



SPECIAL ARTICLE

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Hospital Pharmacy Compounding against COVID-19 pandemic

La farmacotecnia hospitalaria frente a la COVID-19

José María Alonso-Herreros¹, Silvia Berisa-Prado², Carme Cañete-Ramírez³, Carmen Dávila-Pousa⁴, María del Pilar Flox-Benítez⁵, Margarita Ladrón de Guevara-García⁶, Carmen López-Cabezas⁷, Ana María Martín de Rosales-Cabrera⁸, Beatriz Ramos-Martínez⁹

¹Department of Pharmacy, Hospital Los Arcos Mar Menor, Pozo Aledo, Murcia, Spain. ²Department of Pharmacy, Instituto Oftalmológico Fernández-Vega, Oviedo (Asturias), Spain. ³Department of Pharmacy, Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁴Department of Pharmacy, Complejo Hospitalario Universitario, Pontevedra, Spain. ⁵Department of Pharmacy, Hospital Universitario Santa Cristina, Madrid, Spain. ⁶Pharmacy Clinical Management Unit, Hospital Universitario Virgen del Rocío, Sevilla, Spain. ⁷Department of Pharmacy, Hospital Clinic, Barcelona, Spain. ⁸Department of Pharmacy, Hospital Universitario Fundación Alcorcón, Alcorcón (Madrid), Spain. ⁹Department of Pharmacy, Hospital Universitario de la Princesa, Madrid, Spain.

Author of correspondence

José María Alonso Herreros
Servicio de Farmacia Hospitalaria
Hospital Los Arcos Mar Menor
Paraje Torre Octavio, 54
30739 Pozo Aledo (Murcia), Spain.

Email:
josem.alonso@carm.es

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Abstract

As in other areas of the health system, COVID-19 has had a dramatic impact on hospital pharmacy compounding. This area has faced numerous challenges, including the shortage of frequent-use products (hydroalcoholic solutions, lopinavir/ritonavir suspension), the use of new preparations for SARS-CoV-2 (tocilizumab, remdesivir), or requests from overwhelmed wards unable to assume the safe preparation of a high volume of medications (intravenous solutions). The demand for all types of preparations (topic and oral medications, intravenous solutions) has increased dramatically. This increase has highlighted the shortage of resources allocated to this area, which has made it difficult to meet the high demand for preparations. In addition, the pandemic has revealed the scarcity of research on such basic aspects as agent stability and drug compatibility. One of the most relevant conclusions drawn from the COVID-19 pandemic is that the basic areas of hospital pharmacy, along with other, must be maintained and reinforced, as these are the areas that make us essential.

Resumen

Como todo el sector sanitario, la farmacotecnia hospitalaria ha sufrido el impacto de la pandemia de la COVID-19, enfrentándose a la necesidad de cubrir el desabastecimiento de productos de uso frecuente (soluciones hidroalcohólicas, lopinavir/ritonavir suspensión), a nuevas preparaciones surgidas de las nuevas necesidades provocadas por el SARS-CoV-2 (tocilizumab, remdesivir), o a peticiones de plantas desbordadas por la carga asistencial, incapaces de asumir con un mínimo de seguridad la preparación de numerosos medicamentos (mezclas intravenosas). El incremento de actividad ha sido en todo tipo de preparados (tópicos, orales y mezclas intravenosas) y ha puesto de manifiesto la escasez de recursos destinados a esta área, que se ha traducido en serios problemas para afrontar todas las elaboraciones necesarias, así como la falta de investigación en aspectos tan básicos como la estabilidad o la compatibilidad de medicamentos. Probablemente, una de las conclusiones más importantes que podemos extraer tras la COVID-19 es que —sin menospreciar otras áreas de la farmacia hospitalaria que también deben desarrollarse— debemos mantener y potenciar las áreas básicas de nuestra profesión. Aquellas que nos hacen imprescindibles.

KEYWORDS

Drug compounding; Hospital pharmacy service; COVID-19; Pandemic; Lopinavir ritonavir; Hand hygiene; Hydroxychloroquine.

PALABRAS CLAVE

Formulación magistral; Servicio de Farmacia Hospitalaria; COVID-19; Pandemia; Lopinavir ritonavir; Higiene de manos; Hidroxicloroquina.



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Introduction: Challenges and objective

The compounding of medications is a fundamental part of all activities of modern hospital pharmacy (HP). The ongoing pandemic, with an impact on all structures of society, has posed numerous challenges to HPs that had to be solved in record time. Most of these challenges were already known to pharmacological compounding units (formulations not commercially available, shortage of supply, dose adjustment, and resource optimization, among others). However, these problems had to be solved under an unprecedented demand for care and, occasionally, with staff shortage due to infections.

