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Systemic toxicity with topical ophthalmic medications in children

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Drugs applied topically to the eye may be absorbed systemically to a substantial degree, with the potential to cause serious systemic side effects. Children may be particularly vulnerable to systemic effects of topically applied agents as topical doses are often not weight-adjusted. This article reviews cases of serious systemic toxicity which have been described with the use of topical phenylephrine, cyclopentolate, timolol, brimonidine, corticosteroids and chloramphenicol in children. Strategies to minimise systemic absorption should be applied, including use of low drug concentrations and microdrops, and punctal occlusion to minimise absorption via the nasolacrimal duct.

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Introduction

Topical ophthalmic medications are widely prescribed for children by growing numbers of professionals. However, the study of ocular pharmacology in children is often limited to case series and small case reports. Topical application of ocular drugs may cause side effects which involve the eye itself or are systemic; the latter may be significantly underestimated if the clinician and the patient fail to associate a topical medication with a systemic condition[1,2]. As the number and variety of topical agents increase and the number of professionals involved in their prescription grows, the risk of systemic adverse reactions also increases. It is therefore important to raise awareness of the potential systemic dangers of topical eye medications.

Ocular drugs with potentially serious adverse systemic effects include phenylephrine, anticholinergic cycloplegics such as cyclopentolate, glaucoma medications, corticosteroid eye drops and chloramphenicol. Most systemic reactions are a dose dependent extension of the pharmacological action of the drug, with the exception of chloramphenicol, which may cause idiosyncratic blood dyscrasias. This article describes serious toxicity reported with topical ocular drugs, emphasising the need for awareness of potential side effects, and exploring ways of reducing the risk of toxicity in children. Sources of information include literature searches of MEDLINE (1966 until December 2005), EMBASE (1980 until December 2005), as well as datasheets and patient information leaflets for individual drugs.

Systemic absorption after topical application of eye medications

Ocular drugs are most often administered as eye drops or ointments to one or both eyes for diagnostic or therapeutic purposes. The ocular effect becomes manifest when the drug penetrates

the outer and inner parts of the globe and the periocular tissues. However, the eye has several natural barriers which limit the penetration of topically applied drugs such that the local bioavailability of ocular drugs is low. The tear film acts to dilute drug and has natural buffers in proteins and bicarbonates, and the corneal epithelium is five layers thick, which limits absorption into the deeper structures of the eye[3]. Moreover, the residence time of drug on the ocular surface is short. Pharmacological studies have shown that drugs applied topically to the eye are only minimally absorbed into the eye (2-10%) where they exert their local effect[4].

The remainder of the topically applied drug can enter the systemic circulation through an extensive network of conjunctival vessels and via the nasolacrimal duct through the highly vascularised nasal mucosa. Both conjunctival and nasal absorption are rapid, and both bypass first pass metabolism. Some drug entering the nasolacrimal system may be swallowed and absorbed via the stomach[4]. In these ways a large proportion of drug administered ocularly (over 80% in some studies)[5] may enter the systemic circulation rapidly with peak plasma concentrations reached between 5 and 30 minutes after topical instillation[6].

Systemic effects of ocularly administered drugs have been described mainly in adults, though there are smaller case series and case reports in children. It is difficult to estimate frequencies of systemic effects though they are generally reported as being uncommon[2]. In adults, the risk of systemic effects has been shown to be substantially increased in the presence of underlying cardiovascular and respiratory disease, and with the use of intercurrent medications which may interact with the ocularly administered drug[1,2,7]. Systemic absorption has also been found to be greater in the inflamed eye[6].

The dimensions of the paediatric eye are quite similar to the adult's: the eye of the newborn is roughly two thirds of its adult size at birth, and the eye reaches adult size at 3–4 years of age[8]. Ocular doses in children are not weight adjusted and are similar to doses used in adults. However, systemic absorption may have a greater impact in children than in adults due to their lower body mass with potentially higher plasma concentrations reached. In infants, toxicity may be compounded by altered metabolic capacity and an immature blood brain barrier[9]. Thus, in children, a relatively larger dose of topical eye medication can reach the systemic circulation where it may be metabolised at a slower rate, leading to potentially higher plasma levels for a longer period of time[8].

Ocular phenylephrine

Phenylephrine is a sympathomimetic which acts on the pupillary dilator muscle to produce mydriasis for diagnostic or therapeutic procedures. It is used widely in the neonatal period for dilating pupils for retinopathy of prematurity (ROP) screening. Phenylephrine is a selective α-1 agonist, with β activation only at very high doses[10]. Onset of action occurs 30–90 minutes after installation, and effects last for 6–7 hours[11].

