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EFFECTS OF IRRADIATION WITH CONVENTIONAL AND MULTIPLE DAILY FRACTIONATION ON SERUM AMYLASE ACTIVITY

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Abstract

The behaviour of serum α-amylase activity was determined in patients with head and neck cancer treated by radiation therapy. The levels of serum α-amylase activity during conventional and multiple daily fractionation were compared. Starting from the second day of treatment an increase of serum α-amylase activity was observed. The increase and its duration depended on the total daily dose: after the first day of treatment a linear correlation between serum levels and total daily dose could be observed. The size of the amylase increase correlated to the proportion of salivary gland tissue included in the irradiated volume.

Key words: Therapeutic radiology; head and neck cancer, fractionation, serum amylase.

A research program on morphologic parameters and biochemical indicators of radiation injury has been previously developed (2, 5–7, 10, 11, 13, 14, 16). A good evaluation of radiation injury in normal tissues is possible when the ionizing radiations produce the release of specific molecules from the damaged organ into the extracellular fluids (9, 17–19, 21). Previous studies have shown early changes in serum α-amylase activity after radiation exposure of the salivary glands in patients with head and neck tumors (4, 8, 12, 20, 24). In the serum of normal subjects, the amylase activity is mainly of pancreatic origin and increases only in pancreatitis or sialadenitis. Human salivary glands show a high sensitivity to ionizing radiations, although they have a very low proliferative activity. The species-specificity and the organ-specificity of the postirradiation behaviour has been previously demonstrated (1, 3, 4). In man, injury of the salivary glands appears a few hours after irradiation, with acute inflammation, degenerative changes (12, 20, 24) and increases of serum amylase.

In the current study the effects produced by exposure of the salivary glands to radiation in patients with head and neck cancers were determined. Modifications induced by three different schedules of multiple daily fractionation (MF) and by a conventional fractionation (CF) are reported.

Material and Methods

Serum α-amylase activity assays were performed, before and during radiation therapy, in 78 patients with advanced head and neck cancer.

Twenty-six patients had oral cancer, 24 oropharyngeal, 14 nasopharyngeal, 8 laryngeal and 6 paranasal sinus cancer. In all these patients the treatment volume included all the major salivary glands. In a further 16 patients, 11 with oral cancer of limited extension and 5 with cancer of the paranasal sinuses, the irradiated volume included only a part (about 30%) of the total salivary gland tissue; in a further 10 patients with limited laryngeal tumours the treated volumes did not include the salivary glands.

The treatment schedules and the proportions of exposed salivary gland volume are reported in Table 1. Eighty-eight per cent of the patients were males and the mean age was similar in the different groups. The patients were treated through two lateral opposed fields with a ^{60}Co unit. The dose was calculated at the mid-point between the centers of the fields.

Blood samples were collected in fasting patients in the morning before radiation treatment. The time of blood collection and the dose delivered at different days in various treatment schedules, are reported in Table 2.

The method of STREET & CLOSE (22) was used to assay serum α-amylase activity. Results were expressed as IU/100 ml; normal values ranged between 5 and 35 IU/100 ml.

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Table 1

Distribution of patients according to treatment schedules and proportion of irradiated salivary gland tissue

Proportion of salivary glands exposed	100 %	100 %	100 %	100 %	<30 %	0 %
Fractionation schedules	2 Gy×1	1 Gy×3	2 Gy×2	2 Gy×3	2 Gy×1	2 Gy×1
Split between daily fractions (h)	–	3–4	7–8	3–4	–	–
No. of patients	40	13	5	20	16	10

Table 2

Delivered cumulative dose during radiation therapy (Gy) in the different fractionation schedules and time of blood sample collection (*)

Days of treatment ...	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/22/28/40
Blood collection ...	*	*	*	*	*	*	*	*	*	*						* * * *
2 Gy×1	0	2	4	6	8	10	–	–	12	14	16	18	20	–	–	22/32/44/60
1 Gy×3	0	3	6	9	12	15	–	–	18	21	24	27	30	–	–	33/48/60
2 Gy×2	0	4	8	12	16	20	–	–	24	28	32	36	40		split	44/60
2 Gy×3	0	6	12	18	24	30	–	–	36	42	48	52				

The statistical analysis of the data obtained in the different series was done by the Wilcoxon Rank-Sum test.

