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Validation of procedure for checking and releasing antineoplastics medications in an intravenous mixing center in southern Brazil

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Abstract

Objective: Considering Collegiate Board Resolution 220 of 2004, which describes the minimum requirements required for the operation of antineoplastic therapy services, the objective of this work was to propose and validate a process for checking and releasing antineoplastics medications manipulated in the Intravenous Mixture Center in a high complexity hospital in southern Brazil. **Methods:** Prospective descriptive observational study, carried out from January to March 2023 at the Intravenous Mixture Center of a public hospital in Porto Alegre. A pilot study was carried out over a three-week period in which 50% of the antineoplastic preparations produced underwent a final visual check and completion of a checklist with the following points: colors, existence of perforations and/or leaks, foreign bodies or precipitation in the solution, medication compatibility with bag and equipment used and volume in the syringe. The results were presented to the unit's professionals and validated electronically, applying the Content Validity Index, which calculates the proportion of evaluators who agree with individual and total aspects of the instrument. Subsequently, the process was described in a Standard Operating Procedure (SOP) and made available to the sector team. **Results:** A total of 427 syringe/pouch preparations were visually checked with the final product over the course of three weeks. During this pilot, three handling errors were identified, as well as the need to adapt work processes. The topics observed using the checklist were evaluated and validated by the sector's oncology pharmacists. **Conclusions:** The procedure for checking and releasing antineoplastics medications proved to be a necessary procedure for patient safety due to its ability to prevent errors in the production and handling order from reaching the patient. In addition, it is necessary to keep the SOPs and supporting material constantly updated, together with ongoing staff education.

Keywords: pharmaceutical preparations, good manipulation practices, oncology.

Validação de procedimento de conferência e liberação de medicamentos antineoplásicos em uma central de misturas intravenosas no sul do Brasil

Resumo

Objetivo: Considerando a Resolução de Diretoria Colegiada 220 de 2004, que descreve os requisitos mínimos exigidos para o funcionamento dos serviços de terapia antineoplásica, o objetivo deste trabalho foi propor e validar um processo de conferência e liberação de preparações de medicamentos antineoplásicos manipuladas na Central de Misturas Intravenosas em um hospital de alta complexidade do sul do Brasil. **Métodos:** Estudo observacional descritivo prospectivo, realizado no período de janeiro a março de 2023 na Central de Misturas Intravenosas de um hospital público de Porto Alegre. Durante três semanas foi conduzido um piloto em que 50% dos preparos antineoplásicos produzidos passaram por uma conferência visual final e preenchimento de um *checklist* com os seguintes pontos: coloração, existência de perfurações e/ou vazamentos, corpos estranhos ou precipitações na solução, compatibilidade do medicamento com a bolsa e equipo utilizado e volume na seringa. Os resultados foram apresentados aos profissionais da unidade e validados por meio de questionário eletrônico, com aplicação do Índice de Validade do Conteúdo, que calcula a proporção de avaliadores que estão de acordo com aspectos individuais e totais do instrumento. Subsequentemente, o processo foi descrito em um Procedimento Operacional Padrão (POP) e disponibilizado para a equipe do setor. **Resultados:** Foram conferidos visualmente 427 preparos de seringas/bolsas com produto final ao longo de três semanas. Durante esse piloto, foram identificados três erros de manipulação além da necessidade de adequação de processos de trabalho. Os tópicos observados por meio do *checklist* foram avaliados e validados pelas farmacêuticas oncológicas do setor. **Conclusões:** O procedimento de conferência e liberação de medicamentos antineoplásicos se mostrou um procedimento necessário para a segurança do paciente devido sua capacidade de evitar que erros na ordem de produção e manipulação cheguem ao paciente. Além disso, é necessário manter a atualização constante dos POPs e material de suporte, aliada à educação permanente da equipe.

Palavras-chave: preparações farmacêuticas, boas práticas de manipulação, oncologia.

Introdution

Cancer is defined as a disease in which abnormal cells grow disorderly and invade adjacent tissues and organs[1,2]. Incidence rates have been rising as the world's population ages and mortality from other diseases decreases[3]. Worldwide, it is estimated that 19.3 million new cases of cancer and almost ten million deaths from the disease occurred in 2020[2].