Systemic complications of topical phenylephrine are those common to sympathomimetics. Reported side effects in adults include tachycardia, hypertension, arrhythmias, faintness, trembling, pallor, sweating and headaches[10]. Phenylephrine should be used with caution in patients with cardiac disease, and in those on concomitant medications such as tricyclics or atropine, which can compound its pharmacodynamic effects[12].

Phenylephrine 2.5% eye drops are licensed for use in all age groups, whereas the 10% eye drops are unlicensed in children and not recommended in this age group[11]. Small case series have described systemic side effects in neonates and children but side effects may be significantly underreported. Paediatricians should be aware of potential systemic effects of topical phenylephrine in view of the frequency of use in ROP screening.

In a series of 110 neonates undergoing ROP screening, vital sign changes included increases in heart rate (average 7 beats per minute), decrease in oxygen saturation (by an average of 3%) and a small increase in systolic blood pressure (average 4.3 mm Hg)[13]. Changes in this particular series were not clinically significant but the clinician should be aware that such trends may not be well tolerated in sick neonates or in those with underlying cardiac or respiratory problems. A further study showed a significant elevation in systolic blood pressure in 8/10 infants given phenylephrine 2.5% with tropicamide 0.5% versus those given tropicamide only[14]. Changes in vital signs caused by the pharmacological action of the drugs can of course be compounded by physiological changes associated with the stress of physical manipulation of the eyes[15].

There have been isolated case reports of paralytic ileus[16], necrotising enterocolitis[17] and acute gastric dilatation with vomiting and apnoea[18] in neonates in the 24 hour period after ROP screening, using phenylephrine and cyclopentolate. A case series in 50 neonates confirmed a significantly higher incidence of feeding intolerance (abdominal distension and increased gastric aspirates) in the 24 hours after ROP screening, using phenylephrine

and cyclopentolate as mydriatics[17]. Once again, the pharmacological action of the drugs could be compounded by the stress of manipulation. Awareness of the potential gastrointestinal complications after ROP screening using mydriatics should prompt clinicians and nurses to watch more closely for signs of feeding intolerance following ROP screening to help reduce serious complications such as necrotising enterocolitis.

Renal vessels may be sensitive to vasoconstriction induced by sympathomimetics, and there has been a case report of renal failure in a low birth weight infant after phenylephrine eye drop installation[19].

There have been two case reports of hypertension, acute left ventricular failure and pulmonary oedema associated with ocular phenylephrine given intraoperatively, in a 2 month old girl undergoing cataract extraction[20] and an 8 year old boy undergoing retinal detachment surgery[21]. In the latter case, 10% phenylephrine drops were used (unlicensed in children) and extra drops were given in theatre owing to inadequate pupillary dilatation at the time. These cases highlight the need to use the lowest available concentration of topical agents in children and to allow adequate time for the pharmacological action before topping up the dose with potentially serious systemic effects.

Antimuscarininc anti-cholinergics

Cyclopentolate

Cyclopentolate is a synthetic anti-cholinergic agent. It acts as a muscarinic antagonist to produce rapid onset cycloplegia and inhibiton of the parasympathetic constrictor muscle, producing mydriasis useful for ophthalmological screening. It is available in the UK as 0.5% and 1% eye drops. A 2% solution is available in the USA; however, it has been associated with a higher risk of systemic complications in adults and its use should be restricted in children[22]. Onset of action of cyclopentolate is within 30–60 minutes, and effects can last up to a day[23]. Cyclopentolate is not licensed for children under the age of 3 months due to possible association between cycloplegia and development of amblyopia[11].

Systemic complications are due to parasympatholytic (atropine-like) effects. Complications described in adults include dry mouth (salivary gland inhibition), reduced sweating, high fever, flushed skin (vasodilatation to lose heat), and central nervous system effects such as drowsiness, confusion and hallucinations[10].

An increased susceptibility to systemic effects of cyclopentolate has been reported in infants and young children, children with neurological impairment or spastic paralysis, and in those with seizure disorders[24]. The cyclopentolate package insert warns that it should be used with great caution in young children and those with spastic paralysis or brain damage, and should not be used in premature or small infants[25]. However, it is used commonly on the neonatal unit to dilate pupils for retinal examination and following neonatal cataract surgery.

There have been case reports of feeding intolerance in children following ROP screening using a combination of phenylephrine and cyclopentolate (see above), and the parasympatholytic effect of cyclopentolate may well play a role in a transient reduction in intestinal motility[16,17].

Children may be sensitive to central nervous system anti-cholinergic effects and mild effects such as drowsiness may be underreported. Behavioural changes may also occur, and there have been reports of transient psychotic reactions in children after cyclopentolate administration for fundal examination, in a 3 and 8 year old child respectively[26].

