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ORIGINAL ARTICLE

The preventive effect of *N*-acetylcysteine on radiation-induced dermatitis in a rat model

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Summary

Purpose: *We investigated the potential radioprotective effects of N-acetylcysteine (NAC) comparing its effects with that of amifostine (WR-2721), as a representative of clinically used radioprotector, in ameliorating skin injury from irradiation in rats (single dose, 18 Gy to the left hind legs of the rats).*

Methods: *The rats (n=28) were divided randomly and equally into 4 groups: Control (C), Radiation (R), R+WR-2721 (received irradiation and 200 mg/kg of WR-2721) and R+NAC (received irradiation and 1000 mg/kg of NAC). Acute skin reactions were assessed every 3 days by a radiation oncologist and a biophysicist. Light microscopic findings were assessed by an expert pathologist.*

Results: *Clinically and histopathologically, irradiation increased dermatitis when compared with the control group ($p < 0.05$). The severity of radiodermatitis of the rats in the R+NAC and R+WR-2721 groups was significantly lower than in the R group ($p < 0.05$). The protective effects of NAC and WR-2721 on irradiation – increased dermatitis were clinically and histopathologically similar ($p > 0.05$).*

Conclusion: *The study gives clues about the beneficial effects of NAC against radiation-induced dermatitis.*

Key words: *N*-acetylcysteine, radiodermatitis, WR-2721

Introduction

Radiotherapy is an effective modality for cancers. The therapeutic benefit of radiotherapy is limited by radiation-induced skin injuries, which include erythema, dry and moist desquamation, necrosis, ulceration, and/or fibrosis [1]. Most cell damages caused by ionizing radiation are also mediated by reactive oxygen species (ROS) generated from the interaction between radiation and water molecules in cells [2]. Reduced glutathione (GSH), as a multifunctional intracellular non-enzymatic antioxidant, is considered to be the major thiol-disulphide redox buffer of the cell [3].

Studies on various thiol radioprotectants such as WR-2721 (amifostine) have demonstrated preventing properties on radiation-induced damage to the intestinal epithelial and stem cells and skin [4,5]. The suggested mechanisms of sulfhydryl compounds are free-radical scavenging and the facilitation of direct chemical repair at sites of DNA damage by hydrogen atom donation [6,7]. Recently, NAC has been found to protect against several types of ultraviolet radiation (UV) damage on epidermal DNA [8,9]. The protective effects appeared to be based on the ability of NAC to increase GSH levels and probably to neutralize ultraviolet B (UVB) induced reactive species. NAC was selected for our study depending on the results of these studies and its proved safety in humans [10,11].

In the present study, it was investigated whether the application of NAC was effective against gamma irradiation-induced radiodermatitis. Secondly, its effect was compared with that of amifostine**,** as a representative of clinically used radioprotector.

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Methods

Animals

Twenty-eight healthy adult female Wistar rats (Gaziantep University, Faculty of Medicine, Experimental Medicine Research Unit; 8 weeks of age, with average body weight of 170 ± 20 g) were used. All procedures in this study were performed in accordance with the guidelines of the National Institutes of Health for the care and use of laboratory animals and were also approved by the Institutional Animal Care and Use Committee in the Faculty of Medicine at Gaziantep University.

Experimental design

The rats were divided randomly into 4 equal-size groups (7 rats per group), namely, Control (C), Irradiation (R), Irradiation + WR-2721 (R+WR-2721), and Irradiation + NAC (R+NAC) groups. C rats received neither radioprotector nor irradiation, but 2.2 ml of saline were injected intraperitoneally (i.p.). All groups but C (R, R+NAC and R+WR-2721) received gamma irradiation as a single dose of 18 Gy to their left hind legs. Besides irradiation, R rats received 2.2 ml of saline (i.p.), while the R+NAC and R+WR-2721 rats received 1000 mg/kg (i.p.) NAC (containing 300 mg of *N*-acetylcysteine; Asist ampul, Husnu Arsan Ilac, Istanbul, Turkey) and 200 mg/kg (i.p.) WR-2721 (containing 500 mg of amifostine, Ethyol flacon; Er-Kim Ilac, Istanbul, Turkey), respectively. Saline, NAC and WR-2721 injections in the study groups were given 15 min before irradiation. The doses of drugs were chosen according to previous studies [6,12,13]. All rats were irradiated under anesthesia (Ketalar 50 mg/kg i.m., Eczacibasi, Turkey). A cobalt-60 teletherapy unit (Shandong Xinhua SCC-8000F, China) was used for all irradiations. The dose rate was 1.80 Gy/min at a distance of 80 cm. Rats were placed on Plexiglas tray in supine position and irradiated using 2 opposite (anterior and posterior) fields. The dose was calculated at the depth of 1 cm on the left hind leg. The radiation field was shielded with lead blocks to reduce the dose to the rest of the body.

