Drugs and the eye

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For most ophthalmic procedures, surgeons require an immobile patient, akinesia, a normal (16 ± 5 mmHg) or low intra-ocular pressure (IOP) and analgesia. It is the role of the anaesthetist to ensure that these conditions are met whilst maintaining patient safety. However, adverse anaesthetic practice or inappropriate administration of anaesthetic drugs may cause a deleterious rise in IOP, which can cause permanent damage to the eye. This is particularly so in the case of intra-ocular procedures and perforating eye injury, where sudden decompression and prolapse of the lens, iris or vitreous can occur through the surgical incision or perforation. The main determinants of IOP, which is the tension exerted by the contents of the eye on the scleral envelope, are: (i) dynamic equilibrium of aqueous humour production and drainage, (ii) intra-ocular blood volume, and (iii) scleral capacity and rigidity, including extra-ocular muscle tone.

Furthermore, many topical ophthalmic drugs used by the ophthalmologist may have systemic effects of interest to the anaesthetist and be of import to patient safety.

Table 1 Effect of drugs on intra-ocular pressure

Decrease IOP
Opioids: alfentanil, fentanyl, morphine, remifentanil, sufentanil
Induction agents: thiopental, propofol, etomidate
Inhalational agents: halothane, enflurane, isoflurane, sevoflurane, desflurane
Muscle relaxants: vecuronium, rocuronium, pancuronium
Benzodiazepines: diazepam i.v.
Miscellaneous: lidocaine i.v., nifedipine s.l.
Increase IOP
Induction agents: ketamine
Muscle relaxants: succinylcholine
Metoclopramide
No change in IOP
Benzodiazepines: oral preparations, midazolam i.v.
Anticholinergics
Muscle relaxants: atracurium
Nitrous oxide
Anticholinesterases: neostigmine

Key points

Intra-ocular pressure (IOP) is important in ophthalmic surgery

Except ketamine, all intravenous and inhalational anaesthetic agents in present use reduce IOP

Succinylcholine causes a rise in IOP which may lead to further loss of vision in open eye injury

Drugs administered topically in the eye have uncommon but important systemic side-effects.

Effects of anaesthetic drugs on the eye

The effects of these drugs on IOP are summarised in Table 1.

Premedication

Benzodiazepines have sedative and centrally-mediated muscle relaxing properties. Oral preparations do not appear to cause a fall in IOP, though they may attenuate the rise in IOP associated with laryngoscopy and intubation. When given intravenously, diazepam produces a fall in IOP lasting less than 10 min. Midazolam administered i.v. pre-induction has no effect on IOP.

Anticholinergics, given as antisialogogues, have little effect on IOP when given intramuscularly before arrival at the operating theatre or intravenously at induction.

By reducing postoperative nausea and vomiting and consequent rises in central venous pressure, anti-emetics have beneficial effects on IOP. Metoclopramide, given i.v. pre-induction, may cause a small rise in IOP lasting about 30 min. Ondansetron has no effect on IOP when given prior to induction and is, therefore, the anti-emetic of choice in perforating eye injuries.

Induction agents

All intravenous induction agents lower IOP, except ketamine. Ketamine causes a rise in IOP, probably by an increase in systemic blood pressure, choroidal blood volume and contraction of extra-ocular muscles. Thiopental, propofol and etomidate all cause a fall in IOP. The fall is greatest with propofol, but at the cost of a greater reduction in arterial pressure. Induction agents which cause myoclonus, such as etomidate, should not be given in perforating eye injuries.

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Maintenance of anaesthesia

Nitrous oxide does not have a direct effect on IOP. However, it should be avoided in procedures for retinal detachments in which intravitreal injections of gases such as air or sulphur hexafluoride are used. Nitrous oxide, because it is more soluble than nitrogen, will diffuse into any air-filled space faster than nitrogen can leave, which causes an increase in IOP. Postoperatively, the converse occurs; nitrous oxide diffuses out of the gas-containing space more quickly than nitrogen can enter, impairing the outcome of the procedure.

Volatile anaesthetic agents, halothane, enflurane, isoflurane, sevoflurane and desflurane have all been shown to reduce IOP in a dose-dependant manner by up to 50% of baseline values. In the case of sevoflurane, a reduction in IOP occurs despite a paradoxical reduction in intra-ocular compliance. Sevoflurane, when compared with halothane in children undergoing strabismus surgery, has been shown to be associated with a decreased incidence of dysrhythmias and bradycardia attributable to the oculocardiac reflex. In spontaneously breathing patients, it is preferable to avoid agents prone to cause airway irritation since coughing will cause large increases in IOP irrespective of the particular agent or relative depth of anaesthesia.

