Special Article

Drug-Induced Secondary Glaucoma

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Several classes of drugs have potential to cause an elevation of IOP which may occur either by an open-angle mechanism or a close-angle mechanism. Drug-induced elevation of IOP is commonly has an open-angle mechanism. The most commonly recognized medications associated with this mechanism are the corticosteroids. Acute angle closure glaucoma is a potentially blinding side effect of local and systemic drugs, including antipsychotic drugs, antidepressants, monoamine oxidase inhibitors, antihistamines, antiparkinsonian agents, antispasmolytic drugs, mydriatic agents, the sympathetic agents and botulinum toxin, especially in individuals with predisposing narrow angles of the anterior chamber. Sulfamate derivative medications may induce angle closure by a different angle closure mechanism, involving anterior rotation of the ciliary body.

Clinicians should be mindful of the possible drug-induced glaucoma, whether or not it is listed as a contraindication and, if in doubt, ophthalmological consultation is recommended.

Keywords: *Drug-induced glaucoma, Glaucoma*

J Med Assoc Thai 2010; 93 (Suppl. 2): S118-122
Full text. e-Journal: *http://www.mat.or.th/journal*

The term glaucoma refers to a group of diseases that have in common a characteristic optic neuropathy with associated visual field loss for which elevated intraocular pressure (IOP) is one of the primary risk factors. Drug-induced glaucoma should be considered as a form of secondary glaucoma because it is brought about by specific systemic or topical medications. Although there is a high prevalence of glaucoma worldwide, the incidence of drug-induced glaucoma is uncertain. Several classes of drugs have the potential to cause the elevation of IOP which can occur either via an open-angle or a close-angle mechanism.

Opened angle

Drug-induced elevation of IOP is more commonly caused by an open-angle mechanism. The most commonly recognized medications associated with this mechanism are the corticosteroids. One study showed that up to 6% of normal individuals developed marked elevation of IOP 4 to 6 weeks after continuous administration of topical dexamethasone or betamethasone eyedrops[1,2]. Additionally, the number of people responding with an elevated IOP is directly related to the route, frequency and duration of administration. In most cases, glaucoma is found to be associated with a topically applied medication in the form of an eye drop or ointment. However,it can also be found with other alternative routes of administration, such as intravitreal injection, periocular injection, systemic administration and inhalation.

Not at all patients taking corticosteroids develop elevated IOP. Risk factors include preexisting primary open-angle glaucoma, a family history of glaucoma, high myopia[3], diabetes mellitus[4], and a history of connective tissue disease, particularly rheumatoid arthritis.

The exact pathophysiology of steroid-induced glaucoma is unknown. However, it is known that the IOP elevation is a result of an increased resistance to aqueous outflow in the trabecular meshwork[5-7]. Possible mechanisms for steroid-induced elevation of IOP have been proposed, such as accumulation or deposition of extracellular matrix material, reorganization of the trabecular meshwork cytoskeleton, decreased protease and stromelysin activities, increased nuclear size and DNA content, and decreased phago-

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cytic capacity[8-11].

The most effective line of treatment in prevention of corticosteroid-induced glaucoma is through the judicious use of corticosteroids and frequent monitoring of IOP in patients who require prolonged corticosteroid therapy. Once the diagnosis has been made, corticosteroids should be discontinued immediately if the patient's underlying medical condition allows.

In case of topical corticosteroid drops, consider using a low potency steroid drug such as fluoromethalone or medrysone. The less potent steroids, the less likely IOP elevation. Topical nonsteroidal anti-inflammatory medications are alternative agents that have no potential to cause elevated IOP, although they may not have enough anti-inflammatory activity.

If IOP remains elevated after discontinuation of steroid therapy or if steroids must be continued, treatment follows the same line as for primary open-angle glaucoma (antiglaucoma medications, laser and surgery).

