Radioprotection of Salivary Glands by Amifostine in High-Dose Radioiodine Therapy

Karl Heinz Bohuslavizki, Winfried Brenner, Susanne Klutmann, Ralf-Harto Hübner, Stefan Lassmann, Bernd Feyerabend, Jutta Lüttges, Stephan Tinnemeyer, Malte Clausen and Eberhard Henze

Clinic of Nuclear Medicine and Department of Pathology, Christian-Albrechts-University, Kiel; and Department of Nuclear Medicine, University Hospital Eppendorf, Hamburg, Germany

Salivary gland impairment after high-dose radioiodine treatment is well recognized. Because differentiated thyroid cancer has a good prognosis, reduction of long-term side effects is important. This study investigated the radioprotective effects of amifostine in animals and humans receiving high-dose radioiodine therapy. **Methods:** Quantitative salivary gland scintigraphy was performed in five rabbits before and up to 3 mo after high-dose radioiodine therapy applying 1 GBq ^{131}I. Three animals received 200 mg/kg amifostine before high-dose radioiodine therapy, and two served as controls. All animals were examined histopathologically. Quantitative salivary gland scintigraphy also was performed in 17 patients with differentiated thyroid cancer before and 3 mo after high-dose radioiodine therapy with 6 GBq ^{131}I. Eight patients were treated with 500 mg/m^2 amifostine before high-dose radioiodine therapy, and nine served as controls. **Results:** In two control rabbits, high-dose radioiodine therapy significantly reduced parenchymal function by 63% and 46% in parotid and submandibular glands, respectively. In contrast, there was no significant decrease in parenchymal function in amifostine-treated animals. Histopathologically, lipomatosis was observed in control animals but was negligible in amifostine-treated animals. Similar findings were observed in differentiated thyroid cancer patients. In nine control patients, high-dose radioiodine therapy significantly ($p < 0.01$) reduced parenchymal function by 37% and 31% in parotid and submandibular glands, respectively. Three patients exhibited Grade I (World Health Organization) xerostomia. In contrast, there was no significant decrease in parenchymal function in amifostine-treated patients and no incidence of xerostomia. **Conclusion:** Parenchymal damage in salivary glands induced by high-dose radioiodine therapy can be reduced significantly by amifostine. This may increase the quality of life of patients with differentiated thyroid cancer.

Key Words: salivary glands; high-dose radioiodine therapy; radioprotection; amifostine

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Standard therapy in differentiated thyroid cancer requires total thyroidectomy and high-dose radioiodine therapy to completely ablate thyroid remnants. Apart from specific uptake by thyroid tissue, the beta-emitting iodine isotope ^{131}I used for radioiodine therapy is accumulated actively by an adenosine triphosphate-dependent $Na^+/K^+/2Cl^-$-cotransport due to its similar atomic diameter and its comparable electric charge (*1,2*). This causes an undesired accumulation of ^{131}I in parietal cells of the stomach, as well as in acinar cells of salivary glands. Consequently, well-recognized side effects of high-dose radioiodine therapy are transient gastritis and long-lasting xerostomia (*3–5*). Therefore, radioiodine therapy is performed under salivary gland stimulation to decrease impairment of salivary gland function (*4–8*). However, even under salivary gland-stimulating conditions, parenchymal damage could be shown after high-dose radioiodine therapy using quantitative salivary gland scintigraphy (*9–11*). Because differentiated thyroid cancer has a good prognosis, long-term side effects of high-dose radioiodine therapy become important for the patient's quality of life.

Protection of salivary gland function has been the focus of ongoing research in patients with head and neck cancer. The standard treatment of head and neck cancer includes radiotherapy used alone or with surgery. A consequence of radiation treatment is damage of normal tissues in the radiation port, in particular, the salivary glands and oral mucosa (*12*). The most common tissue effects include oral mucositis, xerostomia, dental caries and gustatory dysfunction. Amifostine, an organic thiophosphate, is the first of a new class of drugs known as cytoprotective agents in about 20 yr. Preclinical studies using a rat parotid gland model demonstrated both short- and long-term radiation protection by amifostine against radiation-induced damage (*13–16*) because amifostine is accumulated markedly in salivary glands. These findings provided the impetus for the use of amifostine in patients with head and neck cancer. There are reports of salivary gland protection in early clinical trials with amifostine (*17–19*).

