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PRACTICAL ISSUES AND UPDATES

Overcome the challenges of drug administration in children by developing age-appropriate formulations

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Abstract
Interest in developing age-appropriate formulations of drugs to optimize pharmacological therapy in children continues to grow. With oral formulations being the most common route of administration, several factors relating to the formulation and bitter taste of drugs can impact the acceptability of medications in children. Approaches to improve medication acceptability include the use of alternative delivery systems, taste-masking strategies and the development of new technologies for formulation preparation.

Medication use in children is challenging

Medication use in children is common; however, there are many factors influencing optimal drug therapy in children that may not apply to adults [1]. For instance, although much remained to be discovered, age-related development in children (including infants) changes the pharmacokinetic (e.g. drug disposition) and pharmacodynamic (e.g. effectiveness) profiles of a medication. Moreover, it is also important to consider the risk of adverse drug reactions in children [1].

Major changes in drug regulations have taken place to ensure the safe and effective use of medication in humans. However, despite the changes in regulations, children are often referred as 'therapeutic orphans' due to the widespread use of drugs that lack appropriate labelling for paediatric populations [1].

Multiple factors influence medication acceptability in children

There is growing interest in the development of age-appropriate formulations of drugs to improve their acceptability in paediatric patients. Acceptability refers to the ability of the user (i.e. the patient or their caregiver) to use the medication as instructed by the prescriber. It is a complex concept that incorporates multiple factors including palatability, cost, appearance, age-related development, route of administration and other factors [1].

The problems relating to the administration of medication in children often relates to the formulation of the drug [1]. Oral solid dosing forms are the most commonly dispensed formulations, but factors relating to development, palatability and existing dose formulations can impact the acceptability of their use in children. This article present a summary of challenges in administering oral medication to children and methods to possibly overcome them, as reviewed by Rieder [1].

Overcome swallowing problems by replacing solid oral dosage forms…

Swallowing is a complex process that evolves with time, and children aged < 5 years generally have difficulties swallowing a solid dosage forms (e.g. tablets or capsules) [1]. The traditional approach to overcome this problem includes one of the following:

- *Development of liquid formulations* Most common method, especially to administer antibiotics [2]; typically more expensive than solid dosage equivalents and requires a proper measuring device (e.g. oral syringe) for accurate dosing. Moreover, liquid formulations are typically sold in dry powders and the products are reconstituted with clean water and then often refrigerated due to their limited shelf-life. The utilization of such products

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can be an issue in the developing world because clean water and a refrigerator may not be available.

- *Alternative delivery systems* Can be used for certain therapeutic areas such as ophthalmology (e.g. drops and ointments), dermatology (e.g. topical preparation, patches and micro-needles [3]) and respiratory (e.g. inhalers).
- *Crushing solid dosage form* Commonly used when liquid formulations are not available; often given with food or flavouring agents such as apple sauce. Crushing of drugs, however, is often not practical, as administration of crushed medications with food can alter drug absorption and food may not be able to mask the bitter taste of the drug. Moreover, most solid formulations are not suitable for crushing (e.g. crush-resistant) and pulverization will destroy any specific formulation designs (e.g. long-acting, prolonged/controlled-release, enteric-coatings, etc.) [1]. In addition, grinding certain medicinal products (e.g. cytotoxic drug) can have dual consequences of delivering a potentially inadequate dose to the child while exposing other family members to an active chemotherapeutic agent [4].

…or using innovative solid oral dosage forms

A number of novel solid oral dosage forms have been developed to ease swallowing in children and to avoid the disadvantages of liquid formulations [1]. For example, mini tablets are very small-sized tablets (1–2 mm in diameter) that can potentially be used in very young children, including infants and neonates aged 2–28 days [5–7]. Furthermore, soft melt and gel formulations that use rapid dissolving or melt technology are now commonly used in children instead of liquid formulations, especially for non-prescription medicines [e.g. vitamins, ibuprofen and paracetamol (acetominophen)] [1].

Of note, using a flavouring throat spray such as Pill Glide™ before taking solid medications may help children to overcome swallowing difficulties [1]. In a pilot study, Pill Glide™ significantly reduced the difficulty of taking medicines in ten children aged 6–16 years with known swallowing difficulties or those transitioning from liquid to solid medications [8].

Palatability is a key factor for compliance…

Palatability, including smell, texture and taste, is an important factor to consider for the improvement of medication acceptability in children [1]. Medicines are naturally bitter, which may deter children from taking their medication and lead to poor compliance [1]. For example, in a retrospective study, a third of 119 children with HIV refused to take antiviral therapy because of its poor taste [9]. Moreover, to avoid the unpleasant taste of sodium phenylbutyrate, it was necessary to insert gastric tubes in order to administer this essential drug in some children with urea cycle disorders [10]. Also, texture may be a problem with antibiotics that are administered in the form of suspensions [1].

…but can be tricky to measure

Historically, the palatability of liquid formulations was measured in adult volunteers [1]. However, such test results cannot be directly translated to children because, unlike adults, taste preference changes over childhood (i.e. younger children favour sweeter tastes) [11] and with repeated exposure [12].

