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5-FLUOROURASİL'E ^{60}Co γ-IŞINLARININ ETKİSİ

EFFECTS OF ^{60}Co γ-RAYS ON 5-FLUOROURACIL

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ABSTRACT

Gamma radiolysis of 5-Fluorouracil (5-FU) in aqueous solutions was investigated and G(-5FU) values have been determined. ·OH radicals were found to be responsible for the permanent destruction of 5-FU. No significant radiation decomposition of 5-FU was observed in solutions containing glucose and oxygen, suggesting their possible use as protective agents.

ÖZET

5-Fluorourasil'in (5-FU) sulu çözeltilerinin gama radyolizi incelenmiş ve çeşitli radyoliz şartlarında G(-5FU) değerleri tayin edilmiştir. 5-FU'nun bozunmasından ·OH radikallerinin sorumlu olduğu bulunmuştur. Glikoz ve oksijen içeren 5-FU çözeltilerinde kayda değer bir bozunma görülmemesi, bunların koruyucu ajan olarak kullanılabileceğini göstermektedir.

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INTRODUCTION

One of the main lines of research in oncology is concerned with the investigation of the effects arising from various combinations of different cytostatic agents (1-3). The various possibilities are; combinations of drugs (4), combinations of drug and radiation (5-8), or radiosensitizers or hyperthermia combined with drugs or radiation (9, 10). The aim is to increase the tumoricidal effect of such combinations while reducing the harmful side effects of each therapeutic agents (11, 12). Rational combinations of drugs should be designed by paying special attention to the cell life cycle (Figure 1). During mitosis (M phase), a cell can go either into a resting phase (G_0) or gap phase (G_1) while no DNA is synthesised, although many enzymes are. From G_1, the cell goes to the S phase (DNA synthesis). Another gap (G_2) then occurs before cell division (M). The occurrence of the main segments of the life cycle has to follow the correct sequence.

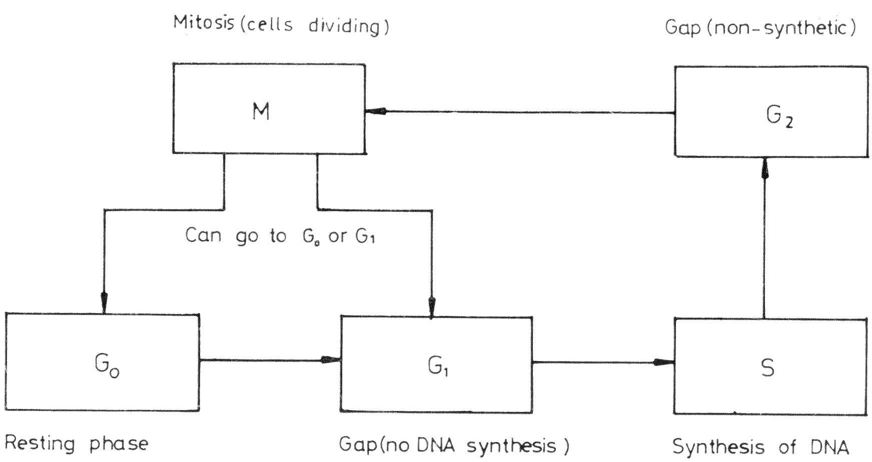

Figure 1 : Life cycle of a cell.

Drugs blocking mitosis act only on cells in the M state, while chemotherapeutic attacks on DNA synthesis are best made during the S phase. However, all the cells in the tumour are not at the same phase of the cycle, which causes a problem concerning tumour annihilation. This problem might be handled, for instance attacking by sequentially at various phases of the life cycle of the tumour cells.

The synthesis of DNA which is the focus of anticancer drug design research is especially important in rapidly dividing cells. Deoxythymidylate (dTMP) is required for DNA synthesis and the cell synthesises this from deoxyuridylate (dUMP) (Figure 2). The vital conversion of dUMP to dTMP can be blocked at the thymidylate synthetase stage.