The basic process usually implemented to address these problems was adopted avoiding uncover "trials":

- Evidence search and appraisal.
- Analysis of the resources needed and options available.
- Authorization according to local procedures (boards, management, protocolization including informed consent, among others).
- Evaluation of results

The website of the Spanish Society of Hospital Pharmacy (SEFH), added to solidarity among centers, has demonstrated to be highly useful for the evaluation and dissemination of evidence and resource sharing and optimization.

Strategies developed to address the problems raised during the COVID-19 pandemic

Shortage of solutions for hand disinfection

The closure of borders and the ban on exports in some countries, along with the increased demand, initially resulted in a sudden shortage of hydroalcoholic gel in Spain, with a special impact on hospital pharmacy services (HPS) for several reasons, namely:

- As hydroalcoholic gel is not considered a medicine, procurement was rarely managed by HPS, which hampered supply.
- Some HPS did not have the capacity to prepare the large volume needed daily (up to 300L/day). In this situation, pharmacy schools played a crucial role.
- The wide variability in the formulations available in the market, which did not always have the required bactericide/viricidal effects.
- Shortage of raw materials and containers.

The SEFH Pharmacological Compounding Group advocated the use of the formulation recommended by the WHO¹, since it was evidence-based, supported by health authorities, and easy to prepare, putting special emphasis on quality controls and precautions for handling. It was also recommended to reuse bottles, which partially solved supply problems.

Preparation of disinfectants and guidance for cleaning compounding areas

In the light of the high stability of SARS-CoV-2 in the environment, the selection and compounding of disinfectants for cleaning surfaces and equipment has become essential. The cleaning of compounding areas (either in ward or in HP) must be carried out in accordance with protocols based on the Best Practice Guidelines for Medicine Compounding in Hospital Pharmacy Services² (BPGMC) issued by the Spanish Ministry of Health. Thus, traces of detergent or dirt must be eliminated, as they may affect the effectiveness of the viricidal agent —authorized against SARS-CoV-2³—, which must be let work for some minutes.

The WHO⁴ also recommends:

- Sodium hypochlorite 0.50-0.05%. During preparation, consider the concentration of commercially-available bleach (4-10%), use cold water, keep the room adequately ventilated, use gloves and eye protection. These dilutions must be protected from light, used within 24 hours, and left on the surface for five minutes. Sodium hypochlorite cannot be mixed with ammonia or acids.
- Ethanol 70%: for hypochlorite-sensitive surfaces.

Other agents (chlorhexidine, benzalkonium, etc.) should be avoided, as they have demonstrated to have limited effectiveness against SARS-CoV-2⁵.

Compounding of oral liquid formulations

As shortage of lopinavir/ritonavir solution (Kaletra®) was foreseeable, we sought an alternative. Replicating Kaletra® was inviable due to the unavailability of its active substances and its composition⁶ (ethanol 42%, propylenglycol 15%), which made it impossible to prepare a replication using tablets containing incompatible excipients. Acceptable results were not obtained from the use of tablets and a lipophilic excipient. Finally, preparing a hydrophilic suspension was ruled out due to a loss of bioavailability of 45-47%⁷ and the characteristics of the active substances⁸.

With respect to hydroxychloroquine, preparing an oral liquid formulation was considered. This drug is highly soluble, with a minimal impact on bioavailability. The European Paediatric Formulary (PaedF) published information on pediatric formulations of active substances used in clinical trials and experimentally in clinical practice⁹. The formulation described by the Pharmacological Compounding Group¹⁰ is consistent with that reported by PaedF. The vehicles used are semi-finished, but they are similar to those described by the United States Pharmacopeia, with prior galenic testing and validation^{2,11}.

Unit dose of lopinavir/ritonavir oral solution

The shortage of Kaletra® solution led some hospitals to prepare unit doses with the period of validity indicated in BPGMC recommendations² and in the literature.

The only information available on the stability of the solution in oral syringes¹² indicates that the product keeps stable for at least 12 hours at 25 °C/60% RH (relative humidity) and for 3 hours at 30 °C/65% RH. Moreover, it contains excipients⁵ that may be incompatible with some plastics; therefore, administration through polyurethane tubes is not recommended.

In this setting, it seems reasonable to establish a period of validity of refilling below the one indicated in general BPGMC recommendations. Further studies are needed to test the stability of the medicine in unit doses.

Preparation, stability and compatibility of intravenous compounds for intensive care units

The COVID-19 crisis has had special relevance in terms of the treatments administered in critical care units (ICUs) for the severity and risk of the disease and the complexity of the preparation and administration of intravenous solutions. This situation has brought out the need for the centralized preparation of intravenous solutions in HPS, assuring their stability.

The scarcity of literature data and the need for the simultaneous administration of several drugs make it necessary that an analysis is performed to assess the physical compatibility of the solution for a safe immediate use in terms of absence of turbidity/precipitates, dilutant/container compatibility, and storage conditions. Preparation of stock solution is only recommended if supported by the literature and microbiological batch validation. The preparation of solutions in the HPS guarantees that the formulation is prepared in a controlled environment and warrants microbiological stability, batch- and patient-level traceability according to BPGMC criteria and recommendations², and an effective management, which is essential in a critical situation.