A number of studies have used facial hedonic scales to assess the palpability of medications in children [1]. In a study assessing the palatability of four antibiotics by using visual analogue and facial hedonic scales, 90% of healthy children said cloxacillin, which is known for its poor taste, was the worst tasting antibiotic [13]. However, this type of assessment is not suitable for children aged < 5 years, as at least some understanding of a numerical scale is needed [1]. Of note, given the ethical issues of conducting palatability testing in healthy children, recent studies have enrolled paediatric patients [1].

Different in vitro methods are being investigated to provide an initial screening of new formulations before conducting palatability tests in patients [1]. The ‘electronic tongue’ (an instrument comprising an array of sensors) is one of the promising in vitro tools for taste assessments [14]. For instance, the test formulation of cetirizine hydrochloride [15] and valaciclovir [14] for in vivo palatability assessment was successfully selected based on the results of electronic tongue measurement [14, 15]. However, given that palatability is not only comprised of taste, but also of texture and smell, the electronic tongue system has some limitations and requires further research [1]. Albeit investigational, bitterness prediction using computer simulations has also provided promising results [16].

Vital to mask bitter taste

Masking the bitter taste of oral formulations is vital to improve compliance in children [1]. Different taste-masking strategies have been employed during the manufacturing process or at the dispensing pharmacy (Table 1). For example, the bitter taste of the drug can be altered by adding flavouring agents, or blocked by creating a physical barrier between the drug and the taste buds (Table 1). With an improved understanding of the genetics and biology of taste, researchers are also exploring other novel taste-masking

Table 1 Examples of taste-masking strategies used to improve medication palatability, as reviewed by Rieder [1]

Taste alteration (organoleptic approach)
Flavouring agents (e.g. sweeteners or syrup) are commonly added at dispensing pharmacies
The palatability of glycerol-based liquid formulation of valaciclovir was non inferior to the reference formulation (suspension made out of crushed tablets) in children in in vitro and in vivo palatability assessments and had a longer shelf life [14]
Orally administered flavoured intravenous ondansetron demonstrated acceptable palatability and did not impact absorption in children presenting with acute gastroenteritis; can be useful in the absence of oral formulations [18]
Taste barrier (creating a physical barrier between the drug and the taste buds)
Techniques require careful and thoughtful design in terms of palatability and biopharmaceutics
May use various techniques, including microencapsulation (encapsulation of the drug using coatings such as polymeric membranes), polymer coating and spray-drying (provide a physical barrier), complexation (formation of inclusion complexes of the drug compounds such as cyclodextrins or ion exchange resins) and hot melt extrusion (heating of the drug and other ingredients to create taste-masked granules)
Important to consider whether an alternative form of drug (e.g. salt) or excipient is more suitable or palatable for the development of new formulations
Microsphere-formulation of prednisone effectively mask the taste of prednisone in healthy young adults [19]
95.5% of parents preferred the microencapsulated form of hydrocortisone for the treatment of adrenal insufficiency in neonates, infants and children [20]
β-cyclodextrin and cherry/sucralose flavouring system effectively mask the bitter taste of cetirizine hydrochloride in in vitro and in vivo palatability assessments [15]
Other approaches
Administering the oral iron chelator deferasirox with food improved palatability and gastrointestinal tolerability with an acceptable pharmacokinetic profile [21]
Bypassing the taste system by creating the ligands that block taste receptors or inhibiting the taste signal cascade [22]
Targeting polymorphism in bitter-taste receptor genes (*TAS2R38*) may improve palatability [23]

strategies (e.g. bypassing the taste system or targeting polymorphism; Table 1) [1].

Advanced and novel taste-masking strategies may create some practical challenges to the correct administration of the formulation [1]. Parents and/or children may find it difficult to follow the instructions for administration, which can lead to medication errors [1]. Providing instructions with illustrations (i.e. pictograms) substantially increased the understanding of medication administration techniques in parents and paediatric patients with low health literacy [17].

Ensure drug regimens are compatible with life style

The issue of short dosing intervals is particular important in children [1]. It may be difficult for school children to receive all doses of medications that require frequent administration at the correct intervals. Similarly, adolescents are unlikely to adhere to frequent administration due to social pressure towards conformity. For instance, compliance (assessed by glucose control) often deteriorates dramatically when adolescent diabetic patients administer their insulin instead of a parent. Adapting the drug regimen to the life style of children is critical. The use of long-acting formulations (e.g. osmotic delivery systems, drug depot systems, patches or microencapsulated particles) that allow once- or twice-daily administration, may lead to improved compliance in children [1].

Pharmaceutical industry needs to partner with regulatory agencies

Over the years, regulatory agencies have had workshops discussing best practices for developing child-specific drug formulations [24, 25]. Nevertheless, there are currently no consistent guidelines on what is acceptable in terms of dosage form, ingredients and taste standards in children [1]. To facilitate harmonious development and approval of child-specific drug formulations, regulatory agencies and pharmaceutical industries should work closely together [1].

Take home messages

- Improving medication acceptability, especially palatability, is important to optimize drug therapy in children
- The use of oral liquid medications, alternative delivery systems and/or the use of innovative oral solid dosage forms may overcome swallowing difficulties in children.
- Masking the bitter taste of medicines, as well as adapting the drug regimen to the life-style of the child, may lead to improved compliance

Compliance with ethical standards

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