

The extemporaneous compounding of paediatric medicines at Mater Dei Hospital

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Educational aims

- To gain further knowledge about extemporaneous compounding of medicines
- To highlight the importance of extemporaneous preparations in paediatric use
- To appreciate the need for the extemporaneous compounding of medicines locally
- To showcase the extemporaneous preparatory service provided at Mater Dei Hospital

Key words

extemporaneous, compounding, off-licence preparation

Extemporaneous compounding is defined as the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient.¹ The lack of commercially available formulations for patients with specific needs poses a challenge to making medicines available to what are considered to be the most vulnerable patients.² This qualifies as off-licence use of a medicine, whereby a licensed medicine is reformulated into a preparation that is acceptable/appropriate for the patient.

Introduction

Children, especially the younger age groups, may require age-appropriate formulations allowing both safe and accurate dose administration.³ Lack of appropriate studies preclude most medications from being labelled for use in paediatric patients.⁴ In order to improve the health of children in Europe without subjecting children to unnecessary trials, or delaying the authorisation of medicinal products for use in adults, the European Union's Paediatric Regulation came into force in 2007.⁵

Since licensed medicines represent the 'gold standard' for quality, safety and efficacy, the underlying general rule is that a licensed preparation is always preferable to a compounded one. Medicines are given a license, now called a marketing authorisation, if the pharmaceutical company has demonstrated the quality, efficacy and safety of the medicine as recommended in the Summary of Product Characteristics (SmPC) when given in the dose and for the disease and age group recommended. The Standing Committee on Medicines has stated that in paediatric practice, the informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary.⁶

There are circumstances in which there is no licensed product or alternative which fully meets the clinical needs of a particular patient and therefore it becomes necessary to extemporaneously prepare a limited quantity of a custom-made product for an individual patient.⁷ Between 15 and 80% of all medicines used in hospitalised children have either not been licensed at all ('unlicensed') or are used outside the specification terms of the product license ('off-licence').⁸

Extemporaneous compounding of medicines carries significant risk, as the risks of using unlicensed medicines are combined with inherent risks associated with the pharmaceutical compounding process.⁷ The risk for the patient is that total accuracy and uniformity of the dose can never be assured and the risk for the operator is that he/she is being exposed to the chemicals whilst reconstituting a preparation. Extemporaneous compounding is defined as the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient.¹ At Mater Dei Hospital, the extemporaneous compounding service caters for both children and adults, to both in- and out-patients and liaises with clinicians, pharmacists and nursing staff to

ensure seamless care. Since the majority of medicines are prepared for paediatric patients, this article will focus on this category of patients.

Extemporaneous medicines can range from oral formulations such as suspensions and solutions, sachets, mouthwashes to topical formulations such as creams and ointments. Examples range from captopril suspension for cardiovascular disease to controlled medicines such as clobazam sachets, both for use in paediatric patients. Oral liquid medicines are commonly prepared extemporaneously because of a relative lack of licensed formulations for children who are unable to swallow tablets or capsules, or for whom the required dose is less than a single tablet or capsule.⁷ A large proportion of extemporaneous compounding lies in converting capsules and tablets to oral liquids or powders. Others are made from the bulk active ingredient, such as oseltamivir powder to prepare oseltamivir phosphate solution.

It can be noted that most medications are marketed without adequate studies and availability of appropriate dosages for infants and children.⁹ Even medications such as phenobarbital and spironolactone, which have been approved for use in paediatric patients, are not available in an appropriate dosage form for this category of patients. One of the aims of extemporaneous compounding is making medicines available to paediatric patients.¹⁰

Legal considerations

Extemporaneous compounding of medicines is usually not covered by the manufacturer in the product's SmPC. An off-license form must be filled in by the prescriber every time there is a new request for an extemporaneous formulation, wherein the prescriber takes full responsibility for the clinical use of the preparation. This should accompany every new prescription. At MDH, off-license forms can either be departmental (e.g. caffeine citrate oral liquid is used by Neonatal and Paediatric Intensive Care Unit (NPICU) in neonates for respiratory distress syndrome) or patient-specific (e.g. sildenafil suspension for pulmonary hypertension in paediatrics) and are downloadable from the hospital intranet via the following link: <http://www.kura.gov.mt/infocentre/forms/result.asp?keys=off-license&SearchMonth=&SearchYear=>. A database of off-license medicinal products is kept by Quality Assurance (QA) section within the Pharmacy Department.

The role of QA is to ensure that services and medicinal products provided/supplied by the Pharmacy Department are of the quality required for their intended use.

