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INCREASED SKIN TOLERANCE TO HIGH VOLTAGE X-RADIATION
IN PATIENTS GIVEN METHOKSALEN

CLINICAL OBSERVATIONS ON 28 CASES

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The relatively limited tolerance of overlying skin may seriously restrict the delivery of optimal amounts of x-ray into deep tumors. Several devices have come into accepted usage in order to spare the skin from as much radiant energy as possible. Among these are the use of multiple portals, grids, and careful selection and application of filters. Topical preparations, too numerous to mention, have been of little value in the attempt to increase skin tolerance to x-ray. In spite of these measures, it is still the integrity of the patient's skin that remains a matter of grave concern to the radiotherapist in his efforts to deliver optimal treatment.

Early in 1958, S. W. Becker, Jr. (1-2) reported that methoxsalen plus ultraviolet energy induced the following changes in skin: Morphologically, there appeared thickening, increased density, and increased adherence of the stratum corneum with the formation of a structure resembling the stratum lucidum. Because of these changes, pigment was retained in the epidermis, with "tanning." Functionally, the remarkable finding was that at the end of his two week experiment, and six months later, twice as much radiant energy was required to induce a minimal erythema in the skin area given methoxsalen plus ultraviolet as in the control area given ultraviolet exposures without the drug. This resistance to burning was impressive.

M. C. Zimmerman (3) confirmed these findings and extended the source of radiant energy used into the Grenz or soft x-ray band. He reported that the administration of 100 r daily for 14 days produced skin pigmentation and low grade inflammation; the former persisted for several weeks. Microscopically changes were noted similar to those described by Becker, Jr.

(The pertinent factors were: Universal X-ray Corp. Grenz X-ray machine: 15 KV; 12 ma; minimum wavelength 0.8 Å; 3 cu cone; TSD, 8 cm.; H.V.L. 0.034 mm. Al.)

In the electromagnetic spectrum the ultraviolet and roentgen bands are continuous, the far ultraviolet having wavelengths approaching the shorter, soft, or Grenz ray band. It seemed reasonable to wonder whether still higher energy from further out in the roentgen band, plus oral methoxsalen, could induce the self-protective changes in skin described by Becker, Jr., and by Zimmerman following the use of ultraviolet energy and soft x-ray, plus the drug. It is the purpose of this paper to report that skin tolerance to high voltage roentgen exposures may be substantially increased by giving methoxsalen to patients undergoing radiotherapy.

First, however, because the psoralens have largely been employed in the field of dermatology, a few basic considerations are in order concerning them. This is a group of chemicals called furocoumarins, several of which have the property of augmenting the self-protective mechanisms of normal skin against ultraviolet energy. It is noteworthy that the protection seems to be secondary; the presence of the drug may increase the inflammatory response to the first several exposures. Then, as pigmentation and the epidermal changes described by Becker, Jr., gradually make their appearance, tolerance to ultraviolet is increased (4-6).

The psoralens are widely distributed in nature. Methoxsalen is found in the seeds of a plant, Ammi majus Linn. which occurs on the Nile Delta and which grows wild in parts of California where it is known as "Bishop's weed." The crude powder has been used in Africa and the Far East for many generations, mainly for the treatment of vitiligo.

In recent years, especially in Europe and in this country, the pure chemical has been employed in a variety of other dermatologic conditions such as light allergy, in fair skinned people who tend to sunburn readily, and to prevent cancers in patients with xeroderma pigmentosum, and others susceptible to excessive solar exposure by reason of occupation (e. g., ranchers).

Although some early reports suggested the drug might induce transitory liver damage, this has been discussed by Sulzberger and Lerner (7) who wrote "this has not been proven in a single case." Two recently published studies on this problem further documented lack of toxicity (8-9). This and other possibilities raised in recent reviews (7, 10-11) seemed remote in the light of what we now know about the widespread distribution of the psoralens in natural foodstuffs. They are present, for example, in members of the lime, fig, parsley, parsnip and other vegetable families, and it has been estimated that an average stalk of celery may contain one mg. or more of psoralens (12). That at least some of these are photodynamically active furocoumarins is suggested by recent correspondence concerning "celery picker's dermatitis" in the Journal of the American Medical Association (13-14).

Finally, the fact that methoxsalen seems to be entirely inert in the absence of some form of radiant energy would attest to its safety. By stopping x-irradiation, drug effect would cease. Similarly, in case of accidental overdosage, the "antidote" would consist of placing the patient in a darkened room for 12 to 24 hours, away from all sources of ultraviolet radiation. Thereafter, normal skin reactivity would have returned.

