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MANUSCRIPT TITLE

Acceptability of a novel levofloxacin dispersible tablet formulation in young children exposed to multidrug-resistant tuberculosis

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CONFLICT OF INTEREST

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KEY WORDS

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ABBREVIATED/RUNNING HEAD TITLE

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ABSTRACT (60 word limit)

Levofloxacin is used for the treatment and prevention of multidrug-resistant tuberculosis in children, but current adult formulations are poorly palatable. A questionnaire administered to caregivers of 27 children taking a novel 100 mg dispersible taste-masked levofloxacin tablet found the new formulation to be more palatable (69%) and easier to prepare (81%) than the adult formulation. This formulation may assist children to better adhere to anti-tuberculous therapy.

INTRODUCTION

There is now consensus that children should have access to medicines that are specifically designed and evaluated for paediatric use (1). Acceptability, defined as 'the overall ability and willingness of the patient to use, and its caregiver to administer, the medicine as intended' may substantially affect a patient's experience of treatment, and their adherence (1, 2). Acceptability of a medication is driven both by the characteristics of the user and by the properties of the medicinal product, including palatability (the taste of the product), swallowability, appearance, dosing, complexity of modification before dosing, and mode of administration (3). There is increasing awareness that children are unique and that acceptability should be studied in children themselves.

Modelled estimates suggest that 2 million children globally are currently infected with multidrug-resistant tuberculosis (MDR-TB; defined as *Mycobacterium tuberculosis* with resistance to at least isoniazid and rifampicin), with 25,000 children progressing to MDR-TB disease each year (4). It is currently unclear whether MDR-TB preventive chemotherapy should be used, with no clear guidance from the World Health Organisation (WHO) (5). The fluoroquinolones are a safe and effective component of treatment regimens for MDR-TB disease in children and an increasing number of observational studies suggest that the fluoroquinolones may also treat MDR-TB infection (6). Treatment of both MDR-TB infection and disease in children require daily fluoroquinolone use for at least 6 months (7).

Adult formulations of moxifloxacin and levofloxacin are not dispersible and are bitter when crushed. Thus, there is an urgent need for child-friendly formulations of fluoroquinolones, and for any new formulations to be appropriately assessed for acceptability in children, prior to their use in clinical trials and routine care.

TB-CHAMP is a phase III, placebo-controlled trial to assess the efficacy and safety of levofloxacin to prevent TB disease in healthy child household contacts of infectious MDR-TB cases. A new, child-friendly dispersible formulation of levofloxacin was developed (Macleods Pharmaceuticals, Mumbai, India) for this study and received WHO Prequalification in February 2018. Here we report on the acceptability to children and caregivers of this novel formulation as part of an open-label pharmacokinetic (PK) lead-in study.

METHODS

Design and population

This study was implemented in Cape Town, South Africa. Participants were children <5 years in household contact with an adult MDR-TB index case diagnosed during the previous 6 months. Exclusion criteria for children included TB disease at enrolment, being on isoniazid or a fluoroquinolone for more than 16 weeks, having been treated for TB in the previous 12 months and known concurrent exposure to an isoniazid-susceptible source case. In Cape Town, the "standard of care" for MDR-TB child contacts is a regimen consisting of levofloxacin (adult 250mg formulation), ethambutol and high-dose isoniazid. On enrolment into the study (first visit), this regimen was temporarily interrupted and children were started on weight-banded doses (15-20mg/kg) of levofloxacin with the novel dispersible formulation. At the second (final) visit at 7-14 days (when steady state was reached and dependent on participant and study team availability), PK sampling and acceptability evaluations were undertaken and the routine regimen was restarted.

Medication

Levofloxacin 100 mg tablets were developed in collaboration with Macleods Pharmaceuticals (Mumbai, India) and are taste-masked (orange-peppermint flavour) and dispersible (product specifications indicate a disintegration time of 1 minute at 15-25°C). The tablets are off-white to pale yellow coloured, capsule shaped, biconvex, uncoated, with a break-line on one side and a plain surface on the other.

Administration

Levofloxacin tablets were administered by study personnel at the initial and second visit when PK sampling was undertaken. The remainder of the tablets were given once daily by caregivers at home with clear instructions provided by the research team. Dosing was

carefully demonstrated at the first visit, and caregivers were shown how to add tablets and water to a syringe or cup, wait for dissolution (2-3 min), administer to the child and then rinse the container with additional water and administer to ensure all tablet residue was swallowed. At home, tablets were administered whole, crushed or dissolved in water, based on the caregivers' choice. The initial water volume recommended by the manufacturer for dispersion was 50 ml per tablet, which was not feasible in this age group. We initially used 10 ml water, which was reduced to 2.5 ml per tablet after the first few participants were enrolled, as we observed that the tablets dissolved easily in small volumes of water, and that both children and caregivers preferred the smaller volumes. Residue in the dosing container necessitated a 2.5 ml water rinse to ensure that the entire dose was swallowed. The simplest way to dose very young children was to place the tablet in a syringe, draw up the required amount of water, invert to allow for full dispersion, and then administer using the syringe.

