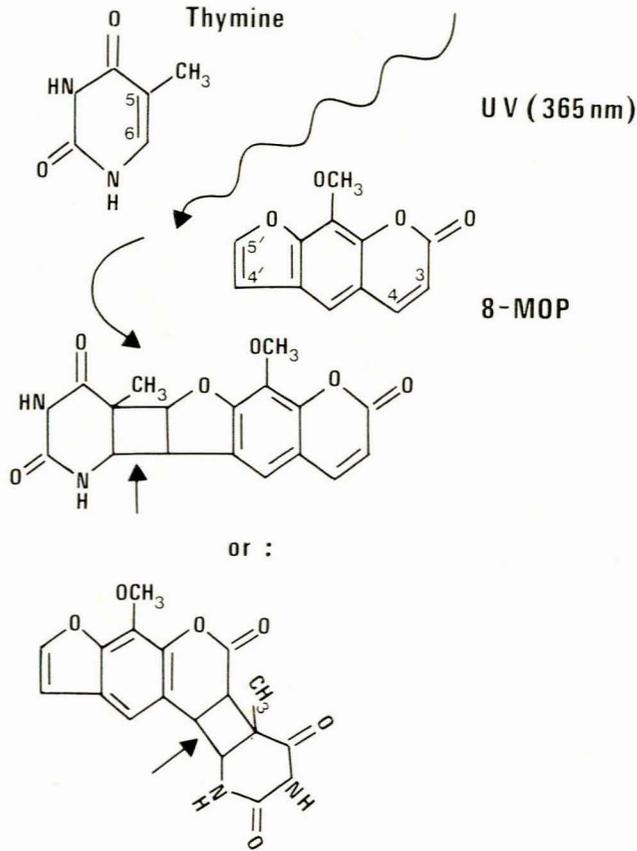


Fig. 2. Photo-addition between psoralen and DNA base.

It is obvious that this principle is mainly applicable to skin diseases caused by increased cell proliferation, such as psoriasis and mycosis fungoides. Stage III of the latter includes ulcerating tumours. The conventional therapy of both diseases consists *inter alia* of intensive exposure to sunlight or UV-B irradiation (290-320 nm). PUVA therapy is also indicated in cases of vitiligo, although the exact mechanism of action is still not clear. It is possible that the desired repigmentation includes stimulation of melanocyte production.

Technique

In order to achieve optimal photosensitization, 8-MOP (20-60 mg, according to body weight) is administered orally 2 hours before every UV-A exposure (peak emission 365 nm). During the initial whole-body exposures, UV-A doses of approximately 1-5 J/cm² are used. Because of the development of pigmentation and therefore of increased resistance, these doses are then increased stepwise. At first, psoriasis and mycosis fungoides treatments are carried out four times per week. When patients are completely symptom-free, i.e. usually after 4-8 weeks, treatment to prevent recurrence is carried out at greater intervals. If the disease recurs, the frequency of treatment is temporarily increased.^{3,10,21} Altogether, the following number of PUVA exposures is required: psoriasis approximately 10-30, mycosis fungoides 20-60, and vitiligo 100-300.¹³

Results

The results have been good, sometimes even very good, and in any case better than those after UV-B irradiation alone (Table I). In more than 90% of psoriasis patients there is complete short-term remission. After a longer time interval, the remission rate is still greater than 70%. Nearly all stage I and stage II patients suffering from mycosis fungoides are cured. Among 4 stage III patients treated, 1 was cured completely whereas the other 3 had incomplete remission. In approximately 75% of vitiligo cases moderate or good repigmentation is attained. It is obvious that more reliable data will only be available

TABLE I. SUMMARY OF RESULTS OF PUVA TREATMENT

Skin disease and required PUVA exposures ¹³	Authors	Number of patients treated	Results		Repigmentation moderate to good (%)
			Short-term remission (wks) (%)	Long-term remission (mo.) (%)	
Psoriasis (10-30)	Parrish <i>et al.</i> ¹¹	21	100	88	
	Wolff <i>et al.</i> ²¹	152	93		
	Braun-Falco <i>et al.</i> ³	259	91	70	
Mycosis fungoides (20-60)	Hofmann <i>et al.</i> ⁵	10 (stage I, II)		90	
	Konrad <i>et al.</i> ¹⁰	15 (stage I, II)	100	100	
	Konrad <i>et al.</i> ¹⁰	4 (stage III, i.e. tumours)		25	
Vitiligo (100-300)	Fitzpatrick <i>et al.</i> ⁷	84*			75
	Parrish <i>et al.</i> ¹²	26			73

* Sun exposure instead of UV-A exposure.

after greater numbers of patients have been treated.