Results

All patients had pretreatment serum amylase levels within the normal range. A sharp, statistically significant increase in the activity occurred after the first day of treatment in all groups of patients (Fig. 1). The peak value, the time for its appearance, and the duration of the increase depended on the fractionation modality. In fact, the values after the first day increased progressively with the total daily dose received; in MF with 2 Gy×3 the peak value was reached already after the first day dose. After the other fractionations the amylase levels further increased after the second day and the maximum value was observed after MF with 2 Gy×2. The values after MF 2 Gy×3 decreased after the first day and reached the pretreatment levels after the fourth day; with the other fractionation schedules these levels were reached first one day later.

A moderate increase was observed during MF with 1 Gy×3 on the resumption of treatment after the first weekly split. A similar increase appeared also in the MF group treated with 2 Gy×2; in these patients the treatment was interrupted for about one week at the total dose of 36 to 40 Gy and an increase observed when the radiation therapy was resumed.

The statistical significance of the observations in the different groups during the first four days of treatment is reported in Table 3. Day by day the levels of statistical significance between all groups of treatment are reported; after the first day dose all differences were statistically significant with the exception of the 2 Gy×3 group in comparison with the 2 Gy×2 group. Significant differences between the various groups were observed also after the second, third and fourth days of treatment.

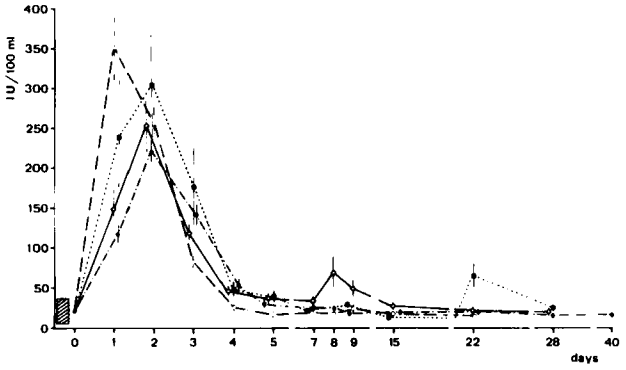

Fig. 1. Serum α-amylase activity (mean ± SEM) at different days after the beginning of various treatment schedules. CF, 2 Gy×1 (●), and MF with 2 Gy×3 (○), 1 Gy×3 (◇) and 2 Gy×2 (■). Control range is marked by a shaded bar.

In the different treatment groups, there was, after the first day, a significant correlation between the increase in enzyme activity and the total daily delivered dose (Fig. 2).

For the few cases treated by the 2 Gy×2 schedule, the correlation coefficient was 0.756, and p(F)—calculated by Fischer's test—was less than 0.02. When the correlation between amylase activity after the first day, and daily dose, was calculated, the values were $r=0.999$ and $p(F)<0.001$.

A similar correlation was not evident at the second treatment day, as the increase of amylase levels in patients treated with a lower daily total dose corresponded to a lower increase or even a reduction in the other groups.

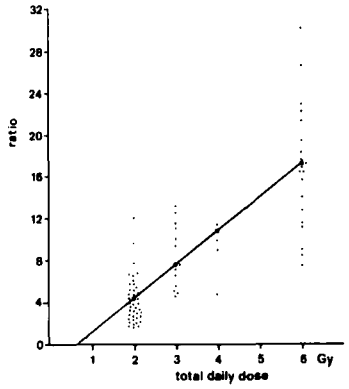

Fig. 2. Calculated linear regression between the increase of α-amylase activity after the first day of treatment and the dose delivered. The ordinate represents the ratio between the value after the first day of treatment and the pretreatment value in each individual patient. r=0.756.