Key points for consideration prior to compounding

The following alternatives should be considered before extemporaneous compounding is undertaken:

1. Soluble or dispersible tablets may be a useful and convenient alternative to the preparation of liquid extemporaneous products. Some tablets can be dispersed or crushed and information on this aspect can be obtained from the Medicines Information Section within MDH. In this case, the dose should be prepared and administered immediately. In general compressed tablets or tablets which are scored or just film coated can be crushed whereas modified release tablets cannot.
2. If a particular medicine is not available as a liquid formulation, another medicine from the same therapeutic classification may well be used, such as the use of a less potent steroid rather than diluting a potent one.
3. Using a suitable preparation intended for a different route of administration, for example, using an injectable solution orally.
4. Use of a 'specials' preparation manufactured in licensed premises (Specials are medicines made in larger volumes by a licensed manufacturer).⁹

Stability

When evaluating the stability of a formulation, its chemical, physical and microbiological stability must be considered.¹ It is highly important that the storage conditions stated on the label are adhered to. Even where a given formulation has been shown to achieve suitable physical, chemical and microbiological stability, the bioavailability and palatability of the preparation may be unproven.

Very few extemporaneous preparations are supported by any data to demonstrate a suitable absorption profile and/or bioequivalence with a licensed preparation. Other issues include concerns about inadequate access to equipment and materials needed to provide a safe extemporaneous dispensing service and the highest possible quality products.

In order to limit degradation and spoilage, products are given a maximum

shelf-life of 28 days, unless the product is not chemically stable, whereby the shelf-life is then given according to the stability of the respective product.⁷ Stability studies for extemporaneous preparations are usually conducted over small periods of time.

Lack of stability data limits many medicines from being made available for use in paediatrics. The armamentarium of formulations available for extemporaneous compounding relies heavily on the availability of stability data and the ingredients required for compounding.

A systematic approach to compounding at Mater Dei Hospital

- Non-sterile extemporaneous preparations must always be compounded upon receipt of a prescription i.e. on demand.
- If a worksheet for the formulation requested is not available and a licensed product or alternative cannot be found, an appropriate formulation must be researched. The details of the new formulation are presented to the prescriber who endorses it.
- A new worksheet and label must then be prepared. The master worksheets are then approved by the Quality Assurance section and endorsed by the Head of Pharmacy. A request for inclusion of the new extemporaneous formulation in the hospital formulary should also be filled in. The original master work sheets are stored by Quality Assurance section which is also responsible for uploading a secured electronic version on the intranet. A separate set of worksheets and labels are drawn up for every preparation compounded (i.e. patient-specific).
- All pharmacists and pharmacy technicians receive training which is certified by Quality Assurance prior to starting duties within the Compounding Section. All the compounding steps are double-checked by a pharmacist before a preparation is released for use.

Premises

At MDH, extemporaneous medicines are prepared in a clean controlled environment containing equipment required for extemporaneous compounding such as a fume cupboard and a powder-containment cabinet for personnel protection from fumes and aerosols generated during compounding. Personnel must don the prescribed garments

Key Points

- Extemporaneous compounding is the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient.¹
- The extemporaneous compounding of medicines, involving the alternation of a licensed formulation, is off-license unless it is clearly indicated in the Summary of Product Characteristics (SmPC) of the product that the extemporaneous process can be performed.
- Extemporaneous preparations have a limited shelf life.
- A licensed, commercially available preparation is always preferable and in its absence, if possible, a licensed alternative should be sought.
- Extemporaneous preparations are patient-specific.

before entering the clean area i.e. mob hat, gloves, overshoes, plastic overcoat and a facial mask for males.

Final comment

The pharmaceutical industry is expected to develop and market dosage forms which are suitable for children, hence relieving the hospital pharmacy from the burden of preparing extemporaneous preparations. However, it remains to be discussed whether this is a realistic expectation. Manufacturers would have to produce formulations that have a limited shelf life, since many existing medicines are intrinsically unstable in any aqueous vehicle, which is possibly the only acceptable formulation for paediatric oral administration. The manufacturer would be placed at a financial disadvantage, considering the small size of the paediatric healthcare market and the economic push for

group purchasing and cost reduction, in order to solve the compounding problems of hospital pharmacies.¹⁰

Conclusion

The aim of extemporaneous compounding is that of meeting the therapeutic needs of vulnerable patients, especially the paediatric population, as a last resort in the absence of a marketed licensed preparation. Prescribers are encouraged to use their clinical judgment when recommending extemporaneous formulations to their patients, and should monitor for safety and efficacy throughout treatment. With the the resulting aim of preparing appropriate dosage forms for paediatric use, a significant responsibility in a pharmacists' work remains the compounding of extemporaneous formulations.

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