Materials and Methods

During the year from July, 1958, through June, 1959, 28 consecutive, unselected white patients were studied. All were ambulatory and in good general condition. None had received previous radiation therapy and none had evidences of prior or present skin diseases. As may be seen in Table 1, 21 were females, 7 were males. The average age was 59 years; one patient was 21, another 37 and the remainder fell in the age range of 50 to 73 years.

With respect to complexion types treated, 12 patients were of light complexion with fair to very fair skin and blond hair, 10 patients were of average complexion with brown hair, and 6 patients were of moderately dark complexion with medium-dark skin and dark brown to black hair. There were no heavily pigmented or swarthy-skinned patients in this series.

The types of lesions for which deep x-ray treatment was administered, together with the numbers of patients with a given diagnosis, were as follows:

Lymphosarcoma of axilla with localized spread (1)

Adenocarcinoma of uterus (6)

Squamous carcinoma of prepuce with metastasis to left pelvis and groin (1)

Adenocarcinoma of ovary (2)

Adenocarcinoma of breast (8)

Carcinoma simplex of breast (1)

Adenocarcinoma of urinary bladder (2)

Bronchogenic carcinoma (3)

Carcinoma of uterine cervix (1)

Giant cell lymphoblastoma of groin invading pelvis (1)

Giant follicular lymphoma of omentum with abdominal dissemination (1)

Hodgkins disease (1)

The system of radiotherapy employed in this series was identical with that employed previously with the exception that each patient received two tablets (20 mg.) of methoxsalen ∇ 2 1/2 to 3 hours prior to each of the first 14 treatments. All patients were cautioned against exposure of treatment areas to sunlight or other forms of radiant energy, and to be careful about casual exposures of exposed skin areas to sunlight.

Technical factors adhered to were as follows: 200 KV, composite filter, 1.6 mm. Cu H.V.L., 50 cm. distance producing 25.4 roentgens/min. in air.

Dependent upon the anatomic site and character of the disease treated in each patient, portals varied in number from two to six and in size from 100 to 400 cms². Two portals were treated each visit, usually five times weekly, for from five to seven weeks, alternating portals where feasible and desirable. The air dose was 200 r to each of the two portals. Wherever possible, more treatments were administered to portals closer to the site of disease than to those further removed. Total skin doses to a major port (frequently the port receiving the most x-ray) varied from a low of 1,820 to a high of 7,000 r with an average of 4,700. Total tumor doses varied from a low of 3,000 to a

∇ The methoxsalen tablets used in this study were furnished by

The Upjohn Company, Kalamazoo, Michigan. The trade name is Meloxine [®].

high of 5,400, with a mean of 4,070 r. All treatments were given under the personal supervision of my associate, Dr. Arnold J. Bajek, or myself.

It has been my custom to reserve the use of topical drugs for the relief of distressing symptoms until the onset of moist desquamation. This has been adhered to in this series for those few patients who required such help.

At the conclusion of this series, in an effort to clarify the mode of action of methoxsalen, a healthy adult volunteer was given a 700 r single air dose to a five cm² area on the right forearm at time zero. (Factors: 200 KV; H.V.L. = 1.1 cu; 1/2 cu + 1 Al filt.; 50 cm. dist.; 13' 24" time at 15 ma.) Twenty mg. of methoxsalen was taken 140 minutes later. At + 350 minutes the same x-ray dose was administered to a five cm² area on the left forearm. Periodic observations were recorded.

In one patient () specimens of skin were taken from irradiated and unirradiated areas at the conclusion of the 14-day course of methoxsalen. Sections were sent to Dr. S. W. Becker, Jr., for staining and interpretation.

A control group was not included for two reasons. First, it would be difficult to do this in a private practice and secondly, it was felt the natural course of skin changes following radiotherapy was too well known to require it.

Results

As may be seen in Table 1, among these 28 patients, eight had no desquamation or insignificant flaking, 13 had moderate dry desquamation, and seven had moist desquamation. The treatment areas shown in Figures 1 and 2 represented the more extreme reactions encountered. Comparing the

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results in this series with those obtained in similar patients prior to the use of methoxsalen, it was my conclusion that the drug had induced approximately a 25 per cent increase in skin tolerance. This seemed a reasonable estimate since the average of the total skin doses in this series is actually 15 to 20 per cent higher than that previously attainable. And only 25 per cent of these patients developed any degree of moist desquamation in contrast to over 75 per cent of earlier patients.

There were no untoward reactions, local or systemic, attributable to methoxsalen. In fact, it was my impression the nausea associated with large doses of irradiation to the abdomen (see patient) for widespread giant follicular lymphoma was milder than would have been expected previously.

