

Novel pediatric delivery systems for second-line anti-tuberculosis medications: a case study

J. Furin,* G. Brigden,[†] E. Lessem,[‡] M. C. Becerra[§]

*Tuberculosis Research Unit, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA; [†]Campaign for Access to Essential Medicines, Médecins Sans Frontières, Geneva, Switzerland; [‡]Treatment Action Group, New York, New York; [§]Harvard Medical School, Boston, Massachusetts, USA

SUMMARY

Tens of thousands of children are sick with multidrug-resistant forms of tuberculosis (MDR-TB), but there are limited child-friendly delivery systems for second-line medications. This case study presents the development of a granular dosing spoon pediatric delivery system for

para-aminosalicylic acid. This product is the first of its kind for MDR-TB and could serve as a model for the development of other urgently needed pediatric delivery systems for second-line anti-tuberculosis drugs.

KEY WORDS: pediatric; MDR-TB; PAS; TB

MULTIDRUG-RESISTANT tuberculosis (MDR-TB) is a major public health threat, and it is estimated that there are more than half a million individuals with MDR-TB in the world today.¹ Data on pediatric MDR-TB are limited, but it is likely that there are at least 45 000–50 000 children who become sick with MDR-TB globally every year.² It is estimated that less than 1% of children with MDR-TB actually receive treatment for their disease,³ although children have excellent outcomes.⁴

There are multiple reasons why children are overlooked in the global response to the MDR-TB pandemic. One barrier is diagnosing MDR-TB in the pediatric population.⁵ Once a diagnosis has been made, the major challenge faced by clinicians is initiating children with MDR-TB on appropriate treatment. Pharmacokinetic data in pediatric populations are lacking, making dosing recommendations unclear.⁶ Further compounding the problem is the lack of pediatric formulations of or delivery systems for most second-line anti-tuberculosis medications.⁷

The lack of child-friendly delivery systems is not unique to the problem of MDR-TB and has been confronted in other diseases, most notably human immunodeficiency virus infection.⁸ One approach has been the development of fixed-dose combinations (FDCs) in dispersible tablet forms. Such delivery systems for MDR-TB treatment are likely decades away, however, and there is an urgent need for child-friendly formulations for treating children currently sick with MDR-TB.

This article presents a case study of the develop-

ment of a pediatric delivery system for granular para-aminosalicylic acid (PAS) as a possible alternative approach to developing pediatric formulations of second-line anti-tuberculosis medications. This is the first such delivery system available for pediatric second-line anti-tuberculosis drugs and can be an instructive case for pediatric MDR-TB drug development.

CASE STUDY

Para-aminosalicylic acid

PAS is a second-line medication used in the treatment of drug-resistant TB.⁹ PAS was originally one of the first medications used to treat TB and was often given with streptomycin before the development of isoniazid. The use of PAS was limited by the large pill burden and the large size of the pills. To improve the safety profile and to ease administration, a gastro-resistant granular form of PAS (Paser[®]) was developed by Jacobus Pharmaceuticals (Princeton, NJ, USA, <http://www.onlinedrugtest.info/companies/jacobus-pharmaceutical-company-pharmaceuticals-company.html>), and this is the formulation most commonly used worldwide. Paser comes in sachets of 4 g PAS. Dosing PAS for pediatric patients can be difficult: as children need doses of between 150 and 300 mg/kg/day, entire sachets must be opened, and weighing out the granules can be labor-intensive.

On 17 December 2010, orphan designation (EU/3/10/826) was granted by the European Commission to Lucane Pharma, Paris, France, for Paser for the

treatment of TB. Lucane, which has a history of working with other designated orphan drugs, was asked to develop a pediatric delivery system for Paser for use in Europe.

Dosing spoon intervention

Lucane determined that the adult granular formulation of PAS (Paser) was amenable to adaptation for pediatric use. Their development strategy found that granule formulations are well suited for the dosing of infants and children for several reasons. First, doses can be calibrated to body weight. Furthermore, granules allow the unpleasant taste of many medicines to be masked, which can be difficult to achieve with liquid forms. Granule forms are also often more stable than liquids, making them easier to distribute and store safely in more inaccessible locations. Finally, although 4 g is the dose of active ingredient to be delivered, the actual weight of the Paser granules can be higher; the dosing spoon takes this into account and allows the correct dose of the active ingredient to be delivered.

