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ORIGINAL ARTICLE

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Stability of commercial solutions of 5-fluorouracil for continuous infusion in an ambulatory pump

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Abstract *Purpose*: The stability of 5-fluorouracil (FU) Roche solutions in a portable infusion pump under prolonged "in-use" conditions (32 °C, in the dark) was studied, especially with respect to the formation of the cardiotoxic compounds fluoroacetaldehyde (Facet) and fluoromalonic acid semialdehyde (FMASAld). *Methods*: The solutions, prepared according to three protocols frequently used at the Anticancer Centre in Toulouse, were analysed by ^{19}F NMR immediately after preparation (T_0) and after 2, 3 or 10 days (T_F) in the pump. *Results*: The commercial solution already contained 64 fluorinated "impurities", among them fluoride ion (F^-), FMASAld and Facet. The concentration of FU did not change significantly between T_0 and T_F, whatever the protocol. The levels of F^- had not increased significantly after 2 or 3 days, but had increased by about 50% after 10 days. The increases in FMASAld levels were low (12–28%) albeit significant in the three protocols. The levels of Facet had increased by a factor of about 2 after 2 or 3 days, and by a factor of >3 after 10 days. The levels of the other fluorinated compounds were constant during the first 2 or 3 days, but had increased by about 30% after 10 days. FU Dakota lyophilizates, analysed immediately after reconstitution, contained neither FMASAld nor Facet. After 2 days at 25 °C, low levels of FMASAld were present but Facet could still not be detected. *Conclusion*: This study showed that special attention must be paid to the risk of increasing concentrations of highly toxic FMASAld and Facet when FU is administered via a pump for long periods of time. It would be preferable not to exceed 3 days of treatment when patients receive FU from a portable infusion pump. This underlines the interest in using a lyophilized formulation of FU in clinical practice.

Key words Fluorouracil · Stability · Cardiotoxic compounds · Ambulatory pump · Lyophilizate

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Introduction

Over the last decade, there have been a number of reports of increased cardiotoxicity in patients receiving high doses of 5-fluorouracil (FU) (see reference 4 and references cited therein). Mechanisms involved in FU-associated cardiotoxicity and their multiple interactions have not yet been identified exactly. Among several hypotheses, we have suggested that toxic degradation products in commercially available FU preparations could be involved in the pathogenesis of FU cardiotoxicity. Indeed, using fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectroscopy, we have found that commercial vials of FU contain cardiotoxic fluorinated "impurities" [7, 8]. They are not true impurities but degradation compounds of FU, resulting from the storage of the drug in the alkaline conditions required for its dissolution.

When the vehicle is Tris buffer (Trometamol), two main degradation compounds are formed. These are the oxazolidine adducts of Trometamol with fluoroacetaldehyde (Facet-Tris) and fluoromalonic acid semialdehyde (FMASAld-Tris) as Tris is known to react with aldehydes. However, when the vehicle is sodium hydroxide (NaOH), ^{19}F NMR analysis of commercial vials of various brands and batches from different countries has revealed 50–100 fluorinated "impurities" resulting from the hydrolysis of FU in this alkaline medium. Facet and FMASAld are also found in these solutions but as free forms since there is no Tris in the vials [8].

Facet and FMASAld are highly cardiotoxic in the isolated perfused rabbit heart model [7, 8]. Indeed, Facet-Tris at doses of 0.56 μmol/kg body weight

(0.09 mg/kg) and 2.36 μmol/kg (0.39 mg/kg) leads to ventricular arrest at 222 ± 15 and 140 ± 15 min, respectively. Similarly, FMASAld-Tris at doses of 2.36 μmol/kg body weight (0.49 mg/kg) and 14 μmol/kg (2.9 mg/kg) shows the same effect at 132 ± 21 and 84 ± 22 min, respectively. Free FMASAld is even more cardiotoxic: injected at a dose of 14 μmol/kg body weight (1.5 mg/kg), the ventricular arrest occurs at 30 ± 4 min. Moreover, cardiotoxic fluoroacetate and 2-fluoro-3-hydroxypropionic acid, from Facet and FMASAld metabolism, respectively, are found in the urine of patients treated with FU [6, 9].

