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CORRELATION BETWEEN INITIAL SALIVARY FLOW RATE AND RADIATION DOSE IN THE PRODUCTION OF XEROSTOMIA

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Xerostomia (dryness of the mouth) is one of the undesirable side effects produced by radiation when treating head and neck areas. It is important to the clinician because of the deleterious effects it has on taste, appetite and the teeth (SILVERMAN & CHIERICI 1965, BLOZIS & ROBINSON 1968, CARL et coll. 1972, DALY et coll. 1972, CONGER 1973, WESCOTT et coll. 1975). Hence, it is useful to know the different factors that influence its course, intensity and duration. If these are well known, xerostomia might be avoidable in some cases. In two previous communications some of them were described (WESCOTT et coll. 1978, MIRA et coll. 1981): field arrangement, amount of salivary glands irradiated, interruption of therapy (split course), dose and initial salivary flow rate. The present communication addresses the correlation between these last two factors.

Material and Methods

The data in the Table are based on 11 patients who had virtually all major and minor salivary glands irradiated with 2.25 Gy per day, Monday through Thursday, up to 45 to 63 Gy. Details of the irradiation technique and saliva collection have been explained by WESCOTT et coll. (1978). Briefly, patients were irradiated with a ^{60}Co teletherapy unit using parallel opposed lateral fields with equal loading. Dosage was fairly uniform within the treated volume, and all salivary glands were considered uniformly irradiated. Unstimulated saliva samples were collected before irradiation, with patients sitting quietly, allowing saliva to drool into a plastic funnel plate in a graduated tube (BECKS & WAINWRIGHT 1943, MASON & CHISHOLM 1975).

Initial flow rate (IFR) values in the table are the mean of pretreatment flow rate measurements. All patients had from 2 to 7 whole saliva samples collected before irradiation.

Saliva samples during the course of treatment were taken several times a week, allowing observation of the progressive downward trend in the saliva flow rate. This continued until the flow decreased to almost total dryness (i.e. below 0.1 ml/min). After this point, this minimum flow rate (MFR; Table) remained constant throughout treatment and subsequent follow-up with minimum daily variations.

The statistical analysis of the correlation of the Figure was done using the F distribution (DANIEL 1974).

Results

Although some variation in initial flow was found within each patient, this variation was small when compared with the pretreatment wide variations among patients (from 0.15 to 1.46 ml/min; Table).

Patients with high initial flow required higher radiation doses to reach minimum flow. Those with

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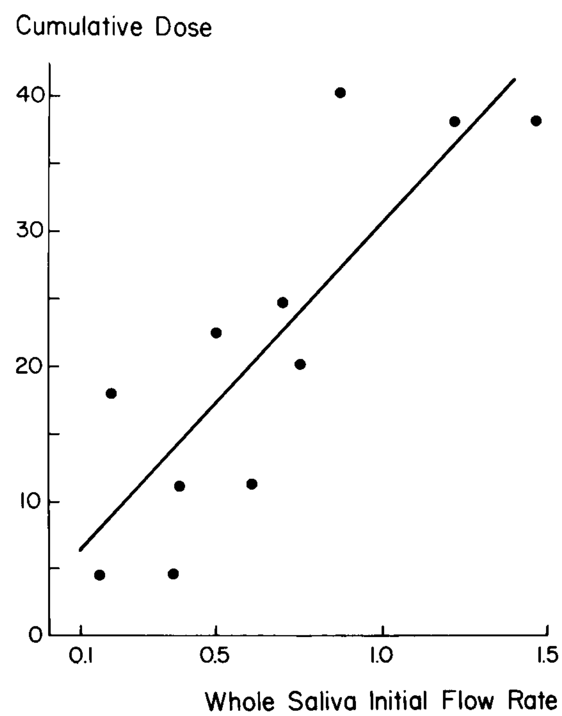
initial flow above 0.75 ml/min had to receive more than 38 Gy, while patients with flow below 0.70 ml/min required usually less than 20 Gy.

The Figure shows a good correlation coefficient ($r=0.837$) between initial flow and the cumulative dose resulting in minimum flow. A linear regression of the data using a least squares fit yielded the relation: MFR dose (D) = 27 Gy × IFR + 3.6 Gy, where D is the dose required to produce minimum flow rate and IFR is the initial flow rate (ml/min). Statistical analysis shows this correlation to be significant ($p<0.01$). This good correlation is also found when the time to develop minimum flow and initial flow was compared. This is of course expected as all the patients were treated with the same dose fractionation. Hence, it will take a longer time to reach higher dosages.

