

Chemical contamination of the primary packaging of 5-Fluorouracil RTU solutions commercially available on the Belgian market.

J.P. Delporte (*), Ph.D., P. Chenoix (*), Ph. Hubert, Ph.D ().**

University Hospital Centre of Liège, Pharmacy Department, Liège – Belgium
Drug Analysis Department, University of Liège, Liège - Belgium

Key words

Antineoplastic agent, contamination, occupational hazards, safety, toxicity

Summary

Different batches of 5-Fluorouracil (5-FU) solutions commercially available on the Belgian market have been tested for contamination by traces of the cytotoxic agent on the primary packaging. Methods for quantitative determinations and for the quantitative recovery of traces of products on vials have been developed and validated. Residues of 5-FU were either detected or quantified ($\geq 5\mu\text{g/vial}$) in most tested batches. Nevertheless the frequency and level of contamination seems to vary depending on the source company. The potential risks of accidental or repeated dermal contacts with cytotoxics are poorly evaluated but nevertheless accepted. That is the reason why it is highly recommended that pharmaceutical companies take all appropriate measures to avoid such contamination and that internal precautionary measures are taken towards the personnel who, in the hospital, could be exposed to such traces of cytotoxics.

Introduction

Much attention is paid to the necessary precautionary measures which need to be taken during the handling of cytotoxic drugs. Severe adverse effects of antineoplastic drugs are well documented, including for example second malignancies, hematopoietic effects, immunosuppression or impaired reproductive function. Actual risks or long-term health effects of chronic unexpected low-level exposures to cytotoxics either by skin contact, dermal penetration or by inhalation are not exactly known. In a cross-sectional survey by questionnaire sent to 4659 nurses, nurse aides, pharmacists and pharmacy technicians,

Valanis et al. [1,2] have observed a small but significant increase of the number of acute symptoms. These included cardiac, gastrointestinal, allergic, infectious and general symptoms within the 3 months before the survey with people exposed to antineoplastic drugs during various handling activities. If the number of declared symptoms can be significantly associated to various parameters like the number of exposures or the extent of adopted protection, the skin contact appeared as the most important predictor of the number of symptoms. Besides potential carcinogenic effects of cytotoxics and many observations like urine mutagenicity, frequencies of lymphocytic sister-chromatid exchange or chromosome gap by people who frequently handle antineoplastic agents have led to define recommendations and protective measures [3,4,5]. Different authors have attempted to demonstrate the effectiveness of recommended measures for the protection of workers by measuring residues of antineoplastic drugs in the air of vertical laminar-airflow safety cabinets [6] (VLASC) or on the immediate working environment , VLASC surfaces, gloves, floor, etc. [7].

More recently Ros [8] and Wilken [9] have emphasised the external contamination of the outside surface of injection bottles or infusion bags. Visible crystals or traces of cytotoxics can be present on the primary packaging. Workers who are routinely involved in the preparation of antineoplastic agents are usually well aware of the potential risks in the handling of the product. They subsequently take appropriate precautions in order to protect themselves against any hazards. By contrast, some workers, not usually involved in this process, but concerned by the general handling of any drug in a manufacture, a pharmacy or an hospital ward (unpacking, transportation,...) can be unconsciously exposed to skin contacts with such agents. That is the reason why Wilken [9] considers that the evaluation of the product safety and the inherent reliability of the company releasing the product on the market place could be good arguments in the selection of a product in the hospital formulary.

The purpose of this study is the evaluation of drug residues on the external surface of commercial injectable solutions of 5-Fluorouracil (5-FU), a pyrimidine antagonist antimetabolite introduced about 30 years ago as an anticancer agent and still widely used for its palliative action in the management of common malignancies in particular cancer of the colon and breast. It is used as a single agent or in combination with other cytotoxic agents.

Method

A 3-step method was implemented:

1. Development and validation of a high-performance liquid chromatography (HPLC) method for 5-FU determinations;
2. Development and validation of a method to recover 5-FU residues spotted on glass vials;
3. Quantitative determination of 5-FU residues on different batches of 5-FU vials available on the Belgian market, issued from different companies.

All precautionary measures were taken in order to protect technicians and environment.

HPLC fluorouracil determinations.

The 5-FU was determined by HPLC, according to a method adapted from McDiarmid and coll. [6], using a μ Bondapack C₁₈ 30 cm column maintained at 20°C, a Varian-Instrument Group pump (model 2010), a Varian-Instrument Group variable-wavelength detector (model 2050UV) with an integrator (model 4290).

