Preservatives can produce harmful effects in paediatric drug preparations

Abstract
Paediatric drug preparations can be made in hospital pharmacies with product manufacturing facilities. These are often aqueous liquids and require preservatives to prevent microbial growth occurring during storage or use.

Introduction
Pharmacists working in hospital or community pharmacies often call on their experience to prepare medications extemporaneously (extemp preparations).

In the UK, NHS hospital trusts — especially those with product manufacturing facilities — are responsible for preparing pharmaceutical preparations for hospital use where there are shortages in commercial sources to meet clinical needs. This is often done for those paediatric products where it is common practice to take an adult dose and turn it into preparations suitable for children — such as the preparation of ciprofloxacin suspension from tablets or the preparation of unit dose by a pharmacy Central Intravenous Additive Service (CIVAS). Some other products are also produced under special licence for rare therapies or in support of clinical investigations.

Most of the extemporaneous preparations are aqueous liquids and as a result they are susceptible to microbial contamination, which can lead to spoilage and undesirable effects in patients. These products thus need to be preserved to maintain their microbial integrity during storage and when in-use. However, the type and quantity of preservatives must be carefully selected in paediatric preparations because of the possible pharmacological actions or toxic effects from this formulation ingredient.

Current practice
A list of preservatives currently used within the London region NHS pharmacy manufacturing units, obtained from a survey, is given in Table I. The survey revealed that chloroform is used widely as a preservative, especially for extemporaneously prepared oral liquid medicines. Chloroform is active against a wide range of microorganisms and it is one of the oldest preservatives used...
in pharmacy. Of concern, therefore, is the reported chloroform toxicity in animals that has led the US FDA and similar agencies in some other countries to ban its use in medicines and cosmetics.

Chloroform has been found to produce hepatocellular carcinomas — liver cancers — in mice and rats, and renal tumours in male rats after oral administration. Aside from the toxic effects there is a possibility of reduction in the preservative effect as a result of evaporation of chloroform from medicinal preparations during storage and routine use.

Despite these unfavourable reports, the British Pharmacopoeia (2001) and Martindale Extra (36th Edition) still allow the inclusion of chloroform in drug preparations up to a concentration of 0.5%w/w or v/v.

Few scientists would argue that the reported adverse effects of chloroform have not been demonstrated in humans. Some believe there is a genuine reason for concern because results from animal studies have been used to predict the toxicity profile of substances in humans — and chloroform is no exception. In our opinion chloroform should not be employed as a preservative for pharmaceutical preparations — especially those intended for use in children.

Methyl and propyl parabens, including their salt combinations, are also used as preservatives for extemps and products.
that are produced as batches.

In our survey benzyl alcohol was used in one cream preparation. Comments from the survey revealed that the use of phenyl mercuric nitrate (0.004%) and thiomersal (0.005%) as preservatives in ophthalmic preparations is diminishing because of side-effects. Future formulation objectives may therefore include the production of ophthalmics without a need for chemical preservation.

Other preservatives, such as propylene glycol, ethanol and benzalkonium chloride are also being used to a varying extents and they also have potential to cause harm when used for the preparation of paediatric medicines.

Review

Some preservatives are toxic and should be restricted in paediatric formulations while others are less toxic but effective. This paper is a concise review of the properties of some of the preservatives frequently used in the preparation of pharmaceutical dosage forms and includes a thorough assessment of their potential risks and benefits, especially in medicines intended for neonates and children. It is hoped that the information we provide will assist formulation pharmacists to select an optimum preservation system for their products.

**Benzyl Alcohol**

Benzyl alcohol is commonly used at concentrations up to 2.0%v/v as preservative in solutions and injectable drugs. Optimum activity occurs at

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solution pH values of less than pH 5. It is active against gram positive bacteria, moulds, fungi and yeast and possesses modest bactericidal activity. It is less effective against gram negative bacteria and ineffective against spores. It is incompatible with methylcellulose.

