Evaluation of Lioxasol for the Treatment of Accidental Local Radiation Injuries: an Experimental and Clinical Study.

Natalia M. Nadejina[1], John W. Hopewell[2], Igor A. Gusev[1], Mohi Rezvani[2], Gerard M. Morris[2], Tatiana G. Protasova[1], Tatiana E. Chelmodaeva[3], Nina I. Fetisova[3] and Lev B. Shagalov[3].

[1]*Scientific Research Center - Institute of Biophysics, Moscow, Russia*
[2]*Research Institute of Oxford University, The Churchill Hospital, Oxford, Great Britain*
[3]*"Pharmazashita" Scientific Productive Association, Moscow, Russia.*

Abstract: The Chernobyl accident caused the development of Acute Radiation Syndrome (ARS) in 134 individuals, these were either treated at Hospital 6 (Moscow) or in hospitals in Kiev. Local radiation injuries (LRI) were found in 54 patients from the 108 ARS patients treated in Moscow over the acute period; 2 additional patients from this group had combined radiation and thermal skin injuries (the total number of LRI patients was 56).

The effectiveness of Lioxasol, an ethyl alcohol based product containing 2-alliloxoethanol, was investigated in these patients. The treatment group was composed of 8 survivors of ARS with a second degree LRI caused by relatively uniform gamma-beta exposure. The control group was composed of 8 patients suffering from ARS also of second degree (7 patients) or first degree (1 patient) reactions caused by external, relatively uniform, gamma-beta exposure between 1956 and 1970.

The time of of re-epithelisation in the treated group was 25.4 ± 3.1 days after irradiation. This was slightly shorter than the 28.3 ± 4.9 days in the control group. However, this difference was not statistically significant ($p>0.05$).

The effectiveness of Lioxasol was further studied on pig skin. Multiple sites in the same animal were irradiated with 22.5 mm diameter $^{90}Sr/^{90}Y$ plaques. The time of onset of moist desquamation and the subsequent healing times were used as end points. Following a single dose of 35 Gy, a dose known to produce moist desquamation in all irradiated sites, Lioxasol was applied topically twice a day. Lioxasol treatment (twice daily), which started the day after irradiation, delayed the time of onset of moist desquamation significantly from 5.1 ± 0.2 weeks to 5.5 ± 0.2 weeks. However, the most marked effect was on the number of sites that healed within 3 weeks of the first appearance of moist desquamation. This was 80 ± 10.3% for sites treated with lioxasol whereas in untreated sites only 26.7 ± 11.4% of the irradiated fields were healed by this time ($p<0.001$). The possibility that this might be explained by enhanced proliferation of cells in the basal layer of the epidermis was tested by examination of the effects of prolonged Lioxasol treatment on unirradiated pig skin. Twice daily applications of lioxasol for 2 weeks resulted in a 28.6 ± 1.7% increase in the ^{3}H-thymidine labelling index of basal cells. This level of elevation in the labelling index was maintained until 10 weeks; when Lioxasol treatment was stopped. There was no quantifiable evidence of hyperplasia in the epidermis but the number of labelled cells, fibroblasts and endothelial cells, was markedly increased in the papillary dermis. Twice daily application of lioxasol for 2-10 weeks produced a 43-58% increase in the number of labelled cells per mm^2. These observations provide a possible mechanism for the actions of Lioxasol in ameliorating localized radiation injury to the skin.

1. Introduction

Non uniform exposure to individuals has been a feature of the numerous radiation accidents that have been associated with the use of nuclear power plants, radiation devices in

medicine and industrial applications of ionizing radiation, since the end of the second world war. Partial body exposures have been associated with extremely high doses to the skin and mucous membranes and relatively lower non-uniform doses to the bone marrow. Extremely high doses to the skin, from beta emitters, have caused severe skin effects which were the primary cause of death in some cases.