Based on the early success of amifostine as a radioprotective agent in patients with head and neck cancer, it seemed worthwhile to investigate the radioprotective effect of the radical scavenger amifostine on salivary gland function after high-dose radioiodine therapy, because both external radiotherapy and radioiodine therapy cause their therapeutic effect by generating free radicals. This study was performed using both normal rabbits and patients with differentiated thyroid cancer to evaluate the effect of amifostine on salivary gland function after treatment with high-dose radioiodine therapy.

MATERIALS AND METHODS

Animal Studies

Five male New Zealand white rabbits, 3 mo old and weighing 2.5 ± 0.1 kg, were used to investigate the radioprotective effect of amifostine on salivary gland function after high-dose radioiodine therapy. Radioiodine (^{131}I) was given intravenously in a quantity of 1 GBq to ablate the thyroid and to destroy salivary gland parenchyma. Before the application of ^{131}I, all animals received 4 mg of dexamethasone (Fortecortin; Merck, Darmstadt, Germany) and 0.5 mg tropisetron (Navoban; Sandoz, Nürnberg, Germany) as an antiemetic treatment. Two groups of rabbits were evaluated in this study: three rabbits received 200 mg/kg amifostine (Ethyol; Essex, Munich, Germany) intravenously, and two rabbits serving as controls received physiological saline solution before high-dose radioiodine therapy.

Salivary gland parenchymal function was quantified using quantitative salivary gland scintigraphy before and at 4, 8 and 12 wk after the application of ^{131}I. Rabbits were placed in a prone position directly onto a low-energy, high-resolution collimator of a large-field-of-view gamma camera (Bodyscan, Siemens, Erlangen, Ger-

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For correspondence or reprints contact: Karl H. Bohuslavizki, MD, Department of Nuclear Medicine, University Hospital Eppendorf, Martinistr. 52, D-20246 Hamburg, Germany.

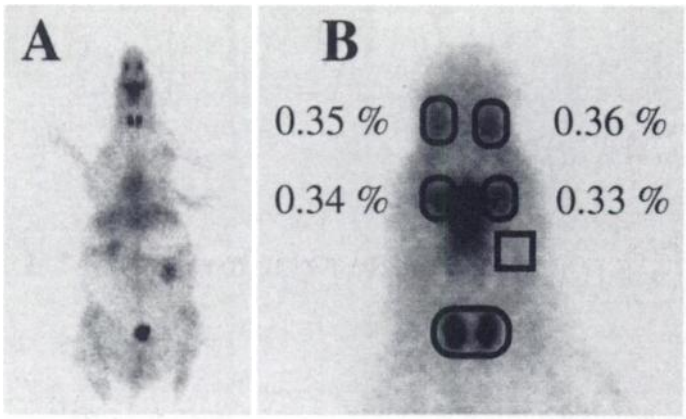

FIGURE 1. (A) Whole-body distribution of ^{99m}Tc-pertechnetate and (B) magnification of head visualizing ROIs used for quantification. Numbers represent uptake of ^{99m}Tc-pertechnetate as a percentage of injected activity in parotid and submandibular glands, respectively.

many). After injection of 100–141 MBq ^{99m}Tc-pertechnetate, sequential images of 1 min each were acquired up to 25 min and stored in a 256 × 256 matrix. Regions of interest (ROIs) used for quantification of salivary gland function included one rectangular background ROI positioned caudal to the left parotid gland and five oval ROIs positioned over both parotid and submandibular glands and the thyroid gland, respectively. The same ROIs were used for measurements performed before and after ^{131}I application. As a measure for parenchymal function, the uptake of ^{99m}Tc-pertechnetate was calculated as a percentage of injected activity. For compensation of noise and, thus, for stabilization of data, uptake was averaged from 21 to 23 min postinjection. Whole-body distribution of ^{99m}Tc-pertechnetate in a rabbit is shown in Figure 1A, and ROIs used for quantification are depicted in Figure 1B.

Twelve weeks after ^{131}I application, all animals were killed to remove salivary glands for histopathological examination. Salivary glands were stained with hematoxylin/eosin in a conventional manner. Animal studies were approved by the local government (XI 330a 72241.11-17).

