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ORIGINAL ARTICLE

Centralized intravenous additive services (CIVAS): The state of the art in 2010

UCRI, unité centralisée de reconstitution d'injectables : le point en 2010

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Summary In hospitals, the major part of the drugs is administered by intravenous way and the majority of the reconstitution of injectable drugs are carried out right before the administration to the patient by the nursing staff. The risks and errors related to the preparation and the administration of the injectable drugs are numerous. The standardization then the centralization of the preparations and reconstitution by the hospital pharmacy make it possible to reduce these various risks and errors. In addition to the preparation of the mixtures of parenteral nutrition as well as doses of anticancer chemotherapy, many other treatments can be taken in charge, such as antibiotics, antiemetics and pain treatments. Consequent equipment is necessary but the realization of these treatments proves non-overdrawn insofar as a certain quantity of production is reached. The reconstitution of the intravenous treatments by a centralized intravenous admixture service guarantees the chemical stability and the microbiological quality of the ready-to-use injectable drugs and contributes to the quality and the total management of the care of the patient.

MOTS CLÉS
Erreurs ;
Perfusion intraveineuse ;
Préparation médicamenteuse ;

Résumé En milieu hospitalier, la majeure partie des médicaments est administrée par voie intraveineuse et la plupart des reconstitutions des injectables sont réalisées juste avant l'administration au patient par le personnel infirmier. Les risques et erreurs liés à la standardisation puis la centralisation des préparations et reconstitutions dans le service de pharmacie hospitalière permettent de réduire ces différents risques et erreurs. Outre la préparation des mélanges de nutrition parentérale ainsi que des doses de chimiothérapie anticancéreuse,

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de nombreux autres traitements peuvent être pris en charge, à savoir les antibiotiques, les antiémétiques et les antidouleurs. Un équipement conséquent est nécessaire mais la réalisation de ces traitements s'avère non déficitaire pour autant que l'on atteigne une certaine quantité de production. La reconstitution des traitements intraveineux par une unité centralisée de reconstitution d'injectables garantit la stabilité chimique et la qualité microbiologique des doses injectables prêtes à l'emploi et contribue à la qualité et au management global des soins du patient.

Place of injectable drugs in hospital treatments

In hospitals, the major part of the drugs is managed by intravenous way. The majority of the reconstitutions of injectable is carried out right before the administration by the nursing team. Lastly, the operating room is generally the only aseptic zone except if the hospital institution has aseptic units for cancer patients.

Several authors tried to quantify the quantity of injectable administrated to the patients.

Turco [1] reports that 24% of the administered doses to hospitalized patients are injectable drugs, while 38% of the patients receive at least an injection per day.

According to Simmons [2], 30 to 50% of the patients receive medications by intravenous way, percentage confirmed by Taxis and Barber (28%) [3].

Kwan and Anderson [4] estimate that 40% of medications and solutions are managed by intravenous way while Rwabihama et al. [5] note that 49% of the patients are under perfusion.

The risks related to the preparation and the administration of the injectable drugs are numerous:

- incomplete and ambiguous regulations;
- procedures of the complex preparations;
- missing of essential technical information;
- multidisciplinary absence of process;
- error of selection of the drug and/or the diluent;
- use of the drug, the diluent or the aqueous solution after expiry date;
- miscalculation;
- physicochemical incompatibility;
- error of patient;
- error of route of administration;
- bad technique of preparation and/or asepsis;
- protection of the operator and/or the environment;
- varied levels of knowledge, experiment and competence in the personnel of care [6].

Forms of the injectable drugs

The pharmaceutical companies provide the injectable drugs in the form of ampuls, flasks of powder, concentrated solutions or mini-perfusions.

Minimal qualities of these forms are physicochemical stability, sterility, the absence of particles and pyrogenic substances as well as long-term validity.

These qualities must be preserved in the administered perfusion to the patient.

Factors affecting drug stability

Many authors studied and detailed the physicochemical factors influencing the stability of the molecules in solution [7–19].

A drug is considered stable in solution insofar as it preserves 90% of the initial concentration (United States Pharmacopeia [USP] standards).

To determine this stability, the concentration of the active ingredient will be performed by high-pressure liquid chromatography or gas chromatography, microbiological test (for certain antibiotics) or by any other specific test making it possible to differentiate the active molecule from its breakdown products.

