

Clinical Challenges in the Usage and Shortage of Mercaptopurine in Pediatric Oncology: Case Report

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Desafios Clínicos no Uso e na Escassez de Mercaptopurina na Oncologia Pediátrica: Relato de Caso

Desafios Clínicos en el Uso y la Escasez de Mercaptopurina en Oncología Pediátrica: Informe de Caso

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ABSTRACT

Introduction: The shortage of pediatric medications is particularly concerning due to the lack of pediatric-specific labeling and limited alternatives, reducing the therapeutic options and increasing the risk of medication errors. Another significant challenge is the absence of appropriate pediatric dosage forms, leading to practices such as tablet splitting or dilution, which can result in toxic or subtherapeutic doses. This article presents two cases that exemplify these obstacles and underscore the critical role of pharmaceutical services, particularly Comprehensive Medication Management (CMM). **Case report:** 1-year-old boy with B-cell acute lymphoblastic leukemia (B-ALL) was prescribed 50 mg 6-mercaptopurine (6MP) tablets, but experienced difficulty swallowing the medication. In case two, the mother of a two-year-old child with B-ALL encountered difficulties obtaining 6MP due to medication shortages. In the first case, caregivers were advised to prepare an extemporaneous oral solution to accommodate the child's inability to swallow tablets. In the second case, the mother was instructed not to use expired medications and was directed to promptly obtain compounded 6MP from the hospital pharmacy to counter the shortage of commercial formulation. **Conclusion:** These cases highlight significant challenges faced by pediatric leukemia patients within a CMM service. Two primary issues were identified: the need to adapt dosage forms for pediatric use and the shortage of 6MP, an orphan drug in Brazil. Children with cancer have unique medication needs, and services like CMM are vital in educating patients and caregivers on proper medication administration, while addressing challenges related to medication access and use effectively. **Keywords:** Resource Shortage for Health; Patient Safety; Medication Therapy Management; Medical Oncology; Pediatrics.

RESUMO

Introdução: A escassez de medicamentos pediátricos é particularmente preocupante em virtude da falta de medicamentos licenciados para pediatria e das alternativas limitadas, o que reduz as opções terapêuticas e aumenta o risco de erros de medicação. Outro desafio significativo é a ausência de formas farmacêuticas apropriadas para pediatria, levando a práticas como a divisão de comprimidos ou diluição, o que pode resultar em doses tóxicas ou subterapêuticas. Este relato apresenta dois casos que exemplificam esses obstáculos e ressalta o papel crucial dos serviços farmacêuticos, particularmente da Gestão da Terapia Medicamentosa (GTM). **Relato do caso:** Menino de 1 ano, com leucemia linfoblástica aguda de células B (LLA-B), que teve a prescrição de comprimidos de 50 mg de 6-mercaptopurina (6MP), mas teve dificuldade em deglutir o medicamento. No segundo caso, a mãe de uma criança de 2 anos com LLA-B enfrentou dificuldades para obter 6MP por conta da escassez do medicamento. No primeiro caso, os cuidadores foram orientados a preparar uma solução oral extemporânea para facilitar a administração em razão da dificuldade de deglutição do paciente. No segundo caso, a mãe foi instruída a não usar medicamentos vencidos e orientada a obter prontamente a 6MP manipulada na farmácia do hospital para contornar a escassez da formulação comercial. **Conclusão:** Tais casos destacam desafios significativos enfrentados por pacientes pediátricos com leucemia em um serviço de GTM. Dois problemas principais foram identificados: a necessidade de adaptar formas farmacêuticas para o uso pediátrico e a escassez de 6MP, um medicamento órfão no Brasil. Crianças com câncer possuem necessidades medicamentosas específicas, e serviços como a GTM são fundamentais para educar pacientes e cuidadores sobre a administração adequada de medicamentos, ao mesmo tempo em que enfrentam de forma eficaz os desafios relacionados ao acesso e uso de medicamentos. **Palavras-chave:** Escassez de Recursos para a Saúde; Segurança do Paciente; Conduta do Tratamento Medicamentoso; Oncologia; Pediatria.