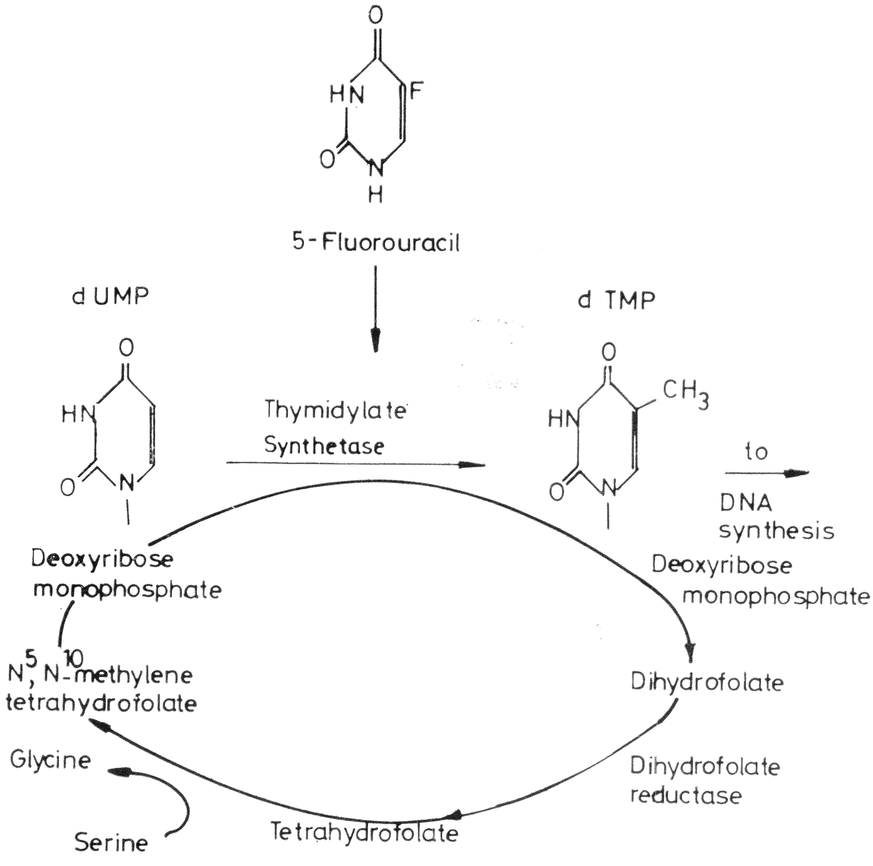

Figure 2 : Deoxythymidylate (dTMP) synthesis.

Fluoropyrimidines, of which the most famous is 5-FU, act primarily as metabolites and cause cell-kill in one of two ways - inhibition of thymidylate synthetase or by incorporation into RNA, thus altering RNA processing and function (6, 7). Accordingly, 5-FU has been used in clinical oncology for more than two decades. 5-FU acts more effectively on the S phase of the cycle which is the most radioresistant phase (7). By killing the radioresistant cells, it increases the apparent effectiveness of radiotherapy (2, 11, 12). However, the possible decomposition of 5-FU irradiated with ^{60}Co γ-rays, has not been investigated, so far. In this study, ^{60}Co gamma radiolysis of 5-FU in aqueous solutions was investigated and G(-5FU) values (the number of 5-FU molecules destroyed per 100 eV energy absorbed) have been calculated.

EXPERIMENTAL

High purity 5-FU was supplied by 'İbrahim Ethem Kimya Evi T.A.Ş.'. 5-FU solutions ($(1.076\text{-}1.92) \times 10^{-4}$ M) were prepared by dissolving 5-FU in triply distilled water and/or in 5% glucose solutions. The aqueous 5-FU solutions were saturated with CO_2, N_2O, N_2 or O_2 before irradiation.

γ-Radiolysis was performed using a ^{60}Co γ-source. The dose rate was 2.90 Gy. min^{-1} as determined by Fricke dosimetry. The total doses absorbed varied in the range of 30-700 Gy. A Cary - 14 UV-VIS spectrophotometer was used for spectrophotometric analyses. The irradiation degradation of 5-FU was determined by measuring the optical density changes at 265 nm (Figure 3). G(-5FU) values of 5-FU obtained at different radiolysis conditions are summarised in Table I.

