

An Overview of Paediatric Drug Delivery

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Dr Tuleu is the Pfizer paediatric drug delivery lecturer at the School of Pharmacy, at the University of London. With a background in pharmaceutical technology and biopharmaceutics, her research interests are centered on gastrointestinal drug delivery with emphasis on colonic targeting where she developed expertise ranging from *in vitro*, animal and clinical evaluation (Gamma Scintigraphy) and on drug delivery systems for neonates, infants and children. Dr Tuleu was invited to give an oral presentation at the British Pharmaceutical Conference in September 2005.

Introduction

The fact that our children are at risk as they are administered inappropriate medicines has been internationally recognised. These medicines are the only ones available yet they have not been clinically tested for safety, efficacy and quality in this age group. Problems resulting from the absence of suitably adapted medicines for children include inadequate dosing information leading to increased risks of adverse reactions. These include death, ineffective treatment through under dosing, non-availability to children of therapeutic advances and extemporaneous formulations for children, which may be poorly, or inconsistently, bioavailable and of poor quality. The International Conference on Harmonisation committee recommends appropriate formulations are used in paediatric drug trials (EMA, 2000). Often, many articles still provide inadequate formulation information in paediatric drug trials, impairing their validity and reliability (Standing *et al.*, forthcoming) because the lack of adequate licensed product requires extemporaneous preparations that are not optimised or standardised.

Drug Handling in Children

To meet the challenge of providing appropriate formulations for a range of age groups and the requirement for a diverse range of medicines, extemporaneous liquid preparations are often used (Yeung *et al.*, 2004; Standing and Tuleu, 2005). These are either prepared at the dispensary or under GMP by special manufacturers holding a license. This does not include extemporaneous manipulations carried out on the ward or, the practice with the most risk, by parents at home. Problems linked with all these formulations are mainly associated with dosing errors and accuracy as well as unknown bioavailability and the use of potentially toxic excipients, impairing the safety of patients. The risk associated with these preparations would be decreased if drugs sponsors were to make in-house information available to the healthcare professionals who perform those operations, without infringing the Medicines Act 1968 which legislates against the promotion of off-label use. For example, providing pure drug to use as analytical standards, information such as stability indicating method

or, ultimately, a validated extemporaneous formula would be highly beneficial.

The Future is Bright

In September 2004, the European Commission released a draft regulation on medicinal product for paediatric use (EC, 2004) in order to work towards an ethical, effective and favourable environment in Europe for paediatric research and development. European regulators are in a great position, being able to benefit from the similar positive FDA experience (FDA, 2002) to achieve the best outcome for children, carers and health professionals. The key objectives of the EU proposed regulation are to increase the development and authorisation of medicines for use in children while ensuring that their medicines are subjected to high-quality research without unnecessary clinical trials and without delaying the authorisation of medicines for adults. Key elements in the proposal are:

- The creation of a new expert committee within the EMA to assess and agree companies' Paediatric Investigation Plans (PIP) while providing free scientific advice.
- A requirement at the time of marketing authorisation applications for data on the use in children. However, a system of waivers and deferrals will ensure that the requirements do not delay the authorisation for medicines in adults.
- A reward for studying medicines for children of a six-month extension to the supplementary protection certificate (SPC); in effect, a six-month patent/SPC extension for the whole use of the product (including adult use).
- For off-patent medicines, eight plus two years of data exclusivity on the paediatric use of the product for new studies awarded (with amended data requirements) via a Paediatric Use Marketing Authorisation (PUMA) and the possibility to use the existing brand name, including a superscript 'P' for brand recognition.

These incentives are very similar to those proposed by the FDA but the EU proposal is more robust. It requires the sponsor to market the paediatric medicine for the approved indication within twelve months, thereby speeding up the availability for patients. It requires:

- Increased safety monitoring for children's medicines (pharmacovigilance).
- A compulsory submission by the industry of existing studies in children, an inventory of the EU therapeutic needs of children and an EU network of investigators and trial centres to conduct the studies required, similar to the Pediatric Pharmacology Research Network in America. The EU proposes a more transparent approach to negative outcomes of the trials in children as any results (positive or negative) will be included in a database of ongoing or terminated studies. The results will also be incorporated on the drug label, regardless of whether the indication is approved or not.

The European Parliament approved this law on the 7th of September 2005 and this awaited legislation is likely to become effective in late 2006, after it is approved by EU council for its passage into law. However, delays in availability of paediatric products for off-patent actives are anticipated as the MICE (Medicines Investigation for the Children in Europe) fund has not yet been sourced. This is equivalent to the National Institute of Health and FDA setting to support old and commercially disregarded drugs. This is a real issue as, generally, generics' manufacturers do not have substantial resources for research and development beyond equivalence studies, nor do they have expertise in complex clinical trials.

These EU regulations will provide an incentive to manufacturers and researchers to develop appropriate paediatric formulations and, hopefully, more high-quality paediatric formulations and drug deliveries will be available from the pharmaceutical industry as a result.

'One Size Does Not Fit All'

Children represent a vulnerable group with developmental, physiological and psychological differences from adults, making age and development-related research targeted at the specific needs of children particularly complex.

This is especially true when it comes to designing appropriate dosage forms for such a heterogeneous population. Developmental changes, especially in early childhood, affecting bioavailability, pharmacokinetic, pharmacodynamic, pharmacogenomics (Kearns *et al.*, 2003) will influence the choice for the optimum medicine for different age groups. As a simple example, neonates and, especially, pre-term have a thinner skin and perfusion is greater. Therefore, unwanted systemic effects can occur where drugs applied locally are absorbed percutaneously. Later on in childhood, the surface-area-to-weight ratio is still greater, also leading to possible toxic effect. Nevertheless, with more knowledge and control, this could prove an asset for painless and passive administration for children systemic uptake.