Continuous slow infusions of FU are very common as they result in an increased antitumor effect and less toxicity. However, the manufacturer's instructions state that dilute solutions of FU are stable for only 8 h after preparation. The aim of this study was to investigate using ^{19}F NMR the stability of commercial solutions of FU, especially with respect to Facet and FMASAld levels, in ambulatory pumps in three protocols currently used at the Anticancer Centre in Toulouse. The stability of new FU lyophilizates was also studied.

Materials and methods

Materials

FU used in the experiments with the pump was the Roche commercial solution (batch FO32Y; Produits Roche, Neuilly, France) containing 1 g FU in 20 ml NaOH, pH 9.1. The study was completed 1.5 years before the withdrawal date of the drug. This batch was quite representative for FMASAld and Facet of the eight FU NaOH solutions from various brands and batches we had previously analysed (Table 1). The ambulatory pump was a model 5100 HF CADD-1 (series number 104716, production number 605150, capacity 100 ml; Pharmacia Deltec, St Paul, Minn.). The Dakota lyophilized formulations of FU, which will soon be available commercially as the manufacturer has recently received the authorization, contained 0.25, 0.5 or 1 g of FU.

Protocols and preparation of FU solutions

The three protocols chosen were those used daily at the Anticancer Centre in Toulouse, and are as follows. Patients received FU Roche at a dose of (a) 1 g/m^2 per day for 4 days with the pump refilled on day 2, (b) 0.75 g/m^2 per day for 5 days with the pump refilled on day 3, (c) 0.3 g/day for 21 days with the pump refilled on day 10.

To prepare the solutions of FU Roche, the average body surface area was considered to be 1.6 m^2. For each protocol, 105 ml FU solution was prepared, and 100 ml was placed in the pump reservoir and the remaining 5 ml immediately frozen and stored at −80 °C pending ^{19}F NMR analysis which was carried out within 7 days. This sample was the initial time (T_0) sample. The pump reservoir was placed in a waterbath at 32 °C in the dark to mimic the conditions of prolonged infusion of a drug via a pump kept beneath the patient's clothing. The liquid running out continuously from the pump was collected in a beaker and discarded. After 2, 3 or 10 days of pump functioning, the remaining FU solution in the pump reservoir was removed and immediately analysed or frozen at −80 °C until analysis, which was carried out within 7 days. This sample was the final time (T_F) sample.

For the first protocol, 86.2 ml of the commercial solution of FU was mixed with 18.8 ml 5% dextrose (to give a theoretical initial FU concentration of 41 mg/ml, i.e. 315.4 μmol/ml) and the flow rate of the pump was set at 39 ml/day. For the second protocol, 84.0 ml of the commercial solution of FU was mixed with 21.0 ml 5% dextrose (theoretical initial FU concentration of 40 mg/ml, i.e. 307.7 μmol/ml) and the flow rate of the pump was set at 30 ml/day. For the third protocol, 79.0 ml of the commercial solution of FU was mixed with 26.0 ml 5% dextrose (theoretical initial FU concentration of 37.5 mg/ml, i.e. 288.5 μmol/ml) and the flow rate of the pump was set at 6–8 ml/day. Three experiments were carried out for the first and second protocols and four for the third.

We checked that there were no evolutionary changes in the samples during storage at −80 °C. We stored three vials of FU Roche commercial solution (batch FO32Y) for 1 month at −80 °C. The data from the ^{19}F NMR analysis are presented in Table 1.

The Dakota lyophilized formulations of FU were reconstituted immediately before ^{19}F NMR analysis in 5, 10 or 20 ml sterile water for injection, giving a theoretical initial FU concentration of 50 mg/ml (384.6 μmol/ml). The ^{19}F NMR spectra were recorded immediately after reconstitution (T_0) and after 2 days at 25 °C in the dark (T_F). The conditions of this study were different as the pharmaceutical company was not interested in the evolution of the lyophilizates in an ambulatory pump. The possible interactions with the container were therefore not taken into account.

The pH of the T_0 samples was measured immediately after preparation, and the pH of the T_F samples was measured after their recovery.

