ORIGINAL ARTICLE

Variations in captopril formulations used to treat children with heart failure: a survey in the United kingdom

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Background and objective: Different liquid formulations of a drug prepared for use in children cannot be assumed to have therapeutic equivalence. The objective of this study was to ascertain the interhospital constancy of unlicensed liquid captopril formulations used to treat children with heart failure in the UK.
Design: A questionnaire-based telephone survey.
Setting: 13 tertiary paediatric cardiac centres in the UK and 13 large hospitals referring patients to these centres.
Participants: The study included pharmacists responsible for providing the pharmaceutical input to children with congenital heart disease or a pharmacist designated to cover paediatric services. Technical staff employed by ''specials'' manufacturers also participated.
Results: Four hospitals dispensed captopril tablets for crushing and dissolving in water before administration; the remaining 22 used nine different liquid formulations of captopril. Only three cardiac centres and their referring hospitals were found to be using the same liquid captopril formulations; 10 centres and their referring hospitals were using completely different captopril formulations.
Conclusions: This survey shows that paediatric cardiac centres and their referring hospitals use a variety of unlicensed liquid captopril formulations interchangeably. This degree of inconsistency raises issues about optimal captopril dosing and potential toxicity, such that its use may influence paediatric cardiac surgical and interventional outcomes.

Captopril is a common and well-established pharmacological treatment for managing children with heart failure. However, its use in this patient group is largely founded on drug efficacy and safety data from studies involving adults with acquired heart disease.[1 2] Although clinicians do not doubt the efficacy and utility of captopril in managing children with heart failure, concerns exist about optimal dosing schedules and toxicity.[1 2] One parameter that may cause significant variation in ensuring optimal dosing and minimal toxicity is its formulation.[3] Currently, licensed captopril is available only in tablet form; many children are either unable or unwilling to swallow tablets. At our institution, we use an unlicensed liquid captopril preparation obtained from a ''specials'' manufacturer. Such manufacturers operate under a specials manufacturing licence, although their medicines do not undergo formal clinical studies and are therefore not licensed with any regulatory authority. Thus, as with many other pharmaceutical formulations obtained from ''specials'' manufacturers, liquid captopril does not have any supporting bioequivalence data.

Although our institution is a regional congenital heart centre, we have no control over the type of formulation dispensed by other hospital pharmacies or even community pharmacies that serve children whose care is co-ordinated in our institution. Although it is difficult to quantify the clinical effect this has, we have noticed large interpatient variability in the duration of time needed to optimise the dose of captopril (with the resulting inconvenience for the patient and family of spending more time in hospital). The variation in the type of liquid captopril formulation dispensed to children in our service raises relevant issues about optimal dosing and toxicity. To determine whether this was a local or national issue, we performed a national survey of all pharmacies linked to a congenital heart service and of neighbouring hospital pharmacies.

METHODS

Ethical approval was not required for this study.

Identification of hospitals and data collection

All tertiary paediatric congenital heart centres (those that perform paediatric cardiac surgery or therapeutic cardiac catheterisation) were identified and paired (except for Royal Victoria Hospitals, Belfast, UK) with hospitals (chosen arbitrarily) that referred patients to that centre. A telephone survey was then conducted by one of the authors (HM) with the clinical pharmacist responsible for providing the pharmaceutical input to children with congenital heart disease or a pharmacist designated to cover paediatric services. On some occasions, additional information was obtained from a pharmacist or technician responsible for formulations. Although each survey generally took no more than 15 min, occasionally repeat phone calls were necessary to obtain information not available at initial contact.

The questionnaire was designed to determine (1) whether the liquid captopril formulation dispensed by the hospital was procured from an external source (either a ''specials'' manufacturer or an NHS manufacturing unit) or extemporaneously prepared; (2) the identity of the external source; (3) whether the participants had any data on the consistency of the liquid formulation dispensed for patients by their hospital and community pharmacies; and (4) the nature of the extemporaneously prepared liquid formulations (excipients, shelf life and stability). Information regarding products procured from external sources was obtained by phoning the manufacturers' technical departments.