Neuromuscular blocking agents

It is important to distinguish the effects of neuromuscular blocking agents themselves on IOP and the associated effects of manoeuvres such as laryngoscopy and endotracheal intubation, which usually accompany their administration. These manoeuvres cause a rise in IOP due to systemic hypertension and straining on the tracheal tube if relaxation is not ideal.

Succinylcholine is as yet unsurpassed in rapidly providing ideal intubating conditions with a short duration of effect. It has, however, long been known to cause an increase in IOP of approximately 8–10 mmHg for about 5–10 min after administration. The rise in IOP due to succinylcholine occurs after the initial reduction in IOP which accompanies administration of an induction agent. IOP does not usually rise after the administration of succinylcholine to pre-induction base-line values, though this cannot always be relied upon. This has led to a long-standing debate about the appropriateness of its use for patients with open globe injuries. The decision to use succinylcholine in an emergency case or in a patient at high risk of aspiration should be one based on the balance between the risk to the eye and benefit in terms of prevention of aspiration or failed intubation.

The cause of the rise in IOP due to succinylcholine has traditionally been ascribed to the increase in extra-ocular muscle tone caused by the drug. This notion has been challenged by some investigators who have shown an increase in IOP after succinylcholine with the extra-ocular muscles detached in subjects undergoing enucleation. Succinylcholine may, therefore, have a direct effect on choroidal blood volume or on aqueous humour formation or drainage. Several agents have been investigated which have been shown to obtund the rise in IOP which accompanies administration of succinylcholine and intubation (*vide infra*).

Non-depolarising muscle relaxants cause a reduction in IOP during steady-state anaesthesia due to their effect on extra-ocular muscles. Rocuronium is a non-depolarising muscle relaxant with a short onset time which does not cause a rise in IOP. It has been proposed as an alternative to succinylcholine in open eye injury and in patients at risk of aspiration undergoing eye procedures. To produce reliable and rapid conditions for intubation, however, a dose 3 times the ED_{95} is required (0.9 mg kg^{-1}). This may cause problems in patients who are unexpectedly difficult to intubate since the duration of action of this dose is considerably longer than that of succinylcholine.

Other commonly used non-depolarising muscle relaxants such as atracurium and vecuronium have been shown to produce little change or to reduce IOP to varying degrees, principally due to their paralysing effect on the extra-ocular muscles. Atracurium is a suitable agent for use in the elderly presenting for eye surgery because of its predictable onset and offset time. These agents do not prevent the rise in IOP which accompanies endotracheal intubation.

Opioids

Ocular surgery is often not particularly stimulating in nature. Opioids are used to prevent the rise in IOP which accompanies intubation, in addition to providing intra- and postoperative analgesia. The mechanisms by which opioids may decrease IOP include relaxing extra-ocular muscles and miosis (improving aqueous drainage). They may also decrease IOP by reducing arterial pressure, though only if systolic blood pressure falls to less than 90 mmHg.

Alfentanil at doses of 10–40 μg kg^{-1} prevents the rise in IOP associated with laryngoscopy and intubation following induction with propofol and muscle relaxation with either succinylcholine or vecuronium. Fentanyl prevents the rise in IOP due to intubation, when used at a dose of 5 μg kg^{-1}. However, at these doses, bradycardia, intra-operative hypotension and postoperative nausea and vomiting may be problematic, particularly in elderly patients. Fentanyl 2.5 μg kg^{-1} also prevents the rise in IOP with intubation but only when used in combination with lidocaine

1.5 mg kg^{-1} spray to the larynx; a manoeuvre not suited to rapid sequence induction of anaesthesia. In North America, sufentanil 1 μg kg^{-1} has been used to similar effect.

Remifentanil is an ultra-short acting μ-receptor agonist with a rapid onset of action. Its ester linkage renders it susceptible to hydrolysis by tissue esterases producing a half-life at the site of action of less than 10 min. Its pharmacokinetic profile is, therefore, well suited to obtunding the rise in IOP which accompanies laryngoscopy and intubation. Remifentanil 1 μg kg^{-1}, administered over 30 s before induction with thiopentone and succinylcholine, attenuates the rise in IOP after intubation to levels less than those recorded prior to induction. Bradycardia, respiratory depression, muscle rigidity and nausea and vomiting can occur but the significance of these problems may have been exaggerated.