Scoring system of skin lesions

Skin reactions were scored every 3 days by a radiation oncologist according to the scale proposed by Abe et al. and other investigators [14-18]. The lesions were scored as follows: 0, normal; 0.5, slight epilation; 1, epilation in about 50% area; 1.5, epilation > 50% area; 2, complete epilation; 2.5, complete epilation with definite edema or dry desquamation in > 50% area; 3, moist desquamation in a small area; and 3.5, moist desquamation in most of the irradiated area.

Skin biopsies, tissue preparation, and histological examination

The study was terminated by sacrificing the rats under Ketalar (Eczacibasi, Turkey) anesthesia (50 mg/kg, intramuscularly) 45 days after irradiation. Skin samples 10 mm × 10 mm were taken for biopsies from the center of the skin flap and corresponding to the central area of the lesion of the left hind legs. The tissue samples were fixed in 10% formaldehyde and embedded in paraffin for histological assessments. Five-micrometer-thick slices from skin biopsies were stained with hematoxylin and eosin for evaluation with light microscopy according to standard procedures. Slides were examined blindly by an experienced pathologist. Damaged areas were scored using a damage score (epidermal atrophy, findings of dermal degeneration such as edema and collagen fiber loss, and hair follicle atrophy) in terms of percentages. The scale used 5 defined damage levels as follows: 0, normal; 1, minimal; 2, mild; 3, moderate; 4, marked; and 5, severe. The semiquantitative scores reflected the population examined as follows: 1, < 5%; 2, 6-20%; 3, 21-50%; 4, 51-75%; and 5, 76-100%. These methods were also referred to in previous studies [14,16,19].

Statistical analysis

Descriptive values of data were represented as mean ± standard deviation (S.D.). Statistical analysis was performed by using the ANOVA test followed by the Tukey HSD post hoc test, after checking for normal distribution with Kolmogorov-Smirnov test. A p-value <0.05 was considered significant and, in all calculations, the SPSS (v 11.5; Lead Technologies, Inc., USA) program was used.

Results

Skin score

Slight epilation (score 0.5) developed as of the 6th day postirradiation in the R and R+NAC groups in 1 of 7 rats in each group. It began in 1 of 7 rats in R+WR-2721 group on day 9, and on the 9th day 0.5 dermatitis score developed in 2 of 7 rats in the R group and only in 1 of 7 rats in each of the R +NAC and R+WR-2721 groups. Score 1 dermatitis (epilation in an about 50% area) be-

gan in 3 of 7 rats and score 1.5 dermatitis (epilation > 50% area) in 1 of 7 rats in the R group on day 18. Score 1 dermatitis developed in 3 of 7 rats in the R+NAC group on day 18. No score 1 lesions were seen in the R+WR-2721 group on the 18th day (score 0.5 developed in 5 animals); score 1 lesion developed in 3 of 7 rats in this group on the 24th day. Epilation >50% area (score 1.5) developed as of the 24th day postirradiation in the R and R+NAC groups (in 4 and 3 of 7 rats in the groups, respectively). However, in the R+WR-2721 group it began on day 27 (in 1 of 7 rats). Complete epilation (score 2) became evident in the R group on the 30th day (in 1 of 7 rats), whereas in the R+NAC group on day 39 (in 1 of 7 rats) and in the R+WR-2721 group on day 45 (in 1 of 7 rats). In the R group score 2.5 dermatitis (complete epilation with definite edema or dry desquamation in >50% area) began in 2 of 7 rats on day 36. Nevertheless, in the R+NAC group it began on the 42nd day (in 1 of 7 rats) and in the R+WR-2721 group on the 45th day (in 1 of 7 rats). Score 3 dermatitis (moist desquamation in a small area) developed as of the 39th day postirradiation in the R group in 2 of 7 rats. No moist desquamation developed in the WR-2721 and NAC groups. Score 3.5 dermatitis (moist desquamation in most of the irradiated area) became evident only in the R group on day 42 (in 2 of 7 rats).

