Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial

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Objectives To assess the acceptability and swallowability of several minitablets when administered as a unit dose compared with an equivalent dose of syrup in children aged 6 months to 5 years.

Study design The acceptability and swallowability of multiple drug-free minitablets in comparison with glucose syrup was assessed in 372 children of 2 age groups (186 in age group 1 [6-23 months of age] and 186 in age group 2 [2-5 years of age]) in a randomized, 3-way, single administration cross-over study. Age group 1 received 25 minitablets, 100 minitablets, and 5 mL syrup. Age group 2 received 100 minitablets, 400 minitablets, and 10 mL syrup.

Results Superiority was demonstrated in age group 1 for acceptability (25 minitablets, $P < .017$; 100 minitablets, $P < .0001$) and swallowability (25 minitablets and 100 minitablets, both $P < .0001$) compared with syrup. In age group 2, noninferiority of acceptability was found only for 400 minitablets ($P < .0003$), not for 100 minitablets. Subgroup analysis revealed a strong sequential effect. For swallowability, noninferiority could be demonstrated for 100 minitablets ($P < .01$) but not for 400 minitablets.

Conclusions Administration of ≥25 minitablets is well-tolerated, feasible, and safe in children aged from 6 months, and was superior to the equivalent dose of syrup. Children aged >1 year accept ≤400 minitablets even better than the equivalent dose of syrup. Minitablets open the perspective for introducing small-sized solid drug formulations for all children, thus, further shifting the paradigm from liquid toward small-sized solid drug formulations. *(J Pediatr 2018;■■:■■-■■).*

Trial registration German Clinical Trials Register (DRKS): DRKS00008843.

Despite the implementation of Europe's Paediatric Regulation[1] in 2006 and the requirement for Paediatric Investigation Plans to achieve marketing authorization for all new medicines, a large portion of currently available medicines for children are not based on scientific evidence but still are given off-label.[2-4] In addition, the current practice of administering liquids or syrup to children results in an unreliable form of dosing.[5] Thus, it is necessary to investigate the efficacy and optimal doses of pharmaceutical substances in different age groups, and to develop age-adapted drug formulations for the most suitable routes of administration.

In practice, the specific requirements for adequate dosing depend on the age and developmental stage of the child. Existing formulations often do not contain the required strength, the child might not be able to ingest standard-size solid dosage forms, and the taste of oral medicines may be unacceptable. This often results in a choice of an alternative drug formulation, such as a suppository. Despite the importance of appropriate drug formulations for children, there is little knowledge in practice about dosage forms in different age groups.[6] In addition, concerns and uncertainties regarding the age at which young children can safely swallow orally administered solids, such as conventional tablets and capsules persist.[7]

The European Medicines Agency's Reflection Paper *Formulations of Choice for the Paediatric Population*[6] states that there may be no single formulation which is ideal for pediatric patients of all ages such that a range of dosage forms in the portfolio will be preferred. They provided a table of recommended dosage forms per age group,[6] although this recommendation was based on evidence from prescriptions for different dosage forms in relation to age, anecdotal reports of very young children being trained to manage oral solid dosage forms, and a questionnaire completed by a small number of medical and scientific experts.

Although the use of solid multiparticulates in children has been recommended by the World Health Organization[8] in 2008, the European Medicines Agency questioned their applicability at an age of <2 years.[9] The final adopted version of this guideline[10] removed an age restriction for solid oral dosage forms by taking into account previous results from different groups on minitablet acceptability.[7,11,12]

In children, the most common oral formulation currently is syrup. However, minitablets are a cheap alternative that provide advantages over liquids in regard to drug stability, potentially toxic excipients, and storage conditions. Several earlier clinical trials with minitablets have shown that the acceptability of a single minitablet in neonates, infants, toddlers, and preschool children is high and in comparison with a liquid is significantly better.[7,11-13]

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An important limitation of minitablets is their low volume available for drug loading. A minitablet of 2 mm in height and diameter may contain a maximum of ≤2.0-2.5 mg of active drug.[14] Because many therapeutic substances require administration of higher doses, it is important to investigate as a next step whether the administration of multiple uncoated minitablets is feasible in young children. One clinical trial investigated the acceptability of a maximum of 10 minitablets in children 2-3 years of age[15]; 75% of 2-year-old and 93% of 3-year-old children accepted the minitablets.