Other agents

Nifedipine 10 mg given sublingually 20 min prior to induction has been reported to attenuate the rise in IOP due to succinylcholine and intubation, though it has not been validated against opioids or in patients with eye disease. Similarly, lidocaine 2 mg kg^{-1} given intravenously 90 s prior to intubation suppresses the rise in IOP associated with intubation.

Systemic effects of drugs used in ophthalmic surgery

Pharmacokinetics and pharmacodynamics

Systemic absorption of topically applied ophthalmic drugs may occur via the conjunctival sac, nasal mucosa or gastrointestinal tract. Diffusion into the circulation occurs slowly via conjunctival capillaries into vessels that eventually drain into ophthalmic and facial veins. Eye drops reach the nasal mucosa via the puncta of the eye and the nasolacrimal duct. Absorption is comparable in speed to that of an i.v. injection. Applying finger pressure over the inner canthus of the eye can reduce absorption. Occluding the nasolacrimal duct in this way for 5 min reduces systemic absorption of drugs by up to two-thirds. Drugs absorbed by the above two routes do not undergo first-pass metabolism in the liver and plasma concentrations may, therefore, be unexpectedly high. Finally, drops which reach the nasopharynx are swallowed by the patient and are subsequently absorbed by the gastrointestinal tract.

Drops from eye droppers vary greatly in size (15–40 drops ml^{-1}) and in the dose per drop which they deliver. Therefore, a toxic dose may easily be administered. Increased systemic absorption occurs from eyes which are hyperaemic or dry and when drugs are administered topically in the supine patient. Children and elderly patients may be less tolerant to agents affecting the cardiovascular system. Serious pressor reactions can follow the administration of catecholamines.

The classes of drugs used in ophthalmic surgery are summarised in Table 2.

Table 2 Topical and miscellaneous drugs used in ophthalmology

Sympathomimetics: phenylephrine, epinephrine, dipivefrine, brimonidine, apraclonidine
Parasympatholytics: atropine, homatropine, cyclopentolate, tropicamide
Parasympathomimetics: pilocarpine, carbachol, acetylcholine
Anticholinesterases: ecothiopate
β-Adrenoreceptor antagonists: timolol, betaxolol, carteolol, levobunolol, metipranolol
Local anaesthetics: cocaine
Diuretics: acetazolamide, dorzolamide, brinzolamide
Steroids
Antibiotics: chloramphenicol

Sympathomimetics

Phenylephrine (2.5%, 10%) is used to facilitate examination of the fundus by causing pupillary dilatation (mydriasis). Epinephrine 1%, 2%, dipivefrine 0.1% (a pro-drug of epinephrine), brimonidine 0.2% and apraclonidine 0.5%, 1% (α_2-adrenoreceptor agonists) are all used in the treatment of chronic open-angle glaucoma. They act by reducing the rate of production of aqueous humour and increase outflow through the trabecular meshwork.

Their systemic side effects include hypertension, arrhythmias and coronary artery vasospasm. They should be used with great caution in the elderly, in children and in those with pre-existing cardiovascular or cerebrovascular disease. The 10% phenylephrine preparation should not be used prior to general anaesthesia. The myocardium is sensitised to these agents and rendered arrhythmogenic by volatile agents (in particular halothane), by acidaemia and hypoxaemia (*e.g.* hypoventilation) and by anaesthetic manoeuvres such as laryngoscopy and intubation. Patients taking oral β-adrenoreceptor blocking agents may experience hypertensive crises from concurrent administration of phenylephrine, possibly due to reduced baroreceptor responsiveness or absence of β-agonist mediated vasodilatation. Epinephrine is often added to the ocular irrigation fluid during cataract extraction and posterior segment surgery. Drug administration errors could occur in these circumstances.

Adrenoreceptor blocking drugs

Timolol (0.25%, 0.5%), betaxolol (0.25%, 0.5%), carteolol (1%, 2%) and levobunolol (0.5%, 1.4%) are β-adrenoreceptor blocking drugs used in the treatment of chronic open-angle glaucoma. They act by reducing the rate of aqueous production. Systemic absorption can cause bronchospasm, bradycardia, hypotension and cardiac failure. When given topically, first-pass metabolism by the liver is avoided and significant plasma concentrations can be achieved. The Committee for Safety of Medicines has advised that even cardioselective agents should not be used in patients with asthma, heart failure or heart block. The possibility of interactions with verapamil and other calcium channel antagonists should be noted. Timolol can aggravate the symptoms of myaesthenia and can mask symptoms of hypoglycaemia in diabetic patients. Other agents which can also cause bradycardias, such as alfentanil and fentanyl, should be used with caution during general anaesthesia.