Various 5-FU solutions ranging from 10^{-4} M to 10^{-1} M were irradiated in order to investigate the concentration effect on radiolysis. Variation of decomposition with respect to initial 5-FU concentration is shown in Table II.

A significant decrease in the radiation decomposition of 5-FU was observed for solutions containing 5% glucose, in comparison to solutions prepared without glucose. Accordingly, the irradiation of glucose containing solutions were extended to doses as high as 4000 Gy. Aqueous glucose solutions irradiated under equal conditions were used as blanks. This was necessary to avoid possible interferences arising from radiolysis products of glucose (16). The results are given in Table III.

DISCUSSION

In aqueous solutions, free radicals derived from radiolysis of water are usually responsible for solute breakdown. The effect of

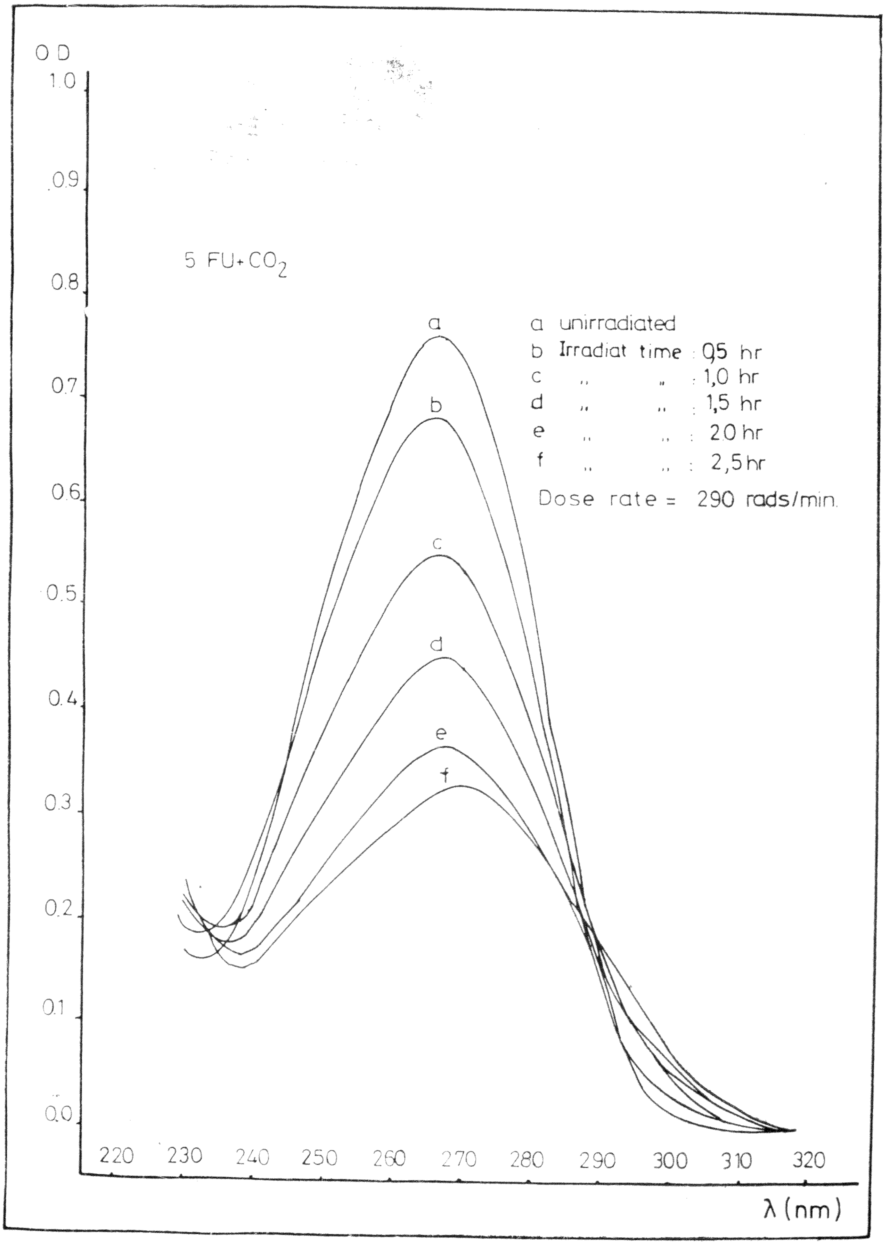

Figure 3 : Gamma radiolysis of $5-FU+CO_2$

TABLE I. G(-5FU) values obtained from the γ-radiolysis of 5-FU solutions of various compositions