Moreover, there cannot be a decomposition of the active ingredient in toxic product and the initial appearance of the solution cannot be modified.

In short terms, when one wants to evaluate or know the stability of a drug in solution, it is necessary to know:

- final concentration of the reconstituted product;
- nature, pH and ionic force of the diluent;
- pH and ionic force of final dilution;
- nature of container (polyvinyl chloride, ethylvinyl acetate, polypropylene, etc.) to avoid the phenomenon of sorption and salting out;
- conditions of storage (refrigerator, ambient temperature, body temperature, protection from light);
- nature of the set of administration (PVC, polyethylene, etc.);
- protection from the light during the administration.

Methods of preparation and/or reconstitution

The principal methods are the syringe, the set transfer, the sophisticated perfusions or the sophisticated flasks.

The syringe is one of the systems most used for the reconstitution of the injectable drugs.

The set transfer is also strongly used, either in the shape of a double needle, or in the shape of a double needle itself surrounded by a plastic protection. Among the sophisticated perfusions, let us quote the minibag, which is equipped at the site of injection with a receptacle making it possible to

receive the vial insofar as this one reaches a diameter of 22 mm.

The ADD-Vantage® system is on the other hand delivered like such. The vial is connected already beforehand to the perfusion.

On the other hand, some flasks are already equipped with a needle of transfer and require at this time to use a perfusion definitely more traditional (Monovial®).

Lastly, there exist now systems of assembly-reconstitution using of the traditional perfusions and the traditional vials (Vial-Mate®).

Microbiological quality of the injectable reconstituted medications

Several authors [20,21] highlighted that infectious complications could occur among patients receiving of the intravenous solutions. The risk of contamination of injectable solutions administrated to the patients is all the more high as the products are prepared in a non-controlled environment.

This risk increases with the number of handling carried out during the addition of additional medications to the solution of perfusion [22].

In 1953, the first report/ratio of microbiological contamination of a perfusion appeared.

O'Hare et al. [23] describe a fatal case of anaphylactic shock following the perfusion of a solution of glucose of 10% contaminated ''by inadvertency'' with *Aerobacter aerogenes*. The same year, Michaels and Ruebner [24] announce that two patients receiving an intravenous therapy developed a pyrexia allotted to a bacillus coliform present in the system of perfusion.

Wilmore and Dudrick [25] postulate that the parenteral solution itself can cause infection and suggest that the contamination can be introduced into the system of perfusion by penetrating not filtered air in the container during the addition of the drugs to the perfusion or during the intermittent administration of parenteral medications.

Holmes and Allwood [26] describe the five types of possible contamination: contamination by air, contamination by touching, administration of additives, site of injection, use of contaminated disinfectants.

Several authors studied the percentage of contamination of solution of perfusion following the addition of various medications: 3% [27], 3.75% [28], 3.8% [29], 4.9% [30], 10% [31], 25% [22].

In 2001, Mansfield [32] observed the preparation of injectable in four hospitals. The results were surprising:

- the surface of preparation was never cleaned;
- in a hospital, 84% of the nurses wore gloves during handling, which was absolutely not the case in the three others;
- no nurse had washed her hands beforehand;
- the bottles were not regularly disinfected (0 to 1.67%), the site of injection of the minibags neither (0 to 1.67%);
- in two hospitals out of four, the window of the room where the constitutions were carried out were open in 58% of the observations.

Errors: review of the literature

A review of the literature makes it possible to quantify the errors of asepsis, the errors of duration of administration, the errors of administration, the errors of labelling, the errors of preparations and the errors of compatibility.

Thus, the errors of asepsis were observed in 19% [33], 58% [33], 71% [34] or 100% [33] of the cases.

The errors of duration of administration take place in 0.2% [35], 1% [36], 6% [37,38], 26% [39] of the administrations.

Errors of administration occur in 3% [40], 6% [35], 10% [33], 23% [41], 24% [33], 36% [42] of the cases.

The labelling is non-existent in 20% [33], 43% [33], 99% [33] of the observations.

Errors of preparations reported in 1% [35], 2% [33], 4% [38], 7% [42], 8% [40], 10% [39], 19% [41], 24% [33], 40% [41], 79% [33].

