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Understanding how to select appropriate liquid medicines for children will ensure they receive the best-available product for their needs

Adult medicine formulations often cannot be given directly to children and dedicated formulations must be manufactured. It is the pharmacist's responsibility to ensure that the manufactured medicine is suitable for their patient, and obtaining such liquid formulations for children can be fraught with difficulties. Steve Tomlin, consultant pharmacist for children's services at Evelina Children's Hospital, highlights the important considerations when selecting an appropriate formulation for use in children.

In the European Union, more than 50% of medicines used in children have never actually been studied in this population.[1] In Australia 25% of the medicines licensed for use in children do not have appropriate formulations for the intended ages.[2] At the end of 2006 a group of experts wrote a *Consensus guideline on the medication management of adults with swallowing difficulties* where they described the problems, in terms of medical and legal consequences, with crushing tablets and opening capsules.[3] It is easy to see that this problem is potentially far greater in children where tablets are often even less appropriate than in adults. It is important that we understand not only how the same issues affect children, but also that we look more closely at what the pros and cons are for the available medicines alternatives.

This paper aims to cover the principles involved in selecting appropriate liquid medicines in children, which are unlicensed or being used outside their licence and to highlight the clinical governance processes for ensuring that the right liquid product is given to the right child.

Replicating research is hampered by lack of experimental detail

A review of the literature identified that 37% of research papers on children's

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medicines did not give enough information for the study to be reproduced accurately and 26% did not state the formulation used. Even when the formulation was stated 51% did not have a paediatric formulation (defined as liquid, chewable tablet or granules).[4] This is a worrying finding when we know that different formulations and manufacturing processes can affect the bioavailability of a drug and therefore the clinical outcome. It is these studies that give professionals some evidence on which to base children's doses. However, if they cannot be faithfully reproduced through lack of adequate methodology detail, this creates a major flaw in the system.

In accepting that crushing tablets or opening capsules is rarely the best option for delivering a quality medicine, then what options are open to us? Importation of a liquid, if it exists, from outside of the UK is one option. Alternatively, a liquid could be made by a pharmacist for an individual patient or a manufacturing unit could make batches of a liquid prepared under a 'specials licence'. None of these options are without potential problems, but an understanding of the important issues can aid choosing the right liquid preparation for the right child. Governance structures for management of these issues must be in place.

Importation

A medicine that has a licence outside of the country of use legally becomes an unlicensed medicine once it is imported. However, if the licence is granted from a country with similar regulatory standards as our own then at least the quality of the product is reasonably guaranteed. This is usually a good option, but can pose problems in terms of the risk of use clinically.

Clinical risks

Problems may arise because the imported liquid may not be licensed for its intended use. For example, tiny (un-measurable) volumes of liquid might be needed for a neonate's dose when taken from a product licensed for adults. Alternatively it may contain excipients that are not suitable in a particular clinical condition for which it is not licensed.

The importation costs may be very expensive. For example, it is not uncommon for one month's supply of an imported liquid to cost 100 times the price of one month's supply of tablets (which have the potential to be crushed and are readily available with a longer shelf-life).

Depending on the country of export the packaging and patient information may not be in English. This can be managed with over-labelling.

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Counterfeit medicines are estimated to account for 6–10% of the worldwide market of medicines at a value of around $35bn[5] (equivalent to around £17.6bn). Although the problem is small in the UK as far as the legitimate pharmaceutical supply chain goes, the first recall of parallel trade counterfeits was ordered in May this year.[6] Counterfeit medicines could contain a lower concentration of the active ingredient. This could therefore lead to altered clinical effect, no effect or fluctuating effect, the consequences of which may vary from inconvenient to life threatening. Alternatively they may contain varying excipients leading to unexpected adverse events or anaphylaxis.[5]

Extemporaneous dispensing

Extemporaneous dispensing is one of the fundamental skills that the pharmacy profession was founded upon. A paediatric pharmacist should have a good understanding of the theory of manufacturing and knowledge of the 'manufacturing ingredients' to inform them of the clinical effectiveness and safety of unlicensed manufactured liquids.