Data collection and statistical analysis

The research team observed levofloxacin dosing on the last day of the trial (day 7-14) to assess how the child took the dose. An acceptability questionnaire was administered to the child's caregiver by the research team to assess study drug acceptability at home. The questionnaire consisted of: i) six items soliciting ranked responses from the caregivers regarding their opinions about drug administration and acceptability and ii) four questions soliciting categorical responses to assess and describe the study drug administration. The ranked responses used 5 point Likert scales and these results were displayed using stacked bar plots, with the 5 point Likert data merged into three categories (Figure 1). All analyses were conducted using Stata 14.0 Special Edition (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX; StataCorp LP.)

Ethical considerations

This study was approved by the Health Research Ethics Committee of Stellenbosch University (M16/02/009), the South African Health Products Regulatory Agency (20160128) and the South African Department of Health (DOH-27-0117-5309). Informed consent was provided by all participants' parents or legal guardians.

RESULTS

Twenty-seven children, median age 1.9 years (interquartile range [IQR] 0.8-2.7), were enrolled; 16 (59%) were male, none were living with HIV and all were clinically well. During observed dosing at the final visit, 22 (85%) children swallowed the entire dose or swallowed the dose with minimal spillage, 3 (12%) children refused the dose and 1 (4%) spat it out (n = 26; one child was not observed as they had incorrectly dosed the child the night before and were thus withdrawn from the PK study). Caregiver responses to the questionnaire indicated that at home one child swallowed the tablets whole, another was given the tablets crushed with food and 25 (93%) drank the tablets dissolved in water. Twenty-two of 27 caregivers (82%) felt the size of the tablet was acceptable and 23/25 (92%) felt that the volume of dispersion was acceptable; 11/27 (41%) gave either food or liquid after dosing, to help the child take the medication.

Further results from the acceptability questionnaire are summarised in Figure 1. The novel levofloxacin formulation was reported to be more palatable (18/26; 69%) and easier to prepare (21/26; 81%) than the adult levofloxacin formulation used. Overall, the novel levofloxacin formulation was very acceptable to children and their caregivers.

The full questionnaire is provided as supplementary material. Data regarding the PK and the safety are reported elsewhere (*in progress*).

DISCUSSION

Our results indicate good overall acceptability of this new 100 mg child-friendly, taste-masked, dispersible formulation. Children swallowed the drug easily and caregivers were satisfied with the tablet size and drug volume when dispersed. 2.5 ml is considered an acceptable volume for children aged 1- <5 years to swallow (7). Infants under 6 months probably need smaller volumes, which may be feasible considering our observation of this formulation. The much improved acceptability of this dispersible formulation over existing adult tablets provides strong evidence for TB programmes to take up this formulation for paediatric MDR-TB therapy, as it is now WHO prequalified and available from the Global Drug Facility (9).

Potential disadvantages of dispersible tablets generally include low dosing flexibility and large volumes needed for dissolution (10). However, we found that by halving these levofloxacin scored tablets, dosing flexibility was adequate. Small dispersion volumes reduced the risk of mis-dosing, although a small rinse was required to ensure that no residue remained. We demonstrate that the large volumes recommended for dispersing these tablets are not required.

Our study was limited by the fact that these young children's reactions and opinions were not directly evaluated. There are methods suitable for use in non-verbal children (such as Facial Action Coding System), however these are highly subjective and dependent on availability of specific expertise. Our study did not involve direct and immediate comparison of

formulations. Caregivers were asked to compare the study formulation with their memory of previous regimens, which is open to recall, acquiescence and sponsor bias. Factors such as mouth-feel and texture were not assessed in this study due to the children's young age.

Further planned work includes the administration of similar assessments to larger numbers of caregivers during the TB-CHAMP trial (both for levofloxacin and matched placebo), in conjunction with adherence data which may allow exploration of any association between adherence and trial outcomes. During the trial, the formulation used will switch from the adult 250 mg formulation to this new dispersible formulation; formal comparisons between the two are planned with a pharmacokinetic bridging study. We are planning separate direct palatability comparison studies in healthy adult volunteers and older children. This work will enable evaluation of ontogenic taste development in children, and also formulation properties such as after-taste, smell and mouth feel/texture. We also plan to conduct more in-depth qualitative work on caregivers and children's experiences of levofloxacin-based MDR-TB preventive therapy.

In conclusion, we found good acceptability of a novel dispersible paediatric levofloxacin formulation in young children. There is a need for further work to more formally evaluate this and other novel antituberculosis formulations in children. Child-friendly formulations are likely to help children and their caregivers adhere better to children's antituberculosis treatment. This levofloxacin dispersible tablet formulation is now available from the Global Drug Facility and TB programmes should consider providing this formulation for children treated for MDR-TB.

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Supplemental Digital Content 1. Questionnaire

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Figure 1. Stacked bar plots representing ranked responses from an acceptability questionnaire in children receiving a novel levofloxacin paediatric formulation (N=27).

*One child was not yet taking preventive therapy when enrolled on this study, hence the n=26.

Footnote: Some categories from the 5-point Likert scale have been merged for the sake of clarity