Initial reports [1] on the Chernobyl nuclear power plant accident in 1986, have accounted for 115 patients, with clinical signs of general acute radiation syndrome (ARS), who were admitted to the Hospital of the Institute of Biophysics, Moscow. Among these patients 56 had a varying degree of radiation-induced skin lesions. Lymphocyte analysis has subsequently shown that two of these cases had not received a total body dose sufficient to result in a general ARS. Skin lesions in these two individuals were caused by the combined effects of radiation and thermal burns.

Initially, the victims of ther Chernobyl accident who developed skin were classified into four groups [1] according to the following criteria: The contribution of the ß- and γ-radiation components to the total dose, the prevalence of distant or contact exposure to the skin and the nuclide composition of the radioactive sources to which an individual was exposed. In the light of additional information, obtained during the last few years, the number of cases allocated to each group has been revised and are slightly different to the initial values. These new values are given in Table 1. In some cases, skin lesions were so severe that they were not compatible with patient recovery even in the absence of any ARS. Deaths in 26 patients in the first 3 months of the exposure were associated with skin lesions involving >50% of the total body surface area (Table 2). This left 28 survivors who had acute local injuries and developed the long term consequences of these injuries. Of these 25 remain alive 10 years after the accident.

Table 1. Dependence of clinical signs of radiation-induced damage to the skin on the depth-dose distribution.

Group	Number of Patients current (original)	γ doses (Gy)	Skin doses (Gy) at: 70 μm	150 μm	Time of onset of severe damage (days) Ist wave	2nd wave	Maximal clinical signs (time of onset in days)
I	17 (15)	2-5.8	8-10	3-4	-	-	Erythema (15)
			60-90	20-30	25-28	~60	Small erosions (35 & 65)
			100	>30	20	45	Ulcerations (30 and 50)
II	6 (6)	4.0-12.7	100	10	10	-	Small erosions (20)
			250	~30	5-7	35	Necrosis (20-30)
			360†				
III	6 (6)	9.0-14	>200	>50	5-10	-	Necrosis (15)
IV	25 (29)	2.0-11.5	150	50	8-10	~30	Ulceration & necrosis (25)
			300†	100	5-7	~30	Total necrosis of skin (20-25)
Total	54 (56)						

†The most exposed cases

Group I: exposed to distant high energy ß-γ sources; Group II: exposed to γ-radiation from smoke constituents of the plume and γ skin contamination from particles of fall out; Group III: high dose ß-γ radiation from smoke and steam (firemen); Group IV: varied group, some with total or local wetting of clothes to generate a thick radiation source on the skin surface (ß-γ irradiation).

Table 2. Number of deaths over the acute period in patients showing a varying severity of radiation-induced skin lesions and the number still alive after 10 years.

Group	No. of patients	No. of acute deaths	Alive at 10 years
I	17	1	14
II	6	4	2
III	6	6	0
IV	25	15	9
Total	54	26	25

Clinical management of localised radiation injuries to the skin involves the development of more effective therapeutic measures for both the acute and for the late periods as well as the elaboration of methodologies for diagnosis and surveillance of the dynamics of the pathological processes at different times after an accident. Main clinical manifestations of different grades of radiation induced skin lesions in radiation accident victims are given in Table 3.

Table 3. The main clinical manifestations and levels of absorbed doses (short-term gamma irradiation) for different grades of local radiation injuries to the skin.

Local radiation injury	Grade of lesion (approximate dose, Gy) I (8-12)	II (12-20)	III (20-25)	IV >25
Initial erythema and time of appearance	Continues for few hours, may be absent	Seen from a few hours to 2-3 days	Seen in all; duration from 3-6 days	Seen in all; its severity does not decrease prior to manifestion of main reaction
Main Reaction				
- latent period	15-20 days	10-15 days	7-14 days	Oedema, pain necrosis, local haemorrhages
- clinical signs	erythema, 'dry' desquamation	erythema, oedema, blisters, moist desquamation	erythema, pain, blisters, erosions	