Apart from an emergency situation, extemporaneous dispensing should only be used as a last resort. Extemporaneous dispensing, while being legal — and sometimes essential — has very little built-in quality assurance. This applies to the formula that is used, the products that are used to produce it, the environment in which it is conducted and the manufacturing process to produce the final product. For this reason licensed products are preferred.

Specials manufacturing

A liquid made under a specials licence has greater quality assurance in the manufacturing process than that of an extemporaneously prepared product. The product that is delivered by the specials manufacturer is made to a high standard, and to a set formulation and manufacturing process. There is no guarantee, however, that that product is suitable for a particular patient with a

particular condition. Knowledge of how a specials manufacturer is going to make a product is essential; some apply the same criteria as those used to produce licensed products, others may not.

It is the responsibility of the dispensing pharmacist to ensure that what is manufactured is suitable for their particular patient. Liquid formulations — unlike most tablets — are cocktails of ingredients, some pharmaceutically active and others not. It is essential that the formulation is understood and appropriate for an individual child.

Unlike a licensed medicine, which is made by a standard, reproducible procedure, a liquid produced by a specials manufacturer will have its own formulation and manufacturing process for an individual medicine. This may vary considerably from another specials manufacturer — so swapping manufacturers could alter clinical outcomes.

An example of this has been published recently. The authors of the paper were looking at the variations in captopril suspension being dispensed from hospitals and they highlighted the need for a consistent approach to product selection.[7] Twenty six hospitals used 13 different liquid formulations for the same medicine and about 80% of referring hospitals dispensed a different formulation to the initiating tertiary hospital. Thus, despite the fact that all the preparations may give an adequate response in their own right, the response may be altered as soon as the formulation is changed.

Similarly, a study of nifedipine modified release looked at the effect of halving, quartering, crushing and suspending the tablets so as to make suitable preparations for children. They found that cutting the tablets increased the drug release and dissolution rates of nifedipine thus changing the pharmacokinetic profile significantly. Crushing and suspending the tablets produced a liquid, which started to degrade after just 15 minutes under light.[8]

Box 1. Formula used to calculate blood alcohol concentration from a formulation containing different strengths of alcohol[12]

$$\text{Blood Alcohol Concentration (in mg/100ml)} = \frac{\text{volume of medicine} \times \%\ \text{alcohol in medicine v/v} \times 0.79^{*}}{0.6^{**} \times \text{weight of patient in kg}}$$

Notes:

*0.79 should be disregarded if using %w/v instead of v/v because it is the specific gravity of ethanol

0.6** is the volume of distribution of ethanol (0.6L/kg)

How safe are the excipients?

Liquid formulations must be considered as a mixture of excipients, some pharmaceutically active and others not. The Food Commission (an independently-funded pressure group) recently criticised medicines manufacturers for including additives that have been banned from foods aimed at the same age groups in children's medicines.[9]

Ethanol

Ethanol is the second most commonly used ingredient in liquid medications after water. Ethanol is known to have risk in terms of acute overdose and chronic consumption. In the US guidelines have been agreed on limits for alcohol content of children's medicines[10] and the European Agency for the Evaluation of Medicinal Products (EMEA) is also producing guidelines.

Ethanol is used as a solvent, flavouring agent and antimicrobial preservative.[10] It is well known to interact with other medicines. Altered drug absorption and impaired degradation of drugs are both associated with acute ethanol administration. Sedation and hypoglycaemia are also common side-effects. Chronic alcohol administration may induce liver enzymes, and then there are the disulfiram type reactions, such as nausea, vomiting, tachycardia and convulsions, which may be produced with medicines such as metronidazole.[11]

The limits for alcohol content set for over the counter medicines in the US for 12 years and older is 10%, between 6 and 12 years is 5% and for under 6 years it is set at 0.5%. In the UK we have Phenobarbitone BP on our shelves with an alcohol content of 38% and infants as the main users of phenobarbitone liquid.