The specimens taken for biopsy from patient were stained with hematoxylin and eosin, and with silver nitrate stain plus hematoxylin counterstain. Dr. Becker, Jr., compared these with his own (see color plate opposite page 264, reference 2), and with sections obtained from Zimmerman following 14 days of Grenz irradiation. He reported both sets of sections removed after x-radiation "had a thickened stratum corneum and some development of a stratum lucidum. These changes were not excessive and the stratum lucidum was not as thick and dense as that seen after methoxsalen and ultraviolet light. The epidermis was slightly thicker than the control specimens. Pigment formation was active in the irradiated specimens; the melanocytes and stratum corneum contained considerable amounts of melanin and macrophages containing melanin were seen in the upper cutis. A few lymphocytes were present in the upper cutis."

Dr. Becker, Jr.'s interpretation pointed out that the exact effect of the psoralens in producing these changes was uncertain because true control sections would have been from skin given the same quantity of x-ray without the psoralen. The changes were, however, less than after ultraviolet plus methoxsalen. This was not unexpected since most ultraviolet energy is absorbed in the upper layers of the skin while most x-ray energy passes through. In any case, he concluded, there was no anatomic change in the sections which would act as a filter to x-ray.

Dr. Becker, Jr., suggested that, in the absence of such a filter, perhaps another mechanism might explain the increase in skin tolerance to x-ray. The reaction of the skin in radioderma-
titis is due to secondary ionization and not to the primary beam. The metabolic products in the skin following oral methoxsalen might act as ion absorbers, thus preventing the secondary ions from producing damage. To test this hypothesis, the experiment described under "Materials and Methods" was carried out, with results shown in Table 2. The differences in the two sides were distinct in that two-plus erythema and edema were present on the control side. With methoxsalen present, there was no edema and at no time was erythema graded above one-plus.

Discussion

Average human skin, exclusive of warm moist areas, will tolerate a maximum of approximately 4,000 r (skin dose) when administered over a six week period, using 200 KV; H.V.L. = 1.6 Cu. This will create a moist desquamation throughout most of the treatment area, more intense toward the center, less intense around the periphery. There is a considerable range of variation depending on a number of factors, which include complexion-type, elasticity, and nourishment of the underlying

tissue bed. This moist desquamation is generally associated with edema, hypersensitivity and pain for three to six, or even eight, weeks and is only slightly altered in duration and degree of discomfort by the wide variety of topical pharmaceutical preparations available.

Fair, blond, lightly pigmented skin will tolerate considerably less than the average maximum, in the range of 3,200-3,600 r (skin dose). And dark, swarthy, deeply pigmented skin will tolerate as much as 4,400 r. These figures are approximate and are applicable with physical factors: 200 KV, H.V.L. = 1.6 Cu, 50 cm. distance, and portal sizes varying from 100 to 400 cm².

The radiation therapist, torn between the desire to administer tumor doses in the cancerocidal range, and the equally strong desire to spare the patient from radiation-induced pain and suffering frequently chooses discretion over valor and limits radiation to sub-desquamation levels. Despite multi-port technics, compression, grid utilization, and other safeguards, the skin is still the greatest single deterrent to the administration of the "adequate" tumor dose. This is so because 200 KV radiation produces its maximum ionization within the skin (primary plus backscatter), in contrast to supervoltage or telecobalt radiation which produces its maximum secondary ionization three or four mm. below the surface of the skin.

The exact mode of action of methoxsalen plus mid and near ultraviolet energy in producing morphologic and functional changes in skin is unclear. It seems definite, however, that the drug produces no discernible effect in the absence of electromagnetic energy (3). The experiences reported in this paper suggest that some components of the energy spectrum I have used in high voltage radiotherapy were also

capable of inducing that effect in the overlying skin.

The mode of action seems to be different when ultraviolet and when x-radiation are delivered to psoralenized skin. In the former case, active wavelengths penetrate only superficially, and because methoxsalen is photodynamically active, skin response to a given dosage is enhanced. For example, a dose producing a minimal erythema without the drug would, with methoxsalen present, induce a more intense erythema than the control. In the case of x-radiation, however, less inflammation occurs when the drug is present than when it is not. It seems possible that methoxsalen or its breakdown products in the skin may indeed act as ion absorbers, as Becker, Jr., has suggested. The reaction in radiodermatitis is due to secondary ionization and not the primary x-ray beam. As ion absorbers, the psoralen might prevent the secondary ions from producing damage. Thus, in contrast to the secondary protection following repeated methoxsalen-plus-ultraviolet exposures, the psoralen apparently acts as a primary protectant against x-radiation injury.