The difference among groups in terms of the severity of radiodermatitis began to become evident on the 18th day (Figure 1). The radiodermatitis mean scores of the groups displayed a statistical difference on the 36th day. The mean score value of R+WR-2721 groups was significantly lower than that of the R group ($p < 0.05$). At the end of the study, on the 45th day, the mean damage scores of both R+NAC and R+WR-2721 groups were significantly lower than those of the R group ($p < 0.01$; Figure 2).

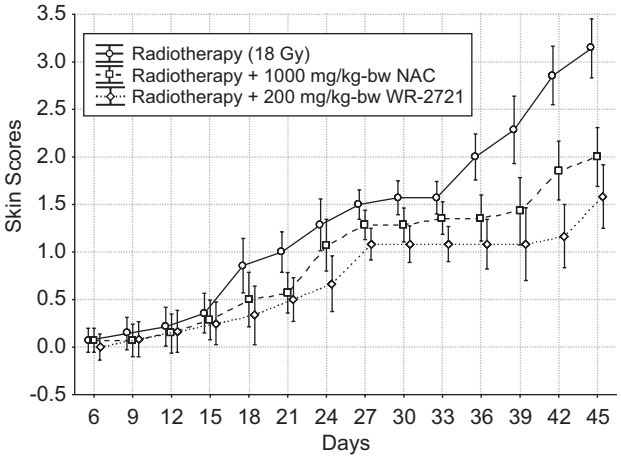

Figure 1. The time courses of the mean clinical skin score after 18Gy irradiation. Each data point (±SE) represents an average of 7 rats.

Histopathological assessments

The histopathological findings in terms of epidermal atrophy, dermal degeneration and hair follicle atrophy are summarized in Table 1. We found a significant difference between R and C rats with respect to the investigated histopathological parameters ($p < 0.05$). Following the application of NAC and WR-2721, there was a marked decrease in the mean values of histopathological parameters in both R+NAC and R+WR-2721 groups when compared to the R group ($p < 0.05$). The mean values of the R+WR-2721 groups were not significantly different from those of the C rats ($p > 0.05$). With the application of NAC, a significant dermal protection was observed in the R+NAC groups in comparison to the R group. In this group, unlike the results of WR-2721 treatment, hair follicle atrophy increased slightly when compared to the C group, and there was no difference in terms of dermal degeneration and epidermal atrophy ($p < 0.05$ and $p > 0.05$, respectively; Figure 2). When R+NAC and R+WR-2721 groups were compared, no statistical difference was present with respect to the 3 histopathological parameters.

Discussion

A considerable proportion of the radiation injuries and, therefore, the temporary treatment discontinuation encountered during external radiotherapy, are related to skin damage [20-22]. Erythema occurs in the second to third week of a fractionated course of radiotherapy, followed by dry and moist desquamation due to the depletion of the basal stem-cell population; when severe, moist desquamation may lead to ulceration.

Table 1. Histopathological values in all groups (mean ± SD)

Groups (n =7 for each group)	*Histopathological values*		
	Epidermal atrophy	*Dermal degeneration*	*Hair follicle atrophy*
C	0	0	0
R	4.57 ± 0.53^{a}	4.71 ± 0.49^{a}	4.71 ± 0.49^{a}
R+WR-2721	0^{b}	0.29 ± 0.49^{b}	0.71 ± 0.75^{b}
R+NAC	0^{b}	0.57 ± 0.53^{b}	$1.29 \pm 1.11^{a,b}$

WR-2721: amifostine, NAC: *N*-acetylcysteine, C: control rats treated with 2.2 ml of saline; R: radiation group received 18 Gy of gamma irradiation to the left hind legs and was treated with 2.2 ml of saline; R+WR-2721: rats exposed to the same irradiation procedure as R rats and treated with 200 mg/kg-BW WR-2721; R+NAC: rats exposed to the same irradiation procedure as R rats and treated with 1000 mg/kg-BW NAC. All values are mean± standard deviation. Statistical analysis was performed using ANOVA test followed by Tukey HSD post hoc test, after checking for normal distribution with Kolmogorov-Smirnov test. [a]Compared to C rats, [b]Compared to R rats; $p < 0.05$. All histological values of the R+NAC and R+WR-2721 rats were not significantly different ($p > 0.05$). The scale used 5 defined damage levels: 0: normal; 1: minimal; 2: mild; 3: moderate; 4: marked; and 5: severe

