Biomedicine & Pharmacotherapy 65 (2011) 17–21

Available online at ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Safety in the preparation of cytotoxic drugs: How to integrate gravimetric control in the quality assurance policy?

J. Lecordier [a,*], Y. Heluin [a], C. Plivard [a], A. Bureau [b], C. Mouawad [c], B. Chaillot [c], J.-J. Lahet [a]

[a] Department of Pharmacy, Jean-Monnet Hospital, 3, avenue R.-Schuman, 88000 Épinal, France
[b] Department of Pharmacy, Vittel Hospital, 191, avenue M.-Barrès, BP 129, 88802 Vittel, France
[c] Laboratory of bioorganic chemistry, School of Pharmacy, University of Dijon, 7, boulevard Jeanne-d'Arc, 21079 Dijon, France

ARTICLE INFO

Article history:
Received 14 September 2010
Accepted 6 December 2010
Available online 5 January 2011

Keywords:
Weight control
Balance
Compounding unit
Antineoplastic agent
Chemotherapy
Isolator

ABSTRACT

Purpose: We present the way to integrate gravimetric control (GC) in a centralized preparation of cytotoxic drugs unit. Two different modalities are described. In the first strategy, the balance is located inside the isolator, whereas in the second, it is located outside in order to remove many technical and ergonomic constraints. These two modalities are compared in terms of benefits and limits.
Methods: GC consists in comparing the observed weight variation with the expected weight variation using a precision balance. According to the B-in strategy, this variation is directly attributable to the weight of the cytotoxic solution injected, whereas with the B-out strategy, the weight of various additional components must be taken into account.
Results: Five hundred and seventy-seven preparations have been weighed. For "B-in" strategy, the 95% confidence interval is [1.02–1.14%] and every preparation is below the threshold of 5%. For "B-out" strategy, the 95% confidence interval is [2.34–2.63%] and 94% of preparations are below the threshold of 5%. B-in strategy is distinctly more precise than B-out strategy and can be applied to all preparations. However, B-out strategy is a feasible option in practice and enables the detection of an important mistake. All in all, results obtained from B-out strategy can be considered as a quality indicator in the production line.
Conclusion: Results of GC are helpful in the final step of release, which the pharmacist is responsible for. Many contributions in the quality assurance policy could justify using of GC in every unit.

1. Introduction

The use of cytotoxic drugs is considered as a high-risk activity that benefits from a restrictive regulatory framework. Centralized preparation has been developed in order to assure the safety of nurses in view of the potential adverse effects of hazardous drugs. It improves the safety in the different steps from prescription to administration [1–3]. However, preparation is a complex process that can provoke multiple errors [4,5]. In France, centralized preparation units are under pharmaceutical responsibility. It is therefore essential for the pharmacist to have tools in order to ensure that the preparation has been done correctly. We present how to integrate gravimetric control (GC) in the preparation process using two different modalities. The electronic balance is located inside the isolator in the first strategy ("B-in" strategy) and outside in the second ("B-out" strategy). These two modalities are compared in terms of benefits and limits.

2. Materials and methods

2.1. Setting

The Jean-Monnet hospital, Épinal, France, is a 325-bed hospital. A centralized pharmaceutical unit for the preparation of antineoplastic drugs was opened in September 2007. This unit uses one isolator (Sieve, Lyon, France) for gaseous sterilization of drugs and medical devices by peracetic acid. Approximately 7200 preparations per year are manufactured by three trained technicians. These preparations are for patients in oncology (80%), pneumology (13%) or other wards (7%). All chemotherapies which are administrated in the hospital take place in this unit. Two third of the preparations are intended for outpatient-hospitalization wards, and are subject to a time constraint.

* Corresponding author. Tel.: +33 3 29 68 75 05.
E-mail addresses: lecordier.julien@gmail.com (J. Lecordier), heluin.yannick@gmail.com (Y. Heluin), claire.plivard@ch-epinal.rss.fr (C. Plivard), abureau@ch-vittel.fr (A. Bureau), charbel.mouawad@u-bourgogne.fr (C. Mouawad), bernard.chaillot@u-bourgogne.fr (B. Chaillot), jean-jacques.lahet@ch-epinal.rss.fr (J.-J. Lahet).

0753-3322/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.biopha.2010.12.014

2.2. Material

The material consists of:

- precision balance XP4002S (Mettler Toledo®, Viroflay, France) with wireless connection (maximum capacity 4100 g – readability 10 mg);
- printer BT-P42 (Mettler Toledo®, Viroflay, France) with wireless connection;
- software Chimio® V 2.9 (Computer Engineering, Paris, France) that is used to assist the preparation of antineoplastic drugs;
- software Microsoft Excel® including Visual Basic Editor® for processing of weighing data;
- software Systat® V 12 (Systat Software, Erkrath, Germany) for data analysis.