To ease dispensing of PAS for children, Lucane developed a pediatric ‘dosing spoon’, calibrated specifically for Paser. The spoon allows providers to dispense Paser in dosing ranges acceptable for children, and has cut-off marks for the different doses of PAS based on weight-band doses (Figure). The spoon has been purchased in small quantities by Médecins Sans Frontières for some of its project sites. It is now available from Lucane and will be included in all European Union packs if the product is granted marketing authorization.

Development

To facilitate the development of pediatric PAS, Lucane did not change the adult formulation. Rather, they worked with the existing formulation and came up with a novel method for dosing, i.e., a pediatric delivery system. Lucane encountered some challenges in creating this pediatric delivery system. It took almost 9 months to develop and validate the device. Furthermore, the number of MDR-TB patients in Europe is relatively small, and the number of children requiring Paser in Europe is unlikely to exceed 200 per year. This small market made registering the device in Europe more difficult. Finally, there are issues



Figure Pediatric dosing spoon.

with the level of calibration and accuracy that can be achieved with these spoons. The spoon is operator-dependent, and requires that the dispenser be familiar with the marking system. Dispensing doses between those calibrated on the spoon (e.g., 750 mg) requires special attention. Despite these limitations, the dosing spoon developed by Lucane is one of the few pediatric-friendly delivery systems for second-line anti-tuberculosis drugs available and the only one of its kind in use today.

DISCUSSION

The lack of child-friendly formulations for second-line anti-tuberculosis medications greatly hinders access to MDR-TB treatment for thousands of children around the world. While some of the second-line medications come as syrups (e.g., linezolid, levofloxacin), they can be cumbersome, difficult to store and require large volumes to be administered daily. Other medications come as injectables (e.g., capreomycin, the aminoglycosides), and while it may be possible to adjust injection doses for children, this mode of delivery can be painful. This case study presents one way in which the pharmaceutical industry has responded to the need for pediatric delivery systems for second-line medications, drugs for which there is a limited market. Similar action is needed for other second-line anti-tuberculosis drugs—particularly medications such as cycloserine (CS) and ethionamide (ETH), for which no such delivery systems exist—to improve the global management of pediatric MDR-TB.

The pediatric pharmaceutical community is aiming for dispersible FDCs as a way of providing safe and effective treatment for children with TB and MDR-TB. However, due to the lack of certainty regarding the dosages required for MDR-TB in children and the number of drugs involved, the development of an FDC for MDR-TB is still some time away. The development of granules and dosing spoons offers an alternative to the standard FDC approach. Other medications such as CS or ETH could be developed into granular formulations with spoon delivery systems at a minimal cost. The granular approach to pediatric dosing has the potential to address the urgent need for pediatric-friendly formulations of and delivery systems for other second-line anti-tuberculosis medications, and it should be pursued in future drug development plans.

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R É S U M É

Des dizaines de milliers d'enfants sont atteints de formes multirésistantes de tuberculose (TB-MDR), mais des systèmes de fourniture des médicaments de deuxième ligne adaptés aux enfants n'existent que de manière limitée. Cette étude de cas expose l'élaboration d'un système de délivrance de l'acide para-aminosalicylique aux

enfants au moyen d'une cuillère permettant le dosage de granulés. Cet instrument est le premier dans son genre pour la TB-MDR et pourrait servir de modèle pour l'élaboration d'autres systèmes de délivrance pédiatrique nécessaires d'urgence pour les médicaments antituberculeux de deuxième ligne.

R E S U M E N

Decenas de miles de niños sufren de formas multidrogo-resistentes de tuberculosis (TB-MDR), pero se cuenta con muy pocos sistemas de administración de medicamentos de segunda línea que sean adaptados para los niños. En el presente análisis casuístico se presenta el desarrollo de un sistema de administración de ácido

p-aminosalicílico en gránulos con cuchara dosificadora para niños. Este producto es el primero en su género para el tratamiento de la TB-MDR y podría servir como modelo en otros sistemas de administración de medicamentos de segunda línea que se necesitan con urgencia en pediatría.