RESULTS

Adequate responses to the questionnaire were obtained from all 13 tertiary paediatric cardiac centres and from 13 hospitals referring patients to these centres.

Four hospitals (three tertiary cardiac centres) dispensed captopril tablets for crushing and dissolving in water before administration; the remaining 22 used nine different liquid formulations of captopril (fig 1). Three of the liquid formulations

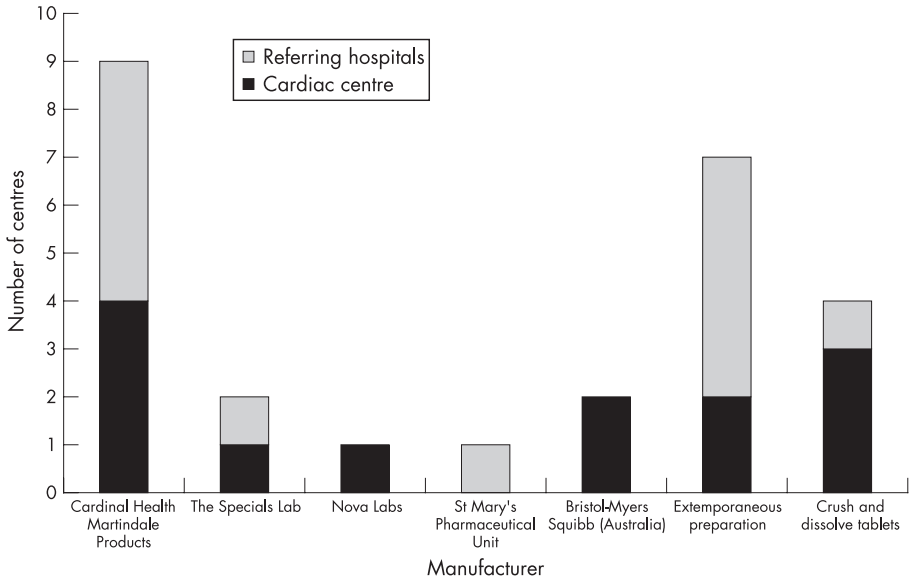

Figure 1 Histogram showing the frequency of use of different liquid captopril formulations identified in the survey (n = 26 hospitals). Bars also show the breakdown for each formulation between tertiary cardiac centres and referral hospitals. ''Manufacturer'' refers to the source of liquid captopril.

were procured from ''specials'' manufacturers, one from an NHS manufacturing unit, four were extemporaneously prepared and one formulation was imported from Australia. This latter formulation is licensed in the source country, but is not currently available in the UK. The 13 tertiary cardiac centres were found to be using six different liquid preparations or to be crushing/dissolving tablets. In relation to the consistency of liquid formulation, only three cardiac centres and their referring hospitals were found to be using the same preparation; the remainder used completely different preparations. In addition, no hospital was found to have any data to support continued use of the captopril preparation dispensed by the hospital in the community. However, all but three hospitals provided letters detailing their source of the captopril liquid. The letters were given to the parents of the patients, who were asked to forward these letters to their doctor and/or community pharmacist. Three hospitals recommended formulations that were different from the formulation dispensed by the hospital.

Extemporaneous and ''specials'' formulations were either aqueous- or oil-based suspensions, or aqueous solutions, and were prepared using a range of excipients (table 1). The shelf life of ''specials'' formulations ranged from 1 to 3 months, whereas extemporaneously prepared formulations had a shelf life of 1–2 weeks. Apart from the Bristol–Myers Squibb formulation, no other manufacturer or hospital had conducted comprehensive stability studies on their final finished product to support the stated shelf life.