Cases involving exposure doses of more than 20 Gy (Grade III-IV lesions) are likely to develop late radiation ulcers even where there is initial healing of acute lesions. This is illustrated by an analysis of representative cases with either Grade I, II or III LRI (Figure 1). Patients with Grade I lesions show full re-epithelialisation with skin scarring or atrophy. The majority of patients with Grade III lesions do, on the other hand, develop late ulceration. This confirms the necessity for early (20-30 days) surgical intervention after local irradiation with doses higher than 20 Gy. After such doses it is important to perform surgical intervention in the period of ulceration and necrosis to reduce the risk of

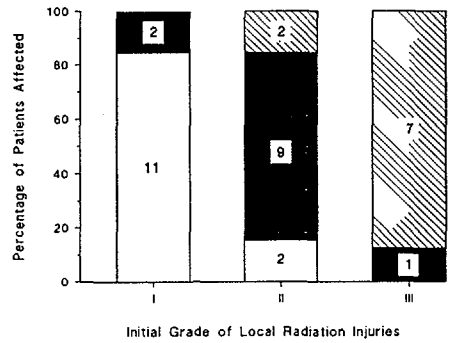

Figure 1: Incidence of late consequences of exposure in patients with an initial diagnosis of either Grade I, II or III LRI. ▨ Late radiation ulcers, ■ Tissue scarring or atrophy □ full re-epithelisation.

the development of anatomical abnormalities and defects of damaged tissues. The following types of operation are performed:

1. The simultaneous dissection of all the damaged tissues, with healing of the postoperative wound. This operation prevents late pathological processes, including the development of late trophic ulcers. Usually such therapy is possible when the LRI are not localised in regions of large blood vessels, nerves and tendons.
2. Transplantation of a skin flap onto an ulcerated defect without any preliminary dissection of the ulcer. This operation is recommended when LRI is localised on the face, fingers or if major arteries, nerves or tendons are located at the base of the ulcer. For the successful survival of a skin flap, the surface of the ulcer should be prepared for transplantation (treatment with vasoactive drugs and local application of agents to clean the surface of the ulcer). The best time for such an operation is after full ulcer cleansing and the appearance of bright-red granulation tissue. Sutures are removed on days 12-14 after surgery and the flap stem is dissected on day 20. According to available experience a free divided skin flap does not always prevent the development of late radiation ulcers.

3. Amputation of damaged part of extremities is carried out in cases of dry gangrene, large necroses of soft tissues with bones opening. The level of amputation depends on the localisation and area of destruction and on the possibility of creating the most favourable conditions for the formation of a viable amputation stump, considering future prosthetics.

4. Necrotomy with skin transplants.

a) free skin graft
b) multilayered pedical skin flap
c) skin-muscular flaps on vascular pedicule (microsurgical method)

Since 1990 the Department of Plastic and Reconstructive Microsurgery of the Russian Academy of Medical Sciences have used microsurgical techniques in association with operations on 7 patients with LRI who had ulcerative and necrotic skin defects at late

times after exposure. In 4 patients, LRI resulted from accidental gamma-irradiation. The absorbed radiation doses varied from 20 to 60 Gy. As the patients had multiple skin lesions, operations were performed in stages. The results of the operations were evaluated by defects healing and recovery of hand function. Substantial increases in hand functional activity were seen as well as the social rehabilitation of the patients.

LRI of the mild and moderate degree (Grades I and II) can be treated using conservative approaches. Such conservative therapies are subdivided into general and local methods. It is the view of the Moscow group that the most effective means of local therapy in cases of LRI, of Grade I-II, are preparations giving the opportunity to use 'blister cover' as a natural barrier to secure against wound infection and to allow the re-epithelization of the eroded surfaces situated under the skin blister. Therefore, we have investigated the effectiveness of a Lioxasol preparation in victims of LRI of the mild and moderate degree of severity.

2. Treatment of LRI with topical application of Lioxasol:

A Lioxasol preparation, in the form of an alcohol aerosol, has been developed at Hospital 6 in Moascow. This compound has been widely used, topically, in the treatment of acute local radiation injuries during the last decade. This was carried out as part of the routine treatment in that hospital and unfortunately, there is no independent study to demonstrate the effectiveness of Lioxasol. This paper reports the results of the clinical course of LRI in patients who received Lioxasol as part of their treatment compared with those patients who did not receive Lioxasol. The analysis of the clinical course of LRI includes the time of occurrence, time to re-epithelisation of radiation ulcers and the duration of the clinical manifestation of lesions.