^{19}F NMR analysis

Spectra were recorded at 282.4 MHz with ^{1}H-decoupling on a Bruker WB-AM 300 spectrometer under the following conditions: probe temperature, 25 °C; sweep width, 41,667 Hz; 32,768 data points zero-filled to 65,536; pulse width, 7 μs (flip angle about 40°); pulse interval, 3.4 s; no exponential multiplication. The chemical shifts (δ) are expressed in parts per million relative to the resonance peak of trifluoroacetic acid (5% w/v aqueous solution) as external chemical shift reference. The concentrations of the fluorinated compounds were measured by comparing the expanded areas of

Table 1 Amounts (μmol/ml, means ± SD) of FU, F^-, FMASAld, Facet and other fluorinated degradation compounds in the commercial Roche solution used in this study and after storage for 1 month at −80 °C, and in FU solutions of various brands and from various batches. The number of experiments corresponds to the measurements of the commercial Roche solution and the different T_0 samples of the solutions prepared, considering a theoretical concentration of 50 mg FU/ml (i.e. 384.6 μmol/ml)

	FU	F^-	FMASAld	Facet	Sum of other fluorinated impurities
Batch F032Y (n = 11)	382 ± 23	0.72 ± 0.06	0.054 ± 0.006	0.025 ± 0.003	1.50 ± 0.11
Batch F032Y after 1 month storage at −80 °C (n = 3)	395 ± 24	0.69 ± 0.06	0.056 ± 0.003	0.025 ± 0.003	1.43 ± 0.04
Mean of eight FU solutions (50 mg/ml) of various brands and batches	407 ± 29	2.5 ± 1.7[a]	0.058 ± 0.012	0.039 ± 0.012	4.1 ± 2.0[a]

[a] The amounts of fluoride ion and other fluorinated impurities were highly different in the various brands and batches

their respective NMR signals with that of the external standard for quantification placed in a coaxial capillary, namely a solution of sodium parafluorobenzoate (FBEN) in D_2O doped at saturation with chromium (III) acetylacetonate ($Cr(acac)_3$) to shorten the longitudinal relaxation time (T_1) of FBEN. The apparent concentration of the FBEN peak was previously calibrated. $Cr(acac)_3$ (about 2.5 mg) was also added to the samples. With the NMR recording conditions used, fully relaxed spectra were obtained and peak areas were therefore directly proportional to concentrations. The areas were determined after the different signals were cut out and weighed.

Statistics

All results are expressed as means ± SD. Statistical significance was determined by the use of Student's *t*-test. A *P*-value of < 0.05 was considered statistically significant.

Results

^{19}F NMR spectra of the FU Roche vial (Fig. 1) and the T_0 samples of the three protocols showed the signals of FU ($\delta = -93.1$ ppm) and 64 fluorinated "impurities", which are degradation compounds of FU formed over time in the basic medium necessary to dissolve the drug. The three identified were fluoride ion (F^-, $\delta = -43.6$ ppm) and the two cardiotoxic compounds, Facet ($\delta = -155.1$ ppm) and FMASAld ($\delta = -126.5$ ppm). In the commercial FU solution (batch FO32Y), F^- which comprised 0.72 ± 0.06 μmol/ml of the FU solution was the main "impurity". FMASAld and Facet comprised 0.054 ± 0.006 and 0.025 ± 0.003 μmol/ml, and the other fluorinated "impurities" 1.5 ± 0.1 μmol/ml (Table 1).

The pH did not change significantly whatever the protocol (Table 2). The concentration of FU was not significantly different between the T_0 and T_F samples (Table 2). The variations measured were in the range of the accuracy of the method (5–10% depending on the concentration [10]). The level of F^- had not increased significantly after 2 or 3 days, but had increased by about 50% after 10 days. The increase in FMASAld levels were low (12–28%) albeit significant in the three protocols. The levels of Facet had increased by a factor of about 2 after 2 or 3 days, and by a factor of > 3 after 10 days. The levels of the other fluorinated compounds were constant during the first 2 or 3 days, but had increased by about 30% after 10 days.

Even if the experimental conditions were quite different, it might be interesting to compare the data with