Composition	G(-5FU)
5-FU + N_2O	3.41
5-FU + N_2	1.76
5-FU + O_2	1.53
5-FU + CO_2	1.27
5-FU + Glucose + CO_2	0.98
5-FU + Glucose + N_2	0.42
5-FU + Glucose + N_2O	0.33
5-FU + Glucose + O_2	0

TABLE II. Effect of initial 5-FU concentration in γ-radiolysis

Concentration	$(\% \frac{\Delta OD}{OD})$			
	N_2O	O_2	N_2	CO_2
1×10^{-4} M	93.4	89.0	70.8	68.6
2×10^{-4} M	88.2	98.9	76.4	75.1
1×10^{-3} M	73.9	71.7	35.7	29.4
1×10^{-2} M	6.2	10.3	7.0	8.8
1×10^{-1} M	5.7	6.2	0.7	3.3

TABLE III. Percentage decomposition of 5-FU solutions containing 5% glucose in γ-radiolysis

Condition	$(\% \frac{\Delta OD}{OD})$	
	2800 Gy	4000 Gy
5-FU + Glucose + CO_2	69.3	
5-FU + Glucose + N_2	62.5	80.3
5-FU + Glucose + N_2O	40.2	68.8
5-FU + Glucose + O_2	5.1	5.6

high energy radiations on water (17) may be summarised as:

$$H_2O \rightsquigarrow 2.7(e_{aq}^-) + 2.7(\cdot OH) + 0.55(H\cdot) + 0.45(H_2) + 0.71(H_2O_2)$$

where the numbers before chemical symbols represent G-values. It can be seen from Table I that the highest 5-FU decomposition occurred in aqueous solutions saturated with N_2O. This could be due to the increased yield of $\cdot OH$ radicals in N_2O-saturated solutions, where e_{aq}^- is converted to an equivalent amount of $\cdot OH$ radical:

$$e_{aq}^- + N_2O \xrightarrow{-H_2O} \cdot OH + OH^- + N_2$$

The decomposition rate was found to be low in aqueous solutions of 5-FU mixed with glucose which acts as scavenger of $\cdot OH$ and $H\cdot$ radicals. This observation suggests that under gamma irradiation $\cdot OH$ radicals are responsible for the permanent destruction of 5-FU.

In oxygen-contained solution, O_2 scavenge e_{aq}^- according to the following reaction:

$$e_{aq}^- + O_2 \rightarrow O_2^-$$

The formed O_2^- radical is a weak reducing species. This is in agreement with the lower decomposition found in oxygenated solutions compared to the decomposition observed in N_2–saturated solutions. Besides, no significant radiation decomposition of 5-FU was observed in solutions containing both glucose and oxygen due to their expected combined protective effects.

Irradiation of 5-FU solutions of various concentrations, saturated with the above cited gases, showed that the decompositions at lower 5-FU concentrations depend on the kind of the gas used. But this dependency vanished at higher 5-FU concentrations where the decomposition found to be low.

Irradiation of CO_2-saturated 5-FU solutions to 4000 Gy in the presence of glucose resulted in $\sim 80\ \%$ decomposition. The lowest decomposition (5.5%) was observed in O_2-saturated solutions. It is thus apparent that glucose in the presence of O_2 is a suitable additive for protecting 5-FU from radiolytic decomposition in aqueous solutions.

As it has been already mentioned, radiotherapy and chemotherapy are, generally, applied together. We conclude that, 5-FU administered in 5 % glucose solutions to patients with malignant tumours can be used safely due to its low 5-FU concentration and the presence of glucose and oxygen, preventing significant radiation decomposition.

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