During mixtures of medications, it was raised, according to the observations, 17% [43], 23% [44] and 86% of compatibility, 2% [45], 3.4% [46], 11% [43] and 18.6% of incompatibility. In addition, 10.3% [46] to 72% [44,46] of the mixtures carried out were not studied in the international literature.

How to reduce these errors?

Standardization of the methods of preparation

The standardization of the methods of preparation and administration makes it possible to the medical staff to prepare the injectable medications according to validated methods. This standardization is based on various sources and certain authors carried out such standardizations [47—49].

Centralization of the preparations and reconstitutions in pharmacy

Parenteral nutrition

It is at the end of the 1970s that become the preparation of the mixtures standardized under horizontal laminar airflow hood (or out of isolator) of binary mixtures (amino acid + glucose) or of ternary mixtures (amino acid + glucose + lipids). The incentives to taking in charge these preparations are:

- an increase in the microbiological quality of the end product, possibilities of contamination being brought back from 18 to two;
- an increase in the physicochemical quality of the end product, mixtures of parenteral nutrition containing up to 50 different molecules;
- a lightening of the nursing team workload.

The improvement of the microbiological quality of the end product was shown in particular by Miller et al. [50] in 1971 who noted that the contamination of the solutions of perfusion resulted from a weak aseptic technique rather than of an aseptic lack of environment.

Table 1 Cefepime during the year 2000.
Céfépime durant l'année 2000.

	Pharmacy	Nursing	Difference
Average/production	33.72		
Preparation time (minute)	3.48	5.51	
Cost (per minute)	0.408	0.533	
Team cost (€)	1.420	2.937	
Cost in material used (€)	0.502	0.233	
Total cost (€)	1.922	3.170	1.248

Allinson et al. [51] in 1979 showed that none of the 360 bottles of perfusion in which one had added a drug under hood to flow of laminar air were contaminated.

Brier et al. [52] in 1981 show that, when one adheres to an aseptic technique, the environment in which the additions are carried out is the most important variable affecting the degree of microbiological contamination of the solutions. The incidence of the contamination under laminar airflow hood is significantly less than the contamination of the solutions carried out on a clean table.

Cytotoxics

It was during the 1980s that hospital pharmacies started to deal with the reconstitution and the preparation of anticancer doses of chemotherapy. These doses are carried out under vertical laminar airflow hoods or in isolators. The incentives are identical to the precedents. With these three elements, the protection of the manipulator towards the toxicity of the handled products is added.

Centralized intravenous additive services (CIVAS)

Beside the mixtures of parenteral nutrition and anticancer cures of chemotherapy, there remains an important quantity of injectable medications, in particular antibiotics, antiemetics and pain treatment.

The incentive of taking in charge these various medications are identical to the precedents.

One-fifth element is added which is the economic aspect. Indeed, the preparation of series of standardized injectable doses is made more quickly, is less expensive in material used for the preparation and is less expensive in labour. Thus developed the CIVAS.

Several works documented this subject [53—55].

Reference books provide data of stability [1,54,56—62].

These books furnish a lot of information on physical stabilities (visual, pH, modification of colouring). Chemical stability is described for 12 hours at 7 days on average. The concentrations used, the containers can be different (flexible PVC bags, polyolefin, reservoirs) and the solutions of perfusion can be different.

Cost of reconstitution of injectable doses

In order to estimate the time and the cost of preparation of injectable drugs, it is necessary to time the make ready time which must include the disinfection of the area of work of the laminar air flow hood, its loading, the preparation in itself, the labelling and the putting in bags, storage with the refrigerator and the cleaning of the work area of the hood.

The most complete studies concerning all the operations relating to the reconstitution and the preparation of an injectable drug at the ward provide the times ranging between 4.71 and 6.51 minutes [63—66], with an average of 5.51 minutes.

Table 1 details these data for the reconstitution at the pharmacy of an antibiotic, cefepime, and compares them with the time and the cost of preparation at the ward by the nursing team [67].

During the year 2000, the average quantity of cefepime ready-to-use bags manufactured by batch is 33.72. The average time of preparation, all operations included, rises to 3.48 minutes.

