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Meeting commentary

Meeting commentary—Formulating better medicines for children

Providing rapid access to medicines for children has been a particular focus area ever since legislation was enacted in the USA in 2002 (USA Public Law 107-109, 2002). In Europe, similar legislation was introduced in January 2007 (European Parliament, 2006), which mandated the development of medicines for children in parallel to that for adults. Overall, the legislation has had a positive effect, with many Paediatric Investigation Plans (PIPs) being reviewed by the Paediatric Committee (PDCO) to date.

However, it is well recognised that developing medicines for children presents many additional challenges to that of developing medicines for adults and it was these that were the subject of a recent and first of its kind conference held in London (Formulating Better Medicines for Children, 2009). The 2-day conference, organised by the European Paediatric Formulation Initiative group (EuPFI), covered the European Paediatric Regulations in an address by Dr Daniel Brasseur (Chair of PDCO) and some experiences obtained to date by the PDCO in reviewing PIPs, in an address by Dr Caroline Le Barbier (EMEA).

To date (March 2009) 396 PIP applications have been received by the PDCO, covering several therapeutic areas including oncology, endocrinology/metabolism and cardiovascular. Reviews focussed on the appropriateness of routes of administration, dosage form, excipients, taste/palatability and delivery devices.

In addition, the conference provided the opportunity for practitioners from different disciplines to discuss all aspects of formulating paediatric medicines, including which materials can be used, how medicines can be formulated to ensure they are of appropriate quality and accepted by children, yet made quickly available; and how children can be encouraged to take the medicines. The format of the conference facilitated this, with formal presentation sessions, a 'soap-box' session on six topical subjects and a 'round table'.

1. Excipients

Nearly all medicines are formulated with excipients that have been used for many years and are generally regarded as safe (GRAS). They are defined in monographs in the various pharmacopoeias and released on certificates of analysis against monograph specifications, using monograph test methods. However, these monographs are usually intended to cover use in adults and some excipients are less well tolerated in children, especially young children whose physiological systems are still undergoing development. In particular there are concerns with solvents, solubilising agents, preservatives and colourants. This is especially true for Preterm Infants as pointed out by Dr Hussain Mulla (see Whittaker et al., 2009).

It was agreed at the conference that there was a lack of consolidated information on the use of excipients in children and attendees were supportive of initiatives to develop public databases to address this need. The EuPFI has been working towards the development of such a database that should be available on the internet in 2010. It is hoped to add into the database general learnings so far from PIP review by the PDCO. New insights that consider developmental toxicology based on existing (published) data and new data generated would also advance knowledge in this area.

2. Products

The manufacture of sophisticated medicines for use in patients is a core skill of the pharmaceutical industry, but such medicines take a lot of time to develop and this can delay making medicines available to children, especially if there is a need to have several 'age appropriate' formulations to cover a wide age range (CHMP EMEA, 2005) This issue is common to conducting clinical trials as well as the supply of commercial product.

2.1. Age appropriateness of formulations

Addressing this topic, Dr Julie Williams (Pfizer), gave an overview of the challenges, including choice of appropriate route and dosage form. She talked through a case study where the inclusion of specific excipients was a pre-requisite to achieving a stable, palatable formulation and advocated a sound science and risk-based approach to paediatric medicine development. Being overly cautious could be detrimental to timely availability of medicines for children.

In guidance notes for the PIP it states "*. . .Applicant shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population. . .*" But there is little evidence-based information in the public domain on the impact of dosage form (formulation, route of administration, dosing frequency, administration device, user instruction) on patients' outcomes (efficacy, safety, tolerability, compliance), claimed Diana A. van Riet-Nales, in her conference address. More work in this area needs to be conducted and published to ensure the right product is developed.

In practice, consumer needs should be taken into account. Jenny Newman (Medicine for Children Research Network Consumer Liaison Officer) introduced representatives from the MCRN Children and Young Person's Advisory Network who requested that the preferences of children be taken into account if medicines are to be administered effectively. One interesting aspect that featured was the 'psychology' of dosing children. This was raised by one 8-year-old presenter who offered 'tricks to help the medicine go down', including 'look away', 'hold nose', 'add nice flavours', 'use assertiveness' and 'use bribery'. It also came up when reviewing who the 'medicine giver' might be. It is not always the parent, who has the highest vested interest in making sure the medicine is taken. It may

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be a 'baby-sitter', another member of the family or a teacher/helper at school.

Solutions to these issues are not simple, but several ideas came out of the conference.

2.2. Platform formulations

Solutions and suspensions for oral paediatric dosing have long been the accepted norm, but this was challenged during the conference. Professor Jörg Breitkreutz (University of Dusseldorf) outlined the recommendations of the report of the informal expert meeting on dosage forms of medicines for children (held under the WHO-led 'Make Medicines Child Size' initiative) which favoured small scale solid dosage forms (multiparticulates) or orally fast dissolving solid dose forms (WHO Report, 2008). This was discussed further by Professor Peter York (University of Bradford), who advocated using divided solid doses as a platform technology, specifically in the form of granules, which could be suspended in water, suspended in an alternative vehicle, or added to selected foodstuffs. There are many advantages to granules, particularly ease of manufacture, use of simpler excipients and greater stability. Extension of this approach to enable combinations products was described, illustrated by a case study of an antimalarial fixed dose combination product of artesunate and amodiaquine, whereby improved stability was demonstrated when the drugs were formulated as separate populations of granules.

Mini-tablets are a variant of this which have been looked at by several companies and were covered in an address by Dr Sabine Desset-Brethes (Novartis). She described how mini-tablets of 2–5 mm in diameter can be counted to achieve the required dose rather than the need for weighing the medicine. An example of commercialised mini-tablet product is Lamisil Oral 'Granules' (terbinafine) approved by the FDA.