There have also been several published case reports of generalised seizures associated with atropine-like side effects such as flushing and tachycardia after ocular cyclopentolate administration in children[27-29].

Tropicamide

Tropicamide is another synthetic anti-muscarinic agent used topically as a mydriatic and cycloplegic. Tropicamide may be the preferable topical anti-muscarinic drug to use in children owing to a reduced propensity to cause systemic effects[30-32]. In adults, tropicamide has been shown to have a lower affinity for systemic muscarinic receptors and negligible receptor occupancy in plasma, explaining the lower incidence of systemic side effects[30]. Moreover, it has a shorter duration of action than cyclopentolate (0.25 days versus 1 day)[23] hence a shorter period of time available for systemic actions.

Case series in neonates undergoing ROP screening have shown tropicamide to be as effective as, yet safer, than cyclopentolate in producing pupillary dilatation for retinal examination[31,32].

Tropicamide is frequently combined with hydroxyamphetamine hydrobromide, an indirectly acting sympathomimetic agent, for mydriasis. This combination may lead to an increased potential for systemic side effects[33].

Topical glaucoma drugs

Timolol

Timolol is a β blocker which acts to reduce intraocular pressure in glaucoma by reducing aqueous humour production. It is not licensed for use in children but has been used successfully in the management of paediatric glaucoma[34-37].

Systemic side effects are those of non-selective β blockade. Reported systemic effects in adults include bradycardia, hypotension, atrioventricular block, bronchospasm, fatigue, confusion, depression, hallucination, worsening of myasthenia gravis, abdominal pain, nausea and vomiting and diarrhoea[38]. Timolol should be used with caution in patients with a history of asthma, congestive cardiac failure and in those receiving β blockers or verapamil[12].

Several cases of severe systemic toxicity in children after the use of timolol eye drops have been described. An 18 month old girl presented with bradycardia, cyanosis and respiratory depression 30 minutes after the administration of timolol eye drops[39]; and an 8 month old boy on maintenance propanolol for supraventricular tachycardia presented with unresponsiveness, bradycardia and hypotension after inadvertent nasal administration of timolol eye drops[40]. Another report has described apnoeic episodes in a 2 week old girl with congenital glaucoma given timolol[41]; apnoeic episodes stopped when the drug was discontinued.

Brimonidine

Brimonidine is a sympathomimetic with selective α-2 adrenoceptor agonist action. It acts by reducing aqueous humour production and increasing uveoscleral outflow to control intraocular pressure in glaucoma[3,42]. It is not licensed in children as it may cause cardiorespiratory depression[11]. Brimonidine passes through the blood brain barrier, hence has the potential to cause central nervous system toxicity, as illustrated by several case series in children.

In a study of 30 children given brimonidine 0.2% for uncontrolled glaucoma, two young children (2.4 and 3.7 years) were repeatedly unrousable soon after the administration of ocular brimonidine, and five others experienced extreme fatigue[43]. In another case series of 83 children on brimonidine for glaucoma, 76% experienced excessive sleepiness or lethargy[44]. The frequency of these symptoms was higher in younger children (< 6 years) and those with weight below 20 kg. In a study of 22 children with glaucoma given 0.2% brimonidine, two children discontinued treatment because of tiredness, and two because of fainting attacks[45].

Infants may be at higher risk of systemic effects associated with brimonidine. A one month old infant with an anterior chamber anomaly of the eye had recurrent episodes of unresponsiveness, hypotension, hypotonia, hypothermia and bradycardia that were found to be associated with administration of brimonidine eye drops[46].

Corticosteroid eye drops

Topical steroid eye drops including prednisolone, betamethasone and dexamethasone are licensed for use in all ages for the treatment of steroid responsive inflammatory conditions[11]. These include treatment of external eye disorders such as allergic conjunctivitis and keratitis, as well as intraocular disorders such as uveitis and post-surgical inflammation[3]. Prolonged use of topical steroids carries the theoretical risk of systemic side effects associated with excessive exogenous steroids, including adrenal suppression, growth restriction and reduced bone mineral density. Such side effects have been described after intranasal and inhaled corticosteroids[47-49]. Sporadic case reports in the literature suggest that ocular steroids carry a similar risk of systemic complications.

In a case series of 13 patients post cataract surgery, instillation of dexamethasone 0.1% eye drops hourly for 3 days led to a significant lowering of plasma cortisol level, demonstrating considerable absorption of ophthalmic dexamethasone[50]. An 11 year old boy with iridocyclitis developed a cushingoid habitus and acanthosis nigricans after he was treated with prenisolone acetate 1% eye drops every 2 hours for 6 months[51]. He subsequently developed posterior uveitis which was treated with periocular injections of methyl-prednisolone; this led to a worsening of truncal obesity and a slowing in linear growth.