DISCUSSION

This survey shows that paediatric cardiac centres and their referring hospitals use a variety of unlicensed liquid captopril formulations interchangeably to treat children with heart failure. Furthermore, informal discussions with hospital pharmacists suggest that it is possible that children with heart failure are dispensed one liquid captopril formulation by a

Table 1 Composition and stability of liquid captopril formulations used to treat children with heart disease in the UK

	Strengths	Expiry (days)	Stability data*	Excipients
''Specials'' manufacturer				
Cardinal Health Martindale Products	Various	90		Fractionated oconut oil, Cab-o-sil
The Specials Laboratory	Various	28	No	Xanthan gum 1%, ascorbic acid
Nova Laboratories (flavoured)	Various	28	No	Flavoured suspension Diluent A in a 1:1 ratio with water, ascorbic acid
Nova Laboratories (unflavoured)	Various	8	No	Suspension diluent A in a 1:1 ratio with water
NHS manufacturing unit (St Mary's Pharmaceutical Unit)	1, 5 and 12.5 mg/ml	35	No	Xanthan gum 0.4%, methyl hydroxyl-benzoate, propyl-hydroxy benzoate
Imported (Bristol–Myers Squibb, Australia)	5 mg/ml	28	Yes	Citric acid, sodium citrate, disodium edetate, sodium benzoate
Extemporaneous formulations				
Southampton General Hospital	1 mg/ml	14	No	Ascorbic acid, water
Bradford Royal Infirmary, Royal Hospitals, Belfast, and St George's, London	Various	14	No	Suspension diluent A
St George's, London	Various	14	No	OraPlus/OraSweet (1:1 ratio)
Queen's Medical Centre, Nottingham, and Gloucester Royal Infirmary	Various	14	No	Suspension diluent A in a 1:1 ratio with water

Suspension diluent A contains xanthan gum 1%, methyl hydroxybenzoate and propylhydroxy benzoate. St George's Hospital, London, provided two extemporaneous methodologies.
*Evidence of comprehensive in-house stability data on the final finished product.

What is already known on this topic

- The lack of suitable oral formulations of medicines for children is often overcome by preparing or procuring unlicensed liquids.
- Such unlicensed formulations are deemed necessary, while accepting that their clinical reliability and performance has not been tested and that their relative bioavailability is unknown.

What this study adds

- A wide variety of unlicensed and untested liquid captopril formulations is used interchangeably in the treatment of children with heart failure.
- This degree of inconsistency raises issues about optimal captopril dosing and potential toxicity, such that its use may influence paediatric cardiac surgical and interventional outcomes.

hospital pharmacy and a completely different formulation by a community pharmacy.

Using different licensed formulations of a drug interchangeably is common and accepted practice where bioequivalence data are available. In relation to captopril and paediatric heart failure, no bioequivalence data exist for the liquid formulations identified in this survey. Hence, it is not possible to be confident that the rate and extent of captopril absorption do not vary according to its formulation. Not surprisingly, the manufacturers of liquid captopril do not guarantee that their formulation performs in vivo, just that their manufacturing process adheres to a quality assurance system.

Therapeutic equivalence between differing formulations should not be assumed, as excipients can significantly affect the rate and extent of drug absorption.[4] For example, it is conceivable that the performance in vivo of an oil-based suspension will not be the same as that of an aqueous-based suspension. The practice of crushing tablets and dissolving in water adopted by some centres may be even worse than using unlicensed formulations, as crushing tablets has the potential for dose inaccuracies as well as altered absorption.[5 6] Such practice is also associated with the highest risk of errors, as there is no record or control of preparation.[7]

Taken together, these issues strongly argue against using unlicensed liquid formulations of captopril interchangeably, as seems to be the case in many UK regions. The present lack of consistency in liquid captopril formulations dispensed to children with heart disease raises issues about efficacy and toxicity. Moreover, failure to optimise captopril treatment in children with heart failure has potential repercussions for both immediate and long-term surgical outcomes, as many children require further and often multiple surgical interventions.

Treatment outcomes for children with heart disease are scrutinised by the Department of Health and various Royal Colleges. However, variances in outcomes owing to drug treatment have received scant attention either by these institutions or by paediatric cardiac specialists. Even less attention has been paid to the influence of using unlicensed drug formulations, interchangeably, on these outcomes. It is estimated that, annually, up to 1000 children will be initiated on captopril for the treatment of heart failure. To ensure optimal treatment, we recommend that: 1) doctors/hospital pharmacies and community colleagues use identical formulations; 2) medicines regulatory authorities and pharmaceutical manufacturers work together to ensure that liquid captopril formulations with supporting bioequivalence data are developed.

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