

Pharmacology

In this section

This section covers the following topics:

- Terminology
 - Fluorescein & ICG
 - Learning Outcomes Fluorescein
 - Learning Outcomes ICG
 - Research Assignment: Fluorescein & ICG
 - Mydriatics & Cycloplegia
 - Learning Outcomes Mydriatics
 - Research Assignment: Mydriatics
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Terminology

- Agonist - A drug having an effect when acting on a drug receptor.
 - Accommodation - Ability of the lens to change for near vision.
 - Acetyl choline - Neural transmitter of parasympathetic nervous system.
 - Adrenergic - Relates to drugs or transmitters action on the sympathetic nervous system.
 - Antagonist - A drug occupying a receptor thus blocking the effect of the agonist.
 - Blocker - See antagonist.
 - Cholinergic - Relates to drugs or transmitters action on the parasympathetic nervous system.
 - Cycloplegic - A drug freezing lens accommodation.
 - Duration of action - Period of time over which drug is effective.
 - Muscarinic - A classification of receptors found in the eye triggered by the parasympathetic nervous system.
 - Mydriasis - Dilation of the pupil.
 - Mydriatic - A drug producing mydriasis.
 - Onset of drug action - When drug starts to have its effect.
 - Parasympathetic nervous system - One of two branches of the autonomic nervous system.
 - Recovery - Time by which drug no longer has an effect.
 - Sympathetic nervous system - One of two branches of the autonomic nervous system.
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Fluorescein & ICG: Fluorescein and Indocyanine dyes for angiography

Fluorescein sodium

Fluorescein sodium is a yellow water-soluble dibasic acid xanthine dye which produces an intense green fluorescent colour in alkaline solution.(pH less than 5). It is used as a topical eyedrop to show defects in corneal epithelium but as a diagnostic aid in ophthalmic angiography it is given by direct intravenous injection. Fluorescein angiography allows examination of the fundus and assessment of iris and retinal blood vessels. Oral fluorescein has been used for diagnosis of retinal vascular disease.

Contraindications;Hypersensitivity to fluorescein. A prior reaction to fluorescein should be entered in the patient's notes.

Cautions; Where patient has a history of hypersensitivity, allergies or asthma. Discontinue if signs of sensitivity develop.

Pregnancy; Category C. Avoid during pregnancy, especially in the first 3 months. There are no reports of fetal complications during pregnancy.

Breastfeeding; Fluorescein is excreted in breast milk.

Adverse Reactions; The injection can cause nausea, headache, gastro-intestinal upset & vomiting. Signs of hypersensitivity include hypotension. There have been incidents of cardiac arrest, thrombophlebitis at injection site, severe shock and convulsions. Hives, itching, bronchospasm, anaphylaxis, fever, transient shortness of breath and dizziness may occur. Where a serious adverse event occurs report it using the Yellow Card Scheme. (www.mhra.nhs.uk ») Extravasation at injection site causes intense pain locally and a dull aching pain in the injected arm.

Patient information; May give patient a strong taste in use. Can cause temporary yellowing of the skin which fades in 6 to 12 hours. Urine becomes bright yellow up to 36 hours after injection of the dye.

Off license use; There is no licensed product available in the United Kingdom for administration of fluorescein for angiography by intravenous or oral route. Companies making these agents therefore do not have a duty to provide professional information or written information for patients.(Ophthalmic Drug Facts 2000)

Administration and dosage; Sodium fluorescein 10% or 20% injection is given rapidly into the antecubital vein, taking precautions to avoid extravasation. If the needle has extravasated stop the injection. When injection of the dye is complete luminescence appears in the retina and choroid vessels in 9 to 15 seconds. If allergy is suspected, perform an intradermal skin test prior to i.v. administration. 0.05ml is injected intradermally and the site examined after 30-60 minutes.

I.V. doses; Adult : 500 - 750mg ; Children: 7.5mg/kg

Oral fluorescein has been used to study lesions of the fundus. Dye begins to appear at the fundus at 15 minutes post ingestion with maximum effect at 45-60 minutes. Fasting can enhance dye serum concentration. Oral administration has a lower incidence of side effects.

Oral doses; 1 to 2 grams as powder, capsules or as a solution in fruit juice.(Noble MJ et al 1984)

Extravasation; Because of its high pH extravasation can result in severe local tissue damage. Complications can include sloughing of the skin, superficial phlebitis and toxic neuritis along the curve of the antecubital area. Administration procedure should involve drawing back blood or using sterile saline to check for correct placement of the cannula before injecting the dye. Solutions should not be used if they contain precipitate and any unused solution should be discarded.

