**Purpose of review**

Acute angle closure glaucoma is a potentially blinding side effect of a number of local and systemic drugs, including adrenergic, both anticholinergic and cholinergic, antidepressant and antianxiety, sulfa-based, and anticoagulant agents. The purpose of this article is to bring this condition to the attention of clinicians using these compounds as well as ophthalmologists called to see the patient.

**Recent findings**

Acute angle closure glaucoma due to pupillary block, treatable by peripheral iridotomy, can be caused by adrenergic agents, either locally (phenylephrine drops, nasal ephedrine, or nebulized salbutamol) or systemically (epinephrine for anaphylactic shock), drugs with anticholinergic effects including tropicamide and atropine drops, tri and tetracyclic antidepressants, and cholinergic agents like pilocarpine. A novel anticholinergic form is the use of periocular botulinum toxin diffusing back to the ciliary ganglion inhibiting the pupillary sphincter. Sulfa-based drugs (acetazolamide, hydrochlorothiazide, cotrimoxazole, and topiramate) can cause acute angle closure glaucoma by ciliary body edema with anterior rotation of the iris-lens diaphragm. Iridotomy is not effective.

**Summary**

Most attacks of acute angle closure glaucoma involving pupillary block occur in individuals that are unaware that they have narrow iridocorneal angles. Practitioners using any of the above drugs should be aware of their potential to cause acute angle closure.

**Keywords**

acute angle closure glaucoma, adrenergic drugs, central nervous system drugs, drug

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**Introduction**

Acute angle closure glaucoma (AACG) occurs in predisposed individuals (hypermetropia, narrow angle, thick lens) when the pupil is mid dilated. At least one-third of AACG cases are related to an over-the-counter or prescription drug. Drugs with α₁ adrenergic or anticholinergic effects can precipitate attacks of AACG mainly by mydriasis. Some drugs with no pupillary effect induce AACG by ciliochoroidal effusion (sulpha-based drugs and anticoagulants). The new term ‘acute angle closure crisis’ replaces the former ‘acute angle closure glaucoma’ when no glaucomatous optic nerve damage is observed before the attack [1]. We will use both terms in this review.

Both local (ocular drops, nasal and nebulized agents) and systemic drugs (e.g. atropine, adrenaline, ephedrine, some psychoactive and antiepileptic drugs) can induce AACG. Using the PubMed database we reviewed the most recent articles (case reports and reviews) published in English, French and German.

Drugs that can induce AACG should be recognized not only because of the risk of AACG but also because certain drugs can induce intermittent angle closure or exacerbate chronic angle closure glaucoma.

**Adrenergic agents**

Alpha-adrenergic agents cause mydriasis that can precipitate an attack of acute AACG in predisposed individuals that have shallow anterior chambers. Phenylephrine drops are commonly used to induce pupillary dilation for ocular fundus examination and may induce AACG in about 0.03% of nonselected patients [2,3]. Apraclonidine (Iopidine: Alcon, Rueil-Malmaison, France) is an α₂-adrenergic agent that has a minor α₁ effect, causing mild mydriasis [4,5]. We observed two cases of AACG caused or precipitated by apraclonidine drops in predisposed patients (personal report, not published). Dipivephrine (Propine: Allergan France Sas, Mougins, France) also has a mild mydriatic effect.

Cases of AACG have been reported after systemic administration of ephedrine for flu, surgical anaesthesia or epinephrine (adrenaline) to treat anaphylactic shock and ventricular fibrillation. Intake of nasal ephedrine and naphazoline in the acute management of epistaxis can induce AACG, which may be bilateral [6,7]. AACG is believed to result more from the reflux through the ipsilateral nasolacrimal duct than from the absorption through the nasal mucosa, even though plasma levels...
can be similar to those achieved with intravenous administration [8].

Nebulized $\beta_2$-adrenergic agents (salbutamol, albuterol, terbutaline) are used for bronchodilation in patients with asthma or chronic obstructive pulmonary disease. They can increase the intraocular pressure and induce transient angle closure. Stimulating ciliary body $\beta_2$-adrenergic receptors promotes aqueous humour secretion. Angle closure is exacerbated by pupil dilation caused by the parasympathetic inhibitory effect of ipratropium, especially when an anticholinergic drug is frequently connected [9–13]. These drugs can be absorbed through the cornea and the conjunctiva after escaping from a face mask. Properly fitted and positioned masks and hand-held nebulizers can minimize ocular deposition of nebulized medication.