There were some difficulties in finding appropriate control patients for some historical reasons. Developments in the nuclear industry and improvements in radiation protection for radiation workers has produced a change in the type of radiation accidents during recent years. In the early periods (1955-1977) local exposures were dominated by accidents with unsealed sources (compounds of radium and nuclear fuel fission products), whereas in the later periods (1980-1992) cases of accidental local exposure were caused by sealed industrial radiography sources (Ir-192, Cs-137). These different types of casualties caused some difficulties in compiling comparable study groups with similar exposure characteristics. The selection of patients was carried out using the following criteria:

- radiation type (taking into account the radiation quality and energy).
- exposure dose or degree of severity of the lesion: if the severity of the lesion was not compatible with the calculated dose clinical assessment was accepted.
- localisation: area effected by local radiation injuries (hands, upper extremities).

1. Effectiveness of Lioxasol in the treatment of LRI caused by local gamma exposure

The multiple origin of the criteria given above caused relatively small numbers of patients to be selected for the control and Lioxasol treated groups. Lioxasol group consisted of 11 patients who suffered from local radiation injury of Grade I-III. The

Table 4. Characteristics of patients with LRI caused by local gamma exposure, who received Lioxasol as part of their treatment.

Patient No.	Patient age at accident (years)	Year of accident	Source	Radiation	Exposure dose (Gy)		Reaction grade	Localisation of LRI	Latency before clinical manifestation (days)	Time to re-epithelisation (days)	Duration of clinical manifestation (days)
					calculated	clinical					
1	52	1988	Sr-Y-90	gamma-beta	-	20	I-II	1st, 2nd finger right hand	12	34	22
2	31	1982	Cs-137	gamma	25	25	II-III	1st - 3rd finger right hand	8	59	51
3	18	1991	Cs-137	gamma	16	16	I-II	1st - 3rd finger right hand	16	30	14
3	45	1982	Co-60	gamma	30	30	II-III	1st, 2nd finger left hand	11	46	35
5	24	1989	Ir-192	gamma	50	25	II	1st - 3rd finger right hand	10	60	50
6	43	1982	Co-60	gamma	25	25	I-II	1st, 2nd finger right hand	10	30	20
7	50	1990	Ir-192	gamma	7	15	I-II	right hand	18	43	25
8	60	1992	Ir-192	gamma	10	15	II	2nd, 3rd finger left hand	13	32	19
9	57	1982	Co-60	gamma	20	20	I-II	1st, 2nd finger right hand	10	62	52
10	45	1984	Ir-192	gamma	280	20	I-II	1st - 3rd finger right hand	10	32	22
11	49	1984	Ir-192	gamma	65	18	I-II	1st, 2nd finger right hand	10	54	44
								Mean (± SE)	11.6±0.9	43.8±3.7	32.2±4.2

control group also included 11 patients who suffered from local radiation injury of Grade I-III caused by gamma radiation between 1951 and 1974.

Lioxasol group: local application of Lioxasol from day 6 to day 26 (100% of cases), Ozocerite (45% of cases), Hippophae oil (9% of cases), Rivanolum (9% of cases), anti-burn ointment (9% of cases), DNA with Dioxidinum (9% of cases), electric puncture (9% of cases), systemic applications of: Solcoseril i.m. (45% of cases), Trental i.v. (45% of cases), Hyperbaric oxigenation (36% of cases), Complamin i.v. (9% of cases), vitamins B-1, B-6, and C i.m. (18% of cases), H Hemodez i.v. (18% of cases), Contrical i.v. (9% of cases), Troxevasinum p.o. (9% of cases), Curantilum p.o. (9% of cases), Cinnarisinum p.o. (9% of cases). A description of these patients is given in Table 4.