Patient Studies

The radioprotective effect of amifostine on salivary gland function also was evaluated in a total of 17 patients. Six male and 11 female patients who were at least 18 yr of age and had a diagnosis of differentiated thyroid cancer, were evaluated in this inpatient study. All eligible patients received 6 GBq ^{131}I as a second treatment course 6 mo after the application of 3 GBq ^{131}I. High-dose radioiodine therapy was performed under salivary gland-stimulating conditions by peroral application of 200 mg ascorbic acid (Cebion; Merck, Darmstadt, Germany) three times per day with an addition of 1 to 2 liters of mineral water during their stay at hospital (*4,6–8*). Before the application of ^{131}I, all patients received 40 mg dexamethasone (Fortecortin) and 5 mg of tropisetron (Navoban) as an antiemetic treatment. Two groups of patients were evaluated in this study: eight patients received 500 mg/m^2 amifostine (Ethyol) intravenously before high-dose radioiodine therapy, and nine patients serving as control group received high-dose radioiodine therapy alone.

Quantitative salivary gland scintigraphy was performed in all patients before and at 3 mo after high-dose radioiodine therapy by intravenous injection of 100–120 MBq ^{99m}Tc-pertechnetate. Sequential images of 1 min each were acquired for 25 min with a conventional large field-of-view gamma camera (Gamma Diagnost Tomo; Philips, Hamburg, Germany), equipped with a low-energy, all-purpose collimator. Images were stored in a 256 × 256 matrix. Five ROIs were used for quantification of parenchymal function: one rectangular ROI in the brain serving as background ROI, and four irregular ROIs over the respective parotid and submandibular salivary glands. The same ROIs were used for measurements performed before and after radioiodine treatment. As a measure for salivary gland function, the uptake of ^{99m}Tc-pertechnetate was calculated as a percentage of the injected activity. For compensation of noise and, thus, for stabilization of data, uptake was averaged from 12 to 14 min postinjection. All investigations were approved by the local ethical committee, and all patients gave their written informed consent.

Statistics

Data are given as mean ± s.d. To evaluate statistical differences between patient subsets, a nonparametric U-test according to Wilcoxon, Mann and Whitney was used, with $p < 0.05$ considered to be statistically significant (*20*).

RESULTS

Animal Studies

Five rabbits were evaluated in this study. Three rabbits received amifostine before ^{131}I and two rabbits served as controls. After application of 1 GBq ^{131}I, both control and amifostine-treated animals exhibited ablation of the thyroid as early as 4 wk after application. This was evident from salivary gland scintigrams in which thyroid uptake of ^{99m}Tc-pertechnetate declined to almost zero (Fig. 2). In parallel, parenchymal

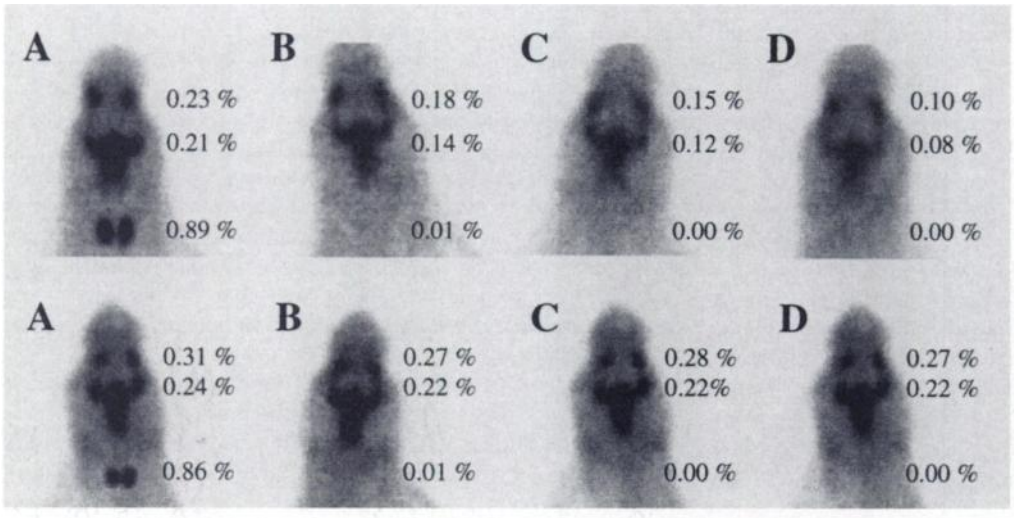

FIGURE 2. Salivary gland scintigraphy in rabbit of control group (Upper) and in rabbit of amifostine group (Lower) (A) before and (B) 4, (C) 8 and (D) 12 wk after application of 1 GBq ^{131}I. Numbers represent uptake of ^{99m}Tc-pertechnetate as a percentage of injected activity in submandibular, parotid glands and thyroid gland (from top to bottom).