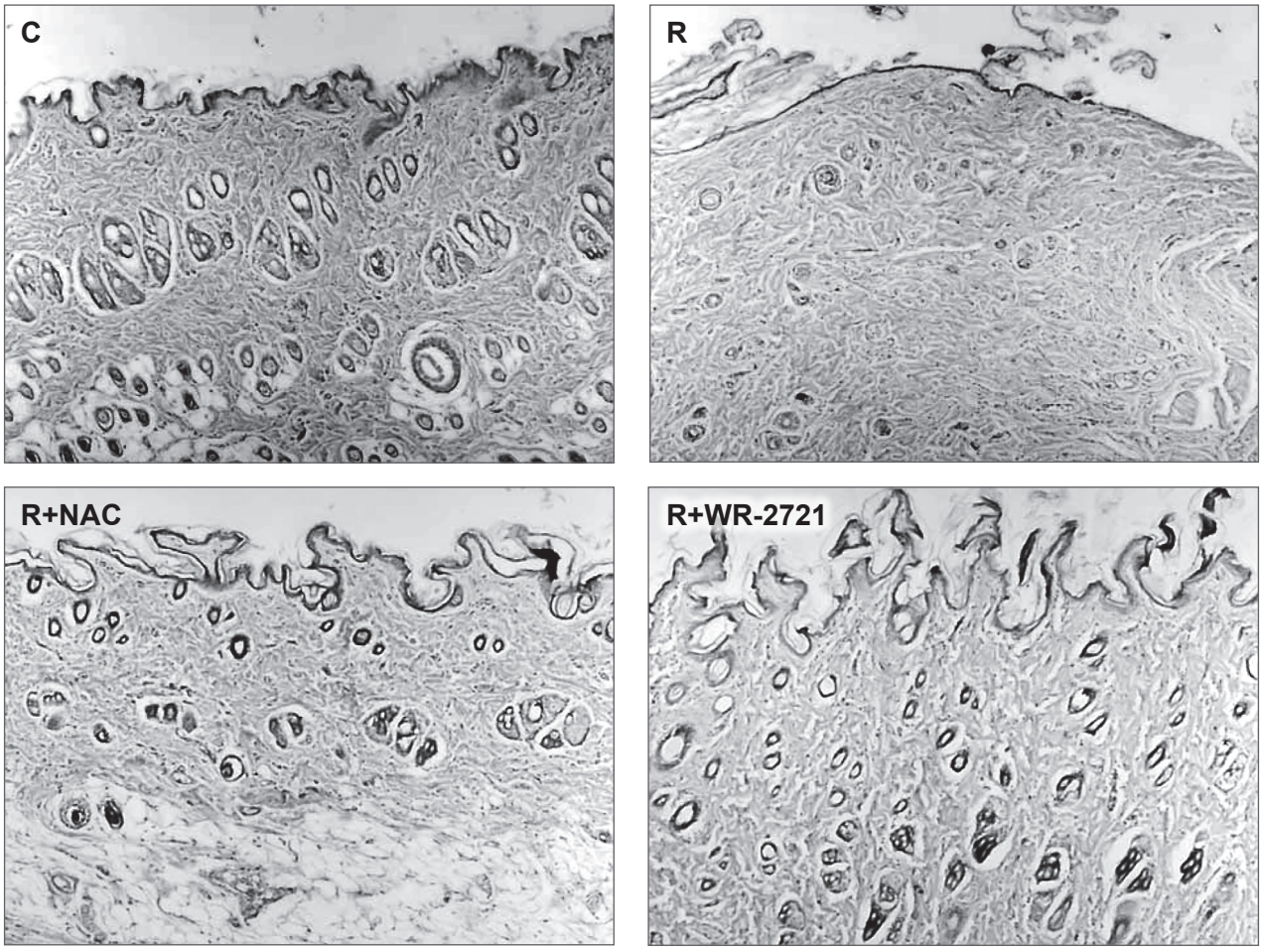

Figure 2. Histological images of all groups in the present study. **C:** Control: skin and skin appendices with normal appearance in the control group. Epidermis, dermis and hair follicles were normal. **R:** Radiation damage on the skin of the radiation group. Epidermal atrophy, dermal degeneration and hair follicle atrophy were observed. **R+NAC** and **R+WR-2721:** The skin was partially protected against the effects caused by radiation in the R+NAC and R+WR-2721 groups. Epidermal atrophy, dermal degeneration and hair follicle atrophy were slight and obscure (H&E ×10).