Non-biological consideration, such as motor and psychological development, ability to coordinate, health status (acute or longterm disease), geographic and socio-cultural background, will also greatly influence the choice of the dosage form for optimal administration in

relation to age groups. Compliance issues are even further complicated by the fact that a third contributor (parents, caregivers, nurses) will also be influential.

Paedia-tricks and Treats!

Paediatric drug delivery is a compromise between applicability and preference to achieve conveniently, efficacy with safety. Few studies have been specifically performed to survey the use of different dosage forms in children and the requirements, advantages and disadvantages of various routes of administration and their respective dosage forms have still to be refined (Danish and Kottke, 2002, Sagraves, 2002). The EMEA reflection paper on formulations of choice for the paediatric population, released for consultation in June 2005 (EMEA, 2005), provides the only non-evidence-based rough guide and is an excellent working document for paediatric formulators. Adequately formulated topical delivery to the skin is generally well tolerated. Ear and eye routes of administration are never welcomed by children but very often are unavoidable. Prolonged released preparations that decrease the frequency of administration could be an improvement. Issues concerning pain and cooperation necessitate that routes of administration that do not involve injection should be explored as alternatives to parenteral routes. Needleless systems, if discomfort is avoided, could be one of those.

Transdermal patches, which can achieve controlled delivery and are painless and easy to apply, could provide a formulation of choice for systemic uptake if adapted to skin maturation, formulated with adhesives with low allergenic potential and in different strength. Asthma is prevalent during childhood; therefore, the pulmonary route is fairly established albeit difficult to self-administer for younger patients. Although it is used for local therapy, in the future it might become more important for systemic drug delivery. Advices for the selection of inhalation devices in relation to age are available on the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk).

Nasal administration is also mainly intended for local effects but it too can provide direct access to systemic circulation. The development of mechanical dispensing systems adapted for dose volume and for dimensions to the patient's nose may prove a valuable alternative to invasive modes of administration, especially for peptides and vaccines. The oromucosal route might be suitable if safety in pre-schoolers is established. Mucoadhesive preparations, especially films, semi-solids and liquids, and those dissolving/disappearing systems in the oral cavity, such as fast-melt, oral strips, might be of interest if they do not interfere with suction and frequent feeding. Nevertheless, as with oral drug delivery (Breitkreutz *et al.*, 1999), one of the major issues with children remains the taste of the preparation.

Monolithic solid dosage form can avoid palatability issues if swallowed intact but there is a great variability in children's

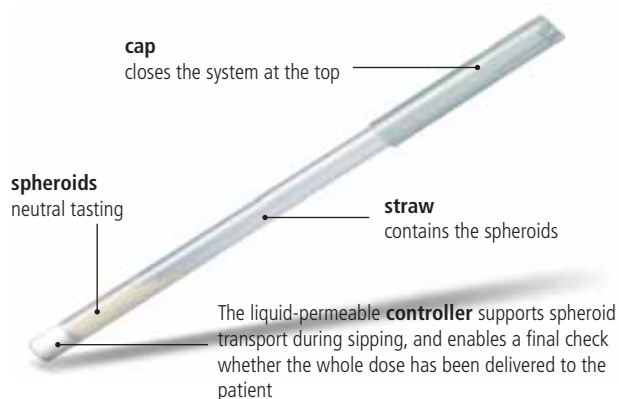


Figure 1 – Dose Sip Technology (Grünenthal GmbH) provides for children a ready easy-to-use pre-measured dose with no bad taste (coating) and possible modified release spheroids.

ability to swallow, although with training younger children could manage it. Stability is improved with solids and modified release can be achieved, but the lack of dose flexibility can be a drawback. The use of mini-platforms, such as mini-tablets, mini-capsules or spheroids with a clever dispensing system, could overcome this problem. A method is illustrated by the Dose Sip Technology (Figure 1) which is a novel patented drug delivery system under development by Grünenthal GmbH for a convenient, efficient and easy administration. It combines both formulation and administration device technology.

Effervescent, powders and granules, orodispersibles and chewable dosage forms stand on the periphery of solids and liquids. These have the advantages of solids in that they are compact and dry but they also have the same palatability issues as liquids with the particular challenge that the quantity of excipients available to improve the taste of the preparation is limited.

Liquid formulation is regarded as the gold standard and the most convenient method in paediatric medication. Along with a simple and accurate dose delivery device, the dose volume to deliver is easily adaptable to the patient's weight. Suspensions can solve some issues around bad taste but solutions generally have better oral acceptability. Organoleptic characteristics of liquid preparation are of great importance but taste is crucial and varies geographically, making global research and development difficult for companies. Flavouring adequately is one issue but novel and efficient taste-masking options are needed to improve compliance issues due to poor palatability. Moreover, formulating liquids involve more excipients which can have an age-related toxicity (Pawar and Kumar, 2002).

Finally, rectal administration of solids is not dose adaptable and absorption is poorly reproducible. It suffers from active non-compliance (poorly accepted by older children or caregivers) or passive non-compliance (premature ejection). Nevertheless, it should not be overlooked for certain therapeutic situations.

Conclusions

In the light of the awaited EU regulations more clinical trials in children will take place and lead to the availability of specific paediatric drug delivery systems. The ideal candidates should be efficacious, tailored, tolerable, convenient, of quality and safe, as should their routes of administration and compliance considerations, their difference in drug disposition and choice of adequate excipients. Although new dosage forms are urgently needed, work on extemporaneous formulation should not be disregarded.

Children represent a fragile and challenging, yet rewarding and potentially large population, for which needs are not met, nor clearly defined. In parallel of investigational work on formulations of choice, measuring/administration devices and packaging innovations should help to meet the needs of children and their caregivers.

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