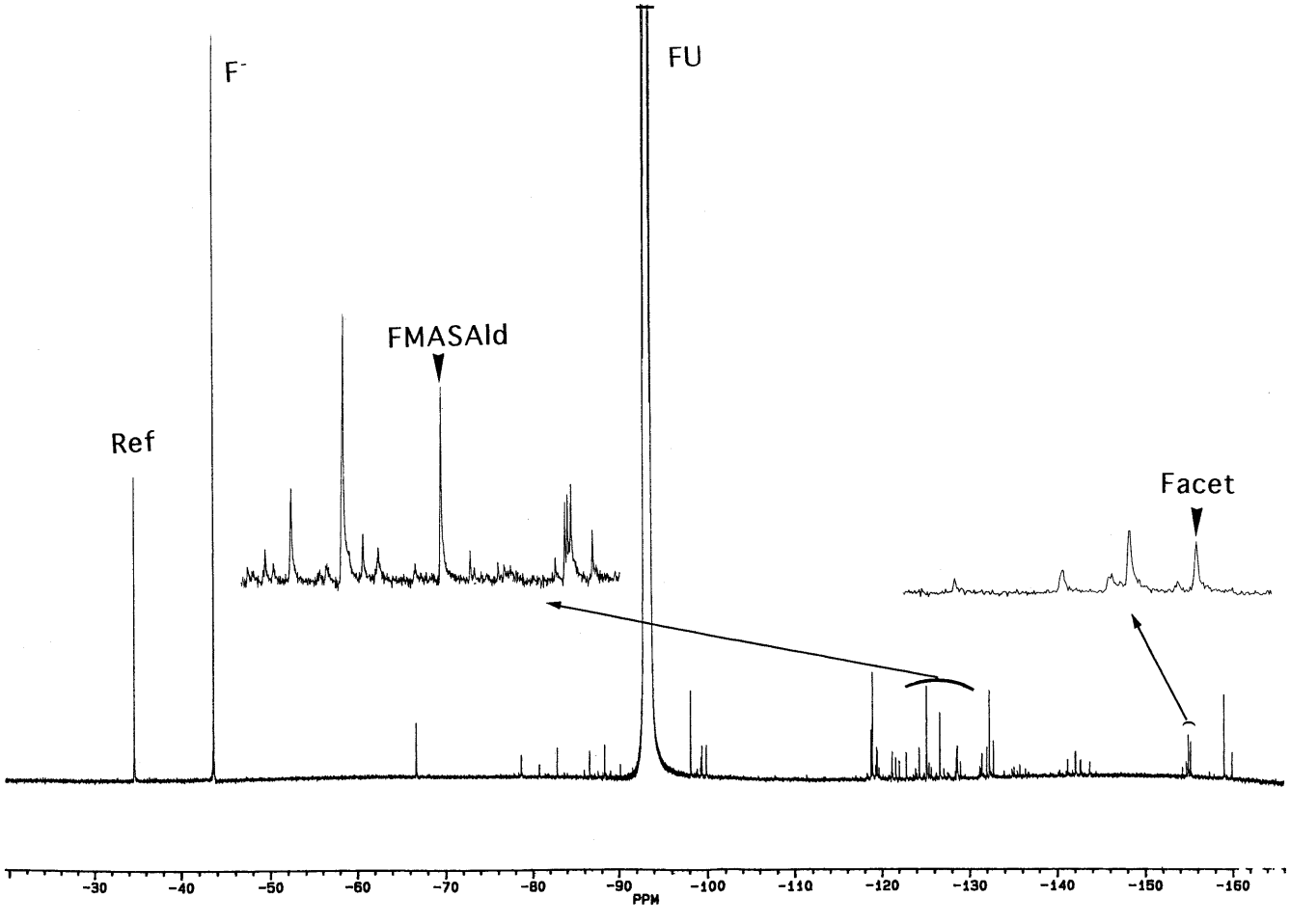

Fig. 1 ^{19}F NMR spectrum of the FU Roche commercial solution (batch FO32Y) immediately after opening the vial (*Ref* reference, *F*$^-$ fluoride ion, *FU* fluorouracil, *FMASAld* fluoromalonic acid semialdehyde, *Facet* fluoroacetaldehyde)

Table 2 pH of commercial Roche solutions, and their contents (μmol/ml, means ± SD) of FU, F^-, FMASAld, Facet and other fluorinated degradation compounds, diluted as described in Materials and methods before (T_0) and after 2, 3 or 10 days (T_F) in a pump at 32 °C (*NS* not significant, *S* significant)

