Effects of Different Shortwave Radiofrequencies on Tumor Growth

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ABSTRACT

The effects on tissue temperature, tumor temperature selectivity, tumor growth retardation, and animal survival of 3 different radiofrequencies (13.56, 3.00, 27.22 MHz) were evaluated in Fischer rats. When non-tumor-bearing rats were treated with an incident power density which was maintained at a constant intensity for the same period of time, the frequencies of 13.56 and 3.00 MHz generated tissue temperatures 5–8°C higher than those generated by the frequency of 27.22 MHz. No preferential temperature elevation was found for s.c. or muscle tissues. In rats bearing a syngeneic methylcholanthrene-induced sarcoma, higher overall temperature levels were obtained during the same time duration in the groups treated with 13.56 and 3.00 MHz when compared to 27.22 MHz. Temperatures recorded in the tumor tissues were significantly higher ($p < 0.05$) than those recorded in the s.c. and muscle tissues when 13.56 and 3.00 MHz were used. When 27.22 MHz was used at the same incident power density or at higher power, this preferential temperature distribution to tumor tissue was not observed.

Tumor growth following treatment was recorded and compared in a sham-treated control group and radiofrequency-treated groups. The mean tumor volume in the animals treated with 3.00 MHz was significantly decreased ($p < 0.02$) at all posttreatment intervals measured. Survival was also significantly prolonged ($p < 0.01$) in this group.

Higher overall temperature levels obtained with both 13.56 and 3.00 MHz using considerably lower incident power density than 27.22 MHz and a preferential temperature distribution to tumor tissue, not found with 27.22 MHz, would indicate a definite superiority of the former 2 frequencies over the latter one. The more pronounced tumor growth retardation and the prolonged animal survival in the group treated with 3.00 MHz could be explained by the finding that 37.5% of the animals had total regression of their tumors for 60 days. The temperature recorded in the tumors of these 3 rats was strikingly higher than that recorded in the tumors of all other animals and was obtained with minimum damage to the surrounding normal tissues. Although we have not as yet been able to pinpoint the cause for such a high tumor temperature and retarded tumor growth in these 3 animals, we can expect similar results when tumor temperature can be maintained above $46^\circ$ for 1 hr in this experimental tumor animal model.

INTRODUCTION

Localized hyperthermia by shortwave RF was initially inves-

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3 The abbreviation used is: RF, radiofrequency.

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treatment, the rats were periodically weighed, and the tumors were measured at 3-day intervals. The observation period was continued until death of the animal.

**RF Apparatus.** This equipment was assembled by Lencon Advanced RF Designs, Greenbelt, Md. It essentially consisted of a frequency synthesizer capable of emitting high-stability signals to an accuracy of 0.001% over a range of 1 to 30 MHz. The signal was then amplified to the desired power through a broadband linear amplifier. An antenna tuner matched the impedance of the load to that of the tissues. Two coaxial cables conveyed the amplified signal to the 2 paddles, positive and ground. These paddles were positioned opposite one another over the site to be treated. The incident power density by the tissues was measured in watts/sq cm, and this was defined as the difference between the forward and reflected power divided by the surface of the paddle:

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\text{Incident power density} = \frac{\text{Forward power-reflected power}}{\text{Paddle surface area}} = \text{watts/sq cm}
\]

The forward and the reflected power were shown on a precision meter located on the linear amplifier.

**Frequencies and Absorbed Power.** With this series of experiments, we used 3 frequencies, 3.00, 13.56, and 27.22 MHz. MHz values of 13.56 and 27.22 have been used and reported previously by us and others (1, 3, 9, 12, 14). The frequency of 3.00 MHz was selected for comparison to the other 2, being at the lower band limit of our synthesizer capabilities. The incident power density (watts/sq cm) was kept constant for the same period of time in all of these experiments; after an initial power of 0.30 watt/sq cm for 5 min, this was incremented and kept constant at 0.35 watt/sq cm for the remaining treatment interval. This setting was kept constant for all RF-treated rats except for those in Group E in which the power was gradually increased to 0.67 watt/sq cm.

**Experimental Design.** Sixty-three rats were divided into 9 experimental groups. The first 3 groups (5 rats each) served as normal controls. The rats in these groups did not have a tumor; the normal thigh was tested using the 3 different frequencies at the constant power outlined previously. The fourth group, used as a control (Group IV), had 8 tumor-bearing rats that were sham-heated, i.e., the rats in this group were anesthetized, temperature probes were inserted into the tissues, RF paddles were positioned, and temperatures were recorded at the same intervals and for the same duration of time as in the other experimental groups. The only difference was that they did not receive any RF power. Five groups of tumor-bearing animals (8 in each group) were treated with RF; 3 groups received RF treatment with the same experimental settings except for the frequency, which varied according to the group treated: Group A, 3.00 MHz; B, 13.56 MHz; and Group C, 27.22 MHz. The other two groups were treated at 27.22 MHz; in 1 group (Group D) the coaxial cables were lengthened 1 m in order to verify if the observed decrease in power seen with this frequency in the previously treated group was due to cable length interference, and the other group (Group E) was treated with a higher power in order to elevate the temperature to the levels obtained with the other 2 frequencies.