The mobile phase was an aqueous mixture composed of 0,05% phosphoric acid adjusted to a pH of 2.5 with a 5 N potassium hydroxide solution. A constant flow rate of 1ml/min was adopted. The detector was set on 266 nm. The retention time was 4.3 min. In these conditions the detection limit and the quantification limit were respectively 0.3 and 1 nG. The standard curve was generated by dilution of a freshly prepared 5-FU solution in distilled water, in order to obtain concentrations of 1, 5, 10, 20, 50 and 100 nG per 50 μ L (50 μ L= capacity of the injection loop). 4 replicates per concentration were carried out. The linearity of the response peak-area/concentration was observed on a Log/Log scale (Hartley, Bartlett and Cochran 's tests, $P < 0.05$) as well as lack of fit test ($P < 0.05$). In the range of concentrations, the method was validated for repeatability ($CV < 2.8\%$ at low concentration levels) and intermediate precision ($CV < 3.2\%$). The mean accuracy of the measure was also verified ($bias < 1.2\%$).

Results

Validation of the recovery of 5-FU residues spotted on vials.

25 μ L of solutions of increasing concentrations of 5-FU were slowly dropped on blank vials first heated at 80°C and rotating around an horizontal axis. Drug deposits were single-blind

prepared and the vials let for drying overnight in a vertical laminar air flow cabinet. 5-FU deposits in a range between 0 and 50 µG were prepared.

To recover the deposit, each vial was rinsed with 3 x 10 mL 0.01N solution of potassium hydroxide carefully dropped with a pipette on its surface. The rinsing solution was adjusted to pH 2.5 with a 85 % phosphoric acid solution, then diluted with the mobile phase up to a 50 mL calibrated volume. This solution is ready for HPLC determination. The data of quantitative recoveries are shown in table 1.

Table 1: Recovery of spotted 5-FU samples

[Table1]

Determination of 5-FU residues on commercial vials.

3 different batches of 3 different origins were tested: Fluorouracil® 500 mG/20mL (Source A: Faulding Pharmaceuticals s.a.), Fluracedyl® 500 mG/10mL (Source B: OPG Pharmachemie) and Fluroblastine® 500 mG/10mL or 1G/20ml (Source C: Pharmacia & Upjohn s.a.). 10 vials of each batch were selected at random for testing. The results of the determinations are presented in table 2 (average of 2 measures on each rinsing solution).

Table 2: External contamination with 5-FU of vials (µG/vial) produced by different pharmaceutical companies.

[Tableau 2]

Discussion

In the recovery method of spotted amounts of 5-FU, the average recovery (\pm SD) from the spotted vials is $97.6 \pm 2.2\%$ in the range of tested amounts. The regression equation between 5-FU determined amounts (y) and spotted amounts (x) is given by : $y = - 0.046 + 0,984 \cdot x$ ($r^2 = 0.999$). The Ho hypothesis ($b=1$), where b is the slope of the curve, was accepted for $p<0.05$. In the same way, the Ho hypothesis ($a=0$), where a is the intercept at the Y axis, was not rejected ($p<0.05$). These results demonstrate the accuracy of the method which is consequently reliable for the purpose of the study.

Of the 90 vials tested, 3 were contaminated by measurable amounts of 5-FU. All 3 were issued from the same company and were present in all tested batches coming from this source (Source C). On 27 vials, traces of 5-FU were detected but in amounts lower than the quantification limit. Respectively 4, 13 and 10 came from sources A, B and C. Roughly we can conclude that the contamination was: source C > source B > Source A, although measured contamination levels are low and never higher than 18 µG per vial.

The results obtained on the few batches of commercially prepared 5-FU are probably not unique and may be expected with other cytotoxics. The origin of the external contamination was extensively discussed by Wilken [9]. The most frequent causes are splashing and foaming during the filling process of the vials or ampoules. Other causes of contamination can result from the breaking of vials during freeze drying, collisions on conveyors and turntables, or during transportation. Nevertheless observed results indicate that precautionary measures taken by manufacturers to avoid that contamination are probably different and do not have the same efficacy.