TABLE 1
Uptake of Technetium-99m-Pertechnetate as a Percentage of Injected Activity Before and at 4, 8 and 12 Weeks After Application of 1 GBq Iodine-131 in Controls and in Rabbits Treated with 200 mg/kg Amifostine*

	Parotid glands		Submandibular glands	
	Mean ± s.d.	Change from baseline	Mean ± s.d.	Change from baseline
Control				
Baseline	0.226 ± 0.042	—	0.295 ± 0.070	—
4 wk	0.140 ± 0.018	38%	0.199 ± 0.046	33%
8 wk	0.106 ± 0.019	53%	0.187 ± 0.067	37%
12 wk	0.080 ± 0.011	65%	0.154 ± 0.057	48%
Amifostine-treated				
Baseline	0.241 ± 0.030	—	0.230 ± 0.074	—
4 wk	0.215 ± 0.038	11%	0.215 ± 0.060	7%
8 wk	0.209 ± 0.032	13%	0.210 ± 0.065	9%
12 wk	0.208 ± 0.023	14%	0.212 ± 0.057	8%

*Numbers represent mean of right and left parotid and submandibular glands, respectively.

function of salivary glands decreased, but not equally, between the two groups of rabbits (Table 1).

Among control animals, ^{99m}Tc-pertechnetate uptake was reduced (versus baseline) by 38%, 53% and 65% in parotid glands and by 33%, 37% and 48% in submandibular glands at 4, 8 and 12 wk after application of ^{131}I, respectively. In contrast, in amifostine-treated rabbits, ^{99m}Tc-pertechnetate uptake was reduced (versus baseline) by 11%, 13% and 14% in parotid glands and by 7%, 9% and 8% in submandibular glands at 4, 8 and 12 wk after application of ^{131}I, respectively (Fig. 3).

All five rabbits were killed at 12 wk after the application of ^{131}I. Histopathological examination of the salivary glands revealed marked differences between the two groups of rabbits (Fig. 4). Salivary glands of control rabbits exhibited more pronounced lipomatosis than those of amifostine-treated rabbits, although no signs of inflammation were noted in any of the animals.

Patient Studies

Seventeen patients with differentiated thyroid cancer and high-dose radioiodine therapy with 6 GBq ^{131}I were evaluated in this study. Nine patients received high-dose radioiodine therapy alone, and eight patients received 500 mg/m^2 amifostine before high-dose radioiodine therapy. Demographic and tumor characteristics of these patients are summarized in Tables 2 and 3, respectively, along with quantification of salivary gland parenchymal function, i.e., uptake of ^{99m}Tc-pertechnetate, at baseline and 3 mo after high-dose radioiodine therapy.

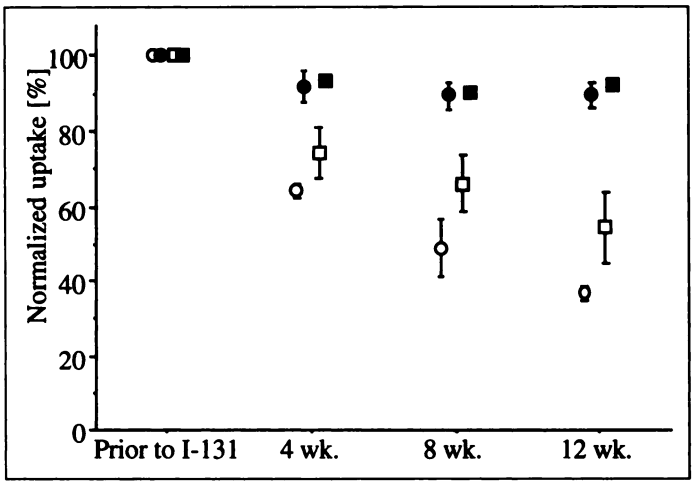

FIGURE 3. Normalized uptake of ^{99m}Tc-pertechnetate in parotid (circles) and submandibular (squares) glands of control rabbits (open symbols) and of amifostine-treated rabbits (filled symbols) before and at 4, 8 and 12 wk after application of 1 GBq ^{131}I.