The question has been raised about possible interference by methoxsalen with the cancerocidal effects of the x-ray beam. This is not possible to answer on the basis of my experience. I can report that where there were palpable masses of radiosensitive tumor tissue, these have regressed at what seems to be the usual rate. In one patient () having giant follicular lymphoma of the omentum with abdominal dissemination, the mass decreased in size promptly.

However the drug-plus-energy-complex acts, in my opinion there is no uncertainty as to the increase in skin tolerance to high voltage x-ray, estimated to be approximately 25 per cent. This occurred in all

patients and was quite enough to be of practical value in terms of delivering more x-ray energy into the tumor area with less discomfort to the patient. My present concern is with the other healthy tissues in the x-ray beam.

It would be desirable to confirm my findings in an institutional setting, using matching drug and placebo tablets. In the meantime, I have started a series who are to receive 20 mg. of methoxsalen prior to each treatment, regardless of number or duration, rather than follow the manufacturer's directions for use in suntanning (14-day course). It is also important to study quantitatively the effects of varying doses of methoxsalen; if it does function as an ion absorber, larger oral doses might be expected to absorb proportionately more secondary ions. It is essential to determine whether interference with tumor-response may be noted. And it would also be of interest to investigate the influence of the psoralen on skin responses to gamma radiation. These are not projects readily carried out in a private practice, but it is my hope that this report will stimulate others to confirm and extend my clinical observations.

Summary

In 28 patients undergoing deep radiotherapy, administration of 20 mg. (two tablets) of methoxsalen (Meloxine[®], Upjohn) two to three hours prior to each of the first 14 treatments induced an estimated 25 per cent increase in skin tolerance in all. This was accompanied by increased pigmentation and the other self-protective skin changes previously described following the use of methoxsalen plus ultraviolet energy. In contrast to skin response to ultraviolet, methoxsalen (or its breakdown products) in the skin seemed to confer primary protection against x-radiation, possibly by absorbing secondary ions. It is hoped this observation will be confirmed and extended by others.

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TABLE 1

Pertinent Details Concerning 28 Patients Given Methoxsalen During the First 14 X-ray Treatments.

Patient	Sex	Age	Complexion Type	Anatomic Site	No. of Ports	Radiation Details				Skin Changes				End Result
						No. of Treatment days	Daily r Skin, Each Port (X)	Total r Skin, Each Port (X)	Total Depth (Approx.) Dose, All Ports	Onset, Character of Erythema (X)	Onset, Character of Desquamation (X)	Duration of Desquamation (X)	End Result	
	M	61	Very fair	Left axilla, chest wall, mediastinum	4	30	270	4600	4000	3rd week +	6th week axilla only +	2-3 weeks	Tanned with little induration	
	F	65	Very fair	Pelvis, lower abdomen	4	29	280	4200	4200	3rd week +	5th week +	2-3 weeks	Pigmented dry peeling, 4 wks.	
	M	65	Average	Left groin, pelvis	2	24	280	6700	4000	3rd week ++	4th week ++	6 weeks	Healed, thickened	
	F	52	Fair	Pelvis, lower abdomen	4	28	274	4100	3720	4th week +	6th week + sl. edema	6 weeks	Tanned with no edema. Slight induration	
	F	53	Fair to average	Pelvis, lower abdomen	6	20	260	1820	3200	5th week ±	None	-----	Sl. tanned, soft	
	F	50	Fair	Post-left radical mastectomy	4	24	280	4480	4000	3rd week +	None	-----	Moderately tanned, soft	
	F	69	Very fair	Post-left radical mastectomy	4	26	280	7000	5200	2-3rd week + to ++	5th week ++ axilla only	6 weeks	Healed. Sl. thickening c telangiectasis	
	M	57	Average	Urinary bladder	4	35 (2 H.M. Grid)	220	4600	5400	2nd week + to ++	5th week + with edema	3-4 weeks	Skin healed, deeply tanned	
	F	65	Very fair	Post-left radical mastectomy	4	23	280	5480	4200	3rd week +	5th week + with edema in axilla	2-3 weeks	Healed, Sl. tanning	
	M	64	Average	Bronchogenic carcinoma	3	30	270	5400	5000	3rd week + to ++	4th week ++	8 weeks	Healed with tan 4x4 cm ² area of scarring	
	M	72	Average	Bronchogenic carcinoma	4	30	270	4300	5200	3rd week ± to +	6th week ± to +	2 weeks	Skin tanned	
	F	37	Dark	Pelvis, mid and lower abdomen	4	25	284	4260	3400	3rd week +	None	-----	Skin tanned	
	M	62	Average	Bronchogenic carcinoma	6	24	270	4300	5300	3rd week +	5th week ±	2 weeks	Skin tanned	
	F	63	Fair	Post-left radical mastectomy	4	26	280	4800	4600	3rd week + to ++	5th week + to ++	3 weeks	Healed, tanned	

Legends

(X) Significant port for brevity, frequently the port receiving most X-ray.