**Temperature Monitoring.** A Bailey BAT8 thermometer (Bailey Instruments, Inc., Saddlebrook, N. J.) was used. The temperature was read from a digital readout. Three inputs allowed for temperature sampling from 3 distinct sites. Thermocouple microprobes were inserted into the tissues through 18-gauge needles, which were then retracted out of the tissue mass. The probe tips were shielded in chemical-resistant Teflon. Calibration with a standardized mercury thermometer of the instrument and microprobes was performed every 2 weeks, and variations at any one time were found to be consistently less than 0.1°C.

**Treatment Intervals.** All animals received one treatment of 1-hr duration. During the treatment, temperatures were measured and recorded at 5-min intervals from the tumor core, the s.c. tissue, and the quadriceps muscle group. In the 3 control groups without tumors, the temperatures were recorded from the s.c. tissue and from both quadriceps and hamstring muscle groups. All temperature measurement sites were within the electromagnetic field. During the temperature reading, the RF was turned off for a total of 15 sec in order to avoid interference due to sensitization of the microprobes by the electromagnetic field. In the control group with tumor, which was sham-heated, temperatures were monitored and recorded in experimental groups.

**Statistical Analysis.** Student’s t test was used to compare the mean tumor growth volumes between the control and experimental groups. The Wilcoxon-Mann-Whitney rank sum test was used to compare mean temperature values during treatment and the mean of the survival days following treatment.

**RESULTS**

The temperatures of the 3 control groups of non-tumor-bearing rats in which the normal thigh was subjected to RF are plotted on Chart 1. At the constant power used, no difference was found among temperatures measured in muscle or in the s.c. tissue, and no significant difference was detected when using 13.56 or 3.00 MHz. A markedly decreased temperature gradient was seen when 27.22 MHz was used.

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**Chart 1.** Mean temperature recordings in the s.c. tissues and quadriceps muscle mass of the non-tumor-bearing rats during the RF treatment intervals. Each group was treated with a different frequency at a constant power. Lower temperature levels were obtained when using 27.22 MHz. The shaded area correlates the incident power density (watts/sq cm) to time in minutes. Bars, S.E.
In the control group (Group IV) with tumor that was sham-heated, there was no elevation of temperature throughout the 1-hr monitoring time.

The tumor-bearing rats treated with 3.00 MHz showed a significant selectivity of temperature for tumor tissue (p < 0.05) when compared to the s.c. and muscle tissues. Tumor selectivity was also seen with 13.56 MHz (p < 0.05), although the mean overall temperatures were somewhat lower than those obtained with 3.00 MHz. When using 27.22 MHz, there was no tumor temperature selectivity, and the mean overall treatment temperature gradients in the neoplastic as well as in the normal tissues were 95% lower than those obtained with the other 2 frequencies. Comparison of tumor and s.c. temperatures and tumor and muscle temperatures with the 3 tested frequencies are represented in Charts 2 and 3, respectively. In the experiments in Group D, the coaxial cables from the RF apparatus to the paddles were lengthened 1 m in order to eliminate any interference due to cable length. The results were similar to those of Group C in which the same frequency with shorter cables was used with minimal overall heating and no tumor temperature selectivity. In Group E, the frequency of 27.22 MHz was again used, and the incident power density was increased in order to bring the tissue temperatures to the values obtained with the other 2 frequencies. Chart 4 depicts the temperatures obtained in Group C with the constant power of 0.35 watt/sq cm and shows the power (0.67 watt/sq cm) necessary to raise the tumor temperature at this frequency in Group E to 43°, a level easily reached with 3.5 watt/sq cm with the other 2 frequencies.

Following RF treatment, the rats were followed at 3-day intervals for 4 weeks and then once a week for 5 weeks. All animals were weighed; no significant difference in weight was observed among any of the groups, and a gain of 25 to 50 g was usually found when the tumors reached large sizes. Small ulcerations resulting in a superficial eschar were present in 60% of the animals treated with 13.56 and 3.00 MHz; temperature selectivity for tumor tissue as compared to muscle tissue was significant (p < 0.05). When 27.22 MHz was used, the muscle mass heated more than the tumor. Shaded area, incident power density. Bars, S.E.
Survival was found at all intervals following treatment in the group treated with the frequency of 3.00 MHz when compared to the other groups. No differences were found among any of the other 3 groups. At the time of RF treatment, there was no statistical difference in tumor volumes among any of the groups. In Group D, treated at 27.22 MHz with long cables, and in Group E, tested at 27.22 MHz with higher absorbed power, the tumor growth was similar to that of the control group and Groups A and C, treated with 13.56 and 27.22 MHz, respectively, with short cables.