Thiol supplementation to maintain tissue redox balance has been investigated, but its toxic side effects in both animal and cell models have limited its application [23,24]. There is currently much concern in procedures that replenish cellular GSH because of raising evidence that GSH plays a principal role in the endogenous defense in the protection of cells against damage by radiation and by reactive oxygen compounds and other toxic substances [2,8,25]. It has been reported that NAC is capable of replenishing intracellular GSH by reducing extracellular cystine to cysteine [26], or by supplying sulfhydryl (–SH) groups that can stimulate GSH synthesis [27], and also it is a potent free radical scavenger as a consequence of its nucleophilic reactions with ROS [28,29].

In the study of Reliene et al., dietary supplementation with NAC was shown to suppress carcinogenesis-associated DNA deletions and oxidative DNA damage in Atm-deficient mice [30]. On the other hand, NAC was able to produce apoptosis in transformed cells but not in normal cells [29]. In previous studies, related mostly with UVA**,** the efficacy of NAC in protecting human cells from irradiation has been indicated [9,31]. Our study was designed on the basis of the antioxidant effect of NAC, proved in case of oxidative stress in previous studies. The present study showed the protection of NAC against radiation-induced dermatitis. The results obtained with NAC might be compared with that of WR-2721.

UV-related carcinogenesis involves depletion of antioxidants and glutathione in skin cells. The protective effect of NAC on the UVB-induced inhibition of epidermal DNA synthesis in rat skin was shown [9]. The similarities in the pathophysiological mechanisms connected with the dermatitis produced by UV exposure as well as gamma-radiation suggested that NAC might be used in the protection against therapeutic irradiation [31].

The protective effect of amifostine is based on

scavenging free radicals and donating hydrogen ions for DNA repair [6,32,33]. However, its toxicity and requirement to be present at the time of irradiation in order to be effective limit its clinical use [32,33]. The radioprotective effect of WR-2721 observed in this study is in parallel to the results of similar clinical studies in the literature. Geng et al. showed that both systemic and topical applications of the prostaglandin E2 or WR-2721 enhanced hair regrowth following radiation [34]. In other randomized studies, it is reported that additional amifostine caused less skin lesions in rectal and gynaecological cancer patients [5,35]. In this study, it may be said that the preliminary findings about the radioprotective effects of NAC on skin were close to those of WR-2721.

There is a small number of studies involving both WR-2721 and NAC [36,37]. Despite some arguments, it can be said that our results are in parallel to the results of the aforementioned studies [37,38]. On the other hand, in the study of Verhey and Sedlacek, WR-2721 and NAC were tested for their ability to protect the normal skin of the mice against damage from single doses of 137Cs radiation and no significant protection was observed [39]. Although in our study it was observed that treatment with WR-2721 provided a slightly better radioprotection than treatment with NAC by the methods of clinical scoring and histopathological assessment, no statistically significant difference could be found between these two agents. As a result, both agents showed a protective effect against radiation-induced skin damage. However, the difference between the results of Verhey and Sedlacek's study and ours may have been due to the different ways of administration of the drugs (topical vs. i.p.).

In other studies on radiodermatitis, investigators used the same damage scoring system with ours but different radioprotectors and radiation doses [16,40]. Thus, even though the dermal protective effect of different radioprotectors was shown in the studies mentioned, it is difficult to compare the results of these studies with ours due to the above-mentioned differences. For instance, Ertekin et al. reported that radiodermatitis (score 0.5) began in 7 of 10 rats in the radiotherapy group on the 3rd day post-irradiation [16]. In our study, slight epilation (score 0.5) developed as of the 6th day postirradiation in the R and R+NAC groups in 1 of 7 rats in each group. And on the 9th day, score 0.5 dermatitis developed in 2 of 7 rats in the R group and only in 1 of 7 rats in each of the R +NAC and R+WR-2721 groups. In the present study the intergroup difference became evident in favor of the radioprotectors in time. On the 45th day, which was the final day of the study, score 3.5 dermatitis developed in 4 of 7 rats in the R group and maximum score 2.5 dermatitis developed in each of the R+NAC and R+WR-2721 groups. Our histopathological findings also supported this clinical observation.

This experimental trial was designed using single-dose irradiation and limited to study skin damage parameters. Nevertheless, our results give clues about the potential radioprotective effect of NAC, shown by other authors, and it could be said that the observed effect in this study is similar to that of WR-2721. NAC, as a safe drug, has been taking a place in clinical practice for different purposes, but not as radioprotector. Further experimental trials are needed to prove this result and to rule out any potential protection of tumor cells.

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