Effect of Heat and Combined Treatments on Normal Tissues

The Problem of Defining Thermal Dose

M. P. Law and S. B. Field

MRC Cyclotron Unit, Hammersmith Hospital, DuCane Road, London W12 OHS, Great Britain

Introduction

The rationale for using hyperthermia to treat malignant disease is based on experimental studies which suggest that tumours may be more susceptible to thermal injury than normal tissues (Field and Bleehen 1979). In particular, solid tumours may have an inadequate vascular supply so that many tumour cells may be in an environment (low nutrient and oxygen supply, low pH) which increases thermal sensitivity. Another consequence of a low blood flow is that removal of heat from a locally heated tumour may be poor so that it reaches higher temperatures than adjacent normal tissues.

Hyperthermia also enhances biological responses to both ionising radiations and chemotherapeutic agents. The factors which increase tumour susceptibility to direct thermal damage, however, are unlikely to increase thermal enhancement of damage caused by other modalities. Indeed, animal studies show that thermal enhancement of radiation damage to tumour and normal tissue is similar for a given degree of hyperthermia (Field et al. 1980; Overgaard 1982). Only if tumour reaches a higher temperature than normal tissue will a therapeutic gain be achieved for the simultaneous application of heat and irradiation (Fig. 1).

A therapeutic gain after combined therapy may be achievable in the absence of a marked temperature difference between tumour and normal tissue if the two modalities are separated in time. This has been demonstrated in both experimental (Fig. 1) and clinical studies (Overgaard 1981) when heat is given 3–4 h after the radiation. In this case the interactive effect of heat and radiation will have decayed and any therapeutic advantage will probably result from a greater susceptibility of acidic tumour cells to heat.

Preclinical studies of hyperthermia should consider the various factors which affect the relative responses of tumour and normal tissues. There is thus a need for systematic investigation of physiological responses of various cells and tissues, including those in man, and studies of underlying mechanisms which may suggest ways of optimising treatment. In order to quantitate such studies, a satisfactory method of expressing thermal does is required. A rigid definition of "thermal dose", however, has not been accepted.
Fig. 1. Thermal enhancement ratio after simultaneous or sequential treatment at various temperatures. In the sequential treatment heat was given 4 h after radiation. Results for a murine mammary carcinoma and its surrounding skin are compared. (Overgaard 1980, 1984)

The Concept of Thermal Dose

Dose is used to provide a means of predicting a biological response following administration of a medicine or something analogous to a medicine and to provide a means of communication regarding the effects of a given amount of a medicine or something analogous to medicine. A dose unit, therefore, must be a well defined and measurable physical quantity. The biological response must be related to the dose in a meaningful and quantitative manner. Proper means of intercomparison should be possible.

Radiotherapists have become accustomed to using energy deposited to describe the dose of radiation as this relates clearly to the resulting biological effect. Absorbed energy, however, cannot be used satisfactorily to predict the biological response to hyperthermia, as illustrated by Hahn (1982). If a thermally insulated culture dish initially at 37°C is heated quickly to 43°C no cells are killed. If the system is kept at 43°C with no energy allowed to enter or leave, cell killing will begin as a result of the cells being at the elevated temperature. The effect of heat depends on the temperature and duration of heating, not on the energy required to produce the temperature rise. Thus for a fixed temperature, time is a reasonable measure of thermal dose.

The problem of using time at a given temperature is that treatments are given at different temperatures and the temperature is probably not constant. One solution is to use some means of relating a given treatment to an equivalent time at a reference temperature. Although different cells and tissues have different sensitivities to heat, there is a general relationship between temperature and time to cause a given response, as described by Dewey et al. (1977). This relationship is given by:

\[ t_2 = t_1 A(T_1 - T_2) \]

where \( t \) is the heating time, \( T \) is the temperature and \( A \) is a factor which depends on the temperature range (Sapareto and Dewey 1984). Mean values for \( A \), ob-