Preparation of hematic derivatives

A consensus document with several updates were issued by SEFH and the Spanish Society of Ophthalmology¹³. The main recommendation is to restrict the use of hematic derivatives to clinical settings where, in doctor's opinion, the condition may worsen and compromise patient's vision.

The exclusion criteria are maintained as usual¹⁴: patients are excluded if they are recovering or have recovered completely from an infectious disease which symptoms, including fever > 38 °C and flu-like condition, disappear.

red at least two weeks ago. COVID-19 patients should be included in this group, but apart from the usual serology tests, the general status of the patient should be assessed.

The applicable precautions are those indicated by the Spanish Agency for Medicines and Medical Devices for platelet-rich plasma¹⁵. However, in order to reduce mobility, it is recommended to elaborate the highest amount of eye drops possible to cover the maximum period of stability. To such purpose, clinical pathways can be optimized by referring patients to their primary care center for blood draws –with prior instructions given to the patient on the safe use and storage of their medicine–, with eye drops included in medicine home delivery.

Dispensing and home delivery to outpatients

HPS has adopted measures to reduce the exposure of outpatients who needed hospital medication, including formulations and solutions of patients in special situation who had to continue their treatment¹⁶.

The measures implemented included teleconsultation, capacity control, reduction of forms/manual signature, and home delivery. The pharmacist/patient relationship in this situation is crucial for coordination with physicians, the continuity of treatments, dose adjustments (especially in the Unit of Pediatrics with neonatal weight gain), the adaptation of formulations, and the selection of the most appropriate number of containers to dispense based on the stability of the formulation. Simultaneously, hospital pharmacists monitor patient tolerance, difficulties, and supervise dose volume, and drug administration, storage and interactions. Medication home delivery is subject to some transportation requirements such as refrigeration and protection from light by the use of fridges, accumulators, protection for fragile containers, and distribution of dosing and administration devices. The role of the pharmacist in pharmacological compounding is not constrained to technical aspects. Pharmaceutical care is essential to guarantee the quality of the design, safety and delivery of the formulation, especially in times of uncertainty.

Optimization of individual protection equipment

The shortage of individual protection equipments (IPE) has forced organizations worldwide to issue specific recommendations for the preparation of sterile formulations¹⁷:

- Prioritize their use for clinicians in close contact with patients.
- Prioritize the availability of sterile gloves, especially IPE, for the risk that the preparation of formulations entail.
- Limitation of the number of operators per day and maximization of preparation times.
- Use of washable masks, gowns, and caps, which must be always clean before entering the preparation area.
- Storage and reuse of single-use gowns during the shift/work day. If they are intact or not visibly dirty, store them in the classified areas. Wash after each shift.

- Wear footwear only for use in the laboratory. Clean regularly.
- For the preparation of hazardous sterile formulations, prioritize the use of gowns and gloves that meet regulations on cytostatic agents (List 1 of the National Institute for Occupational Safety and Health [NIOSH]). Do not reuse.

In the absence of IPE:

- Adopt a risk-based approach and limit the preparation of stocks.
- Assign dates of expiration as short as possible.
- Increase the frequency of cleaning and disinfection.
- The shortage and reuse of gowns may increase the risk of microbial contamination. Implement strategies to minimize risks while the quality of formulations is guaranteed through microbiological controls, among others, thereby assessing the efficacy of these processes.

Lessons learned. Future applicability in pharmacy services

After the pandemic, we should be aware –without prejudice to the other tasks of HP– that pharmacological compounding is one of the main functions of HP. In most hospitals, the demand for formulations from clinical services has raised dramatically due to the shortage of supply, the safe preparation of formulations in the pharmacy, and the lack of resources in the ward, which shows one of the greater challenges of pharmacological compounding: the shortage of resources. This shortage of resources is caused by the use of questionable cost-utility criteria, management tendencies (outsourcing) and other factors that have not resisted SARS-COV-2. All in all, the most relevant lesson learned is that solidarity and cooperation with other services and entities such as faculties, the industry, laboratories, and SEFH allowed us to respond to an overwhelming demand for pharmacy care. Without them, we could not have done it.

This problem does not only result in a lack of capacity to prepare such a number of intravenous solutions, liters of disinfectant, or unit doses, but it also illustrates the scant research on basic aspects such as drug stability or compatibility.

This situation is not only brought about by HPS or hospitals, but it is the result of health authorities' consideration this type of research as something secondary. There are no regulations on the preparation of disinfectants and the availability of active substances, which would have allowed us to design specific formulations enteral tube administration or to solve the shortage of medications. These lessons are no news to us. They have been learned year after year.

COVID-19 has been a final test. The question is whether these lessons will have been learned for the next tests (second wave in September?) (future public health crises?).

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