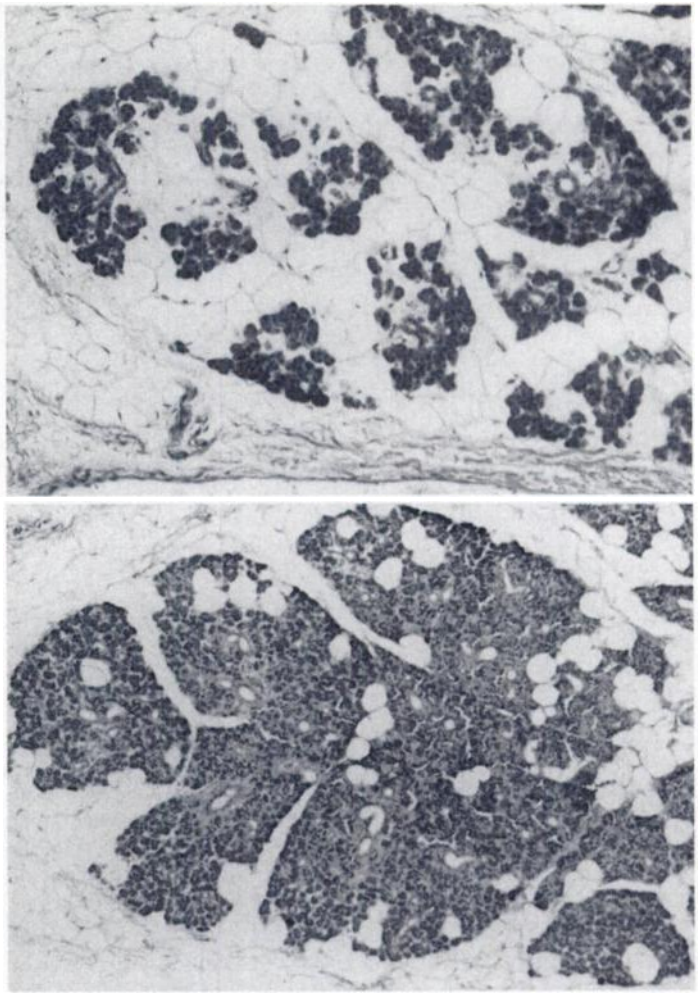

FIGURE 4. Hematoxylin/eosin-stained slices of parotid glands of control group (upper) and of amifostine-treated group (lower) 12 wk after application of 1 GBq ^{131}I. Note a significantly more pronounced lipomatosis in control animal. Magnification ×125.

In control patients, parenchymal function significantly ($p < 0.01$) decreased by 35% and 32% (from baseline) in parotid and submandibular glands, respectively (Table 2 and Fig. 5). In contrast, parenchymal function of salivary glands in amifostine-treated patients was reduced by <1% and <7% (from baseline) in parotid and submandibular glands, respectively (Table 3 and Fig. 5). This reduction was not statistically significant ($p = 0.862$).

Three patients treated with high-dose radioiodine therapy alone exhibited Grade I (World Health Organization) xerostomia versus no patients treated with amifostine. Salivary gland scintigraphy of a control patient with xerostomia revealed marked decrease (versus baseline) in ^{99m}Tc-pertechnetate uptake after 3 mo of high-dose radioiodine therapy in both parotid and submandibular glands (Fig. 6, upper). Scintigrams of an amifostine-treated patient showed little, if any, reduction in ^{99m}Tc-pertechnetate uptake versus baseline (Fig. 6, lower).

TABLE 2

Age, Sex, Histology, Tumor-Node-Metastasis (TNM) Stage, Uptake of Technetium-99m-Pertechnetate Before (Baseline) and 3 Months After 6 GBq Iodine-131 and Change of Uptake as Percentage of Pretherapeutic Uptake (Δ Uptake) in Nine Control Patients*