As it is a complex disease, its treatment is equally complex, requiring multidisciplinary teams and different approaches. Its management may involve surgical, radiotherapeutic and systemic procedures, in combination or not[4]. Because it is a disease that involves different types of interventions, patient safety is extremely important in all processes. In 2000, the Committee on Quality of Health Care in America[5] estimated that between 44,000 and 98,000 patients die each year in the USA as a result of medical errors, and that more people die each year from medication errors than from accidents at work. Among the possible medical errors, medication errors are very common and can cause a lot of harm to patients[6].

The systemic treatment of cancer very often involves the use of antineoplastic medications and, as with other medication therapies, errors can occur in prescribing, preparation, dispensing and administration[6]. Antineoplastic medications interfere with the survival, proliferation and migration mechanisms of tumor and healthy cells. They have a narrow therapeutic index, i.e. they have a high potential for causing adverse events, and are considered potentially dangerous medications, requiring high vigilance at all stages of their use[7]. The pharmacist is the professional responsible for various processes involving medications and is of great importance in ensuring patient safety, especially in the preparation of antineoplastic medications.

Collegiate Board Resolution (RDC) No. 220 of 2004[8], issued by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA), describes the minimum requirements for the operation of antineoplastic therapy services. This standard requires checking before, during and after the preparation of antineoplastic therapies. After handling, the preparation must be checked visually to see if there have been any perforations and/or leaks, if there are any foreign bodies or precipitates in the solution.

The Good Practices for the Preparation of Antineoplastic Therapy establish general guidelines for application in the following operations: analysis of the medical prescription, preparation, transportation, and medications' disposal[8]. At the study site, the final check of the production stage was not carried out, leaving a gap in the prevention of potential failures in the final product handled.

Given the complexity of preparing antineoplastic medications and the legislation in force, the purpose of this study was to propose and validate a process for checking and releasing antineoplastic preparations handled at the Intravenous Mixtures Center in a highly complex hospital in southern Brazil.

Methods

The study followed a prospective descriptive observational design, in an Intravenous Mixtures Center of a large public hospital in southern Brazil. The High Complexity Oncology Center performed 36,000 antineoplastic medication administration procedures in 2022.

Among the efforts to make the management of antineoplastic medications safer is the use of a checklist as a valid tool for checking procedures and standardizing the conduct of the professionals involved. A checklist can be described as a checklist that allows systematic observation of a process[9].

An instrument was proposed for checking the preparation of antineoplastic drugs, in the form of a checklist (Figure 1) in which the characteristics determined by RDC No. 220[8] were checked. The checking procedure was carried out outside the medication handling room, by a pharmacy assistant, before the syringe or bag containing the final product was sent to the unit where it would be administered.

Figure 1. Checklist for checking syringes/bags with final product - preparation of antineoplastic medications (Porto Alegre, Brazil, 2023).

Checking antineoplastic medications	✓	x	NA
Coloring	☑	☑	☑
Leaks/Bag integrity	☑	☑	☑
Particles/Foreign bodies	☑	☑	☑
Serum	☑	☑	☑
Equipment	☑	☑	☑
Syringe volume	☑	☑	☑

Subtitle: ✓ compliant; x non-compliant; NA not applicable

The points checked were, as follows: visual inspection of the final product, observing the existence of perforations and/or leaks, foreign bodies or precipitation in the solution, compatibility of the medication with the bag and the equipment used. As a pilot stage, 50% of the syringes/balls of antineoplastic medications prepared by the Mixing Center over three weeks in February 2023 were analyzed.

If any non-compliance was observed, the syringe or bag should be returned to the handling room along with the completed checklist. The pharmacist responsible for the handling should be informed of the non-conformity by telephone in order to assess the appropriate corrective procedure for each case.

The information on the compatibility of the medications with the bag and the equipment was provided by the establishment's technical team, based on information from the medications' package leaflets and the literature. After applying the instrument, the results were presented to the six pharmacists in the sector and the validity of the checklist was assessed.

The Content Validity Index (CVI) was used to validate the instrument, which assesses the proportion of evaluators who agree with individual and total aspects of the instrument[10]. The checklist was validated by a committee of six pharmacists with a mean of 12 years' experience in oncology and working at the study site. Each item on the checklist was given a score by the evaluators from one to four, as follows:

1 = unclear or unrepresentative

2 = not very clear or not very representative

3 = quite clear or needs minor revision to be representative

4 = very clear or representative

Items that receive scores of one or two should be revised or eliminated, whereas those that receive scores of three and four indicate agreement and the instrument's validity. Thus, each item's CVI was calculated from the sum of scores three and four and subsequent division by the total number of responses, as exemplified by the following formula:

$$CVI = \frac{\text{sum of the number of "3" or "4" responses}}{\text{total number of answers}}$$

The instrument's total score was calculated by adding the mean values of each item and dividing by the number of items considered in the evaluation. It is suggested that the minimum score be 0.8 to indicate agreement in the representativeness of the instrument[10].