2.3. Gravimetric control applied to cytotoxic drugs

Weighing techniques are used to ensure the accuracy of injectable products. In the majority of cases, the preparation of antineoplastic drugs consists in injecting a cytotoxic solution into a bag of infusion. The additive syringe is currently visually inspected just before the injection but this method is imprecise and unsecured. It is possible to determine the exact dose of cytotoxic drug injected by weighing [6]. GC consists in comparing the observed variation weight (OVW) with the expected variation weight (EVW).

2.4. Gravimetric control with balance outside of the isolator

Antineoplastic preparations require a sterile environment in the work zone (class 100–ISO5). Therefore, safety cabinets (isolator or vertical laminar flow hoods) are necessary. Unlike the vertical laminar flow hood, the isolator represents a real physical barrier. Though, this method is more complex because of the multiple steps taken between the first and final weighing. Indeed, OVW and EVW are due not only to the weight of cytotoxic solution injected, but also to other components added (e.g. infusion set). Therefore, this method requires a specific organization.

2.5. Experience

2.5.1. Before the implementation of weighing

The quality assurance policy consists in the application of internal procedures. All stages of prescription/preparation/administration are computer-aided. Validation by the pharmacist is required for each preparation before manufacturing and delivering it to the patient. During preparation, selected drugs, solvents and accessories are double-controlled and the traceability of batches is ensured. The technicians are supervised during cytotoxic preparation (visual inspection of the additive syringe) is performed. Additional safety is expected with the weighing.

2.5.2. Weighing inside the isolator

When the balance is placed inside the isolator, GC consists in the execution of two weighings per preparation: just before the injection (initial weighing) and just after (final weighing). This weight depends on the volume injected and the density of the cytotoxic solution [6]. The volume depends on the prescribed dose of the cytotoxic drug and its concentration. For each active ingredient, the value of density is collected from the supplier beforehand. Each weighing is consistently printed and identified by the preparation number and by a timestamp that differentiates final weighing from initial weighing.

2.5.3. Weighing outside of the isolator

2.5.3.1. Identification and selection of factors that contribute to the expected variation weight. When the balance is placed outside of the isolator, the variation of the weight of the bag is attributable not only to the cytotoxic solution injected, but also to other components: bag of solvent, infusion set (various references are required), luer lock stopper, solvent added or removed... The knowledge of all factors that contribute to the EVW and OVW is fundamental. Firstly, if a factor is not taken into account, a variation between EVW and OVW will be observed and the precision will be affected. Secondly, it is useful to apply a constant weight as far as possible (e.g. 0.38 g for a luer lock stopper). For each component, values of weight and variations have been measured from at least ten units of two different batches [7]. Individual weighing of each bag of diluent (5% dextrose or 0.9% sodium chloride) is essential because of important variations of weight.

2.5.3.2. Development of a computer tool to process data of weighing. We have developed a computer tool to process weighing data and to make easier in practice the determination of EVW [8]. This application considers concentration and density of active ingredient, prescribed dose, other components added or taken off. Results are expressed in percentage of variation between dose to prepare and dose actually prepared. Results are computed from the variation between OVW and EVW, to check that the variation is solely due to the cytotoxic solution injected. Each result makes mention of all contributed factors taken into account for computing. Obtaining many results from identical preparations (same product, same dose, same other components) makes it possible to understand their fluctuations. A database of components and weights has been progressively built for more efficiency.

2.5.3.3. Weighing in practice. For each preparation, the bag of solvent is previously weighed (initial weighing). For more precision, each bag is weighed after packing has been removed (the supplier ensures that the bag can be exposed to the sterilization agent). Then, drug vials, the bag of solvent (large volume of parenteral solution) and other components are introduced into the isolator. After sterilization, admixture takes place inside the isolator. Then, after a rinse cycle inside the isolator, final weighing is completed outside of the isolator. Printed weighing data and preparation data form are stored by the application. Once the validation has been processed (result expressed in %), a weighing form is automatically printed and data are simultaneously saved. In each case, the threshold of the deviation acceptance is fixed to 5%, which means that the results are considered as unacceptable if the variation between the dose to prepare and the dose actually prepared as reported by weighing results is higher than 5%.

2.6. Data analysis

For each strategy, a global analysis of variations is conducted, and a comparison is performed between "B-in" and "B-out" strategies. Results are then broken down for each active ingredient. The statistical test used is Student's *t*-test for independent samples ($P < 0.05$). The null hypothesis is H0: no difference between samples means.

3. Results

3.1. Weighing with "B-in" strategy

For B-in strategy, 577 preparations (about a month's production) have been weighed. Mean of variations between OVW and EVW is 1.08%. The 95% confidence interval is [1.02–1.14%].