		pH	FU	F^-	FMASAld	Facet	Sum of other fluorinated impurities
2 days (n = 3)	T_0	9.14 ± 0.05	324.6 ± 12.1	0.61 ± 0.05	0.043 ± 0.006	0.019 ± 0.003	1.17 ± 0.08
	T_F	9.11 ± 0.02	312.5 ± 23.1	0.64 ± 0.01	0.055 ± 0.007	0.041 ± 0.005	1.15 ± 0.13
Student's t-test			NS	NS	S	S	NS
3 days (n = 3)	T_0	9.11 ± 0.04	299.0 ± 30.7	0.56 ± 0.04	0.041 ± 0.002	0.021 ± 0.001	1.16 ± 0.04
	T_F	9.12 ± 0.03	279.9 ± 9.3	0.61 ± 0.02	0.050 ± 0.003	0.037 ± 0.004	1.19 ± 0.02
Student's t-test			NS	NS	S	S	NS
10 days (n = 4)	T_0	9.20 ± 0.06	287.2 ± 10.0	0.54 ± 0.05	0.041 ± 0.004	0.018 ± 0.002	1.19 ± 0.09
	T_F	9.09 ± 0.09	295.1 ± 12.6	0.79 ± 0.17	0.046 ± 0.003	0.061 ± 0.002	1.52 ± 0.08
Student's t-test			NS	S	S	S	S

Table 3 pH of reconstituted lyophilized formulations of FU Dakota (50 mg/ml, 384.6 μmol/ml), and their contents (μmol/ml) of FU, F^-, FMASAld, Facet and other fluorinated degradation compounds, before (T_0) and after 2 days (T_F) at 25 °C

	pH	FU	F^{-a}	FMASAld	Facet	Sum of other fluorinated compounds
T_0	8.75 ± 0.02	392.1 ± 12.4	0.03 ± 0.02	0	0	0
T_F	8.76 ± 0.05	380.4 ± 15.7	0.06 ± 0.03	0.0095 ± 0.0015	0	0.024 ± 0.001

[a] The values of the SD are high since the initial and final levels of F^- differed by a factor of 2.3–3 in the three lyophilized formulations of FU analysed

those obtained for the degradation of FU Dakota lyophilizates at 25 °C for 2 days. The ^{19}F NMR spectra of the T_0 samples showed the presence only of FU and F^-, the level of F^- being 25-fold less than in the commercial Roche solution (Table 3). After 2 days at 25 °C, three degradation compounds were found, FMASAld ($\delta = -126.5$ ppm) and two unknown fluorinated products at $\delta = -122.8$ and $\delta = -133.1$ ppm (Fig. 2). Facet was not formed. The amounts of F^-, FMASAld and the sum of other fluorinated compounds were respectively 12-, 6- and 62-fold less than in the commercial Roche solution (Table 3).

Discussion

Stability studies of FU solutions in infusion-pump reservoirs (cassettes, syringes or bags) are numerous [2, 3, 5, 11, 13–15, 17, 19–22]. Most of them have shown that FU is stable over time periods of 3 to 28 days at temperatures ranging from 4 °C (storage conditions) to 30–37 °C (ambulatory "in-use" conditions) [3, 5, 11, 13–15, 17, 20–22] and even 8 weeks at 37 °C in an implantable medication pump [19]. Barberi-Heyob et al. [2] have shown that the stability of FU commercial solutions dosed at 50 mg/ml is good in cassettes and syringes after 7 days of storage at 21 °C or 37 °C in darkness (less than 3% and 6% of FU loss, respectively). However, even in darkness, the diminution of the active component reaches 8–15% and 12–20% after 15 and 30 days of storage, respectively.

HPLC with UV detection is a reliable method for FU determination with coefficients of variation for assay reproducibility ranging between 0.4% and 10% [2, 3, 5, 11–15, 17, 20–22, 24]. However, it is not an appropriate method for detecting and quantifying the degradation compounds from the alkaline hydrolysis of FU, namely urea, F^-, and aldehydes (fluorinated or not) [7, 8, 18, 23], all compounds which are non-UV-assayable. Despite a notable decrease in FU peak height in the stability study of Barberi-Heyob et al. [2] and in a study of forced degradation by heat and addition of concentrated HCl or NaOH solution [17], no degradation peak appeared on HPLC chromatograms.

It therefore seems evident that a better knowledge of FU stability will be gained by assaying its degradation compounds. Urea analysis can be performed using TLC [3] or an enzymatic assay [17]. The mean urea content in recently arrived FU vials has been estimated at 1.2–1.3% [3, 12]. However, some of the urea formed reacts further giving ammonia and carbon dioxide [18]. The level of urea is not therefore an accurate measurement of FU degradation. On the other hand, the determination of all the fluorinated hydrolysis compounds of FU would allow the determination of the true level of degradation, the measurement of F^- being an indicator of the level of nonfluorinated degradation compounds.