The applicability of photosensitizers is not limited by acute side-effects caused by them in combination with UV-A radiation, namely pruritus, nausea and skin irritation, but there is still some uncertainty about possible carcinogenic late effects. Although it is known that mutations and cancer are induced mainly by UV radiation with a wavelength shorter than 320 nm, an oncogenic effect of PUVA therapy cannot be excluded with certainty, because of the interaction between psoralen and DNA. At the moment this still overshadows the application of photochemotherapy.

RADIOSENSITIZATION

For immunological and cell kinetic reasons, more than 99% of the cells have to be destroyed to achieve permanent cure of solid tumours. However, radiation cannot be used to an unlimited extent, since the normal tissue must be protected as much as possible, and this is the limiting factor. Furthermore, not all tumour cells are equally radiosensitive. Those with a lesser oxygen content (up to 50% of experimental tumours) are much more radioresistant and are often responsible for the failure of radiotherapy. We have therefore been striving for years to improve the efficiency of radiotherapy by several methods, including the use of true radiosensitizers.

The observation that the radiosensitizing effect of a chemical compound is based on its electron affinity made the search for suitable sensitizers much easier. It has also been found that only hypoxic tissue is sensitized to X- and gamma-radiation. This, as well as the fact that radiosensitizers can only function if they are present at the desired place during irradiation, i.e. that they must be administered before the exposure, is explained by their possible mechanism of action (Fig. 3). Because of its electron affinity, the sensitizer probably competes with endogenous radioprotectors such as glutathione (GSH) for reaction with the damaged biomolecule. If the sensitizer succeeds in reacting with the bioradical, i.e. the radioprotector, and repair is thus excluded, this leads to stabilization of the lesion.¹ In the presence of oxygen, the latter is accomplished by the oxygen already present; this

is why other radiosensitizers are not effective under such conditions.

Radiosensitizers would be of no practical value if they sensitized not only the tumour but also the normal tissue. Because they act exclusively under hypoxic conditions, which occur only in tumours, a selective effect is guaranteed. In contrast to photosensitizers, which can act only at the surface of the body, radiosensitizers are effective in deeper-lying tumours. A prerequisite for this is, of course, that these compounds accumulate in the tissue and that radiation is used with sufficient energy, i.e. with the necessary penetration depth.

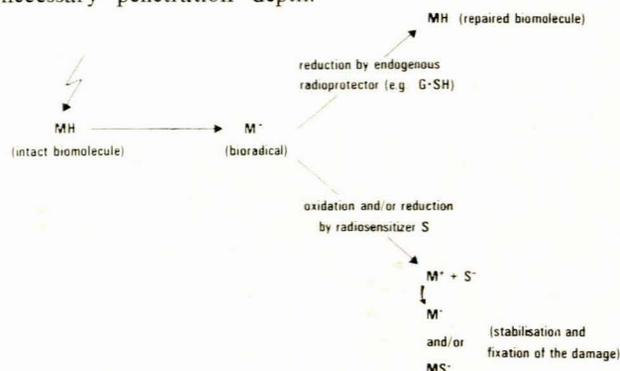


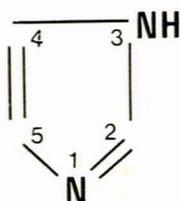
Fig. 3. Possible mechanism of action of the radiosensitizers.

Two Effective Compounds

So far, two compounds have proved themselves in this connection: the nitro-imidazoles, metronidazole (Flagyl) and misonidazole (Ro 07-0582; Fig. 4). They are characterized by high efficiency, good accumulation in the tumour, relatively good compatibility, and low toxicity. Quantitatively the radiosensitizing effect is expressed through the so-called enhancement ratio, i.e. the relation of the radiation dose without sensitizer to the radiation dose with sensitizer, which gives the same effect (if there is sensitization, then this ratio is always greater than 1). Both agents were tested on different biological models and on all occasions misonidazole proved itself to be the better radiosensitizer (Table II).