RESUMEN

Introducción: La escasez de medicamentos pediátricos es particularmente preocupante debido a la falta de medicamentos licenciados para pediatria y a las alternativas limitadas, lo que reduce las opciones terapéuticas y aumenta el riesgo de errores de medicación. Otro desafío importante es la ausencia de formas farmacéuticas adecuadas para pediatria, lo que lleva a prácticas como la división de comprimidos o la dilución, lo que puede resultar en dosis tóxicas o subterapéuticas. Este informe presenta dos casos que ejemplifican estos obstáculos y resalta el papel crucial de los servicios farmacéuticos, particularmente de la Gestión de la Terapia Medicamentosa (GTM). **Informe del caso:** Niño de 1 año, con leucemia linfoblástica aguda de células B (LLA-B), recibió la prescripción de comprimidos de 50 mg de 6-mercaptopurina (6MP), pero tuvo dificultad para tragar el medicamento. En el segundo caso, la madre de un niño de 2 años con LLA-B enfrentó dificultades para obtener 6MP debido a la escasez del medicamento. En el primer caso, se aconsejó a los cuidadores preparar una solución oral extemporánea para facilitar la administración debido a la dificultad del paciente para tragar. En el segundo caso, se instruyó a la madre a no usar medicamentos vencidos y se le orientó para que obtuviera rápidamente 6MP en la farmacia del hospital, a fin de mitigar la escasez de la formulación comercial. **Conclusión:** Estos casos destacan los desafíos significativos que enfrentan los pacientes pediátricos con leucemia en un servicio de GTM. Se identificaron dos problemas principales: la necesidad de adaptar las formas farmacéuticas para su uso en pediatria y la escasez de 6MP, un medicamento huérfano en el Brasil. Los niños con cáncer tienen necesidades específicas en cuanto a medicación, y servicios como la GTM son fundamentales para educar a los pacientes y cuidadores sobre la administración adecuada de medicamentos, enfrentando de manera eficaz los desafíos relacionados con el acceso y el uso de los mismos. **Palabras clave:** Escasez de Recursos para la Salud; Seguridad del Paciente; Administración del Tratamiento Farmacológico; Oncología Médica; Pediatría.

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INTRODUCTION

Approximately 400,000 children and adolescents (0-19 years old) are diagnosed with cancer worldwide each year making it one of the leading causes of death^{1,2}. Among the types of childhood cancer, leukemia is the most frequent and represents 30-40% of the malignant cases^{3,4}. Mercaptopurine (6MP) is a key drug used during the induction, remission, and maintenance phases of leukemia treatment, particularly for acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML)⁵. However, 6MP is available in 50 mg tablets, often requiring splitting or crushing for pediatric dosing, and it interacts with milk, which is commonly consumed by children in Brazil^{6,7}.

Additionally, 6MP is classified as an orphan drug, and its shortage poses a significant challenge in treating leukemia. In general, the impact of drug shortages is problematic for health systems, being characterized as a global problem that currently affects all types of countries, from the least to the most developed^{8,9}. Drug shortages have been linked to higher relapse rates and increased toxicity risks in pediatric cancer patients¹⁰. In 2022, Brazil faced a shortage of 6MP due to regulatory issues related to bioequivalence studies, complicating treatment for leukemia patients. In this context, clinical pharmacists play a pivotal role in mitigating the impact of drug shortages by ensuring appropriate therapeutic alternatives, assessing potential drug interactions, and closely monitoring medication adherence. Their involvement in patient education and therapeutic drug monitoring is crucial for maintaining treatment efficacy and minimizing adverse effects, ultimately safeguarding patient outcomes amid supply disruptions¹¹.