3. Palatibility

3.1. Taste-masking

There are many technologies that can be used for taste-masking (Douroumis, 2007; Ayenew et al., 2009), but the underlying question 'are we trying too hard to mask the unpleasant taste of medicines?' was raised. In some instances (cultures, age groups) it is expected that medicines are unpleasant and that the degree of unpleasantness is directly related to potency. Hence pragmatic approaches may well be to target 'taste-neutral' preparations by first intent and consider taste-masking opportunities at the point of dosing, for example dosing with food or dispersing in flavoured solutions or by adding flavouring agents directly.

Traditional taste-masking utilises a taste-barrier approach, preventing access of drug to taste receptors to achieve neutral taste, e.g. by applying polymer-based coatings. However, Dr Scott Siegel (Redpoint Bio Corp) proposed the use of biochemical bitterness blockers. He described some exploratory compounds with high potency for blocking TRPM5 channels reversibly, which could be incorporated into product formulae. It is hoped that these compounds will eventually be granted GRAS status as a pharmaceutical flavouring.

3.2. Taste-testing

It is well recognised that the best way of testing taste is in children themselves and it has been reported that meaningful results can be obtained with very young children (Davies and Tuleu, 2008). However, child taste panels are difficult to set up and run. Alternatives such as electronic tongue and nose are still under development and some way from being universally applicable. Animal palatability tests are finding favour, but the most practical option is still the use of adult taste panels. It is known that differences exist between adults and child taste perception but it may be possible to 'calibrate' such panels to predict child preferences and minimum acceptability levels (Cram et al., 2009).

4. Industry-verified and extemporaneous preparations

Simple formulations require less development than sophisticated final commercial product and can enable much quicker clinical evaluation in children. This theme was touched on several times during the conference, most notably by Dr Jenny Walsh (AstraZeneca), who advocated the use of 'industry-verified' preparations. These are often simple product approaches such as powder in bottle or powder in sachet that can be manipulated at the point of dosing, using well defined methods of preparation that ensure products of appropriate quality. Such an approach can even utilise already existing adult products, providing well defined and verified methods of preparation are available. Such verification would include stability, dose uniformity and bio-performance assessment.

Development of this approach may help hospital pharmacists who often have to make 'extemporaneous preparations' on demand to treat patients. This was illustrated in examples from Dr André Rieutord (Hôpital Antoine-Béclère, France) who looked into the risk-benefit of making 'extemporaneous preparations' vs. the difficulty of importing medicines not available in France for example. Having 'industry-verified' methods available may have a positive effect on the risk-benefit.

The heterogeneity of practices for 'extemporaneous preparations' in Europe was reviewed by Maria João Carvalho (University of London). She noted that liquids were common in the UK, capsules in France and cachets in Poland. National compounding associations and national formularies influence what is done in practice. In Portugal, extemporaneous dispensing is prohibited for drugs with narrow therapeutic indices whereas in Poland many drug substances can be mixed in one preparation. A European working group on compounding has been formed by the European Directorate for the Quality of Medicines (EDQM) which may help develop common standards across Europe.

5. Global perspectives

Alongside the issues (and possible solutions) discussed above, Dr Fabrice Mouveaux (Sanofi-Aventis), reminded the conference of the need to develop products suitable for populations in all countries, where taste and dose form preferences need to be understood. In particular, he outlined a case study for a product that needed to be reformulated for Japan. Expanding this further, Dr Atieno Ojoo (UNICEF), made a plea for all to remember the special extra requirements of developing countries. The supply chain infrastructure seen in developed nations may not exist; there may not be any fresh water to reconstitute antibiotic preparations for example, cold storage may not be possible and there may not even be medicine bottles for dispensing smaller quantities when the medicine is received in bulk. WHO and UNICEF plan to make paediatric medicines a priority including developing formularies, provision of information at the point of care and guidance on procurement and supply.

6. Conclusions

The conference provided a useful overview of 'the state of play' in the development of paediatric dosage forms and highlighted the need for a follow up meeting in Autumn 2010 organised under the auspices of APV.

References

Ayenew, Z., Puri, V., Kumar, L., Bansal, A.K., 2009. Trends in pharmaceutical taste masking technologies: a patent review. Recent Pat. Drug Deliv. Formul. 3, 26–39.
Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMEA), 2005. Reflection paper: formulations of choice for the paediatric population. EMEA/CHMP/PEG/194810/2005 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/paediatrics/19481005en.pdf. Last accessed on June 04, 2009.
Cram, A., Breitkreutz, J., Desset-Brèthes, S., Nunn, T., Tuleu, C., 2009. Challenges of developing palatable oral paediatric formulations. Int. J. Pharm. 365, 1–3.
Davies, E.H., Tuleu, C., 2008. Medicines for children: a matter of taste. J. Pediatr. 153, 599–604.
Douroumis, D., 2007. Practical approaches of taste masking technologies in oral solid forms. Exp. Opin. Drug Deliv. 4, 417–426.
Formulating Better Medicines for Children, First EuPFI conference, 2nd to 3rd March 2009, London, UK.
Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.
USA Public Law 107-109, Best Pharmaceuticals for Children Act, January 2002.
Whittaker, A., Mulla, H., Turner, M.A., Currie, A.E., Field, D.J., Pandya, H.C., 2009. Toxic Additives in Medications for Preterm Infants. Arch. Dis. Child Fetal Neonatal Ed. 94, F236–F240.
WHO Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. WHO Headquarters, Geneva, Switzerland, Dec. 2008. Available at URL http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf last accessed on June 04, 2009.

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