A number of neonatal deaths and severe respiratory and metabolic complications — especially in low-birth weight premature infants — have been associated with the use of this agent in bacteriostatic saline intravascular flush and endotracheal tube lavage solutions.1,2

Benzyl alcohol toxicity has been ascribed to the build-up of benzoic acid — exacerbated by the immature conjugation pathway in neonates. Thus, the same caution should be applied to preparations containing benzoic acid or sodium benzoate. Benzoates substantially increase the unbound bilirubin concentration (UBC), but this is attenuated after a 42-fold dilution.3

The use of benzyl alcohol should be avoided in neonates if possible. If benzyl alcohol is present in a paediatric preparation and its use is essential, the total dose should not exceed 100mg/kg per day. This is an arbitrary figure based on the knowledge that 100mg/kg/day has caused death from gasping syndrome in very low birth-weight premature babies.4

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Many commercially available neonatal preparations contain sodium benzoate or benzoic acid but the amount of preservatives ingested from normal doses in these preparations is well below 10mg/kg/day. It is advisable to avoid administration of preparations containing these preservatives to severely ill neonates such as premature infants with metabolic acidosis or respiratory distress.

Parabens
Methyl and propyl hydroxy benzoates are generally safe in neonates. Parabens are included in some parenteral products that have been used extensively in neonates, such as gentamicin injection.

The concentrations used in pharmaceutical formulations vary depending on the dosage form with injectable or parenteral preparation having the lowest. Methyl parabens (0.18%) and propyl parabens (0.02%) have been used to preserve various parenteral formulations. The parabens are most active at a pH range of 4–8 and their activity decreases with increasing pH. They are most active against yeast, mould and gram positive bacteria and less against gram negative bacteria. Their activity is enhanced in some formulations when combined with propylene glycol or phenyl ethyl alcohol.

In vitro studies indicate that both methyl and propyl paraben bind to albumin and methyl paraben displaces bilirubin from albumin.6 Despite this displacement, hyperbilirubinaemia has never been demonstrated in vivo when preparations containing the preservatives are given in normal doses.7

The excretion of methyl paraben by the urinary route in preterm infants is variable during the first few days of extrauterine life. Whether there is an accumulation of preservatives in the body and whether after repeated injections the albumin binding capacity for bilirubin is affected, remains to be determined. It is not uncommon for preterm infants to have neonatal jaundice.8 However, as a precaution, products containing parabens should be avoided as much as possible in acutely ill

<table>
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<tr>
<th>Preservatives</th>
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<th>Sterile preparation</th>
<th>External medication</th>
<th>Extemporaneous preparations</th>
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<td>*Benzenalkonium chloride (BC)</td>
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<td>*Thiomersal (TH)</td>
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Table 1. List of Preservatives being used within the London region NHS pharmaceutical manufacturing units

* = ophthalmic products
neonates presenting with jaundice, kernicterus or hyperbilirubinaemia.

Benzalkonium Chloride
Benzalkonium chloride is a commonly used bactericidal preservative in suspensions, nasal sprays, eye drops and nebuliser solutions. In ophthalmic preparations benzalkonium is effective at concentrations of 0.01-0.02% w/v.

In nasal and otic preparations benzalkonium is effective at a concentration range of 0.002-0.02%. Disodium edetate (0.1%) is usually added to enhance antibacterial activity against Pseudomonas spp.

When benzalkonium chloride has been used as a preservative in nebulised solutions of anti-asthmatic agents, it has been reported to cause bronchoconstriction and was associated with the precipitation of a respiratory attack.9,10,11

In nasal sprays this product can exacerbate rhinitis and it can induce irritation or keratitis in eye preparations. It is worth noting that these properties are not peculiar to benzalkonium and they could be manifest by other preservatives. It is advisable, therefore, to avoid the use of benzalkonium chloride in paediatric products especially in anti-asthma preparations.2 Potential sources of benzalkonium in products for children with asthma and concurrent sinusitis include nasal saline, nasal corticosteroids and nasal decongestant solutions.