Erythema Scale

0 = No visible effect
 ± = Slight
 + = Moderate
 ++ = Marked

Desquamation Scale

0 = None
 ± = Flaky-dry
 + = Moderate, dry, not painful may have edema
 ++ = Moist, painful, edematous

TABLE 1 (Continued)

PRIVACY ACT MATERIAL REMOVED

Patient	Sex	Age	Complexion Type	Anatomic Site	Radiation Details				Skin Changes				Legends	
					No. of Ports	No. of Treatment days	Daily r Skin, Each Port (X)	Total r Skin, Each Port (X)	Total Depth (Approx.) (including intra-vaginal)	Onset, Character of Erythema (X)	Onset, Character of Desquamation (X)	Duration of Desquamation (X)		End Result
	F	69	Average	Pelvis, lower abdomen	4	26	270	3000	3200	4th week ± to +	None	None	Desquamation of (X)	Skin healed, tanned
	F	55	Average	Pelvis, lower abdomen	4	25	280	3640	3600	4th week +	±	6th week	2 weeks	Healed, tanned
	M	63	Average to dark	Urinary bladder	3	20	220	4400	(incomplete)	2nd week +	None at 3rd wk.	3rd wk.	3 weeks	Treatment continues
	F	73	Average	Post-left radical mastectomy	4	23	280	6200	4660	3rd week + to ++	± to +, in axilla	5th week	4 weeks	Well healed tanned
	F	71	Average to dark	Pelvis, lower abdomen (en-dometrial)	4	25	280	3640	3400	3rd week +	±	5th week	4 weeks	Well healed tanned
	F	58	Fair	Left groin and pelvis	2	22	284	6248	4800	2nd week + to ++	++	4th week	6 weeks	Desquamated only where adhesive tape was applied. Now healed
	F	67	Fair	Pelvis, lower abdomen	4	28	270	4320	3800	3rd week ± to +	+	5th week	3-4 weeks	Healed, sl. tanning
	F	57	Average to dark	Left breast lateral chest wall	5	26	280	5500	4000	2nd week + to ++	+	3rd week	4 weeks	Healed, tanned
	F	57	Average	Pelvis, lower abdomen	4	28	280	4480	3600	2nd week +	None	None	-----	Sl. tanning
	F	55	Average	Abdomen	2	32	284	4820	3400	3rd week +	±	6th week	5 weeks	Healed, tanned
	F	21	Average	Left supra-clavicular, mediastinum	4	37	270	5400	4000 +	3rd week + to ++	± to +	5th week	4 weeks	Healed, tanned
	F	64	Average	Left supra-clavicular, area	1	17	270	4590	3400	2nd week + to ++	+	Treatment continues	Treatment continues	
	F	58	Average	Post-left radical mastectomy	4	17	260	4160	3000	2nd week +	+	3rd week	5 weeks	Treatment continues
	F	56	Average	Post-right radical mastectomy	4	23	270	3800	4000	3rd week +	+	4th week	5 weeks	Healed, tanned

PRIVACY ACT MATERIAL REMOVED

TABLE 2

Right Forearm			Left Forearm		
Time			Time		
Hours	Minutes		Hours	Minutes	
0	0	700 r to five cm ² area	0	0	
1	20	Faint pink tint (±)	2	20	20 mg. methoxsalen p.o.
5	5	Perceptible erythema	5	50	700 r to five cm ² area
6	20	Deeper erythema (+) with slight edema			
7	20	Erythema ++ with edema, slight local warmth	7	20	Faint pink tint (±)
9	20	No change	9	20	Perceptible erythema (± to +)
10	20	No change	10	20	No change; no edema
11	20	No change	11	20	No change
14	5	Edema, local warmth subsiding. Erythema now (+)	14	5	Erythema subsiding. No edema
18	5	Pink blush slightly deeper in color than left forearm areas	18	5	No change
22	5	Erythema unchanged (+)	22	5	No change (±)
28	50	Erythema (+) very slight edema	28	50	Erythema (±) no edema

FIG. 1 (Pt. T.P.) shows cervical and anterior mediastinal treatment areas two days following completion of treatments: 5400 roentgens skin dose; dry, painless desquamation, healing completely in four weeks, skin tanned, no edema or induration. This was one of the more marked dry desquamatory reactions seen in the 13 patients who showed this \pm to +.