Periocular injection of drugs allow for greater intraocular penetration into the vitreous and retina than topical drops, but involve larger volumes of drug with potentially greater systemic penetration[3]. Adrenal suppression and growth retardation have occurred after periocular injections for capillary haemangiomas in infants[52].

The clinician and patient should therefore be aware of the possibility of systemic effects associated with the long-term exposure to topical steroid eye drops as well as after periocular injections.

Ocular chloramphenicol

Chloramphenicol is an inexpensive and effective topical antibiotic treatment for superficial eye infections which is licensed for use in all age groups in the UK[11]. In contrast to the other classes of topical ocular medications described above, where there may well be under-awareness of possible systemic complications, chloramphenicol eye drops probably represent a case of "over-awareness" of the possibility of systemic complications. This has led to such radical steps as calls for abolition of treatment with topical chloramphenicol[53]. Systemic chloramphenicol therapy has been associated with a risk of idiosyncrastic aplastic anaemia with maximum risk of death of 1:50,000–1:90,000[54]. Topical chloramphenicol carries a theoretical but not conclusively proved risk of idiosyncratic aplastic anaemia. Sporadic case reports have described aplastic anaemia following the use of topical chloramphenicol, yet in several cases the causal association with topical chloramphenicol has been questioned[55,56].

A review in the UK showed that despite more than 200 million cases of topical chloramphenicol being dispensed between 1966 and 1996, there have been only 11 reports (non-fatal) of topical chloramphenicol-related blood dyscrasia[54]. A further population-based prospective case-control surveillance of aplastic anaemia showed the incidence of aplastic anaemia amongst users of ocular chloramphenicol was 0.36 cases per million weeks of treatment whereas the incidence among non-users was 0.04 cases per million weeks[55]. In summary, the risk of serious blood dyscrasias with ocular chloramphenicol seems real but extremely remote.

There are no specific data on risk of aplastic anaemia in children following topical chloramphenicol and no data to suggest an increased risk in children. The only known factor to be associated with vulnerability to chloramphenicol toxicity is family history[54], hence a history of drug reactions in the child as well as in family members is worth eliciting before prescribing chloramphenicol eye medications.

Strategies for reducing systemic absorption and toxicity of ocular drugs

With the exception of chloramphenicol, most systemic effects of topical ocular medications are dose related, and exaggerated by administering high doses (concentrations) of topical agents and by low bodyweight[9]. Several steps have been identified which may reduce the amount of drug absorbed systemically. Such steps should be followed wherever possible when administering topical ophthalmic drugs to children.

- *Use the lowest available concentration of the topical agent.*
  An example is that phenylephrine 10% drops should be avoided in children as they have a greater chance of producing systemic effects in comparison to the 2.5% strength.
- *Do not exceed the recommended number of drops.*
  The volume of most topical preparations is 10–25 microlitres, hence the conjunctival sac in children holds only 1–2 drops[3]. Volumes in excess of this can spill over into the nasolacrimal duct, allowing for further systemic absorption.
- *Avoid unnecessary repetition of doses.*
  This may mean delaying procedures whilst waiting for sufficient time for maximum pharmacological effect to be achieved from the eye drops, instead of early repeat administration.
- *Occlude the nasolacrimal passage after topical administration.*
  Finger pressure on the lacrimal puntus at the medial canthus of the eye immediately after installation of eye drops for at least 60 seconds reduces systemic absorption by reducing entry into the nasolacrimal duct[6,11].
- *Blot away excess drops after administration.*
  This helps minimise the volume of drug administered, and may initiate reflex blepharospasm which reduces movement down the nasolacrimal duct[11].
- *Use microdrops in infants if available.*
  Microdrops are associated with lower risk of systemic action but comparable local effect. 5 microlitre microdrops of mydriatics have been shown to cause equivalent pupil dilatation to 26 microlitre drops in infants[57].
- *Use formulations with lower systemic absorption.*
  Different formulations may have different degrees of systemic absorption, and those with lower absorption may be more suitable for use in children. For example, timolol ophthalmic gelling vehicle has been found to have reduced systemic absorption in comparison to the ophthalmic solution[58].

Conclusions

Great care needs to be taken in local application of ocular drugs, which can produce serious systemic side effects. Clinicians and patients/parents should be aware of possible systemic side effects, and steps should be taken to minimise systemic

absorption of drugs. Extra care should be taken in children on intercurrent medications which may exaggerate the pharmacological effect of ocular agents, and in those with cardiac or respiratory compromise who may tolerate additional changes poorly. Paediatric patients should be monitored closely for systemic effects even after "routine" administration of ocular agents such as for retinopathy of prematurity screening.

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