^{19}F NMR is the method of choice for this kind of study. It makes possible a direct study of any solution without prior treatment, avoiding the problems encountered in extraction recovery and chemical derivatization. Moreover, all fluorine-containing compounds can be detected simultaneously and quantified in a single run. The detection threshold of ^{19}F NMR ranges between 1 and 5 μM, depending on the spectrometer magnetic field [1]. Even with a sensitivity limit of 5 μM,

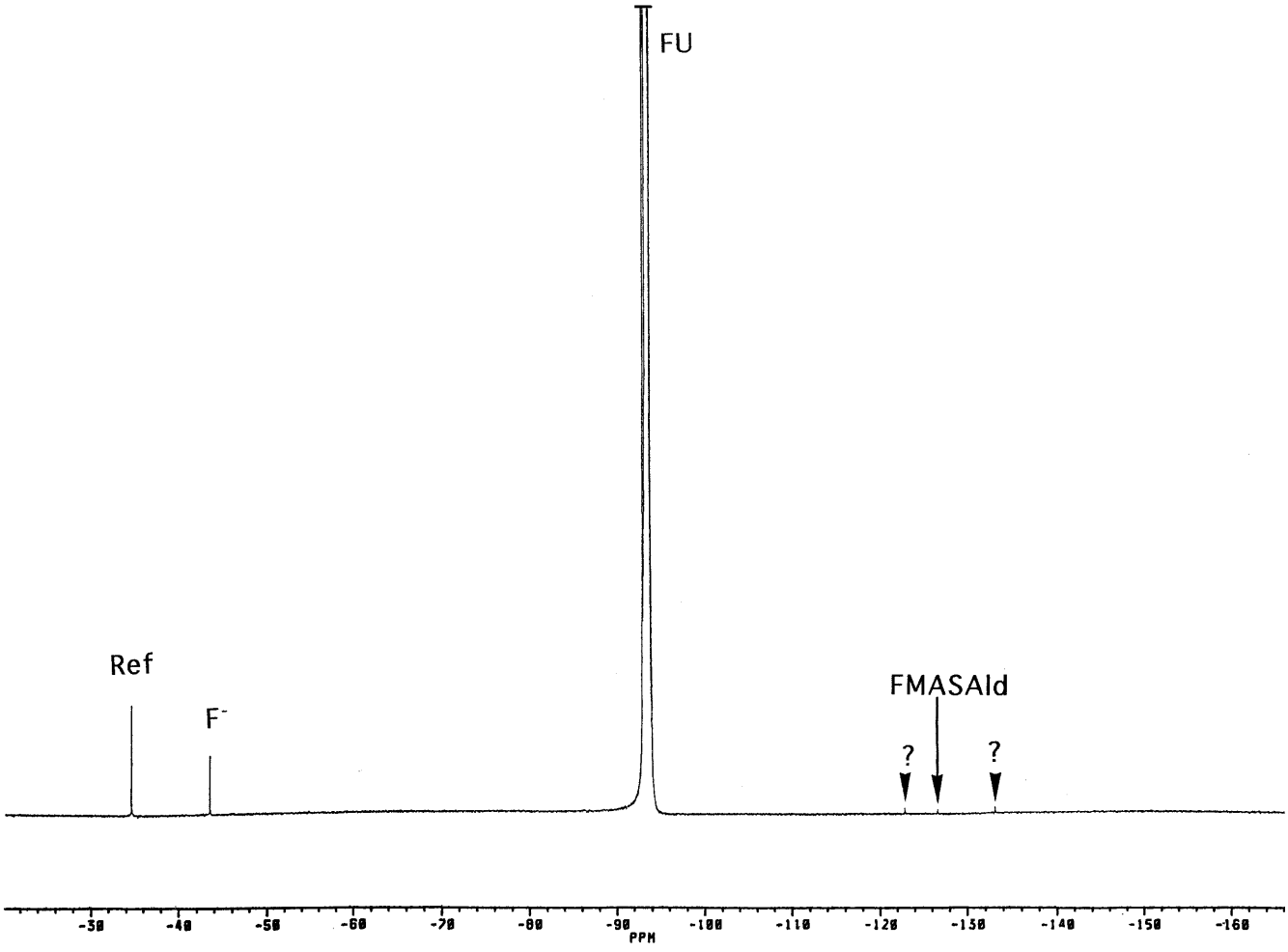

Fig. 2 ^{19}F NMR spectrum of a reconstituted FU Dakota lyophilizate after 48 h at 25 °C (*Ref* reference, *F⁻* fluoride ion, *FU* fluorouracil, *FMASAld* fluoromalonic acid semialdehyde, *?* unknown compounds)

all the fluorinated degradation compounds of FU present in the commercial vials dosed at 50 or 25 mg/ml representing at least 0.001% or 0.002% of initial FU respectively can be detected.