This study reports challenges in managing 6MP shortages in pediatric leukemia patients enrolled in the Comprehensive Medication Management (CMM) service at a pediatric oncology hospital in São Paulo. The service provided pharmaceutical care to children aged 0-19 years with leukemia. Two primary challenges were highlighted: (1) the need to adapt 6MP dosage forms for pediatric patients, and (2) the impact of 6MP shortages. Two cases to illustrate these challenges are described in the present case report.

The study was approved by the hospital's Scientific Committee and the Ethics Committee of *Universidade Federal de São Paulo*, report number 6129438 (CAAE (submission for ethical review): 27115319.4.0000.5505), with informed consent obtained from all participants, in compliance with Directive number 466/12¹² of the National Health Council (CNS).

CASE 1

A 1-year-old boy diagnosed with Common B ALL, stratified as high risk according to the protocol criteria developed by Berlin-Frankfurt-Münster Study Group in 2009, attended his first pharmaceutical consultation accompanied by his caregivers. Before starting the early intensification phase of the ALL BFM 2009 protocol, which recommends the use of 60 mg/m² of 6MP orally, caregivers, including the patient's pregnant mother, were informed about safe practices for chemotherapy administration at home.

Given the patient's inability to swallow the tablet whole, caregivers were instructed to prepare an extemporaneous oral solution by dispersing the tablets in potable water for immediate administration. This method ensures that the child receives the appropriate dosage while maintaining treatment efficacy. Additionally, comprehensive safety guidelines for handling oral chemotherapy were reinforced to minimize risks associated with exposure to cytotoxic agents. Particular attention was given to the potential hazards for pregnant individuals, emphasizing that direct contact with the medication could pose significant teratogenic and toxicological risks.

To mitigate these concerns, the child's father was strongly advised to assume full responsibility for handling, segmenting, and administering the oral chemotherapy at home. He received clear instructions from a clinical pharmacist on best practices for handling medications, including the use of protective equipment, proper disposal of contaminated materials, and hygiene measures to avoid inadvertent exposure.

CASE 2

A mother of a 2-year-old boy diagnosed with Common B ALL, stratified as intermediate risk according to the protocol criteria developed by Berlin-Frankfurt-Münster Study Group in 2009, requests pharmaceutical guidance regarding 6MP shortages. The patient was in the maintenance phase of the ALL IC-BFM 2009 protocol, which recommends oral administration of 50 mg/m² of 6MP. However, due to shortages, patient caregivers tried to buy medicine at pharmacies, without success. She reported that 6MP tablets expired at home and wanted to know if she could continue to administer them to the child or if there was another therapeutic alternative.

A temporary contingency measure was implemented by the hospital pharmacy service, which involved the use of compounded 6MP due to a shortage. At that time, no recommendations permitted the administration of expired 6MP tablets. As 6MP is intended for hospital use only,

it is not commercially available in Brazilian pharmacies. Consequently, the patient's caregiver was advised not to administer expired medications and to visit the hospital to obtain compounded 6MP as soon as possible. This decision was made to ensure uninterrupted treatment for the child while the hospital worked to resolve the shortage.

In a collaborative effort, clinical pharmacists ensured that patients received necessary information on the administration of the new 6MP formulation and that treatment outcomes were closely monitored for effectiveness and safety.

DISCUSSION

The overall survival rate for pediatric acute lymphoblastic leukemia (ALL) exceeds 90% with modern treatment regimens, largely due to personalized long-term maintenance therapy using daily doses of mercaptopurine (6MP)¹³. Drug shortages, however, compromise treatment intensity, leading to negative outcomes, clinical delays, and ethical concerns¹⁴.