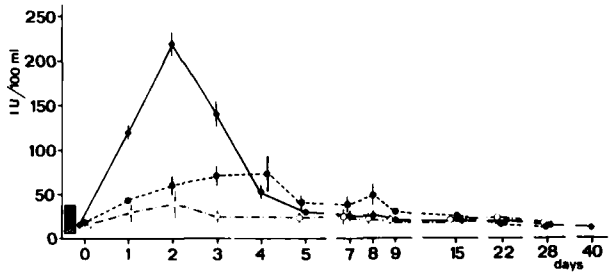

Fig. 3. Serum amylase activity (mean ± SEM) during radiation therapy in patients treated with CF and exposure of the whole salivary gland tissue (◆), of about 30% of this tissue (●), and without exposure of the salivary glands (○). Control range is marked as a shaded bar.

In the patients in whom only a part of the salivary glands was exposed to irradiation, the increase of serum amylase activity was much less pronounced (Fig. 3). The levels showed a gradual increase until the fourth day and then a decrease; however, the values remained around the upper limit of the control range.

The patients treated against volumes not including the salivary gland tissue showed only a slight increase of amylase after the second day. The values always fell within the normal range.

Discussion

The present and the previous studies (4, 8, 20, 24) on the serum α-amylase activity have demonstrated the reliability of this parameter as a biochemical indicator of early radiation injury in salivary gland tissue. The observations can be summarized and interpreted in the following way:

Table 3

Statistical significance of differences between values of serum α-amylase activity during the first 4 days of different treatment schedules, calculated by the Wilcoxon Rank-Sum test

	Pretreatment values	2 Gy×1	1 Gy×3	2 Gy×2
Day 1				
2 Gy×1	<0.01			
1 Gy×3	<0.01	<0.01		
2 Gy×2	<0.01	<0.001	<0.05	
2 Gy×3	<0.01	<0.001	<0.001	NS
Day 2				
2 Gy×1	<0.01			
1 Gy×3	<0.01	<0.05		
2 Gy×2	<0.01	<0.01	<0.05	
2 Gy×3	<0.01	<0.01	NS	NS
Day 3				
2 Gy×1	<0.01			
1 Gy×3	<0.01	NS		
2 Gy×2	<0.01	NS	NS	
2 Gy×3	<0.01	<0.01	<0.05	<0.05
Day 4				
2 Gy×1	<0.01			
1 Gy×3	<0.01	NS		
2 Gy×2	<0.05	NS	NS	
2 Gy×3	NS	<0.01	<0.01	<0.05

1) An initial 2 Gy fraction is high enough to induce a rise in the serum α-amylase activity but does not completely destroy the salivary tissue. The latter fact is confirmed by the observation that a second fraction, delivered after one or more days, induces a new rise in the amylasemia (8).

2) The increase in enzyme activity is strictly dependent on the volume of salivary glands included in the irradiated volume. The observation that the duration of the increase is longer in patients with only partial salivary gland exposure might be explained by incidental exposure, during progression of treatment, of small parts of salivary gland tissue, initially excluded from irradiation.

3) The α-amylase increase and the time of its peak value depends on the fractionation modality: it appears earlier and is higher with an increasing daily delivered total dose.

The results can be explained by death of serous cells or by changes in the permeability of their cell membranes. Some months after treatment the salivary glands were fibrotic and acini were absent; the small ducts were dilated, with deposition of collagen (15). An impairment of salivary function at this time has recently been demonstrated by sequential sialography (23).

The exhaustion of the amylase increase after 4 to 5 days may be due to irreparable cellular injury. However, when MFs with 1 Gy×3 or 2 Gy×2 were resumed after the first weekly split pause, or after a split pause in the third week of treatment, a new slight increase in the amylasemia was observed; this seems to demonstrate a partial recovery of

the tissue. It should be noted that this phenomenon did not appear during CF or during MF with 2 Gy three times a day.

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