Survival was recorded for all the animals in the tumor-bearing control group and in Groups A, B, C, and D. A significant (p < 0.01) prolongation of survival was found in the group treated with 3.00 MHz (Chart 6). The rats in Group E (not included in Chart 6) did not show any prolongation of survival when compared to the controls. In the group treated with 3.00 MHz, total regression of tumor was noted in 37.5% of the animals, and one rat was cured for over 4 months. At autopsy, no tumor could be detected in this rat. The temperatures recorded during the treatment interval for each rat of Group A treated with 3.00 MHz were graphed (Chart 7).

DISCUSSION

Although different frequencies in the shortwave radio band have been used in experimental animals with good tumor...
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identical experimental conditions. All our experiments were conducted on young Fischer rats of approximately the same weight. The methylcholanthrene-induced sarcoma was treated 13 days after inoculation of the cells when the tumor size was approximately 1 cm. Among all groups at the time of treatment, there was no statistically significant difference in tumor size. When the tumor volume, as measured with the prostate spheroid formula, was compared to the actual weight expressed in g, a direct correlation was found for 36 tumors of different sizes (p < 0.001). This indicated the accuracy of the formula which was used to measure tumor volume in all our animals. All experiments were performed with the same RF apparatus; the intensity of the absorbed power was kept constant in all experiments except in Group E, in which it was purposely increased in order to raise the tumor mass temperature to 43°. In the control groups with no tumors, in which the normal thigh was treated, as well as in the groups bearing a tumor that were treated with the 3 tested frequencies, it was apparent that when 27.22 MHz was used, temperature levels in the tumor as well as in the normal tissues were well below the temperature levels obtained with the other 2 frequencies and that, in order to reach similar levels, the absorbed power had to be increased to 0.67 watt/sq cm, which is almost double the power used with the other 2 frequencies. Most reports in the literature have not used a constant and uniform system of reporting the absorbed power used, which has made it difficult to compare results. In all our experiments, the incident power density has been expressed constantly with the formula described previously.

When using 27.22 MHz at low power (0.35 watt/sq cm) or at high power (0.67 watt/sq cm), we did not observe any tumor temperature selectivity. When using 13.56 or 3.00 MHz, significantly higher temperatures were noted in the tumor mass when compared to those of the s.c. and muscle tissue. This finding is consistent with our previous work (1). An explanation as to why tumor tissue temperature rises above that of the surrounding tissue cannot at present be given with certainty. It has been postulated to be due to a decreased dispersion of heat by the tumor (9). Decreased blood flow through the tumor capillary network could account for a reduction in heat dissipation. Morphological studies of tumor vasculature have shown an irregular, inordinate capillary network in some neoplastic tissues (6) that would explain a slower blood flow through the tumor. Scanty blood supply to primary human and experimental tumors was also found using a quantitative method with radioactive microspheres (20). A 20-fold decrease in tumor blood flow compared to normal organs was demonstrated by both a direct and indirect method in experimental animals (4). Similar results were obtained in rabbits with transplanted V-2 carcinomas when regional tumor blood flow was determined by 85Kr clearance technique (5). Although we can ascertain that anesthesis has certain effects on the blood flow, nevertheless, all the animals were managed under the same conditions. The fact that we were not able to obtain preferential tumor heating in any of the experimental groups using 27.22 MHz is difficult to explain on the sole basis of tumor blood flow, since we used an identical tumor model for the other frequencies. One possibility to be considered is that the dielectric properties of tumor tissue at this frequency might be similar to those of the s.c. and muscle tissues, while at 13.56 and at 3.00 MHz they might be more diverse. This could account for different energy absorption by the different tissues. We believe that further studies should be pursued to obtain definitive evidence on temperature profiles by measuring the actual absorbed power by the treated tissues.

Tumor growth retardation and prolonged animal survival were found only in the group treated with 3.00 MHz. Similar results were expected in the groups treated with 13.56 MHz as well as in the group treated with 27.22 MHz (in which the power was increased to 0.67 watt/sq cm) because similar mean tumor temperatures were obtained. When the animals in the group treated with 3.00 MHz were individually analyzed, it was found that 3 animals of this group had temperatures in their tumors recorded at a level strikingly higher than that for the rest of the animals in that same group (Chart 7) or actually higher than that for any of the animals in any of the groups. Those 3 animals were the ones with tumor growth retardation and prolonged survival. We have not been able to pinpoint the cause for such a good response to the RF treatment in these 3 animals, since all experimental settings were similar.

In conclusion, similar tissue temperature elevations were obtained when frequencies of either 13.56 or 3.00 MHz were used at the same absorbed power. However, when the frequency of 27.22 MHz was used, higher absorbed power was required to obtain similar tissue temperature elevations in this tumor model. Statistically significant tumor temperature selectivity was obtained with 13.56 or 3.00 MHz, but not with 27.22 MHz. When temperatures were maintained above 46° for 1 hr in this particular animal tumor model, tumor growth retardation and prolonged survival could be expected. Preferential tumor heating could be obtained with minimal damage to the surrounding normal tissues.

REFERENCES

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