Management of adverse events; Procedures should be in place for the care of patients experiencing adverse events and drugs such as adrenaline 1 in 1000, antihistamines, steroids and oxygen should be available.

Complications of intravenous fluorescein angiography; Based on the Fluorescein Angiography Complication Survey (FACS) (1984), complications are classified as mild, moderate or severe. FACS evaluated 222,000 cases in 1984 and the findings are tabled below.

Mild	Nausea or extravasation resolving rapidly	Reassurance.
Moderate (1 in 63)	Urticaria, fainting, taking some time to resolve but no long term problems	Consider systemic antihistamines, e.g. diphenhydramine or chlorpheniramine . Raise legs, consider smelling salts.

Severe (1 in 9,000- death 1 in 222,000)	Respiratory, cardiac, neurological- prolonged.	Treat intensively as threat to patient safety.
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Butner and Macpherson (1983) reported 241 adverse reactions in 5000 patients. Pacurariu (1982) in a study of 2,600 patients observed men and younger patients to experience side effects more frequently. Cavallerno (1996) has recommended that the procedure should not be performed on pregnant or nursing mothers.

Managing side effects

Side effects such as the warm flush or early nausea within 30 seconds of injection can be explained to the patient in advance. There is no conclusive benefit to giving antihistamines before hand although this may be justified for patients with a history of urticaria. For some patients, anxiety surrounding the whole experience may need controlling with a dose of a benzodiazepine, such as diazepam. It is good practice to have a local policy in place for the management of patients should extravasation occur.

Indocyanine Green

It is a sterile, water soluble, tricarboyanine dye with a peak spectral absorption and emission at 800 to 810 nm in blood or plasma. Indocyanine green contains about 5% sodium iodide. Transmission of energy by the pigment epithelium is more efficient than in visible light. As the dye is nearly 98% bound to blood proteins there is minimal leakage of dye from the choroidal vessels. It is useful in angiography of the choroid. Outside of ophthalmic use it is used to determine cardiac output, liver function and liver blood flow.

Contra-indications; Prior allergy to shell fish, iodine or ICG.

Warnings; Pregnancy; category C- It is not known if ICG can harm the foetus or can affect the normal gestation. Avoid using in the first 3 months of pregnancy. Breastfeeding; It is not know if this dye is excreted in breast milk.

Precautions; Radioactive iodine uptake studies should not be done within a week of having ICG. Use with caution in patients with a prior allergy to iodides.

Adverse Reactions; Anaphylaxis or urticaria has occurred in patients with no prior allergy to iodides. Ensure resuscitation equipment and trained staff are available.

Administration and dosage; Use 40mg ICG in 2ml of aqueous solvent. It is stable for up to 10 hours once reconstituted and must be protected from light.

Patient information; Symptoms reported include restlessness, itching, urticaria, tachycardia, hypotension and breathlessness. Very rarely injections of ICG can cause nausea and anaphylaxis. There are no known effects with ICG that impair ability to drive. Alcohol should be avoided before and after ICG angiography.

Toxicity of ICG; Hope-Ross and colleagues (1994) evaluated 1,923 procedures in 1,226 patients and identified a 0.3% rate of adverse reactions. Regillo's study of literature identified 18 severe reactions and 3 deaths. An estimated incidence of death for ICG approximates at 1 in 300,000 patients compared to 1 in 200,000 patients with iv fluorescein.

Learning Outcomes Fluorescein

Pharmacology for Ophthalmic Photographers. Learning outcomes-Fluorescein IV and oral;

1. To be familiar with the fluorescein products available for angiography.
2. To be aware of the doses and time course of such agents.
3. To be able to inform patients of likely topical and systemic side effects relevant to the clinical setting.
4. To be aware of medical conditions or drug histories which would contraindicate the use of fluorescein.
5. To be aware of the precautions which need to be taken to minimise cross contamination and prevent infection in the clinical setting.
6. To be aware of adverse reactions and the mechanism for reporting adverse events.
7. To be aware of the procedures and protocols laid down by local trust management specifying the dose, strength and administration of fluorescein.
8. To be aware of appropriate storage and safe handling of ophthalmic medicines.

9. To be familiar with the local care plan for patients should extravasation of the dye occur.
 10. To be aware of the responsibilities surrounding the use of unlicensed products both within the trust and the clinic setting.
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Learning Outcomes ICG

Pharmacology for Ophthalmic Photographers.