Some other drugs that have indirect sympathomimetic activity can induce AACG: anticholinergic agents (atropine, homatropine and cyclopentolate used to relax the ciliary muscle and dilate the pupil have long-acting anticholinergic action, and more frequently induce AACG [16,17].

**Anticholinergic agents**

Tropicamide is a short-acting anticholinergic commonly used to induce pupil dilation for fundus examination. Atropine, homatropine and cyclopentolate used to relax the ciliary muscle and dilate the pupil have long-acting anticholinergic action, and more frequently induce AACG [16,17].

Ipratropium bromide (Atrovent: Boehringer Ingelheim France, Paris, France) is an antimuscarinic drug usually prescribed in combination with salbutamol in acute exacerbation of chronic obstructive pulmonary disease. Many cases of AACG associated with nebulized ipratropium have been reported [10–13]. Fifty percent of patients with preexisting narrow angles who received a nebulized salbutamol and ipratropium combination manifest transient AACG [11]. As supposed for aerosolized $\beta_2$-adrenergic agents, ipratropium escapes from the face mask, diffuses through the cornea producing pupil dilation and, in eyes with susceptible angles, angle closure [10].

Atropine is often used to treat bradycardia, especially related to general anaesthesia. Postoperative AACG was reported in patients after general anaesthesia for abdominal, orthopaedic, facial and endoscopic surgery [18]. Several factors are likely to induce postoperative AACG in predisposed individuals: anticholinergic drugs (atropine, scopolamine, and muscle relaxants), adrenergic drugs (ephedrine, epinephrine). Moreover, the peroperative period carries the risk of psychological stress and darkness-induced mydriasis that may increase the risk of glaucoma attacks. Ates et al. [19] recommend practising an oblique penlight illumination test by anaesthesiologists to estimate anterior chamber depth and determine the population at risk. Patients at risk for AACG in the postoperative period can be administered topical pilocarpine therapy to prevent any attack. Since symptoms of AACG may be overlooked or misinterpreted in a sedated or comatose patient, any patient who has a red eye and a subjective vision loss postoperatively should be examined urgently.

Corridan et al. [20] reported a case of AACG which occurred shortly after a series of injections of botulinum toxin around the eyelids for blepharospasm. Botulinum toxin injected pericularly diffuses towards the ciliary ganglion and there impedes the cholinergic innervation of the pupil. This complication, though rare, should be taken into consideration in predisposed patients who undergo this procedure.

**Cholinergic agents**

Pilocarpine is used in some forms of glaucoma to constrict the pupil and increase aqueous outflow through the major outflow pathways. It can, however, induce AACG due to anterior movement of the iris-lens diaphragm, thus resulting in complete angle closure [16]. Eyes with zonular weakness or exfoliation syndrome seem to be particularly prone to developing miotic-induced angle closure [21]. Ritch et al. [22] reported chronic angle closure developing after several years of miotic therapy in eyes that initially had wide open angles.

Acetylcholine and carbachol are topical medications used to constrict the pupil during intraocular surgery, especially cataract extraction. They can induce pupillary block in susceptible patients [16].

**Antidepressants, antianxiety agents**

Tri and tetracyclic antidepressants are known to have important anticholinergic side effects. They have frequently been associated with AACG in predisposed individuals [21,23,24].

Selective serotonin reuptake inhibitors (SSRIs) have a lower incidence of cholinergic side effects than tricyclic antidepressants. Nevertheless, many reports of AACG associated with paroxetine [25–29], venlafaxine [30,31,32], fluvoxamine [33], citalopram [34] and escitalopram [35] were reported. The weak anticholinergic and adrenergic activity and the mydriatic effect of increased levels of serotonin are possible mechanisms of AACG. De Guzman et al. [30] and Zelefsky et al. [35] have identified by ultrasonography supraciliary effusion that precipitates the AACG. Ophthalmological consultations should be considered before starting treatment with SSRIs in predisposed patients [36].
Sulfa-based drugs

Some sulfa-based drugs have been associated with rare AACG: acetazolamide [16], hydrochlorothiazide [37], and cotrimoxazole [16].

Topiramate is a sulfamate-substituted monosaccharide antiepileptic agent. Since it was approved in 1995, several case reports have been published addressing its ocular side effects, including AACG, transient myopia and uveal effusion [38–42,43**,44*,45]. The majority of adverse cases have occurred in females (89%), in paediatric patients as well as adults. Eighty-five percent of cases occurred in the first 3 weeks of treatment with topiramate, in five cases within hours after doubling the dose and in only one case it occurred 49 days from the onset of therapy [39]. Patients were typically taking topiramate doses within the normal therapeutic range. In only a few cases was the presentation unilateral. No risk factors are known for this syndrome [41].