After carrying out the pilot stage, the legal basis, the results observed and the necessary adjustments to the procedure for checking the preparation of antineoplastic medications were compiled and presented to the sector's oncology pharmacists in the form of an infographic. The format was developed with the aim of making the team aware of the importance of the proposed checking process in a clear and objective way, drawing attention to the errors that could be avoided. After analysis and approval of the checklist, the checking procedure was described in a Standard Operating Procedure (SOP).

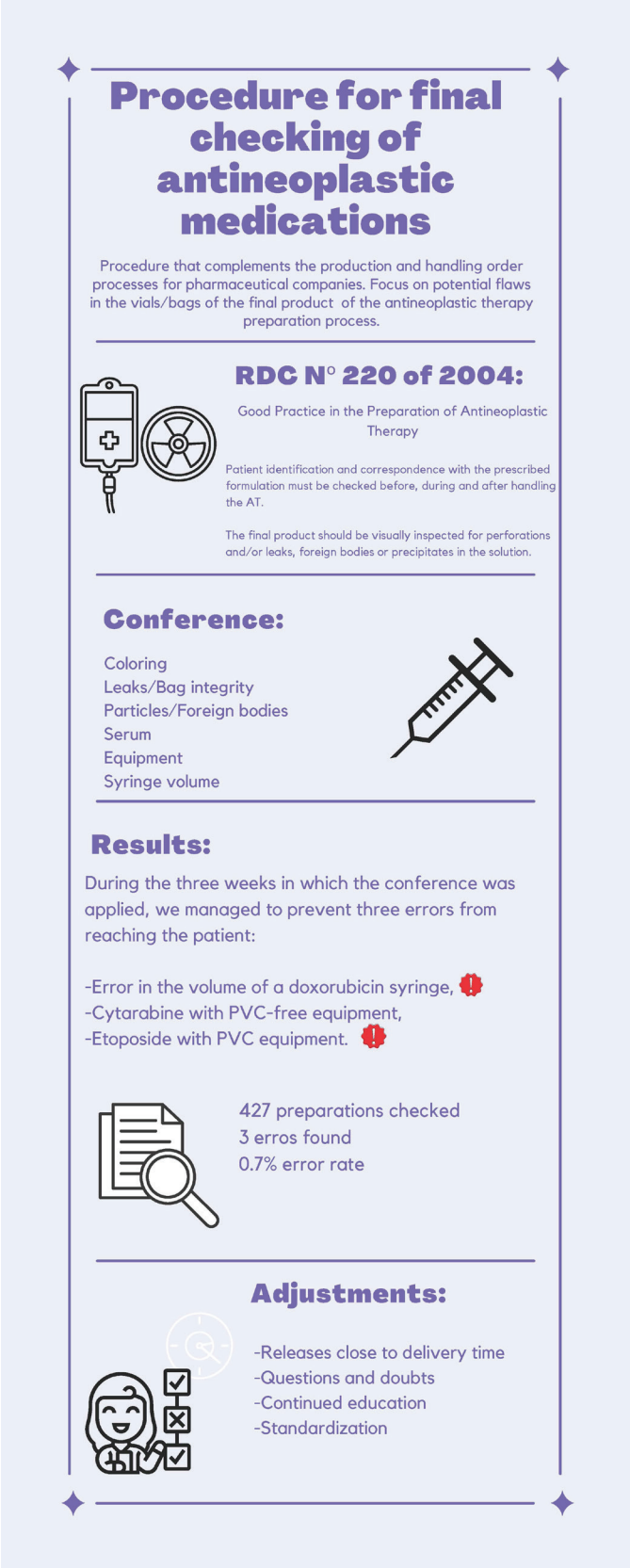
This work complies with ethical precepts and was approved by the Research Ethics Committee of the Federal University of Health Sciences of Porto Alegre (UFCSPA) under opinion number 5851490.