A stable drug is defined as a drug retaining 90–95% of its nominal concentration [3, 20, 22, 24], or a concentration 90–115% of the theoretical concentration [17] (or 90–105% for the French Regulating Agency for drug and drug-related products [12]). If we consider these definitions, this study showed that the concentration of FU was unaffected by 2, 3 or 10 days in a pump at 32 °C (Table 2). These data are in agreement with those already reported by all the authors cited above [2, 3, 5, 11, 13–15, 17, 19–22].

The new findings of this study concern the evolution of the cardiotoxic FU degradation compounds, namely FMASAld and Facet. These compounds are already present in the commercial FU solution, FMASAld at 0.014% relative to FU concentration and Facet at 0.007% (Fig. 1, Table 1). These concentrations are close to those already reported for FU-NaOH solutions at a pH of about 9.2: from 0.010 to 0.018% for FMASAld and 0.006 to 0.016% for Facet, depending on brands and the batches analysed, and most probably on the time between manufacture and analysis [8]. This represents significant progress with respect to the old formulation of FU in Tris. In this case, the stable "depot" forms FMASAld-Tris and Facet-Tris represented 0.65–1.57% and 0.12–0.61%, respectively [7, 8]. The most noteworthy progress would be the use of lyophilized formulations of FU as they contained neither FMASAld nor Facet (Table 3).

This study showed that the variations in the levels of F^- and the sum of fluorinated impurities, except FMASAld and Facet, are only significant after 10 days of storage of a FU solution in a portable-pump reservoir at 32 °C. On the other hand, even if the concentrations of cardiotoxic FMASAld and Facet were low in the FU Roche solution, they showed significant increases after 2, 3 and 10 days (Table 2). The increase was particularly noticeable for Facet after 10 days. It would thus be preferable not to exceed 3 days of treatment when patients receive FU from a portable infusion pump. In FU lyophilizates after 2 days at 25 °C, low levels of FMASAld were also found but Facet could still not be

detected (Table 3). This underlines again the interest in using a lyophilized formulation of FU in clinical practice even if there are disadvantages in terms of safe handling and dose accuracy resulting from the need to reconstitute a dried powder before use. A solution to these problems (degradation of FU in the commercial solutions, reconstitution of the lyophilizates) might be the use of oral preparations of FU. Oral chemotherapy has numerous pitfalls. However, oral FU prodrugs such as capecitabine, UFT and S-1 are currently in clinical trials and seem to provide a more favourable toxicity profile and equivalent antitumor efficacy compared with standard regimens [16].

The presence of cardiotoxic compounds in commercial FU solutions is one of the several hypotheses proposed to explain the cardiotoxicity of this drug (see reference 4 and references cited therein). It must be underlined that there is no clinical demonstration that Facet and FMASAld are involved in FU-related cardiotoxicity as there are no commercially available preparations of FU devoid of "impurities". Moreover, we have previously demonstrated that FU itself is metabolized into cardiotoxic fluoroacetate and 2-fluoro-3-hydroxypropionic acid [1]. However, special attention must be paid to the risk of increasing concentrations of highly toxic FMASAld and Facet when FU is administered in a pump for long periods of time.