Patient age (yr)/sex	Histology	TNM stage	Parotid glands			Submandibular glands		
			Baseline	3 mo	Δ uptake	Baseline	3 mo	Δ uptake
19/F	Papillary	$pT_2 N_1 M_0$	0.46	0.21	54.3	0.42	0.13	69.0
41/F	Follicular	$pT_3 N_1 M_1$	0.38	0.34	10.5	0.34	0.32	5.9
37/M	Papillary	$pT_2 N_0 M_0$	0.42	0.27	35.7	0.38	0.17	55.3
55/F	Papillary	$pT_4 N_1 M_0$	0.59	0.41	30.5	0.55	0.46	16.4
40/M	Papillary	$pT_1 N_1 M_0$	0.37	0.18	51.4	0.29	0.15	48.3
65/M	Follicular	$pT_3 N_0 M_1$	0.61	0.51	16.4	0.71	0.42	40.8
39/F	Papillary	$pT_2 N_1 M_1$	0.44	0.12	72.7	0.24	0.11	54.2
52/F	Papillary	$pT_3 N_0 M_0$	0.31	0.29	6.5	0.23	0.16	30.4
43/M	Papillary	$pT_2 N_1 M_0$	0.54	0.32	40.7	0.63	0.51	19.0
Mean ± s.d.			0.46 ± 0.10	0.29 ± 0.12	35.4 ± 22.0	0.42 ± 0.17	0.27 ± 0.16	31.7 ± 21.1

*Numbers represent mean of right and left parotid and submandibular glands, respectively.

DISCUSSION

Quantitative Salivary Gland Scintigraphy

Salivary gland scintigraphy performed in a standardized method, as previously described (*21*), allows the quantitative evaluation of salivary gland parenchymal function. It is characterized both by an excellent intraindividual observer variability and reproducibility that allows the detection of changes in parenchymal function in the range of about as low as 5%–10% (*10,11*). This enables both the early detection of beginning Sjögrens syndrome by salivary gland scintigraphy, as compared with other imaging modalities (*22*), and the detection of parenchymal impairment of salivary glands after low-dose radioiodine therapy (*10,11*). Therefore, quantitative salivary gland scintigraphy proves to be a suitable imaging modality for quantitative evaluation of salivary gland function.

Radioprotective Effect of Amifostine

The protective capacity of thiol-containing compounds against normal tissue damage from radiation has been recognized for over 40 yr (*23*). In a broad-based search for radioprotective compounds, amifostine was selected from over 4400 compounds screened by the Walter Reed Army Institute as the agent with the best profile. In preclinical studies, amifostine was shown to protect mice, rats, guinea pigs, dogs and monkeys from lethal doses of irradiation. The normal tissues that are reported to be protected from radiation toxicity include salivary glands, bone marrow, immune system, skin, oral mucosa, esophagus, kidney and testes (*24–27*). Importantly, in studies in tumor-bearing animals, there was selective cytoprotection of normal tissues from the cytotoxic effects of ionizing radiation with no protection of tumor (*25,28*).

When administered intravenously, amifostine is rapidly cleared from plasma with an alpha half-life of <1 min and a beta half-life of <10 min (*29*). In contrast to its brief systemic half-life, there is prolonged retention of the drug and its metabolites in normal tissues (*30*). In the first 30 min after amifostine administration, drug uptake into normal tissues such as salivary glands, liver, kidney, heart and bone marrow demonstrated up to a 100-fold greater difference than in tumor tissues, and half-life of amifostine in salivary gland parenchyma was shown to be more than 24 hr (*30*). Biodistribution studies show that the highest tissue levels of amifostine and its metabolites are found in salivary glands (*31–35*), but accumulation in thyroid tissue was found to be negligible (*26,36*).

The mechanism of amifostine's selective protection has been shown to be related to its preferential rapid uptake into normal tissues with negligible or slow uptake into tumor tissues (*30,33,37*). This selectivity results, in part, from differences in pH and alkaline phosphatase at the capillary endothelial level, both being higher in normal tissue compared with tumor tissue. These conditions favor the conversion and uptake of amifostine to the active protective thiol, WR-1065, in normal tissues (*38*). Once inside the cell, WR-1065 acts as a scavenger of oxygen free radicals (*39*).

The radioprotective effect of amifostine on salivary gland

TABLE 3

Age, Sex, Histology, Tumor-Node-Metastasis (TNM) Stage, Uptake of Technetium-99m-Pertechnetate Before (Baseline) and 3 Months After 6 GBq Iodine-131 and Change of Uptake as Percentage of Pretherapeutic Uptake (Δ Uptake) in Eight Patients Treated with 500 mg/m^2 Amifostine*