Results

The checklist was applied to 427 preparations over a three-week period in February 2023. Coloration, leaks/integrity of the bag, particles/foreign bodies, serum, equipment, and syringe volume were observed. During the study period, three errors were found among these preparations, indicating an error rate of 0.7%. The errors found correspond to one syringe final volume error and two syringe and medication compatibility errors. The volume error was detected in a doxorubicin syringe. This volume was correctly divided between two syringes as there is a recommendation to fill up to three quarters of the syringe's maximum capacity when handling chemotherapy medications[11] to avoid losing the plunger during handling and to allow space for handling the dose. Two packaging/medication incompatibility errors were observed. In one etoposide preparation, a syringe was used with polyvinyl chloride (PVC), present in some serum[12] packaging, which is incompatible with the medication. In a cytarabine preparation, a non-PVC tube was used, and it is possible to use a common tube, as there is no incompatibility.

After carrying out the pilot, the results observed were compiled and presented to the oncology pharmacists in the sector by means of an infographic (Figure 2). During the infographic presentation, based on the errors identified in the pilot, questions were raised about details of the work processes, such as the use of subcutaneous needles or luer-type connectors in preparations for subcutaneous use and rounding the volume of the medication in syringes. Based on the questions raised, the unit's team drew up a Standardization of Preparations material with information on the characteristic color of the medications, compatibility with diluents and materials, the appropriate dilution volume, in order to detail all the handling processes, ensuring uniformity in preparation and the quality of the medications handled. This material was also suggested as support material for checking the syringes/bags with the final product.

Figure 2. Results of the evaluation of the final checking procedure for the preparation of antineoplastic medications (Porto Alegre, Brazil, 2023).



The content of the checklist was validated using an electronic questionnaire answered by the sector's pharmacists. The results are shown in Table 1. The Content Validity Index was calculated according to the answers obtained in the questionnaire. The CVI calculation results for all the items on the checklist were 1, indicating agreement with the instrument's representativeness.

Once the checklist had been validated, a SOP for checking was drawn up, detailing the processes for checking, filling in the checklist and notifying any non-conformities.

Table 1. Results of the validation of the content of the antineoplastic medication preparation checklist (n=6) (Porto Alegre, Brazil, 2023).

	Coloring	Leaks	Particles/Foreign bodies	Serum	Equipment
Unclear/unrepresentative	0	0	0	0	0
Not very clear/not very representative	0	0	0	0	0
Quite clear/needs minor revision	3	1	1	0	0
Very clear/representative	3	5	5	6	6

Discussion

During the three weeks of the pilot, three errors were identified, indicating an error rate of 0.7%. This rate is compatible with that presented in a systematic review, which found an overall error rate between 0.004% and 41.6% and a preparation error rate between 0.40% and 0.50% [13].

In relation to the errors detected, the volume error in the doxorubicin syringe occurred when the manufacturer of the syringes used in the sector changed. This may indicate a critical point in the handling of injectables - the change of suppliers of materials and medications, since each manufacturer may present the same product with a different presentation, generating confusion during handling. In relation to the packaging/medication incompatibility errors, it is possible that there was an exchange of inputs when preparing the two medications, as the serum bags were the same and only the equipment was different.

Considering the World Health Organization's (WHO)[14] classification of failures, the errors found can be classified as near misses, as they were all avoided by checking before they reached the patients. However, if the conference had not identified these incidents and they had reached the patients, they could have caused harm to the patient (adverse event) in the cases of the volume error in the doxorubicin syringe and the compatibility of the equipment with PVC/medication in the etoposide. On the other hand, the error with the pump without PVC/medication in cytarabine would be an incident without harm to the patient. The errors found were presented to the team in order to draw attention to the work processes involved, as well as demonstrating that the use of the checklist was useful as a barrier in the administration of drugs with preparation problems.

The checklist was validated by calculating the Content Validity Index, as the result indicated agreement on the suggested items. This index is a tool used in different instrument validation scenarios, such as the validation of an educational tool on insulin therapy for adults with diabetes mellitus, an educational e-book for a neonatal care unit to improve care and a family therapy protocol applied to mental health[15-17].

The points considered in the checklist proved useful for a final check according to the needs of the study site. It should be borne in mind that the center produces around 1,700 syringes or medication's bags per month for the onco-hematology outpatient clinic, as well as other preparations such as antineoplastic medications for inpatients, sedatives, antibiotics for pediatrics and high-cost medications. Therefore, the checking stage must be incorporated into the work routine in a feasible way, in order to increase the safety of the preparations.

One difficulty in implementing the conference was the concentration of demand for the preparation of syringes/medication bags in the morning and early afternoon. This higher demand occurs during these shifts, due to the need for long infusions of medication to be given to patients during the outpatient clinic's opening hours, or because many protocols demand that after the infusion of antineoplastic medication, patients seek oral medication at the Special Medicines Pharmacy (Farmácia de Medicamentos Especiais, FME) or due to transportation difficulties faced by patients from cities outside the greater Porto Alegre area. Due to these factors, the unit's team proposed checking only 50% of the preparations made during peak demand times and/or during the employee training period. Checking all the preparations during the staff's adaptation to this new routine could generate anxiety and result in inappropriate checks.