References

1. Arellano M, Malet-Martino M, Martino R, Gires P (1998) The anticancer drug 5-fluorouracil is metabolized by the isolated perfused rat liver and in rats into highly toxic fluoroacetate. Br J Cancer 77: 79
2. Barberi-Heyob M, Watelet M, Merlin JL, Bléger C, Schroeder B (1995) Stabilité des préparations de 5-fluorouracile en fonction de différents paramètres. Bull Cancer 82: 1025
3. Baud-Camus F, Crauste-Manciet S, Klein E, Richard L, Brossard D (1996) Stability of fluorouracil in polypropylene syringes and ethylene vinyl acetate infusion-pump reservoirs. Am J Health Syst Pharm 53: 1457
4. Becker K, Erckenbrecht JF, Häussinger D, Frieling T (1999) Cardiotoxicity of the antiproliferative compound fluorouracil. Drugs 57: 475
5. Dine T, Kahlfi F, Duban M, Gressier B, Luyckx M, Brunet C, Meersseman X, Goudaliez F, Cazin M, Cazin JC (1999) Effects of PVC bags sterilization process on the 5-fluorouracil stability. Biomaterials 20: 655
6. Forni M de, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, Canal P, Chevreau C, Carrié D, Soulié P, Roché H, Boudjema B, Mihura J, Martino R, Bernadet P, Bugat R (1992) Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 10: 1795
7. Lemaire L, Malet-Martino MC, Forni M de, Martino R, Lasserre B (1992) Cardiotoxicity of commercial 5-fluorouracil vials stems from the alkaline hydrolysis of this drug. Br J Cancer 66: 119
8. Lemaire L, Malet-Martino MC, Martino R, Forni M de, Lasserre B (1994) The Tris formulation of fluorouracil is more cardiotoxic than the sodium salt formulations. Oncol Rep 1: 173
9. Lemaire L, Arellano M, Malet-Martino MC, Martino R (1996) A novel metabolite of 5-fluorouracil in humans: 2-fluoro-3-hydroxypropionic acid. Proc Am Assoc Cancer Res 37: 1225
10. Malet-Martino MC, Martino R (1992) Magnetic resonance spectroscopy: a powerful tool for drug metabolism studies. Biochimie 74: 785
11. Martel P, Petit I, Pinguet F, Poujol S, Astre C, Fabbro M (1996) Long-term stability of 5-fluorouracil stored in PVC bags and in ambulatory pump reservoirs. J Pharm Biomed Anal 14: 395
12. Martel P, Pinguet F, Petit I, Poujol S, Astre C, Fabbro M (1997) Stability of the principal cytostatic agents during storage at unusual temperatures. Int J Pharm 149: 37
13. Milano G, Renée N (1995) Etude de compatibilité physico-chimique 5-fluorouracile (nouvelle préparation française)-acide folinique. Bull Cancer 82: 189
14. Milano G, Etienne MC, Cassuto-Viguier E, Renée N, Bousselet M, Guillot T, Lecompte D (1993) Long-term stability of 5-fluorouracil and folinic acid admixtures. Eur J Cancer 29A: 129
15. Northcott M, Allsopp MA, Powell H, Sewell GJ (1991) The stability of carboplatin, diamorphine, 5-fluorouracil and mitozantrone infusions in an ambulatory pump under storage and prolonged "in-use" conditions. J Clin Pharm Ther 16: 123
16. Pazdur R, Hoff PM, Medgyesy D, Royce M, Brito RA (1998) The oral fluorouracil prodrugs. Oncology 12 [Suppl 7]: 48
17. Rochard EB, Barthès DMC, Courtois PY (1992) Stability of fluorouracil, cytarabine, or doxorubicin hydrochloride in ethylene vinylacetate portable infusion-pump reservoirs. Am J Hosp Pharm 49: 619
18. Rudy BC, Senkowski BZ (1977) Fluorouracil. In: Florey K (ed) Analytical profiles of drug substances. Academic Press, New York, p 221
19. Sadjak A, Wintersteiger R (1995) Compatibility of morphine, baclofen, floxuridine and fluorouracil in an implantable medication pump. Arzneimittelforschung 45: 93
20. Sewell GC, Allsopp M, Collinson MP, Tyrrell C, Prentice AJ, Copplestone JA (1994) Stability studies on admixtures of 5-fluorouracil with carboplatin and 5-fluorouracil with heparin for administration in continuous infusion regimens. J Clin Pharm Ther 19: 127
21. Stiles ML, Allen LV, Tu Y-H (1989) Stability of fluorouracil administered through four portable infusion pumps. Am J Hosp Pharm 46: 2036
22. Stiles ML, Allen LV, Prince SJ (1996) Stability of deferoxamine mesylate, floxuridine, fluorouracil, hydromorphone hydrochloride, lorazepam, and midazolam hydrochloride in polypropylene infusion-pump syringes. Am J Health Syst Pharm 53: 1583
23. Tomankova H, Zyka J (1977) Study of the stability of pyrimidine series cytostatics, ftorafur and fluorouracil injections. Microchem J 22: 70
24. Wang D-P, Chang L-C, Lee DKT (1995) Stability of fluorouracil-metoclopramide hydrochloride admixtures. Am J Health Syst Pharm 52: 98