Learning outcomes-Indocyanine Green;

1. To be familiar with the forms of product available for angiography.
 2. To be aware of the doses and time course of the dye.
 3. To be able to inform patients of likely topical and systemic side effects relevant to the clinical setting.
 4. To be aware of medical conditions or drug histories which would contraindicate the use of Indocyanine Green.
 5. To be aware of the precautions which need to be taken to minimise cross contamination and prevent infection in the clinical setting.
 6. To be aware of adverse reactions and the mechanism for reporting adverse events.
 7. To be aware of the procedures and protocols laid down by local trust management specifying the dose, strength and administration of fluorescein.
 8. To be aware of appropriate storage and safe handling of ophthalmic medicines.
 9. To be familiar with the local care plan for patients should extravasation of the dye occur.
 10. To be aware of the responsibilities surrounding the use of unlicensed products both within the trust and the clinic setting.
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Research Assignment: Fluorescein & ICG

Research assignment- fluorescein & ICG

Fluorescein

Butner and McPherson reported 241 adverse reactions in 5,000 consecutive angiograms, an incidence of 4.82%, with no life threatening reactions. The FACS study suggests a serious incident rate of 1 in 9000.

Use the recommended sources to examine the incidence and severity of adverse reactions experienced. Consider your local work load to predict the number of adverse reactions you are likely to see in a year.

Fluorescein & ICG

It is good practice to have a local policy in place for the management of patients should extravasation occur. Using the internet, drug manufactures and local information sources produce an evidence based policy for prevention and management of dye extravasation.

Indocyanine Green

With approximately 1 million doses of ICG sold, Regillo estimated an incident of death to be 1 in 333,333 compared to 1 in 222,000 for fluorescein angiography. This suggests ICG angiography could be a safer procedure. Carry out an internet search of evidence since these publications to support or disprove this suggestion.

[back to top ^](#)

Mydriatics & Cycloplegia

Pharmacology for Ophthalmic Photographers

Mydriatics and cycloplegics

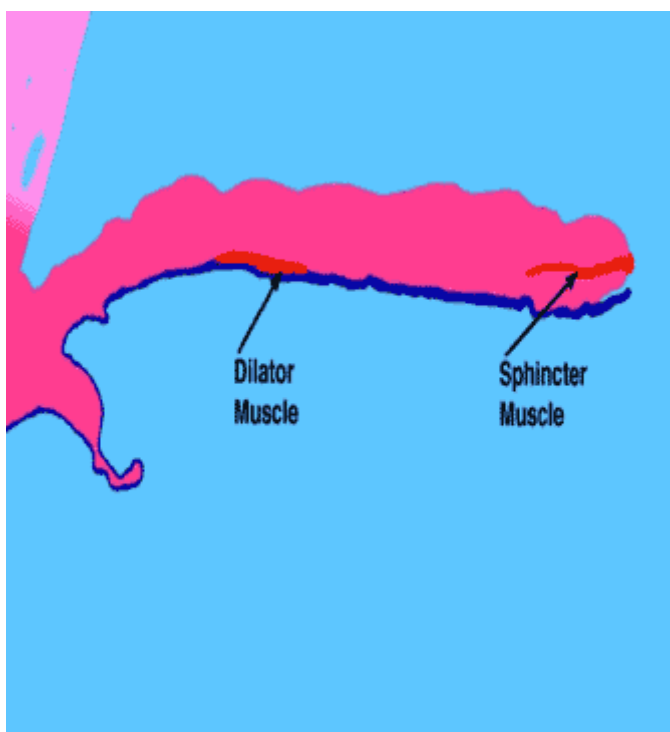
For diagnostic, imaging or photographic purposes these are administered as topical drops. Mydriasis (pupil dilatation) and cycloplegia (paralysis of accommodation) are achieved by drugs effecting on the autonomic nervous system.

Short acting mydriatics such as Tropicamide allow examination of the fundus of the eye. Longer acting agents such as Cyclopentolate and Atropine are preferable for producing cycloplegia for refraction in children (BNF 45, march 2003).

Autonomic nervous system (ANS) and the eye.

Stimulation of the parasympathetic neural supply to the eye results in release of acetyl choline to produce an effect via drug receptors on the iris sphincter and ciliary muscle. Of the different receptor sites, those relevant in the eye for cholinergic action are the muscarinic receptors of which there are five. (M1 to M5). They affect lacrimal glands, cornea and lens as well as pupil size and accommodation. In the human eye over 60% of the receptors are type M3. Cholinergic drugs (muscarinic) mimic the action of acetylcholine or release it. Cholinergic antagonists block the receptors and consequent transmitter release. The normal response of the pupil to light, for example, is neural transmission of acetyl choline to stimulate the sphincter muscle to constrict the pupil. Prior instillation of an anti-cholinergic drug, however, occupies the muscarinic receptors blocking the normal constrictor response.

