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Cardiac and central nervous system toxicity with timolol eye drops in an infant: case report and discussion

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An 8 month old boy on maintenance propranolol for paroxysmal supraventricular tachycardias presented with a depressed level of consciousness, bradycardia and hypotension, triggered by the accidental nasal administration of the ophthalmic β blocker timolol. Timolol eye drops are not licensed for use in children, and safety data has been derived mainly from adult studies. There is a theoretical possibility that children may be more vulnerable to the systemic side effects of ocularly applied agents because of their smaller body mass. A discussion of the mechanisms of how topical application of timolol led to adverse cardiac and central nervous system reactions in a child illustrates how topical agents can be serious players in paediatric drug toxicity.

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Introduction

Timolol is a β blocker which is used ophthalmically in the treatment of glaucoma. It is not licensed for use in children, but several case series have shown it to be effective in reducing intraocular pressure in paediatric glaucoma[1-4].

Safety data for timolol in children has been derived largely from use in adults. It is well known that administration of drugs by the ocular route can result in systemic absorption with the possibility of systemic effects[5,6]. Children may be particularly vulnerable to systemic side effects of topical agents as most topical doses are not weight adjusted, leading to higher systemic concentrations in view of their relatively smaller body mass[7]. Thus, seemingly "trivial" amounts of topically administered drugs can lead to systemic toxicity and drug interactions, as illustrated by the case below.

Case report

An 8 month old boy was brought into the children's emergency department with excessive lethargy and floppiness; his parents had also noted that his heart rate was particularly low. He was on a maintenance dose of propranolol 10 mg twice daily (2.5 mg/kg/day), on which his heart rate was usually in the range of 85–100 beats per minute.

On examination the child was hypotonic and difficult to rouse, though apyrexial with normal blood glucose and no systemic features of infection. His pupils were noted to be constricted bilaterally. His respiratory rate was low for his age at 20 breaths per minute, but he was maintaining good oxygen saturations of above 94% in air. His heart rate was 72 beats per minute, significantly low for a child of his age, taking into consideration the therapeutic β blockade. His blood pressure was

initially low at 60/40, and his peripheries were cold with thready peripheral pulses. Capillary refill was prolonged at 2.5–3 seconds. A capillary blood gas showed a mild metabolic acidosis with a base excess of –8.

In view of the signs of excessive β blockade, a thorough drug history was taken. The child's parents confirmed that he had been given his normal dose of propranolol, and that he was on no other medication apart from normal saline nose drops (two drops per nostril as necessary) for a blocked nose caused by a mild viral illness. At this stage the child's grandmother volunteered that she had left her bottle of glaucoma eye drops (timolol 0.5%), which bore a remarkable similarity to the saline nose drops, in the bathroom cabinet. The child's mother realised that she had mistakenly given the child two drops of timolol per nostril about an hour before the child had become unwell.

A diagnosis of excessive β blockade caused by a drug interaction was made and the child was admitted to the high dependency unit for observation. A bolus of 10 ml/kg of 0.9% saline was given, after which his blood pressure remained within the normal range. He was on maintenance intravenous fluids overnight. Propranolol was omitted for 24 hours, and his level of consciousness and heart rate recovered completely after 16 hours. The time to recovery equates to 4 times the half life of timolol, after which time plasma levels are expected to be negligible.

Discussion

Propranolol is a non-selective β adrenergic receptor blocker. It acts as a class II anti-arrhythmic drug through membrane stabilising activity that decreases the automaticity of contractions and slows conduction through the atrio-ventricular (AV) node. Propranolol has been used extensively in children with paroxysmal supraventricular tachycardias caused by AV re-entry pathways.

Timolol is a non-selective β blocker which is used orally to treat hypertension and topically as an ophthalmic solution to treat glaucoma. It decreases intraocular pressure in glaucoma by decreasing aqueous humour secretion from the ciliary epithelium. Timolol has been demonstrated to have 8 times the potency of propanolol in β blockade[8].

Toxicity with timolol

Systemic administration of timolol can lead to side effects typical of non-selective β blockade, and reported systemic side effects in adults include bradycardia, hypotension, lethargy, confusion, abdominal pain, diarrhoea and bronchospasm[9]. Timolol should be used with caution in patients with a history of cardiovascular disease, asthma, and those receiving systemic beta blockers or verapamil[5].

Toxicity after oral ingestion of β blockers has been well documented in children. A 7 year retrospective review of acute β blocker exposures in children at a regional poison centre in the US showed that mild to moderate symptoms occurred in eight of the 378 exposed children. Symptoms described were lethargy, bradycardia and hypotension[10].