Parasympatholytics

Atropine (0.5%, 1%), homatropine (1%, 2%), cyclopentolate (0.5%, 1%) and tropicamide (0.5%, 1%) are used as mydriatics. Systemic absorption leading to side effects is more common with atropine. Peripheral anticholinergic symptoms such as dry mouth, flushing, tachycardia and arrhythmia occur as do central nervous system side effects such as confusion and ataxia. These symptoms occur particularly in children after repeated doses, but may not arise until minutes or hours after administration and may last for up to 24 h. Convulsions have been reported after application of ocular atropine. Tropicamide and homatropine have a shorter duration and have less marked anticholinergic effects than atropine. Side-effects are uncommon, but can occur especially in children. Confusion and even acute psychosis has occurred after administration of cyclopentolate. It is thought that the dimethylated side chain on the molecule is responsible for the preponderance of central side-effects.

Parasympathomimetics

Pilocarpine (0.5–4%) and carbachol (3%) act by causing contraction of the ciliary muscle which opens up trabecular drainage channels. They are used in the management of intraocular hypertension. Acetylcholine (1% for intra-ocular irrigation) is occasionally used to prepare the eye for anterior segment surgery requiring rapid, complete miosis. Although rare, systemic side effects from these drugs have been reported including exacerbation of asthma and bronchospasm, excessive diaphoresis, nausea and vomiting, bradycardia and hypotension. Acetylcholine solution can theoretically cause resistance to non-depolarising muscle relaxants and reversal of block.

Ecothiopate, a long-acting anticholinesterase of the organophosphorus group, has been withdrawn from general use in the UK, but remains available on a named-patient basis for use under expert supervision. Cholinergic side effects have been described and its use should be discontinued for at least 3–4 weeks prior to anaesthesia involving drugs metabolised by plasma cholinesterase.

Local anaesthetics

Many ophthalmic procedures are carried out under local anaesthesia without ill effects. Use of topical cocaine solutions, however, which are occasionally used for dacryocystorhinostomy, has been reported to be associated with systemic absorption and significant adverse side effects. When using cocaine, the dose should not exceed 1.5 mg kg^{-1}. Peak plasma concentrations occur at 15–60 min after administration and can be detected for up to 6 h in plasma. Systemic reactions can occur with a dose as little as 20 mg. These include confusion, apprehension, convulsions and hyperpyrexia. Cardiovascular toxicity manifests as hypertension, tachycardia and arrhythmias but can be treated symptomatically with benzodiazepines and α-adrenoreceptor blocking agents. Cocaine should not be used in patients taking monoamine oxidase inhibitors, tricyclic antidepressants or other drugs which modify adrenergic function.

Corticosteroids

Prednisolone 0.5% and dexamethasone 0.1% are absorbed systemically when given topically. There is no unequivocal evidence of clinically significant consequences.

Miscellaneous agents

Felypressin is a synthetic polypeptide which is contained in some injectable preparations of prilocaine. It is a vasoconstrictor which has been reported rarely to produce hypertension and other pressor responses.

Diuretics, particularly carbonic anhydrase inhibitors, are used i.v. or orally in the management of raised IOP. Acetazolamide reduces aqueous humour formation. It was originally developed as a sulphonamide derivative and, as such, blood disorders and rashes occasionally accompany its use. It can also reduce the effectiveness of oral hypoglycaemic agents and cause electrolyte disturbances. It increases the pH of urine thereby reducing urinary excretion of basic drugs. Dorzolamide and brinzolamide are recently introduced topical carbonic anhydrase inhibitors and

are sometimes used in the long-term control of raised IOP in those patients who cannot tolerate topical β-blockers. Although systemic side effects are less common than with acetazolamide, sulphonamide-like idiosyncratic side effects do occur, albeit rarely.

Topical chloramphenicol (0.5%) can cause blood dyscrasias and a full blood count should be checked. Fortunately, the anaemia which rarely accompanies its use resolves after cessation of therapy.

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See multiple choice questions 99–103.