Anti-Cancer Drugs 1995, **6**, pp. 163–164

Letter to the editor

Addition of heparin in 5-fluorouracil solution for portal vein infusion has no influence on its stability under clinically relevant conditions

M Barberi-Heyob, JL Merlin, M Vigneron[1] and T Conroy[2]

Laboratoire de Recherche en Oncologie, Centre Alexis Vautrin, [1]Pharmacie, Centre Hospitalier Régional Universitaire (CHRU) and [2]Département d'Oncologie médicale, Centre Alexis Vautrin et Service de Chirurgie C (CHRU), Avenue de Bourgogne, Brabois 54511 Vandœuvre-les-Nancy, France. Tel: (+33) 83 59 85 06; Fax: (+33) 83 44 60 71.

Adjuvant systemic chemotherapy and combined radiotherapy plus chemotherapy both increase survival rate in high risk colon and rectal cancers, respectively. Portal vein infusion of 5-fluorouracil (5-FU) has also been advocated as a rational therapeutic approach, given that malignant cells reach the liver and other sites of the body via the portal circulation. In 1985, Taylor *et al.*[1] reported a controlled study comparing surgical resection alone to a 7-day perioperative course of intraportal 5-FU and heparin. Results were strikingly positive, with a significant survival improvement in favor of the 5-FU group. More recently, Fielding *et al.*[2] reported a randomized study comparing a control group to a group treated with intraportal 5-FU + heparin or heparin alone. They demonstrated an increase in survival for patients receiving 5-FU + heparin which was significant for Dukes' C carcinoma. Heparin alone produces no survival benefit. A meta-analysis of six trials using adjuvant intraportal 5-FU demonstrated a 31 ± 8% reduction in the mortality rate in favor of the treated group.[3] In adjuvant studies, heparin is added in the 5-FU infusion to prevent catheter obstruction and portal vein thrombosis. In such conditions, and in order to determine whether 5-FU remains stable when mixed with heparin, the 5-FU concentrations were measured under conditions simulating the temperature and light conditions encountered during the storage and clinical use of this mixture. To determine drug concentrations, the average body surface area was considered to be 1.7 m^2 and the daily dose of 5-FU was fixed at 500 mg/m^2. The formulation of 5-FU (50 mg/ml, Fluoro-uracile®; Produits Roche, Neuilly, France) in sodium hydroxide was used. The 5-FU solutions were diluted in 0.9% sodium chloride, 5% dextrose and 2500 UI heparin were added in the 500 ml polyvinyl chloride (PVC) plastic bags (Tutiflex™; Aguettant, Lyon, France). This gave a theoretical initial 5-FU concentration of 0.8 mg/ml. The PVC bags were maintained for 24, 48 or 72 h either at room temperature (25°C) in the presence of light to simulate clinical use or at 4°C in the dark to simulate conservation in the refrigerator. At the time

Table 1. Evolution of 5-FU concentrations (mean ± SEM) and pH values in PVC plastic bags and in different storage conditions

Sampling times (h)	4°C (dark)		25°C (light)	
	5-FU concentrations (mg/ml)	pH	5-FU concentrations (mg/ml)	pH
0	0.799 ± 0.007	8.48	0.799 ± 0.031	8.48
24	0.794 ± 0.013	8.59	0.782 ± 0.013	8.49
48	0.792 ± 0.015	8.53	0.813 ± 0.015	8.43
72	0.769 ± 0.015	8.57	0.774 ± 0.027	8.47

Theoretical 5-FU concentrations in containers were 0.8 mg/ml.

Correspondence to M Barberi-Heyob

of each sampling, 5 ml of each solution was used for an immediate determination of 5-FU concentration. All determinations were performed in triplicate by high-performance liquid chromatography (HPLC) with UV detection at 268 nm as already reported.[4] With this HPLC method and for concentrations above 500 ng/ml, the coefficient of variation for interassay reproducibility was less than 7.3%.[4] As described in Table 1, 5-FU remains stable in both conditions tested. However, after 72 h of storage, we observed a decrease of 4.6 and 3.2% at 4 and 25°C, respectively; however, these slight alterations of 5-FU concentrations represent the usual inter-experimental variations and are not relevant in clinical practice. In any case, neither precipitate formation nor change in solution transparency were observed, indicating that light and ambiant temperature have no effect on 5-FU concentrations in PVC plastic bags containing dextrose and heparin. In addition, pH values remained stable in both conditions tested. The protection of PVC plastic bags from light is not required for this admixture and in therapeutic conditions. In view of our results (Table 1), the stability of 5-FU mixed with heparin in clinically relevant conditions appears satisfactory.

To our knowledge, this is the first stability study of 5-FU-heparin mixture in PVC bags submitted to different storage conditions.

References

1. Taylor I, Machin D, Mullee M, *et al.* A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985; **72**: 359–63.
2. Fielding LP, Hittinger R, Grace RH, *et al.* Randomised controlled trial of adjuvant chemotherapy by portal-vein infusion after curative resection for colorectal adenocarcinoma. *Lancet* 1992; **340**: 502–6.
3. Gray R, James R, Mossman J, *et al.* AXIS, a suitable case for treatment. *Br J Cancer* 1991; **63**: 841–5.
4. Barberi-Heyob M, Merlin JL, Weber B. Analysis of 5-fluorouracil in plasma and urine by high-performance liquid chromatography. *J Chromatogr Biomed Applic* 1992; **581**: 281–6.