Conclusion

As with other antineoplastic agents, the potential long-term risks of accidental or repeated contacts with such small amounts of 5-FU is uncertain but any risk, as small as that detected, would seem unacceptable. Hospital pharmacists could pressurise pharmaceutical companies to take appropriate measures to reduce the contamination of any packaging (boxes, vials) or to reduce the risk of material breakage during manufacture or transport. Any cytotoxic supplying must be clearly identified on the external packaging.

Hospital pharmacists however must take internal precautionary measures by ensuring that the personnel in the pharmacy, on the wards, in goods reception area, or those dealing with the reception and consignment of cytotoxic drugs are aware of potential risks and have received appropriate instructions for safe handling eg wearing of gloves when such products are handled or receive help from a specialised department in case of breakages.

References

1. Valanis B.G., Wollmer W.M., Labuhn K.T., Glass A.G. Acute Symptoms Associated with Antineoplastic Drug Handling among Nurses. *Cancer Nursing*, 1993,16, 288-95.

2. Valanis B.G., Wollmer W.M., Labuhn K.T., Glass A.G. Association of Antineoplastic Drug Handling with Accute Adverse Effects in Pharmacy Personnel, Am. J. Hosp. Pharm. 50, 1993, 455-62.
3. de Werk NA, Wadden RA, Win L. Chiou, Exposure of Hospital Workers to Airborne Antineoplastic Agents, Am.J.Hosp.Pharm. 1983, 40, 597-601.
4. LeRoy ML, Roberts MJ, Theisen JA, Procedures for Handling Antineoplastic Injections in Comprehensive Cancer Centers, Am.J.Hosp.Pharm. 1983, 40, 601-603.
5. Association Francophone des Pharmaciens Hospitaliers de Belgique, Les cytostatiques en pharmacie Hospitalière, AFPHB Edition, 1996.
6. McDiarmid MA, Egan T, Furio M, Bonacci M, Watts SR, Sampling for Airborne Fluorouracil in a Hospital Drug Preparation Area, Am. J. Hosp. Pharm., 1986, 43, 1942-5.
7. Sessink JM, Anzion RB, Van den Broek PHH, Bos RP, Detection of Contamination with Antineoplastic Agents in a Hospital Pharmacy Department. Pharm.Weekblad (Sc.Ed.) 1992, 14, 16-22.
8. Ros JJW, Simons KA, Verzijl JM, De Bijl GA, Pelders MG, Praktische toepassingen van een gevalideerde analysemethode voor het aantonen van sporen cyclophosphamide op injectieflacons en in de oncologische dagverpleging. Ziekenhuisfarmacie, 1997, 13, 1968-71.
9. Wilken A. Beobachtungen zur Aussenkontamination der Primärverpackungen von Zytostatika, Krankenhauspharmazie, 1997, 37-39

Introductory sentence

Batches of 5-Fluorouracil solutions commercially available on the Belgian market have been tested for contamination by traces of the cytotoxic agent on the primary packaging in order to assess occupational hazards with the people involved in the handling of such products.

Address for correspondence

Prof. Dr. J.P. Delporte
CHU of Liège
Pharmacy Department B35
4000 Liège - Belgium
Phone 32 4 366 71 39
Fax 32 4 355 71 42
Email jpdelporte@chu.ulg.ac.be

[table 1]

Theoretical Spotted Amount (μG)	Measured Amount (μG)	Per cent Recovery (%)
0.0	0.0	-
5.0	4.6	92.4
7.5	7.2	95.7
10.0	9.9	98.7
12.5	12.4	99.2
15.0	14.4	95.9
20.0	20.0	100.0
25.0	24.9	99.5
30.0	29.4	98.1
40.0	39.4	98.5
40.0	39.4	98.5
50.0	48.9	97.7

(

[Table 2]

Vial number	Source A			Source B			Source C		
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
1	d(**)	-	-	-	d	-	-	d	-
2	-(*)	-	-	-	-	-	-	4.8	-
3	-	-	-	d	-	d	-	d	-
4	d	-	-	d	d	d	-	d	d
5	-	d	d	-	d	-	-	d	18.1
6	-	-	-	-	d	-	-	d	-
7	-	-	-	-	d	-	-	d	d
8	-	-	-	-	d	-	6.5(***)	d	-
9	-	-	-	-	d	-	d	-	-
10	-	-	-	-	d	d	-	-	-

(*) - no amount of 5-FU detected; (**) d: 5-FU detected but in amount lower than the limit of quantification; (***) : amount of 5-FU detected and quantified in µG/vial