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Patient centric formulations for paediatrics and geriatrics: Similarities and differences

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ABSTRACT

Paediatrics and geriatrics both represent highly heterogenous populations and require special consideration when developing appropriate dosage forms. This paper discusses similarities, differences and considerations with respect to the development of appropriate medicine formulations for paediatrics and geriatrics. Arguably the most significant compliance challenge in older people is polypharmacy, whereas for children the largest barrier is taste. Pharmaceutical technology has progressed rapidly and technologies including FDCs, multi-particulates and orodispersible dosage forms provide unprecedented opportunities to develop novel and appropriate formulations for both old and new drugs. However, it is important for the formulation scientists to work closely with patients, carers and clinicians to develop such formulations for both the paediatric and geriatric population.

Paediatric and geriatric patients do not fall into the category of 'standard patient' due to altered pharmacokinetics, different acceptable dosage forms, formulation composition and route of administration. In the paediatric population, there are distinct physiological differences between neonates, infants, children and adolescents. However, relating this information to adult data when determining an appropriate dosing regimen is complicated (Bartelink et al., 2006). In neonates and infants, immaturity of enzymes, volume of distribution and clearance may result in differences in pharmacokinetics. In older people, these differences cannot be defined by age alone. Pharmacokinetics are strongly influenced by morbidity, co-morbidity, multiple drug use or reduced organ function. The ICH Harmonised Tripartite Guideline: Studies in Support of Special Populations: Geriatrics E7 highlights the need to conduct pharmacokinetic studies in healthy geriatric subjects or volunteers with the disease to be treated by the drug of interest. It is not uncommon for clinical trials to exclude older patients, for reasons such as concomitant conditions, polypharmacy or frailty, yet this data is essential to maintain safety and optimise medication for the older population (Ford, 2000; Mangoni and Jackson, 2004). If age-related differences are found that could be of medical importance, a larger, multiple-dose PK study may be necessary to permit statistical comparisons between different patient cohorts at steady state (International Conference on Harmonisation, 1993). Similarly, the Paediatric Regulation was introduced in 2007 to ensure that medicines for use in children are of high quality, ethically researched and appropriately authorised.

In both paediatric and geriatric population groups, challenges exist in the development of formulations that will offer a predictable and safe drug release in the patient, whilst also being presented in an acceptable dosage form to ensure safety and compliance. Manufacturing complexity and cost are also important considerations. From an industry perspective, the paediatric population represent a small market, with many illnesses short term. Adopting a patient centric approach for such a small target group can be difficult financially, requiring significant labour and resources. The geriatric population, on the other hand, are a wider group with a broad range of therapeutic, hence pharmaceutical, needs. By considering the similarities between the paediatric and geriatric population, labour and resource costs may be minimised whilst maintaining this patient focus. This paper outlines some of the paediatric and geriatric formulation needs from a patient centric perspective, with a focus on novel oral systems such as fixed-dose combinations, multi-particulates and orodispersible dosage forms. Patient centric formulation development refers to considering the end user from the beginning of the formulation process and right through the development to an end product.

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1. Excipient and other formulation issues

Excipients of medications that may be acceptable in adult formulations may not be suitable for special populations such as paediatrics and geriatrics. For example, high sodium intake disturbs electrolyte balance, causing water retention and increasing the risk of cardiovascular conditions including stroke, hypertension and heart failure, particularly in older adults (George et al., 2013). Despite this, a recent review of cardiovascular formulations listed in the British National Formulary (BNF) found instances where effervescent, dispersible and soluble tablets prescribed for cardiovascular disorders contained sodium levels higher than the recommended daily intake of sodium in adults (2.4 g or 104 mmol) (Hanning et al., 2015; Joint Formulary Committee, 2013). In addition, only 40% of medicines listed in the BNF for cardiovascular disorders specified dose recommendations that could be adjusted for older patients, taking into consideration factors such as comorbidity, polypharmacy and vulnerability to adverse effects (Hanning et al., 2015).

For children the situation is even more critical, as the vast majority of medicines prescribed for children with cardiovascular problems are unlicensed and often manipulated at the point of administration or only available as extemporaneous formulations (Standing and Tuleu, 2005). Implications of this include dosing accuracy, unknown bioavailability of extemporaneously prepared formulations, use of excipients that may be toxic and a lack of access to modified release preparations for children. Although the introduction of the European Union regulation on medicinal products for paediatric use in 2007 has endeavoured to improve rational, evidence-based prescribing and age-appropriate formulations for children, a significant number of products still lack paediatric information (Breitkreutz, 2008; Frattarelli et al., 2014; Sachs et al., 2012).

