Interaction between 5-hydroxytryptamine and antitumoural drugs

SIR,—The recent observation made by Uroic, Rabadjija & Supek (1964) about the increased toxicity of mustine hydrochloride (nitrogen mustard) in animals pretreated with 5-hydroxytryptamine (5-HT), prompted us to report data dealing with the interaction between 5-HT and alkylating agents.

Tumour-bearing female mice of Swiss strain, average weight 22 ± 2 g, kept in groups of 10 in Makrolon cages at room temperature (22°) and relative humidity 60%, were used in all experiments. Sarcoma 180 was implanted subcutaneously in the intrascapular area in fragments of 10 mg average weight. Ehrlich carcinoma was transplanted in the same area using 0·2 ml (about 3 million cells) of the ascite form.

Treatment started 6 days after transplantation of the tumour and was given daily for 6 days. Animals were killed two days after 5-hydroxytryptamine creatinine sulphate was given intraperitoneally, 10 min before DL-sarcolysine or 5-fluorouracil. The results obtained are reported in Table 1.

TABLE 1. COMBINATION OF 5-HT WITH DL-SARCOLYSINE OR 5-FLUOROURACIL IN TUMOUR-BEARING MICE**

Treatment (mg/kg/i.p. × 6 days)		Tumour	Tumour weight	Leucocyte counts	Spleen weight	Intestinal DNA
Saline		E	100 ± 8	100 ± 12	100 ± 9	100 ± 5
5-HT	62·5	"	110 ± 15	82 ± 12	68 ± 6	—
5-HT	250	"	75 ± 14	84 ± 13	61 ± 2	119 ± 6
DL-Sarcolysine	2·1	"	91 ± 15	83 ± 7	58 ± 5	—
5-HT +	62·5					
DL-Sarcolysine	2·1	"	79 ± 15	70 ● 8	38 ± 3	—
5-HT +	250					
DL-Sarcolysine	2·1	"	71 ± 12	43 ± 1	28 ± 3	—
DL-Sarcolysine	6·3	"	79 ± 11	37 ± 4	17 ± 1	90 ± 3
5-HT +	62·5					
DL-Sarcolysine	6·3	"	63 ± 13	54 ± 5	10 ± 2	—
5-HT +	250					
DL-Sarcolysine	6·3 *	"	31 ± 6	42 ± 5	9 ± 1	77 ± 4
5-Fluorouracil	29	"	51 ± 6	51 ± 4	51 ± 3	121 ± 16
5-HT +	250					
5-Fluorouracil	29	"	25 ± 3	27 ± 2	34 ± 3	79 ± 8
Saline		S180	100 ± 24	100 ± 15	100 ± 14	100 ± 3
DL-Sarcolysine	4·2	"	67 ± 19	19 ± 2	30 ± 3	94 ± 2
5-HT +	500					
DL-Sarcolysine	4·2	"	15 ± 4	7 ± 1	13 ± 1	90 ± 3
DL-Sarcolysine	6·3	"	48 ± 12	16 ± 1	14 ± 1	90 ± 5
5-HT +	500					
DL-Sarcolysine	6·3 †	"	21 ± 5	8 ± 1	10 ± 1	72 ± 5

* Mortality 3/8.
† Mortality 4/10.
E = Ehrlich carcinoma; S 180 = sarcoma 180.
** The effect of the various treatments are expressed as % of the control values (± s.e.). Intestinal DNA was determined according to Ceriotti (1955).

It is evident that 5-HT tends to increase the antitumoural effect of DL-sarcolysine particularly at given doses. However, the toxic effects of DL-sarcolysine on the leucocyte number, spleen weight and intestinal desoxyribonucleic acid (DNA) are also enhanced by 5-HT. Furthermore its effect is not specific for a nitrogen mustard derivative because the activity of 5-fluorouracil was also increased by the amine.

In other experiments, 5-HT at a dose of 250 mg/kg i.p., was given in Ehrlich carcinoma-bearing mice 10 min before equitoxic doses (1/2 of the LD50 determined after 6 days of treatment) of the following antitumoural drugs: DL-sarcolysine (6·3 mg/kg) cyclophosphamide (125 mg/kg) triethylenemelamine (1 mg/kg) 5-fluorouracil (29 mg/kg) and Mitomycin C (7-amino-9α-methoxymitosane) (2·65 mg/kg). On the 7th day the combinations 5-HT and triethylenemelamine and 5-HT and Mitomycin C were lethal for all the mice (10 per

group) whilst in the other combinations or treatments with the drugs alone no toxicity was recorded.

In our opinion the latter data show that the observed interactions between 5-HT and a nitrogen mustard derivative are not specific. Furthermore the effect of 5-HT is unlikely to have a therapeutical interest after systemic administration because of the large dose of 5-HT involved and the lack of a specific effect on the tumour growth.

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