Systemic toxicity with topical timolol has been less well described in children. Although the timolol product information suggests that children may be more susceptible to systemic side effects, a Medline and Embase search (1966 to August 2005) found only two other published case reports in the literature of significant systemic toxicity in children after the administration of timolol eye drops[1,12]. One of the cases was an 18 month old child who presented with bradycardia, respiratory distress and cyanosis 30 minutes after the administration of timolol eye drops[11]. The other case report described apnoeic spells in a 2 week old premature child with congenital glaucoma given timolol; this was probably as a result of central nervous system toxicity in an immature brain[12]. Our case is unique in that it describes cardiac and central nervous system toxicity after the inadvertent administration of timolol eye drops to a child already on systemic β blocker therapy.

Acute overdosage with β blockers should be managed in hospital, with ventilatory and cardiovascular support as necessary. Severe bradycardia and hypotension should be treated with intravenous atropine; cardiogenic shock unresponsive to atropine should be treated with intravenous glucagon[13]. Intravenous isoprenaline and cardiac pacemakers may be used to increase the heart rate. Symptomatic bronchospasm should be treated with β_2 agonists in the first place; intravenous aminophylline may be necessary.

Systemic absorption of timolol eye drops

Timolol eye drops can be absorbed systemically into the conjunctival vessels, and via the nasolacrimal duct system through the nasal epithelium. Some of the drug passing through the nasolacrimal system can also be swallowed and absorbed via the stomach[6]. The 0.5% topical solution contains 5 mg timolol per ml. The recommended dose is one drop in each eye twice a day, and each drop

contains 200 microg[9]. In comparison, the oral dose to treat hypertension is 5–30 mg twice daily. Peak plasma levels are reached 1–2 hours after oral administration,and the plasma half life of timolol is approximately 4 hours[14].

In a study using healthy volunteers the plasma concentration of timolol after the administration of one drop of the 0.5% solution in each eye (total dose 400 microg) was found to be 0.3–0.5 ng/ml. In comparison, plasma concentration after a 5 mg oral dose was found to be 10–20 ng/ml[9]. This equates to approximately 50% bioavailability systemically after intraocular administration in comparison to oral administration. Other reports from healthy adult volunteer studies have shown the biovailability of topical timolol to be even higher at 70–80%[15].

The plasma concentrations reached after intraocular administration of timolol seem so trivial that one could easily question whether the erroneous administration of topical timolol to a child carries any significance at all. However, studies in healthy volunteers concluded that timolol at plasma concentrations below 1 ng/ml competitively antagonised cardiac and non-cardiac effects of isoproterenol (a potent beta receptor agonist) infusions[16]. This suggests that beta blockade can be caused at relatively low plasma levels of timolol, even those achieved from systemic absorption after ocular application. In children, the smaller body mass leads to potentially higher concentrations of drug. For the child in our case report, four drops of 0.5% ophthalmic timolol in an 8 kg child would have been sufficient to reach plasma levels for β blockade.

Nasal absorption

The fact that timolol was administered nasally may well have increased the systemic availability of the drug above that expected from ocular administration. The nasal cavity has a large surface area and is richly vascularised, providing the means for rapid drug transport into the systemic circulation[17]. Moreover, absorption via the nasal epithelium avoids first pass hepatic metabolism. Some drugs given nasally may gain direct access to the brain via the olfactory nerve tract[18].

Pharmacokinetic factors

Timolol is metabolised extensively in the liver, primarily by the cytochrome P450 2D6, and up to 80% is excreted by the kidney, mainly as metabolites[14]. Acquisition of adult glomerular filtration rate as well as full maturation of most hepatic isoenzymes is only reached at 8–12 months of age[19]. Metabolic and excretory immaturity may still have played a role in enhanced systemic toxicity in an 8 month old child.

Cytochrome P450 2D6 is known to have genetic polymorphisms leading to phenotypes with poor or extensive metabolism. In healthy volunteers given timolol eye drops, those with poor metabolising genotypes had higher maximum plasma concentrations and longer elimination half lives than extensive metabolisers[20]. Although 2D6 genotype is not routinely tested and was not tested in our patient, poor metabolisers may well be more prone to systemic adverse effects and drug interactions.

Conclusion

This case report has demonstrated how acute cardiac and central nervous system toxicity can occur after "regular" doses of topical timolol in a child. The risk of toxicity is increased with intercurrent medications which can cause a pharmacological interaction. Topical agents should be remembered as a potential cause of systemic toxicity, hence efforts should be made to reduce systemic absorption, for example by occluding the nasolacrimal duct after administration of eye drops. Moreover, this case has illustrated that different medications can be found in similar looking containers (in this case ophthalmic timolol and saline nose drops), emphasising the need for clear labelling and careful checking of drugs given to children.

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