In 2016, a German manufacturer altered the binding agent in 6MP. While the European Medicines Agency approved the change without bioequivalence studies¹⁵, in Brazil, the Brazilian Health Regulatory Agency (Anvisa) requested a bioequivalence study to approve the new 6MP formulation. Significant differences in the drug's peak concentration led to a decision of non-bioequivalence. Given the severity of the situation and the imminent risk of shortage, the laboratory holding the product requested exceptional authorization to import 23,000 units of the drug. This authorization was contingent upon active monitoring of patients receiving the product, as well as the submission of documentation and a risk minimization plan. In addition, an urgent measure was taken to extend the expiration date for four batches of the drug that were already produced, marketed and in use in the country. This extension was supported by studies demonstrating the drug's stability during this period, which ensured that no significant health risks existed for patients using the drug beyond the initially established expiration date. Unfortunately, by the end of 2022, a shortage of the 6MP was already a reality in Brazil^{6,16,17}.

The US Food and Drug Administration – FDA reported that drug shortages have been a recurring problem despite efforts by the public and private sectors to prevent and minimize them. A five-year survey (2013-2017) identified 163 drugs that were in short supply during that period. In some cases, the product has been off the market for more than eight years⁹. Shortages raise a particular concern in pediatrics given that many drugs lack transitory pediatric labeling and there are scarce alternatives, resulting in fewer

therapeutic options. In addition, incorrect substitutions are often associated with medication errors¹⁸.

Further to these shortages, the lack of appropriate dosage forms for children in Brazil has been a continuous concern. Dispersing tablets or diluting oral solutions is a common practice to achieve therapeutic doses, but compounded forms may lead to toxic or subtherapeutic dosing¹⁹. Studies have shown environmental contamination from home chemotherapy, making it unsafe to compound 6MP in non-clinical settings. When unavoidable, caregivers must be fully informed of the risks and trained in proper safety precautions²⁰. Standardizing procedures for dispersing 6MP in water to create an oral suspension, as suggested by Tessman et al.²¹, can reduce risks and improve safety for children, adolescents, and their caregivers.

Ideally, liquid formulations of 6MP would be commercially available. While some countries have approved 6MP oral suspensions, they are not yet available in Brazil. The Institute for Safe Medication Practices Canada (ISMP Canada) recommends minimizing the need for caregivers to compound medications, developing pediatric-specific guidelines for manufacturers, and advancing the availability of safe pediatric formulations²².

A limitation of this study is that its findings reflect the experiences of a single institution, which may not be generalizable to a broader population. However, the cases described emphasize the challenges of 6MP shortages and the lack of appropriate pediatric dosage forms, while also suggesting possible mitigation strategies.

CONCLUSION

Children and adolescents with cancer have specific healthcare needs due to medication use. The shortage of drugs for pediatric oncology, exacerbated by the increasing frequency of supply disruptions, represents a critical challenge. A key contributing factor is the pharmaceutical industry's limited interest in researching, developing, and manufacturing new drugs for this population due to insufficient incentives. Additionally, the complexity of the pharmaceutical production chain has intensified, which is influenced by factors such as the availability of active pharmaceutical ingredients, raw materials, and packaging components. The COVID-19 pandemic has exposed the global vulnerability of supply chains, further intensified by market demand fluctuations, nationalist policies, and extended transit times, highlighting a longstanding issue.

Although resolving this problem in the short term is unlikely, it is crucial to emphasize that mitigating drug shortages in pediatric oncology will require increasingly innovative and multidisciplinary strategies from clinical professionals. Coordinated efforts among



all stakeholders – governments, the pharmaceutical industry, healthcare professionals, patient associations, and health insurance providers – are essential to developing collaborative programs and comprehensive plans to ensure the availability of these medications. Finally, this case report illustrates how a CMM service for children and adolescents with ALL implemented strategies to support and care for this vulnerable population in the context of ongoing drug shortages.

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CONTRIBUTIONS

Thuane Sales Gonçalves contributed to the study design and drafting of the manuscript; Lídia Freitas Fontes contributed to the writing of the manuscript; Flávia Borelli Gomes Nascimento critically reviewed the content; Paulo Caleb Júnior de Lima Santos and Mariana Martins Gonzaga do Nascimento supervised the study, and conducted a critical review of the content. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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