Oral drug delivery is the most popular route of medicine administration. Advantages include ease of ingestion, avoidance of administration discomfort/pain, low manufacture cost, versatility and expected better patient compliance (Sastry et al., 2000). Many individuals find it difficult to swallow tablets and hard gelatin capsules and this difficulty is especially prevalent in paediatric and geriatric patients (Lindgren and Janzon, 1991; Patel et al., 2015). Co-administration with food is often recommended to ease ingestion of medication, although this practice might have an impact on the oral bioavailability of the drug. Depending on the active moiety and the type of food this can result in an increased or decreased exposure (Martinez and Amidon, 2002). Therefore, recommendations need to be made in a case-by-case basis. Critically, food preferences may vary between paediatric and geriatric individuals, so a variety of food types need to be considered. Not only food, but also oral vehicles (syrups and gels) and thickening agents (which can be added to a drink to increase its consistency) have been investigated and proposed. These administration aids could be supplied along with the drug product, could be commercially available as a separate product, or could be extemporaneously prepared in community pharmacies as required (Kluk and Sznitowska, 2014). Caution must be taken with recommending these products until sufficient scientific evidence with regards to the safety of this practice is generated. In fact, preliminary data suggest that thickening agents could hinder release of drugs from crushed tablets (Manrique et al., 2014). Further research in this topic is required to enable safe administration of medication with food and thickening agents.

2. Fixed-dose combinations

Fixed-dose combinations (FDCs) are a way of administering multiple medications in a single dosage form. Their primary advantage is to reduce complexity of therapy and improve medication compliance by reducing pill burden in patients with co-morbidities. Therefore, FDCs address two key determinants of poor medication compliance–polypharmacy and the complexity of treatment regimen. FDCs have been shown to decrease the risk of medication non-compliance in patients with chronic conditions (Bangalore et al., 2007). In addition, the combination of drugs with different mechanism of action can achieve greater efficacy (synergistic effect) with a lower occurrence of adverse events compared to increasing the dose of the monotherapy (Garber et al., 2002; Panaccione et al., 2014). Other advantages include the simplification of drug handling and lower packing and shipping costs. FDCs are primarily advantageous for geriatric patients with polypharmacy, however, can also be helpful for paediatrics in conditions requiring combined medication, such as tuberculosis and HIV. Although some commercial FDC preparations exist, such as Rifater® and Rifanah® (Sanofi-Aventis) for the treatment of tuberculosis, these are not licenced for use in children. However, these preparations could be considered in older children provided that the dose of each drug is appropriate given the weight of the child (BMJ Group, 2011).

FDCs also have some potential limitations. FDCs restrict individual dose titration of each active ingredient which, indeed, discourages adjustment of doses to the individual patient's need (Blomberg et al., 2001; World Health Organisation, 2003). This is of critical importance when the combined drugs exhibit different pharmacokinetics and/or pharmacodynamics. Unless each active ingredient is available as a separate drug product, FDCs encourage polypharmacy irrespective of the appropriateness of drug combination for a particular patient (World Health Organisation, 2003). The incorporation of various drugs in single dosage forms pose unprecedented technical challenges which arise from incompatibilities of the combined drugs (Singh et al., 2001). Furthermore, the final dosage form may become significantly larger, obstructing oral administration (Desai et al., 2013). This is of particular importance if an individual suffers from dysphagia or struggles to swallow tablets, which are common features in the geriatric and paediatric population. Some of these challenges might be overcome via the preparation of multi-particulate formulations or oral fast dissolving dosage forms.

3. Multi-particulate formulations

Compared to single dose units, which usually take the form of a tablet, multi-particulate formulations are smaller, multiple unit systems of mini-tablets or pellets that are either filled into capsules or compressed into tablets that disintegrate into the original pellet size on administration (Newton, 2010). In some cases, the dose may be adapted to meet patient requirements, for example the administration of a quantity of pellets based on body weight. The utilisation of specialised counting and dosing devices may be necessary in these instances (Wening and Breitkreutz, 2011) and new research is on-going in this area.

Commercial examples of multiparticulate formulations include Depakote® capsules (divalproex sodium) and Creon® capsules (pancrelipase), whereby the capsules can be swallowed whole, or if swallowing is an issue the capsule contents may be sprinkled onto soft food. As discussed previously, the type of food that is used as the vehicle in these instances is important, although often little instruction is given.

Multi-particulate formulations are a good choice for the development of FDC products since individual dosage units containing different entities can be combined in the final dosage form (e.g. filled into capsules). This approach clearly presents fewer limitations from a pharmaceutical development perspective than the combination of drugs in the same dosage unit, particularly