Patient age (yr)/sex	Histology	TNM stage	Parotid glands			Submandibular glands		
			Baseline	3 mo	Δ uptake	Baseline	3 mo	Δ uptake
21/F	Papillary	$pT_3 N_1 M_0$	0.37	0.35	5.4	0.33	0.31	6.1
31/F	Follicular	$pT_3 N_1 M_1$	0.61	0.64	−4.9	0.63	0.65	−3.2
48/M	Papillary	$pT_4 N_1 M_0$	0.42	0.41	2.4	0.38	0.36	5.3
51/F	Papillary	$pT_4 N_0 M_0$	0.57	0.58	−1.8	0.46	0.43	6.5
72/F	Papillary	$pT_2 N_1 M_1$	0.25	0.24	4.0	0.26	0.25	3.8
68/F	Papillary	$pT_1 N_1 M_1$	0.34	0.37	−8.8	0.24	0.21	12.5
58/M	Papillary	$pT_3 N_0 M_0$	0.31	0.27	12.9	0.21	0.18	14.3
41/F	Papillary	$pT_3 N_0 M_0$	0.48	0.49	−2.1	0.51	0.51	0
Mean ± s.d.			0.43 ± 0.13	0.42 ± 0.14	0.9 ± 6.8	0.38 ± 0.16	0.36 ± 0.17	6.7 ± 5.8

*Numbers represent mean of right and left parotid and submandibular glands, respectively.

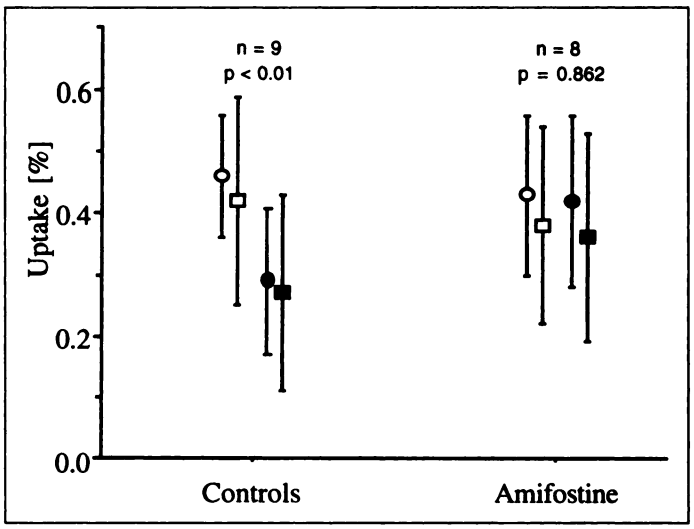

FIGURE 5. Uptake of ^{99m}Tc-pertechnetate in salivary glands of control group and amifostine-treated group before (open symbols) and 3 mo after (filled symbols) application of 6 GBq ^{131}I. Circles = parotid gland; squares = submandibular glands. Data represent mean ± s.d.

function was evaluated in preclinical studies using a rat parotid gland model (*15,16*). Using gland weight and amylase content as indicators of effect, both short- and long-term radioprotection by amifostine against radiation-induced damage was demonstrated (*13–15*). These findings along with those from biodistribution studies provided the rationale for the use of amifostine in patients with head and neck cancer receiving external radiation therapy.

Takahashi and coworkers (*18*) studied ^{67}Ga uptake as an indicator for irradiation-induced damage in salivary glands of patients with head and neck cancer and showed that pretreatment with amifostine resulted in a significantly increased number of ^{67}Ga-negative salivary glands after irradiation. Some studies of head and neck tumors have yielded promising results

