

BLOOD LEVELS OF 5-FLUOROURACIL DURING INTRAVENOUS INFUSION

SIR,—Several clinical studies agree that intravenous infusion of 5-fluorouracil (5FU) over a period of five days is less toxic than bolus intravenous injections of drug daily for five days (Moertel *et al.*, 1972; Seifert *et al.*, 1975), although there is disagreement about the frequency of response of gastrointestinal tumours so treated (Moertel *et al.*, 1972; Moertel and Reitemeier, 1969). Blood levels measured after oral and intravenous administration of 5FU have shown the former to be unpredictable, but in the latter case the drug has constant kinetics with a half-life in plasma of 10 min (Cohen *et al.*, 1974). Measurements of 5FU levels during infusion of the drug have not been reported.

We have recently described a new sensitive assay method for measuring 5FU in plasma by extracting the drug from plasma using a novel procedure followed by gas chromatography and mass spectrometry, with a sensitivity down to approximately 8×10^{-8} M or 10 ng/ml (Hillcoat *et al.*, 1975). Using this method, plasma levels of 5FU have been determined in six patients with malignant disease of the gastrointestinal tract receiving 5FU at 30 mg/kg/day/litre

of 5% dextrose, by gravity infusion. One patient, J.H., had the infusion repeated three months later. The results are shown in the Table. Most patients showed fluctuating levels often of a considerable degree. Patient G.A. on three occasions had high levels with a peak value of 2.4 times the average peak value found. This patient showed only minor marrow toxicity (the nadir of peripheral granulocyte count was 67% of pretreatment levels) and mild stomatitis. Patient J.B., on the other hand, had a nadir of 43% but showed lower blood levels, although higher than those in the remaining patients. Thus, blood levels of 5FU did not relate to toxicity in this small series. Only patient G.A., with the highest and most sustained blood levels, had a clinical response to treatment. Patient J.H., on his second infusion, showed very similar blood levels of 5FU to those observed during his first infusion.

The rate of infusion may have played a role in the marked variation in drug levels observed (up to 80 fold) and may result from inability to maintain constant flow rates by this method. Proper administration of this drug may require infusion by

TABLE.—*Plasma Levels of 5-fluorouracil in Patients Treated by Infusion of Drug for 5 Days*

Day	G.A.		J.B.		J.H. 1 ³		J.H. 2 ⁴		E.C.		B.A.		A.T.	
	Time ¹	5FU ²	Time	5FU	Time	5FU	Time	5FU	Time	5FU	Time	5FU	Time	5FU
1	1	0					8	200	1	16	3	30	2	107
	18	342	24	370	18	94	13	28	17	5	16	66	20	0
2					25	20	32	80	41	59	40	142	26	42
	42	361	48	470	42	44			48	5	47	93	44	<5
3					49	42	56	85			64	49	50	0
	66	887	72	83	66	214	63	108	72	88	71	23	68	35
4					73	150	80	43	89	99	88	494	74	328
	90	143			90	28	87	158	93	95	96	232	92	53
5							104	82	113	119	112	81	98	136
	114	365	116	53	120	68	111	133	117	54	120	0	116	403
													122	120

¹ Hours; ² ng/ml (100 ng/ml = 7.7×10^{-7} M); ³ Feb. 5; ⁴ May 3.

peristaltic pump to sustain blood levels.

Further studies of this type are indicated, especially to relate blood levels to toxicity and to clinical response.

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IMPLICATIONS OF THE OSMOLALITIES OF SOME COMMONLY USED TISSUE CULTURE MEDIA

SIR,—The culture of human tumour cells *in vitro* is an essential prerequisite to the better understanding of tumour biology. Such cultures are needed for studies of the mechanisms of specific tumour immunity and the effectiveness of various chemotherapeutic agents. However, the universally poor results reported of attempts to culture human tumours *in vitro* lead one to conclude that the standard tissue culture media (originally devised for animal—normal rodent—tumours) might not be suitable for the long term culture of human tumour cells.

As part of a study of the possible variables affecting the growth of human tumour cells *in vitro*, the osmolalities of various tissue culture media have been determined and the influence of varying the osmolality of the medium on the growth of human tumour cells has been studied.

Single strength media obtained commercially (Gibco-Biocult, Paisley or Flow Laboratories, Irvine) were used for osmolality determinations. Osmolalities were measured on a Model 65-31 Osmometer (Advanced Instruments Inc., Massachusetts, U.S.A.).

All osmolalities were determined at least twice on separate occasions and in 2 cases have been confirmed by the manufacturer.

Thirteen of the more commonly used tissue culture media have been tested both with and without the addition of 20% foetal calf serum, and the results are shown in the Table. Two separate batches were tested of 5 of the media. In 3 instances one batch was hypotonic and the other was hypertonic. Both batches of the other two media were hypertonic. In addition, all but 2 (Hams F10 and Diploid growth medium) of the media tested only once were hypertonic for human cells. The high percentage of hypertonic media found here is disturbing because study of the growth of tumour cells in primary culture indicates that they grow less well in hypertonic medium than in hypotonic medium (unpublished results). The osmolalities of most of the media are nearer to that of rodent sera than to human serum. The fact that foetal calf serum is hypertonic for human cells should also be considered.

The variation between different batches of the same medium (*e.g.* M 199, RPMI 1640