Closed angle

Several classes of medications have been reported to induce or precipitate acute angle-closure, especially in individuals with preexisting occludable angles. The causes of closed angle glaucoma associated with these agents are also varied. Lists of nonsteroidal drug-induced glaucoma were showed in Table 1[12]. The most common cause of close-angle in these patients appears to be pupillary block mechanism. The medications includeantipsychotic drugs, antidepressants, monoamine oxidase inhibitors, antihistamines, antiparkinsonian agents include antipsychotic, antispasmolytic drugs, mydriatic agents, the sympathetic agents and botulinum toxin[13]. Sulfamate derivatives may induce angle closure glaucoma by a different mechanism, involving anterior rotation of the ciliary body. The pathophysiology of drug-induced angle-closure glaucoma is usually pupillary block from pupillary dilation. Medications have a direct or secondary effect, either to stimulate sympathetic or inhibit parasympathetic activity causing pupillary dilation which can precipitate acute angle-closure glaucoma in patients with occludable angles[12].

The mechanism of sulfamate derivatives involves anterior rotation of ciliary body and/or choroidal effusion, resulting in narrowing of the angle (Fig. 1). Pupillary dilation and occludable angles are not necessary. The exact mechanism that causes the ciliary body rotation is unclear[14].

The followings review prominent classes of medications which can induce angle-closure.

Antipsychotic drugs

The antipsychotic drugs such as perphenazine (Trilafon® and Fluphenazine (Prolixin®) have been reported to induce angle-closure glaucoma. The mechanism of angle closure is believed to be the anticholin-

Table 1. List of nonsteroidal drug-induced glaucoma[12]

Antipsychotic agents and their derivatives
Phenothiazines (Chlorpromazine HCl, Perphenazine)
Thioxanthenes (Chlorprothixene, Thiothixene)
Butyrophenones (Haloperidol)
Dibenzoxepins (Doxepin HCl)
Antidepressants
Tricyclic antidepressants (Amitriptyline, Imipramine)
Nontricyclic antidepressants (Fluoxetine, Mianserin HCl)
Monoamine Oxidase inhibitors (Phenelzine sulfate, Tranylcypromine sulfate)
Antihistamines (Benadryl, Orphenadrine citrate, Promethazine)
Antiparkinsonian agents (Artane)
Antispasmolytic agents
Sulfa derivatives agents (Acetazolamide, Topiramate, Tetracycline, Quinine, Spironolactone, Acetylsalicylic acid)
Autonomic drugs
Sympathomimetic agents (epinephrine, Phenylephrine, Amphetamine)
Parasympathomimetic agents (Atropine, Tropicamide, Cyclopentolate HCl)
Inhalation agents (Salbutamol, Ipratropium)
Botulinum toxin

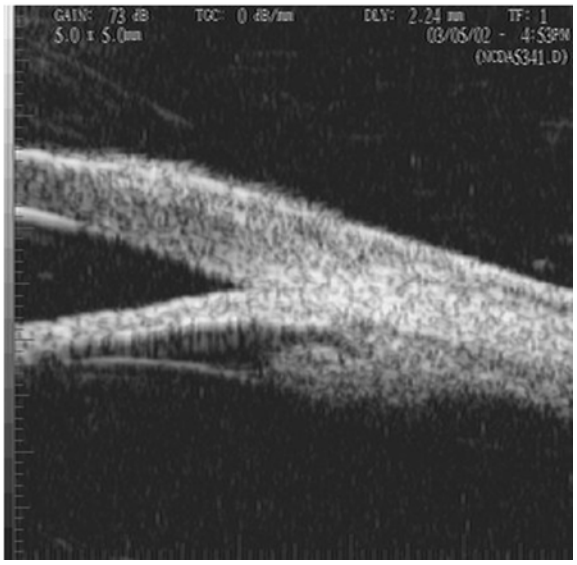

Fig. 1 Anterior rotation of ciliary process

ergic effect[12].

Antidepressant drugs

The tricyclic agents such as amitryptilline and imipramine and the nontricyclic agents such as fluoxetine and mianserin hydrochloride have been documented to precipitated an attack of angle closure[12].