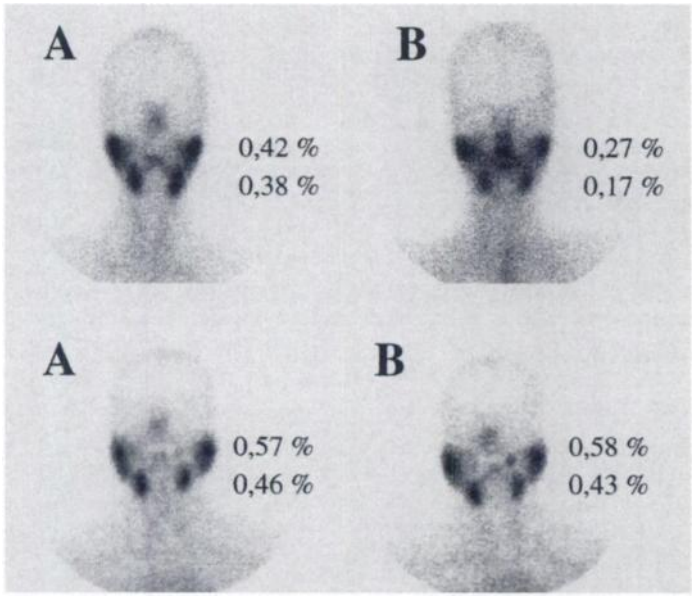

FIGURE 6. Salivary gland scintigraphy of control patient (upper) and of patient treated with amifostine (lower) (A) before and (B) 3 mo after application of 6 GBq ^{131}I. Numbers represent uptake of ^{99m}Tc-pertechnetate as a percentage of injected activity in parotid and submandibular glands (top to bottom). Parenchymal function was decreased significantly by high-dose radioiodine therapy in control patient, whereas it was not affected in amifostine-treated patient.

concerning the reduction of radiation-induced salivary gland damage (*17,19*).

Because the radiation effects of external radiation and radioiodine therapy are, in general, caused by the same mechanisms, i.e., the production of free radicals, it seemed promising to evaluate the radioprotective effect of amifostine against radioiodine-induced salivary gland damage.

Our studies were performed using both normal rabbits and patients with differentiated thyroid cancer. In these studies, a thyroid ablative activity of radioiodine was administered in the presence or absence of amifostine. Salivary gland function was measured quantitatively through the uptake of ^{99m}Tc-pertechnetate using salivary gland scintigraphy.

Animal Studies

In rabbits we showed a clear radioprotective effect in the salivary glands of amifostine-treated animals. This effect was observed at a dose of 200 mg/kg, a dose that exhibited radioprotective activity in other animal species (*24*). Evidence for salivary gland protection by amifostine was observed with salivary gland scintigraphy and histopathological examination. Salivary gland scintigraphy revealed significantly lower reductions in ^{99m}Tc-pertechnetate uptake (as compared with baseline) in parotid and submandibular salivary glands of amifostine-treated animals versus controls. Technetium-99m-pertechnetate uptake was reduced by 11%, 13% and 14% in parotid and by 7%, 9% and 8% in submandibular glands at 4, 8 and 12 wk after radioiodine application, respectively. These reductions were significantly lower than those measured in control animals. In these animals, ^{99m}Tc-pertechnetate uptake was reduced by up to 65% in parotid glands and by up to 48% in submandibular glands. Similar results were observed after histopathological examination, as more pronounced lipomatosis was observed in control animals than in animals pretreated with amifostine. These results are in accordance with several papers in which lipomatosis is described as a typical late effect of radioiodine treatment (*40–42*).

In this study, 1 GBq ^{131}I was applied for complete ablation of the thyroid and for concomitant parenchymal impairment of the salivary glands. In fact, the activity applied caused a complete thyroid ablation in the animals of the control group as well as in the animals pretreated with amifostine as early as 4 wk after application of ^{131}I. This is in accordance with the observation that amifostine accumulates in only a marginal amount in the thyroid (*26,36*). This observation yields the prerequisite for the application in differentiated thyroid cancer since the protection of thyroid tissue or metastases of differentiated thyroid cancer has to be excluded.

Patient Studies

In our patient study we investigated 17 patients with differentiated thyroid cancer. Nine patients served as controls, and in these patients significant decreases in ^{99m}Tc-pertechnetate uptake of 35% in parotid glands and 32% in submandibular glands were observed after high-dose radioiodine therapy with 6 GBq ^{131}I. In addition three control patients exhibited Grade I (World Health Organization) xerostomia. These results are in accordance with data reported in the literature (*3–5,10,11*).

In contrast, parenchymal function of salivary glands was not reduced significantly in patients treated with amifostine before high-dose radioiodine therapy, as demonstrated by a negligible reduction of ^{99m}Tc-pertechnetate uptake in both parotid and submandibular glands. In these patients, amifostine was administered intravenously at a dose of 500 mg/m^2. Doses up to 910 mg/m^2 have been used in chemotherapy trials, and up to 240 mg/m^2 (as a daily dose) have been used in radiation trials.

Moreover, no xerostomia was observed in these patients. Thus, we could demonstrate radioprotection of salivary glands in patients with differentiated thyroid cancer. Future studies are warranted, including a placebo-controlled double-blind study.

CONCLUSION

Parenchymal damage in salivary glands induced by high-dose radioiodine therapy can be reduced significantly by amifostine in patients with differentiated thyroid cancer. This may increase the quality of life of these patients.

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