Control group: local applications of Cintomicinum emulsion (36% of cases), Sintoson (27% of cases), Rivanolum (18% of cases), peach oil (18%), Lanolin (18% of cases), Locacorten (9% of cases), glycerine (9% of cases), Hippophae oil (9% of cases), Furacilinum (9% of cases), paraffin baths (9% of cases); systemic application of: vitamin B-1 i.m. (36% of cases), polivitamins p.o. (27% of cases), vitamin C i.m. (18% of cases), Nikoshpan p.o. (18% of cases), Galidore p.o. (18% of cases), Glivenol p.o. (9% of cases), hyaloid i.m. (9% of cases), Neocompemsan i.v. (9% of cases), vitamin A p.o. (9% of cases). A description of these patients is given in Table 5.

The latency period for the clinical manifestation of LRI was 11.6 ± 0.9 days in the Lioxasol group. This was found to be longer than 7.5 ± 1.4 days in the control group. This difference was statistically significant ($p<0.05$). The time taken for the re-epithelisation of skin lesions was 43.8 ± 3.7 days and 54.9 ± 8.3 days in Lioxasol and control groups, respectively. Although the time taken for the re-epithelialisation of skin lesions after exposure was shorter in Lioxasol group the difference did not prove to be statistically significant ($p = 0.2$). This was also true for duration of the clinical manifestation of the reaction ($p = 0.1$).

2. Effectiveness of Lioxasol in LRI caused by local beta exposure:

Here the Lioxasol treatment group consisted of patients with acute radiation syndrome (ARS) from the Chernobyl accident whose lesions were caused by beta irradiation. A major difficulty associated with patient selection was the assessment of physical dose to the skin of these patients. This was due to the following reasons:

- beta-radiation intensity was unknown and/or rapidly changing depending on the time and distance from the radiation source. These included those changes caused by decontamination procedures.
- the presence of short-lived beta emitters, which were not taken into account.
- uncertainty associated with the exposure time.

Therefore, patient selection was based mainly on the clinical assessment and the severity of skin lesion.

Lioxasol group comprised of 8 patients with Grade II ARS caused by relatively uniform gamma exposure. All patients were observed to have LRI of the skin of Grade I-II caused by beta-gamma exposure. The characteristics of this group of patients are given in Table 6.

Table 5. Characteristics of patients with LRI caused by local gamma exposure who did not receive Lioxasol as part of their treatment.

Patient No.	Patient age at accident (years)	Year of accident	Source	Radiation	Exposure dose (Gy)		Reaction grade	Localisation of LRI	Latency before clinical manifestation (days)	Time to re-epithelisation (days)	Duration of clinical manifestation (days)
					calculated	clinical					
1	25	1951	Uranium fission products	gamma	10	25	II-III	hands	5	100	95
2	24	1958	Br-82	gamma	10	15	II	right hand	13	41	28
3	31	1974	Rn-106	gamma	20	20	II	1st finger right hand	1	20	19
3	26	1969	Uranium fission products	gamma	15	15	II	hands	10	54	44
5	30	1973	Co-60	gamma	30	30	I-II	1st - 3rd finger left hand; 1st, 2nd finger right hand	5	31	26
6	28	1967	Co-60	gamma	20	20	II-III	hands	5	90	85
7	28	1957	Ra-224	gamma	20	20	II	1st, 2nd finger left hand	1	38	37
8	23	1974	Uranium fission products	gamma-beta	20	20	I-II	hands	13	33	20
9	34	1968	Sc-46	gamma	15	15	II-III	left hand	14	87	73
10	22	1971	Uranium fission products	gamma	30	30	II	hands	6	30	24
11	34	1968	Brem-stralen	gamma	20	20	II	1st finger left hand	10	80	70
								Mean (± SE)	7.5±1.4	54.9±8.3	47.4±8.1

Table 6. Characteristics of patients with ARS caused by relatively uniform gamma exposure and with LRI caused by local gamma-beta exposure (Chernobyl, 1986) receiving Lioxasol.