Citalopram and paroxetine are an antidepressant of the selective serotonin reuotake inhibitor (SSRI) class which can induce acute angle-closure[15,16]. The pathophysiologic mechanism of SSRI remains unclear, even though anti-cholinergic effects or an increased level of serotonin, which cause partial pupillary dilation have been implicated[13].

Antiparkinsonian drugs

Trihexyphenidyl HCl (Artane)® has been reported to exacerbate angle-closure[17]. This side effect is belived to reflect the anticholinergic action of this agent.

Antihistamine

Although the anticholinergic effect is mild, orphenadrine citrate (Norgesic®), an H1 antihistamine, has been shown to precipitate an attack of angle-closure[12].

Inhalation agents

The anticholinergic action of ipratropium and the effect of salbutamol on aqueous humor production have been reported to induce angle-closure[18].

Botulinum toxin

Periocular botulinum toxin injection has been shown to produce an attack of angle-closure. The mechanism is due to the effect of this drug on the ciliary ganglion, producing pupillary mydriasis[12].

Sulfamate-derivative drugs

The sulfamate-derivative drugs such as acetazolamide[19,20], sulfamethoxazole/trimethoprim[19] and topiramate[21-23] have been reported to induce acute angle-closure. Although the mechanism is unknown, it may be associated with ciliochoroidal effusion with forward displacement of the lens-iris diaphragm, resulting in anterior chamber shallowing and acute angle-closure[14].

Treatment of nonsteroidal drug-induced glaucoma

Initial management is discontinuation of the precipitating drugs. If the etiology is due to pupillary block, the patient is treated similarly to the primary acute angle-closure. If the etiology is due to sulfamate-derivative medications, treatment is primarily supportive along with discontinuation of the medication. As the mechanism of angle closure dose not involve pupillary block, peripheral iridectomy and topical miotics are not useful[23,24].

If the IOP remains uncontrolled, additional therapies such as topical IOP-lowering medications[21], cycloplegic drugs[25], high dosage steroids[26] and a suprachoroidal drainge[27] may be considered.

Summary

It is recommended that all patients who have to use chronic corticosteroid medications should have a full ophthalmic examination and aregular evaluation by an ophthalmologist to minitor their ocular conditions and IOP.

Patients older than 40 years old should have routine eye evaluations to be screened for narrow anterior chamber angles. If the drugs must be used, IOP should be monitored closely.

Clinicians should be mindful of the possibility of drug-induced glaucoma, if in doubt, ophthalmological consultation is recommended.

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ต้อหินที่เกิดจากยา

สุมาลี บุญยะลีพรรณ

ต้อหินเป็นโรคที่เกิดจากความเสื่อมของเส้นประสาทตา โดยมีความดันตาสูงเป็นปัจจัยเสี่ยงสำคัญ มียาหลายชนิดในปัจจุบันที่มีผลข้างเคียงทำให้ความดันตาสูงขึ้น ซึ่งเกิดได้ทั้งจากกลไกมุมเปิดและมุมปิดของช่องหน้าลูกตา สาเหตุส่วนใหญ่ของต้อหินมุมเปิดที่เกิดจากยา คือการใช้ยาสเตียรอยด์เป็นระยะเวลานาน ส่วนต้อหินมุมปิดที่เกิดจากยาพบว่ามีหลายชนิดด้วยกัน เช่น ยาต้านจิตเวช ยารักษาโรคซึมเศร้า ยารักษาโรคพาร์กินสัน ยาขยายม่านตาทุกชนิด ซึ่งทำให้เกิดต้อหินมุมปิดแบบเฉียบพลันโดยเฉพาะในผู้ป่วยที่มีมุมตาแคบอยู่เดิม ส่วนยากลุ่มซัลฟาสามารถทำให้เกิดต้อหินมุมปิดได้เช่นกันแต่มีกลไกที่แตกต่างกัน ดังนั้นแพทย์ทุกท่านควรระมัดระวังในการใช้ยาชนิดที่อาจมีผลข้างเคียงทำให้เกิดความดันตาสูง ถ้ามีข้อสงสัยในผู้ป่วยรายใดควรปรึกษาจักษุแพทย์