Chlorobutanol (Chlorbutol)
Chlorobutanol has antibacterial and antifungal properties and it is used at a preservative concentration of 0.5% in injections and in eye drops. Patients who were given high doses of salicylamide or morphine infusions preserved with chlorobutanol showed chlorobutol-induced somnolence.12,13

A delayed cellular type of hypersensitivity reaction to chlorobutol used to preserve heparin when it was given by subcutaneous injection, has also been reported.15

Chlorobutanol should not be used to preserve injectable preparations that are intended for neonates and children. Eye drops, nasal and dental preparations may be preserved with chlorobutanol especially where their sedative and analgesic properties are of advantage.

**Cumulative intake of preservatives**
The cumulative or concomitant intake of preservatives from multiple drug therapy given to neonates and children, should be calculated. The very ill neonates and premature babies, especially those with kernicterus or conditions predisposing to hyperbilirubinaemia, should not be given products containing parabens, at least until their condition resolves.

**Conclusion**
There is considerable risk associated with the extemporaneous preparation of pharmaceutical products especially those meant for use in neonates and young children.

Pharmacists must assess these risks and make efforts to transfer extemporaneous products to batch manufacture. This transition will involve formulation study, scale-up and stability surveillance. Adequate information must also be sought on all formulation ingredients so that the problems of incompatibility and toxicity to patients can be resolved before formulation.

We recommend that chloroform should not be used as a preservative in medicines that are intended for use in children because of its toxicity. The next edition of the British Pharmacopoeia should consider this recommendation and delete chloroform from the list of preservatives allowed for inclusion in drug preparations intended for human consumption. There are other, equally effective and less toxic, alternatives.

Parabens and benzyl alcohol can be used as preservatives in children’s medicines, but should be used with caution in children with jaundice. Nebulised solutions for asthmatic patients should not be preserved with benzalkonium chloride and injections intended for neonates should not contain chlorobutanol. However, chlorobutanol is useful as preservative in eye drops, nasal and dental preparations where their sedative and analgesic properties may be an advantage.

To improve the delivery of a professional pharmacy service, we recommend mandatory labelling of all inactive ingredients such as preservatives in all formulations. This must be included on the packaging materials of all prescription and over the counter drugs, whether produced extemporaneously or commercially. This would facilitate an evaluation of the risks associated with specific formulation ingredients and thus speed up the decision-making process on the suitability of medications for neonates and children.

**Acknowledgement**
The authors are grateful to all the London region NHS pharmacy manufacturing units that participated in the survey.

**References**
A neonate in an acute-care unit receiving an aqeous infusion. Special care must be taken in the choice of preservatives for neonatal aqeous drug preparations


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Lantus® 100 IU/ml solution for injection (insulin glargine). Prescribing Information: Presentation: 1 glass vial/pack containing 10ml solution (100 IU insulin glargine, equivalent to 30.5mg) or 5 glass cartridges/pack each containing 3ml solution (100 IU insulin glargine, equivalent to 9.9mg) or packs of 5 OptiSet® pens each containing 3ml solution (80 IU insulin glargine, equivalent to 2.8mg). (Excipients: zinc chloride, manganese, potassium hydroxide, sodium citrate, sodium chloride and water for injection). Indications: for the treatment of adult, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required. Dosage and Administration: Lantus should be administered subcutaneously once daily, at any time, but at the same time each day. In children, the efficacy and safety of Lantus have only been determined when given in the evening. The dosage of insulin glargine should be individually adjusted. Close metabolic monitoring is recommended during transitions from oral insulins to Lantus and in circumstances that increase susceptibility to hypo- or hyperglycaemia. Lantus must not be mixed with other insulins or diluted.

Contraindications: Hypersensitivity to insulin glargine or to any of the excipients.

Precautions and Warnings: Lantus is not the insulin of choice for treatment of diabetic ketoacidosis. The safety and efficacy of Lantus has not been assessed in children below 6 years of age.

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