Patient No.	Patient age at accident (years)	Radiation	Exposure dose (Gy)		ARS grade	Acute LRI grade and area of skin damage (%)	Localisation of LRI	Time to re-epithelisation of radiation ulcers or start of pilation (days)
			calculated	clinical				
1	37	gamma-beta	10	25	II	1 - 15%	face, hands, lower legs	34
2	36	gamma-beta	10	15	II	1 - 20%	face, breast, lower legs, buttocks	19
						2 - 1%		
3	64	gamma-beta	20	20	II	1 - 5%	face, neck	17
3	27	gamma-beta	15	15	II	1 - 20%	face, neck, breast, feet, lower legs, thighs	39
						2 - 2%		
5	55	gamma-beta	30	30	II	1 - 12%	face, neck, breast, lower legs, buttocks	25
6	39	gamma-beta	20	20	II	1 - 12%	face,neck, breast, lower legs	12
7	35	gamma-beta	20	20	II	1 - 10%	neck, face, hands, forearms, lower legs	23
8	30	gamma-beta	20	20	II	1 - 6%	breast, hands, forearms, feet	34
						2 - 6%		
							Mean (± SE)	25.4±3.1

Table 7. Characteristics of patients with ARS caused by relatively uniform gamma exposure, and with LRI caused by local gamma-beta exposure, not receiving Lioxasol as a component of their treatment.

Patient No.	Patient age at accident (years)	Year of accident	Radiation	ARS degree of severety	Acute LRI, degree of severety and area of radiation skin damage	Localisation of LRI	Time to re-epithelisation of radiation ulcers or start of pilation (days)
1	37	1956	gamma-beta	II	I - 25% 2 -3 %	face, inner hand, forearms, inner elbows	40
2	36	1970	gamma-beta	II	1 - 30% 2 - 5%	face, hands, forearms, thighs	30
3	64	1956	gamma-beta	II	1 - 6%	face, inner hands	18
3	27	1956	gamma-beta	II	1 - 14%	hands, lower thirds of forearms, face	20
5	55	1956	gamma-beta	II	1 - 15%	face, neck, breast, hands	20
6	39	1956	gamma-beta	II	1 - 8%	face, hands	19
7	35	1970	gamma-beta	II	1 - 35% 2 - 15%	neck, face, right hand, back, abdomen, breast, legs	60
8	30	1956	gamma-beta	II	1 - 9%	face, hands, elbows	19
						Mean ± SE	28.3 ±4.9

The control group was also comprised of 8 patients suffering from Grade II ARS (7 patients) and Grade I (1 patient) caused by a relatively uniform external gamma-beta exposures between 1956 and 1970. All patients entered in control group also had gamma-beta skin lesions of Grade I and II (Table 7). Average area of Grade I and II injured surface of skin was similar in both groups.

The appearent difference between times to re-epithelisation of 25.3 ± 3.1 days in Lioxasol group and 28.3 ± 5.3 days in control group was not significantly different ($p>0.05$). However, it must be borne in mind that both control and Lioxasol patients received other treatments too. The true effect of Lioxasol could be better determined in an experimental set up where comparable groups of animals could be treated with Lioxasol only.

3. Experimental investigation of the effectiveness of topical application of Lioxasol on radiation damage:

1. Animal model

Acute radiation-induced damage to pig skin can best be quantified by assessing the dose-related incidence of moist desquamation, an easily recognised clinical change in the appearance of the skin. After beta-irradiation from standard 22.5 mm diameter $^{90}Sr/^{90}Y$ plaques (dose-rate ~3 Gy/min), the dose associated with a 50% incidence of the effect (ED_{50} ±SE) following an acute single exposure is 27.3 ± 0.5 Gy [2, 3]. The latency period for the first appearance of this effect (4.75 ± 0.16 weeks) at least for doses of 22 - 45 Gy, is independent of the level of the radiation dose. The severity of moist desquamation and hence the time taken for a desquamated area to heal is dose-related. This model was used to study the effectiveness of the topical application of Lioxasol.

2. Topical application of Lioxasol:

For these studies 22.5 mm diameter sites were irradiated with a single dose of 35 Gy or 65 Gy of β-rays from $^{90}Sr/^{90}Y$ plaques.