Table

Relation between initial flow rate and cumulative dose before occurrence of minimum flow rate

Case No.	Initial flow rate (ml/min)	Minimum flow rate after	
		Cumulative dose (Gy)	Days of first irradiation
1	1.46	38.25	35
2	1.21	38.25	33
3	0.87	40.50	33
4	0.75	20.25	19
5	0.70	24.75	20
6	0.61	11.25	9
7	0.50	22.50	16
8	0.39	11.25	7
9	0.37	4.50	3
10	0.19	18.00	13
11	0.15	4.50	2
Mean ± SD	0.65±0.41	21.27±13.17	17.3±12



Relation between initial flow rate (ml/min) and cumulative dose (Gy) required to produce minimum flow rate, i.e. irreversible xerostomia. Initial flow is the mean of serveral whole saliva samples taken before irradiation. Diagram applies only when whole glands are treated 4 to 5 times a week, total weekly dose 9 to 10 Gy.

Discussion

Information from the literature about the dosage and time required to produce xerostomia is scarce and somewhat contradictory. Doses of 15 Gy (BLOZIS & ROBINSON) and 20 Gy (ENEROTH et coll. 1972 a) have been reported; time to produce dryness between 2 and 6 hours after irradiation (KASHIMA et coll. 1965), by the third week (RUBIN & DOKU 1976), about the middle of the third week (ROBINSON 1964) and after 1 to 3 weeks of treatment (DESJARDINS 1931). Dosage and time are influenced by several factors (WESCOTT et coll. 1978, MIRA et coll.). Hence, no simple answer to this question seems to exist.

The mean preirradiation whole saliva flow rate was similar to that described by others (SCHNEYER & LEVIN 1954, HOLMES 1964). The large individual variations in the patients are also consistent with published data (BECKS & WAINWRIGHT, DAWES 1972, ENEROTH et coll. 1972 a).

A detailed explanation about the reasons for the linear correlation between the two parameters (Figure) is beyond the scope of this communication, and it is not properly known. The present findings are similar to those described by ENEROTH et coll. (1972 a), although they did not attempt to develop a linear correlation. They found that glands with high initial flow were larger than the average, while those with low initial flow were smaller. They were of the opinion that the fact that higher doses were needed to extinguish large glands was because these had a lesser sensitivity to radiation than the small ones. This explanation was not accepted by WESCOTT et coll. (1978) who stated that the decreasing of the salivary flow rate by radiation follows an exponential decay type of curve (this was already suggested by ENEROTH et coll. (1972 b). In this model, when the decreasing rate constant is similar, the same amount of radiation will decrease the flow rate by the same percentage. As minimum flow is always about 0.1 ml/min, patients with high initial flow (around 1 ml/min) will require a decrease of the flow rate of 90 per cent to reach dryness, while those with low initial flow (around 0.2 ml/min) would need only 50 per cent reduction. Assuming the same decreasing rate constant in the two cases, the patient with high initial flow will require a three times higher dose than the patient with low flow. This is consistent with the present observation. Hence, if both types of patients (with high and low initial flow) have the same decreasing rate constant, it is not possible to speak about different sensitivities to radiation. It is possible the explanation is that large glands, having either more or larger secretory acini, secrete more amount of saliva than small ones and need a larger percentage of flow rate reduction to reach the minimum flow, thus higher dose according to the previous explanation. Unfortunately, the size of the glands was not measured in the present series.

Some clinical applications of the Figure may be envisaged. In most institutions of radiation therapy the resting saliva flow rate is not routinely determined. However, if this was measured, the graphic would be a good predictor of the level of the radiation dose required to produce xerostomia, provided entire glands are irradiated, using similar fractionation as the present series, i.e. 4 to 5 times a week, totally 9 to 10 Gy weekly. If it is assumed that all salivary tissue (hence all salivary glands) have similar sensitivity to radiation, the diagram could serve a practical purpose in patients with unilateral head and neck tumors where only one side has to be irradiated. In that case, the contralateral glands could be somewhat spared by the use of electron beam, wedge pair technique, etc. Recovery of salivary function occurs before, but not after reaching the minimum flow rate (WESCOTT et coll. 1978, MIRA et coll.). Hence, an effort should be made in these patients to keep the dose to the contralateral salivary glands below the dose indicated in the Figure, corresponding to the patient's measured initial flow. In this case there will be a chance for recovery of the flow rate to pretreatment levels. DESJARDINS suggested that xerostomia can be prevented by sparing one side and MURTHY & HENDRICKSON (1980) one parotid gland. If minimum flow is reached, no recovery can be expected, with subsequent permanent xerostomia after treatment, and all the deleterious effects associated with it. When determining the initial flow rate the mean of several samples should be used as each patient has a significantly varying flow rate.

SUMMARY

Dose and initial flow rate are two of several factors that influence the outcome of xerostomia when irradiating head and neck tumors. These two parameters were analysed in 11 irradiated patients where most salivary glands were in the radiation field. Unstimulated whole saliva samples were collected before, during and after the irradiation. The results indicate a statistically significant linear correlation between initial saliva flow rate and the accumulated dose causing irreversible xerostomia. This phenomenon is explained. A diagram is made that could be used (in head and neck tumors where one side could be spared) as an indicator of the maximum dose the salivary glands in the contralateral non-involved side can receive before reaching irreversible dryness.

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