Little is known about the effects of ethanol in children and especially in infants, neonates and premature neonates. Woods DJ has adapted a formula originally produced by the American Academy of Pediatrics to estimate the blood alcohol concentration from different strengths of ethanol[11] (Box 1).

Central nervous system effects of alcohol are usually present with blood alcohol concentrations of 100mg/100ml, but have been reported at levels as low as 1mg/100ml. Based on this the American Academy has established 25mg/100ml as the blood alcohol concentration not to be exceeded following a single dose of alcohol-containing medicine.[12] Although a study in 2003 of liquid medicines used in liver and cystic fibrosis children found that the medicines used gave calculated peak blood alcohol concentrations of up to 8.88mg/100ml, there was no inadvertent use of liquids with high ethanol content, such as Phenobarbitone BP, or with children taking numerous medicines of high ethanol concentrations.[13]

There are many more excipients that can cause problems in children either because of their disease, their age or their immune status. The example of alcohol highlights some of the issues in terms of not knowing what the safe limits of these

excipients are and not knowing how different age groups will handle those excipients in terms of pharmacokinetics and pharmacodynamics.

The future and interim measures

There are many initiatives in the UK and across Europe to try to ensure that more medicines are licensed for children with appropriate formulations. However, for the foreseeable future we will be left trying to obtain liquids that are not covered by a manufacturer's licence.

For now, children's liquid medicines will be continue to be obtained through adapting other dosage forms, extemporaneous dispensing, specials manufacturing or importation. All these processes have potential risks if the suitability of the product for the individual child is not thought through carefully. However, by ensuring professionals understand the issues surrounding product selection children can be assured that their liquid medicine is the best available option for their individual needs.

References

1. Conroy S Choonara I, Impicciatore P *et al*. Survey of unlicensed and off label drugs used in paediatric wards in European countries. *Br Med J*.2000; **320:**79–82.
2. Tan E, Cranswick NE, Rayner CR, Chapman CB. Dosing information for paediatric patients: are they really therapeutic orphans? *Med J Aust* 2003; **179(4):** 195–8.
3. Wright D et al. Consensus guideline on the medication management of adults with swallowing difficulties. In: Kelcey G, editor. *Guidelines — summerising clinical guidelines for primary care*. 30th ed. Berhamstead: Medendium Group Publishing Ltd, October 2006, p373–6.
4. Standing JF, Khaki ZF, Wong ICK. Poor formulation information in published paediatric drug trials. *Paediatrics* 2005; **116(4):** 559–62.
5. Pharmaceutical Journal News. Guidance for pharmacists: how to detect and report counterfeit medicines. *Pharm J* May 2006; **276:** 627–8.
6. Pharmaceutical Journal News. First recall of parallel trade counterfeits ordered. *Pharm J* June 2007; **278:** 635.
7. Mulla H, Tofeig M, Bu'Lock F *et al*. Variations in captopril formulations used to treat children with heart failure: a survey in the United Kingdom. *Arch Dis Child* 2007; **92:** 409–11.
8. Tuleu C, Grange J, Seurin S. The need for paediatric formulation: oral administration of nifedipine in children, a proof in concept. *J Drug Deliv Sci Technol* 2005; **15(4):** 319–24.
9. Pharmaceutical Journal News. Additives in child medicines opposed by food group. *Pham J* March 2007; **278:** 302.
10. Smolinske SC. *CRC handbook of food, drug and cosmetic excipients*. 1st ed. Florida, CRC Press, 1992.
11. Woods DJ. *Formulation in pharmacy practice*. 2nd ed. Pharminfotech; 2001 (CD-ROM).
12. American Academy of Paediatrics. Policy statement. Ethanol in Liquid Preparations intended for children. *Paediatrics* 1984; **73:** 405–7.
13. Saunders C, Langley C. An assessment of the alcohol content of medicines commonly used in paediatric liver and cystic fibrosis patients. *Int J Pharm Prac* 2003; R37.

Declaration of interest

The author wishes to state that he has no conflicts of interest to declare related to this article.

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