The underlying mechanism has been better characterized with ultrasound technology. Ciliary body oedema causes relaxation of the zonules, which allows lens thickening. Anterolateral rotation of the ciliary body about its attachment to the scleral spur leads to anterior displacement of the lens and iris and concomitant shallowing of the anterior chamber. Choroidal detachment and supraciliary effusion are frequently present. Secondary angle closure glaucoma occurs without pupillary block, therefore peripheral iridotomies are ineffective [43**,45,46]. Fluid movement in choroidal effusion could be related to drug-induced changes in membrane potential associated with topiramate. The finding of effusion in only a few patients taking topiramate, however, suggests that it is an idiosyncratic reaction [43**].

The management of topiramate-related AACG requires stopping the drug in concert with the prescribing physician, because decreasing the dose may exacerbate pre-existing systemic conditions. In all reported cases, none has subsided without discontinuation of the drug. If the drug is stopped and medical management is instituted, however, intraocular pressure may return to normal in a period of hours to days [37,38]. If unrecognized as a drug-related event, serious outcomes could occur (seven cases of permanent vision loss have been reported).

Anticoagulants

Acute secondary angle closure glaucoma after massive vitreous, choroidal or subretinal haemorrhage is a rare complication of anticoagulant therapy. Risk factors are overtreatment with anticoagulants, exudative age-related macular degeneration and nanophthalmos [47–49]. Both heparin and low molecular weight heparin (enoxaparin, warfarin) have been reported to cause AACG.

To manage increased intraocular pressure, anticoagulative treatment should be discontinued and the symptoms managed as for AACG. Peripheral iridotomy is not effective in the management. Surgery may be needed to drain choroidal effusion or haemorrhage [46].

Histamine H1 and H2 receptor antagonists

Histamine H1 receptor antagonists (brompheniramine, chlorpheniramine, dexampheniramine, dexchlorpheniramine, dimethindene, pheniramine, tripipramine) are used to treat manifestations of allergic disease. Histamine H2 receptor antagonists (cimetidine, ranitidine) are used to treat gastroesophageal reflux and duodenal ulcers. Both of them have a weak anticholinergic effect, which can induce mydriasis and AACG in predisposed patients [16].

Other drugs

One case of recurrent bilateral AACG after combined consumption of ‘ecstasy’, a synthetic amphetamine derivative, and marijuana in a 29-year-old woman was reported [50]. Ecstasy increases the release of monoamine neurotransmitters (serotonin, noradrenaline and dopamine) and inhibits the uptake of serotonin from the synaptic gap. It induces mydriasis and AACG in predisposed persons.

Yalvac reported two cases of AACG in association with topical administration of latanoprost [51]. He speculates that latanoprost induces a swelling of the ciliary muscle, pushing the iris-lens diaphragm anteriorly and initiating the AACG in predisposed patients.

Conclusion

A variety of drugs can cause AACG in susceptible individuals (Table 1) [52]. Different mechanisms may be at

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<th>Table 1 Classification of drugs inducing acute angle closure glaucoma by administration route</th>
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Source: Tripathi et al. [16].
play, including pupillary block for which a peripheral iridectomy can be curative, ciliary or suprachoroidal effusion, or even vitreous haemorrhage with forward movement of the iris-lens diaphragm and shallowing of the anterior chamber. Iridectomy for these latter causes is ineffective.

The problem is to know which eye is at risk. Most attacks involving pupillary block occur in individuals that are unaware that they have narrow iridocorneal angles. Physicians using these drugs cannot practically send each and every patient to an ophthalmologist for gonioscopy and it is not helpful to ask the patient if they have glaucoma since they would be asymptomatic. With open angle glaucoma, there is virtually no risk of AACG. With angle closure glaucoma already treated by iridotomy, filtering surgery, or cataract extraction, there is also no real risk. There is no ideal solution to the problem except to warn medical practitioners to be wary of patients wearing thick hyperopic glasses that magnify objects. One could also recommend use of the lateral penlight method to estimate anterior chamber depth.

Practitioners using any of the above drugs should be aware of their potential to cause acute angle closure. Any patient presenting with signs or symptoms of AACG should be referred immediately to an ophthalmologist.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 177):

Drug-induced acute angle closure glaucoma  Lachkar and Bouassida  133