The cost per minute rises to 0.408 € at the pharmacy and 0.533 € at the ward, the cost of the material used being respectively of 0.502 and 0.233 €.

The cost of preparation of a bag of cefepime rises to 1.922 € in pharmacy and 3.170 € at the ward, with a difference of 1.248 € on account of the reconstitution in pharmacy.

If storage in a freezer is used, it will be necessary to add to this timing the time necessary to store the bags in the freezer just as the time necessary with placing these bags in the microwave oven. Various timings were carried out during time for certain molecules [67].

Table 2 shows that the average quantity of bags manufactured at the same time is higher (55.83 minutes), since the guarantee of long-term stability is ensured by freezing [68].

If the preparation time is a little higher (3.89 minutes instead of 3.48 minutes), the cost in material used is weaker (0.301 € instead of 0.502 €).

The difference on account of the reconstitution in pharmacy rises then with 1.282 € instead of 1.248 € [67].

Various timings were carried out for four other molecules [69—72], ceftazidime, cefuroxime, piperacilline + tazobactam and vancomycine, without or with microwave freeze-thaw treatment.

Table 3 allows the comparison of the unit time of production for these molecules, between the years 2000 (without freezing) and 2005 (with microwave freeze-thaw treatment).

During the first period, the average quantity produced by batch varies from 24.60 to 45.67 units, according to the molecules, with unit times of production varying 3.09 to 3.60 minutes.

Table 2 Cefepime during the year 2005.
Céfépime durant l'année 2005.

	Pharmacy	Nursing	Difference
Average/production	55,830		
Preparation time (minute)	3.89	5.51	
Cost (minute)	0.408	0.533	
Team cost (€)	1.587	2.937	
Cost in material used (€)	0.301	0.233	
Total cost (€)	1.888	3.170	1.282

Table 3 Comparison of the unit time of production (minute) and quantities produced in 2000 and 2005.
Comparaison du temps unitaire de production (minute) and les quantités produites en 2000 et 2005.

	2000		2005	
	Mean time	Produced quantity	Mean time	Produced quantity
Cefepime	3.48	33.72	3.89	55.83
Ceftazidime	3.28	45.67	3.83	53.25
Cefuroxime	3.54	33.72	3.58	55.83
Piperacilline + tazobactam	3.60	40.13	3.99	52.64
Vancomycine	3.09	24.60	3.48	52.75

During the second period, the average quantities produced by batch are higher (52.64 to 5.83) and average times of production a little higher (3.48 to 3.99 minutes).

The difference on account of the reconstitution in pharmacy varies from 1.224 to 1.432 € (Table 4) [67].

On the basis of indirect load ''pharmacy'' provided by the financial management of the hospital institution, including the cost of material (Table 5) and the ratio of surfaces of the CIVAS within the service of pharmacy, it is easy, by a rule of three, to calculate the indirect loads per m^2. This value, multiplied by the number of m^2 occupied by the CIVAS, will be then divided by the number of amounts annually produced in order to identify the cost by produced amounts. At the University Hospital of Mont-Godinne, these values rise

Table 4 Comparison of the team costs (€) between pharmacy and nursing.
Comparaison des coûts en personnel (€) entre la pharmacie et le nursing en 2005.

	2000		2005
	Mean time (minute)	Produced quantity	Difference pharmacy/nursing (€)
Cefepime	3.89	55.83	−1.282
Ceftazidime	3.83	53.25	−1.295
Cefuroxime	3.58	55.83	−1.408
Piperacilline + tazobactam	3.99	52.64	−1.224
Vancomycine	3.48	52.75	−1.432

Nursing team cost/minute: 0.533 €; pharmacy technician cost/minute: 0.408 €.

Table 5 Material (€).
Matériel (€).

2 meters width vertical laminar air flow hood	12,576.74	2	25,153.48
Additional extractor for vertical laminar air flow hood	1295.00	2	2590.00
520 liters freezer	1298.97	3	3896.91
500 liters refrigerator	793.26	4	3173.04
Microwave oven	744.20	4	2976.80
Thermowelding machine HB 65	5925.54	3	17,776.62
Personal computer for printer	1308.00	1	1308.00
Printer	1859.20	1	1859.20
Peristaltic pump	5697.56	3	17,092.68

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