After irradiation skin sites were sprayed twice daily with the aerosol form of Lioxasol and sites allowed to dry. Treatment with Lioxasol was stopped when skin sites developed moist desquamation. The effects of Lioxasol treatment, as compared with untreated skin sites, on the opposite flank of two pigs, are shown in Table 8.

Table 8. Effects of Lioxasol treatment as the latency and healing of moist desquamation in pig skin after irradiation with 35 Gy of $^{90}Sr/^{90}Y$ ß-rays.

	Lioxasol sites	Control sites
Latency (wks)	5.53 ± 0.18	5.07 ± 0.17
Healing time (wks)	>2.0 ± 0.46	>4.37 ± 0.64
Sites unhealed at 11 wks	1/15	5/15
Sites healed after 3 wks	12/15	4/15

Treatment with Lioxasol slightly, but significantly, delayed the time of onset of moist desquamation by 3-4 days ($p<0.05$). The delay in the clinical manifestation of skin damage was also approximately 4 days in accident cases after gamma-irradiation. The marked reduction in the healing time for moist desquamation was somewhat difficult to interpret since some sites remained unhealed 11 weeks after irradiation when the study was completed. However, assessment of the number of sites, healed after 3 weeks, which was 80 ± 10.3% in the Lioxasol treated group and only 26.7 ± 11.4% in the control group was highly significant. ($p<0.01$).

Following the higher dose of 65 Gy to pig skin Lioxasol had no significant effect in the latency for the appearance of moist desquamation after irradiation and on the very delayed healing of this reaction.

4. Effects of Lioxasol on the cell proliferation kinetics of pig skin:

In addition to quantifying the effectiveness of the above treatment protocol, it was also envisaged that studies in animals might be used to determine possible mechanisms of action of the therapeutic procedure. In this respect, experiments were designed to determine the effects of Lioxasol on the proliferation kinetics of basal cells in the epidermis of pig skin. The response of this cell population is the key to responses of the skin. Counts of the number of labelled cells, endothelial and fibroblasts, were also made in the papillary dermis.

Lioxasol was applied topically, twice daily, to unirradiated skin. The experimental findings related to labelling index of the epidermal basal cell layer and the number of labelled cells/mm^2 in the papillary dermis are given in Table 9.

Table 9. Basal layer labelling index (±SE) of pig epidermis and in the papillary dermis at various times after the topical administration of Lioxasol.

Time after compound administration (weeks)	Basal layer labelling index (%)	Labelled cells/mm^2 Papillary dermis
0	8.4 ± 0.4	14.3 ± 0.6
2	10.8 ± 0.4	22.6 ± 1.5
4	11.2 ± 0.3	21.7 ± 1.8
6	10.9 ± 0.6	20.4 ± 1.2
10	11.3 ± 0.7	20.5 ± 1.2

A clearly defined enhancement of cell proliferative activity in the basal layer was demonstrated in pig skin after the administration of Lioxasol. This peaked at a level that was ~29% higher than controls, at 2 weeks after the start of administration. Thereafter, the labelling index remained relatively constant. There was no quantifiable evidence of hyperplasia in the epidermis after the topical application of Lioxasol.

Cell proliferative activity was also accentuated in the papillary dermis. Changes in number of labelled papillary dermal cells paralleled those for the epidermal labelling index (Table 9). Peak values for labelled papillary dermal cells were in the range ~20-22 per mm^2.

The time taken for radiation-induced moist desquamation to heal (4 to 5 weeks in control pigs) was reduced in pigs receiving Lioxasol. This enhanced healing response was

probably related, at least in part, to the acceleration in epidermal cell proliferation induced by the compound.

References

[1] A. Barabanova & D.P. Osanov: Int. J. Radiat. Biol. 57, 775-782, 1990
[2] G.J.M.J. van den Aardweg, J.W. Hopewell and R.H. Simmonds: Radiotherapy & Oncology 11:73-82, 1988
[3] J.W. Hopewell and G.J.M.J. van den Aardweg Int. J. Radiat. Oncol. Biol. Phys. 14:1047-1050, 1988