The sympathetic branch of the ANS responds to sympathomimetic drugs acting on adrenergic receptors. Adrenergic nerve stimulation to the eye increases pupil size, opens the eye wider & affects both ocular blood flow and flow of the aqueous. Adrenergic receptors have become subgrouped into α and β types and these are located at different sites in the eye. α receptors are greater in number in the human iris and β receptor sites are greater on the ciliary muscle. The iris sphincter has no β receptors.



Mydriasis

- Anti-cholinergic effect on sphincter muscle (radial)
- Sympathomimetic effect on dilator muscle

Mydriatics

Anti-cholinergics: Atropine, Cyclopentolate, Homatropine, Tropicamide

Sympathomimetics: Phenylephrine.

Cycloplegic cholinergics antagonists

These agents are used to produce both mydriasis and cycloplegia although mydriasis has a longer onset.

Eyedrops	Action	Clinical uses	Comments
Atropine 0.5%, 1%	Longest acting, up to 7 days	Used for refraction and amblyopia in children	Be aware of toxicity in children if swallowed. Hyperactivity in children
Homatropine 2%	Recovery 1 -3days	Reduces pain due to ciliary spasm	Stings less than cyclopentolate
Cyclopentolate 0.5%, 1%	Recovery within 24 hours	Refraction- useful as time to	Restrict to 0.5% in infants &

		maximum cycloplegia & mydriasis coincide	children with spastic paralysis or brain damage.
Tropicamide 0.5%, 1%	Fastest acting. Maximum mydriasis 20 - 40 minutes.	Routine choice for anterior chamber examination.	Safest where high blood pressure & increased heart rate. Less dependant on iris pigmentation than other anticholinergics.

Phenylephrine added in diabetics where resistance to anticholinergic dilatation

Cholinergic antagonists- side effects and cautions

Local (ocular) effects; blurring, photophobia.

Systemic effects; dry mouth, facial flushing, convulsions in children, restlessness and hallucinations possible in the elderly.

Cautions; allergy, risk of inducing angle closure where prior history, possibility of elevating intra-ocular pressures.

Contra-indications; hypersensitivity to the drug, adhesions (synechiae).

Phenylephrine is an α adrenergic agonist. It contracts iris dilator muscle and the smooth muscle of the conjunctival arterioles, causing blanching. Maximum dilatation is 45 to 60 minutes after instillation. Recovery on average is 3 hours for 2.5% drops and 6 hours for 10% drops. Increased drug concentrations gives more rapid onset but the maximum effect may still take up to 60 minutes. Different rates of mydriasis have been observed between blue eyed and brown eyed individuals. Time to mydriasis is often longer with non caucasian brown eyes. It is likely that the eye pigment absorbs the drug causing both delayed onset and recovery.

Phenylephrine side effects and cautions

Local (ocular) effects; blurring, watering, photophobia, keratitis and rebound miosis (small pupil).

Systemic (whole body) effects; short term raised blood pressure, headache, increased heart rate (tachycardia) and blanching of the skin.

Contraindications to use of 10% phenylephrine; elderly patients with preexisting cardiac disease. Patients taking mono-amine oxidase inhibitor (MAOIs) antidepressants, tricyclics or methyl dopa. Side effects are more likely with the higher concentrations. If administering the drops by soaking onto pledgets 10% should not be used neither should it be given by irrigation.

Learning Outcomes Mydriatics

Pharmacology for Ophthalmic Photographers.

Learning outcomes- Mydriatics and cycloplegics;

1. To be familiar with the range of topical agents used to dilate the pupil or freeze accommodation prior to an ophthalmic visual/ diagnostic procedure.
2. To be aware of the onset and duration of action of such agents.
3. To be able to inform patients of likely topical and systemic side effects relevant to the clinical setting.
4. To be aware of medical conditions or drug histories which would contraindicate the use of a specific agent.
5. To be able to instil drops safely and to be aware of the precautions which need to be taken to minimise cross contamination and prevent infection in the clinical setting.
6. To be aware of adverse reactions and the mechanism for reporting adverse events.

7. To be aware of the procedures and protocols laid down by local trust management specifying the dose, strength and frequency of the authorised drops.
8. To be aware of appropriate storage and safe handling of these ophthalmic medicines.

Research Assignment: Mydriatics

Research assignment

Mydriatics and Cycloplegics

According to the British National Formulary (BNF 45, March 2003); 'Patients should be warned not to drive for 1-2 hours after mydriasis.' Using evidence from the internet and reading list to support you, write a case agreeing or disagreeing with this statement. If you disagree what would be a more appropriate warning when patients ask, 'am I safe to drive? '