We focused our standardized assessment methodology on measuring acceptability including swallowability as defined and standardized in our previous studies,[11-13] which have proven to be reliable measures to objectively assess the suitability of oral formulations for children and assist in the determination of appropriate oral pediatric formulations. The main goal of the present study was to investigate the maximum number of uncoated minitablets toddlers and infants are able to accept and swallow.

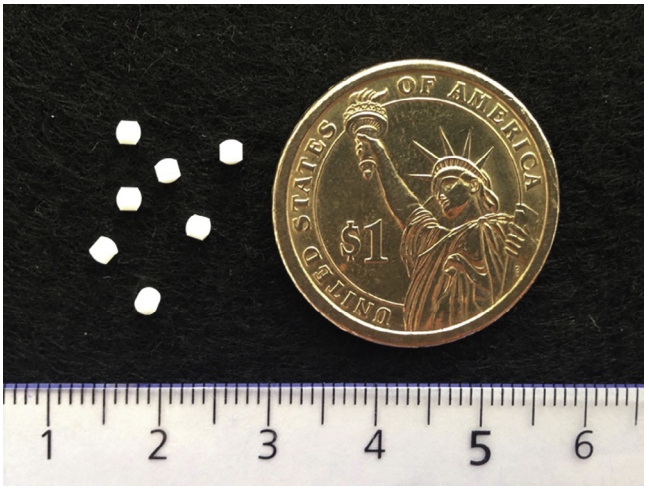

Figure 1. Dimensions of uncoated 2-mm diameter minitablets (left) in relation to a $1 US coin (right).

Methods

The primary objective of this trial was to demonstrate noninferiority in acceptability of 25 uncoated minitablets administered at a time in comparison with 5 mL glucose syrup in children between 6 and 23 months of age (age group 1). The primary outcome measure of acceptability was defined as an aggregate of the evaluation criteria swallowed and chewed (**Table I**; available at www.jpeds.com) according to the validated evaluation criteria defined in our previous studies.[11-13] The secondary objectives were to compare the noninferiority of acceptability and swallowability of administration of further doses of multiple minitablets and syrup in both age groups, that is, 100 uncoated minitablets in age group 1 and 100 and 400 uncoated minitablets in children between 2 and 5 years of age (age group 2), and to monitor potential adverse events.

Design

This study was performed in a single-center, open, randomized, single dose, 3-way cross-over design with 2 age groups to investigate noninferiority of acceptability of 2 different numbers of uncoated placebo-containing minitablets compared with that of glucose syrup.

The study was conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Guideline on Good Clinical Practice[16] with a risk-adapted level of monitoring and adequate insurance coverage. The study received a favorable opinion from the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University, Düsseldorf, Germany (No. 5044R) and was registered in the German Clinical Trials Register (DRKS: DRKS00008843). Because the study medication did not contain an active ingredient, the trial did not fall under the German Drug Law and, thus, was not subject to review and approval from the German competent authority, the Federal Institute for Drugs and Medical Devices.

Study Population

Parents of children between 6 months to 5 years of age at University Children's Hospital, Düsseldorf, Germany, were approached. The recruitment took place between June 30, 2015, and January 18, 2016. Age group 1 included infants 6-23 months of age and age group 2 includes those 2-5 years of age.

Apart from age and signed informed consent by both parents as well as, when possible, by the child, further inclusion criteria were boys and girls able to swallow the formulations, and parents and children who were compliant and willing to accept the study procedures. The exclusion criteria were any impairment of swallowing either solids or glucose syrup as a consequence of chronic or acute illness or oral deformation, family history of lactose intolerance, premedication and concomitant medication that causes nausea, fatigue, or palsy, and patients shortly after surgical intervention.

Formulations

All formulations were placebos. The uncoated minitablets of 2 mm in diameter and a height consisted of lactose, cellulose, magnesium stearate, and anhydrous colloidal silicone dioxide, produced according to Good Manufacturing Practice at Nextpharma (PHARBIL Waltrop, Waltrop, Germany) for this study. The glucose syrup was produced by Fagron (Barsbüttel, Germany) and diluted to 15% at the trial site. A minimum of 25 and a maximum of 100 minitablets and 5 mL syrup for age group 1 was chosen and for age group 2, the minimum was 100 and the maximum 400 minitablets and 10 mL syrup; these respective maximum formulations would equate with a drug dose of approximately 250 mg and 500 mg of a drug, respectively, allowing for the administration of up to 80 mg/kg per day of the active drug (**Figure 1**).

Administration

Children suitable for enrollment into the study were randomized to the sequence of placebo formulations. After an

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