With a view to balancing the patient's well-being and safety, it is important that the check is carried out effectively, but does not increase the patient's waiting time, which is why the checklist model with six topics, which generally cover the main errors that a final visual analysis of the preparations can explore, proved to be appropriate. In addition, establishing that the checklist should be filled in by consulting the compatibility chart of the medications with the standardized bag and equipment, provided by the Intravenous Mixtures Central team, helps to standardize the procedure, and allows particularities of certain protocols and medications to be included in the material and easily consulted. In addition, the inclusion of medications or changes in the medications' presentation used by the sector are frequent, which can lead to changes in the form of dilution. It is therefore necessary to update the material without having to change the checklist topics.

Checking the preparation of antineoplastic medications is especially important when you realize that, even though there is an electronic system that generates the production order for preparing the medications, there are some gaps. After the patient has undergone a consultation, the medication is prepared. The system requires each component of the infusion to have its barcode checked electronically. If there is a mistake at this point and an unsuitable medication, serum or equipment is checked, the system issues a signal pointing out the error and does not allow the process to continue. However, some protocols allow dilution to be carried out in different serum volumes, depending on the

medication's dose, and the system does not differentiate between these, requiring the professional to memorize these exceptions. None of the errors found during the pilot were related to these points, but it is clear that during the training of new professionals in the sector these points could be critical in the process.

Resolution No. 288 of 1996[18] specifies that the pharmacist is the professional responsible for preparing antineoplastic drugs and other drugs that may cause occupational risk to the handler, as well as being responsible for various processes involving antineoplastic drugs such as: acquisition, storage, standardization, handling, pharmacotherapy review, among others. It is therefore their responsibility to ensure that good practice in the preparation of antineoplastic therapy[12] is respected. The training of all professionals involved in the preparation of antineoplastic medications is therefore of great importance, and the pharmacist plays a major role in educating the team. ANVISA Resolution No. 220 establishes general guidelines regarding the training of professionals involved in the preparation of antineoplastic therapies and defines that individual duties and responsibilities must be formally described and available to all those involved in the process. In addition, the professionals involved in the preparation of antineoplastic therapy must receive initial and ongoing training, ensuring that they are trained and updated, duly documented[8].

From this standard, it can be inferred that it is essential to have all procedures described and standardized, with the SOP being the instrument of choice. In addition, all SOPs must be reviewed periodically or whenever routines change and must be easily accessible to the professionals involved.

The human resources training in antineoplastic therapy services must be continuous and constantly updated. The processes are subject to potential failures, which can occur due to human error, a lag in the process, failure to update health education, incorrect handling, or an unsuitable environment for carrying out the process[19]. To this end, the SOPs can be instruments for both training and updating employees in conjunction with training actions provided by oncologist pharmacists. According to the Manual of Good Practices for the Manipulation of Antineoplastics from the Brazilian Company of Hospital Services[12], it is recommended that training be provided by the oncology pharmacist after new employees are hired, as well as ongoing training every six months or whenever there are changes in routines or needs. It is also essential that oncology pharmacists are committed to their own continuing education, checking for updates on legislation with ANVISA and the Federal and Regional Pharmacy Councils.

External validity can be cited as a limitation of this study since it was focused on the reality of the institution where it was developed. In any case, the instrument can be adapted in other cancer centers, as it seeks to meet the requirements of current legislation in an objective and feasible way. Furthermore, the study was developed in the form of a pilot project and may require some adjustments in order to fully and effectively implement the conference process.

Conclusion

The procedure for checking and releasing syringes/bags of antineoplastic medications proved to be a necessary procedure for patient safety due to its ability to prevent errors in the production and handling order from reaching the patient. To incorporate it into the service, it should be planned and incorporated gradually, until the team adapts to the new routine. The SOPs and supporting material should also be constantly updated, along with ongoing staff education.

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Collaborators

EES: Conception and design, article writing, data analysis and interpretation; KHS: Conception and design, data analysis and interpretation, article writing, relevant critical review of intellectual content; MCW: Conception and design, article writing, relevant critical review of intellectual content.

Conflict of Interest Declaration

The authors declare no conflicts of interest in relation to this article.

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