TABLE II. ENHANCEMENT RATIOS ATTAINED

Model and criterion	Authors	Enhancement ratio		Concentration/dose of radiosensitizer
		Metronidazole	Misonidazole	
Hypoxic mammalian cells <i>in vitro</i> (survival)	Asquith <i>et al.</i> ¹	1,9		8 mmol/l
	Asquith <i>et al.</i> ²		2,5	4 mm
5 different mouse tumours <i>in vivo</i> (remission, re-growth, etc.)	Several authors cited by Phillips ¹⁶	1,6	2	1 mg/g
		(average)	(average)	0,2 - 0,3 mg/g
Hypoxic human skin <i>in vivo</i> (pigmentation)	Dische <i>et al.</i> ⁴	1,1		200 mg/kg
	Dische <i>et al.</i> ⁴	(average)	1,6	80 mg/kg
Human tumours <i>in vivo</i> (re-mission, regrowth)	Thomlinson <i>et al.</i> ¹⁹		1,2	4 g
	Jentzsch <i>et al.</i> ⁹		1,5	60 - 80 mg/kg
			(estimate)	



Imidazole

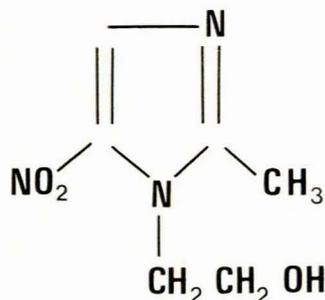
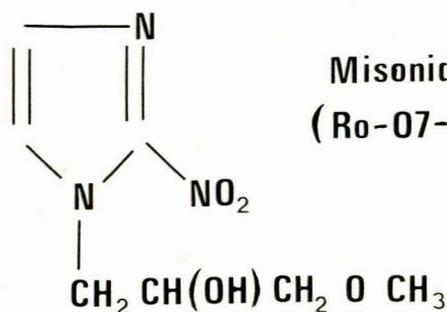
Metronidazole
(Flagyl)Misonidazole
(Ro-07-0582)

Fig. 4. Structure of the radiosensitizers.

Both substances are already in use in radiation treatment of human tumours in various countries, including South Africa.¹⁵ As a guideline, the treatment scheme of Jentsch *et al.*,⁹ who treated (mainly) brain tumours, may be studied. According to this, approximately 4.5 g misonidazole is administered orally 3-4 hours before irradiation (tumour dose: 400 rad). During each of the first 2 weeks, two such fractions are given. Subsequently five fractions per week are given (each of 170-200 rad) for a total of 3-4 weeks. The last treatment week resembles the first one, the total radiation dose to the brain tumour being 5 500-6 000 rad and the total misonidazole dose being 27-30 g. The authors estimate that the enhancement ratio per fraction achieved with this treatment scheme is 1.5. Furthermore, Urtasun *et al.*²⁰ have shown

that after unsuccessful radiation treatment, patients with brain tumours lived an average of 4.5 months longer when their tumours had been sensitized with metronidazole. Because of radiosensitizers, the effective radiation dose to the tumour is nearly always greater than that actually administered, so that a greater percentage of tumour cells is destroyed, thereby either increasing the cure rate or retarding recurrence.

Despite its promising radiosensitizing effect, however, administration of misonidazole has led to severe though reversible polyneuropathies;^{5,9} the total misonidazole dose should not exceed 29-30 g. Metronidazole is also said to be neurotoxic in large doses, so that the radiotherapeutic usefulness of these two compounds is unfortunately much reduced.

CONCLUSION

In conclusion, photosensitizers and radiosensitizers are important therapeutic aids. As their application in dermatology and oncology is relatively new, our knowledge is increasing daily (incidentally, the photosensitizer 8-MOP acts under certain conditions as a radiosensitizer and the radiosensitizer misonidazole acts as a photosensitizer).^{6,17} Perhaps it will soon be possible to define the risks which at present still exist (late effects of photosensitizers, early effects of radiosensitizers) and to avoid them.

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