Journal of Advances in Medicine and Medical Research

34(22): 197-205, 2022; Article no.JAMMR.92132
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Ophthalmic Uses of Atropine: A Review

Ugochukwu A. Eze [a], Godswill I. Nathaniel [b*] and Godswill Pepple [c]

[a] Department of Ophthalmology, Federal Medical Centre, Asaba, Delta State, Nigeria.
[b] Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria.
[c] Department of Ophthalmology, Rivers State University Teaching Hospital, Port Harcourt, Rivers State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. The article conceptualization was done by author UAE. The literature review was done by authors GIN and UAE. The writing of the initial draft was done by author GP. Author UAE edited the manuscript; then author GIN reviewed and wrote the final draft. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i2231593

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/92132

Review Article

Received 12 July 2022
Accepted 20 September 2022
Published 23 September 2022

ABSTRACT

Atropine has been used in medical practice for decades and is one of the essential emergency drugs. Its applications in ophthalmology have also followed a long trajectory. Therefore, this review is intended to explore the various uses of Atropine in ophthalmology. Atropine uses in strict ophthalmic indications have extensive diagnostic and therapeutic outlay including Examination under anesthesia, cycloplegic refraction, myopia, and amblyopic management, post trabeculectomy management, synechiae treatment, floppy iris syndrome, and uveitis management. The side effects have been shown to be dose-dependent with no long-term sequelae. Atropine has remained an important medicine in ophthalmic practice globally.

Keywords: Atropine; ophthalmic uses; indications.

1. INTRODUCTION

Atropine occurs as a tertiary amine (alkaloid) extracted from a perennial bushy herb known as "deadly nightshade" (Atropa belladona) [1]. Belladonna is an Italian word which means beautiful lady, owing to the historical uses of its extract by women to dilate their pupils [2].

**Corresponding author: E-mail: godswill.nathaniel@uniport.edu.ng;*

Atropine is also derived from plants of the Solanacae family. It has a broad spectrum of central and peripheral actions, and principally causes mydriasis and cycloplegia in the eyes, while the systemic effects include reduction of body secretion (such as nasal, salivary, bronchial, gastric, and sweat glands), reduction in heart rate and smooth muscle function in the bladder and gastrointestinal tract [1].

Atropine is a soluble odorless, bitter, colorless crystal or white crystalline powder with a molecular weight of 289.4 [3]. Molecular formula C17H23NO3.

2. PHARMACOLOGY

It is classified as an anticholinergic or antispasmodic agent. Acts by binding competitively to muscarinic acetylcholine (M1 – M5) receptors, thus inhibiting its functions [4,5].

Atropine is long-acting, it is well absorbed (in the gastrointestinal tract (GIT), mucous membranes, and eyes) and distributed as it readily crosses the blood-brain barrier and the placenta. It has a bioavailability of 90% while 50% is bound in plasma with a plasma half-life of 2-5 hours. Its ocular effects last for days. Hepatic oxidation is responsible for its partial metabolism while about 30-50% is excreted unchanged in the urine [1,6]. This review aims to highlight the different ocular uses of atropine from existing literature.

Atropine has a wide range of therapeutic indications; in surgery, it can be used for anesthetic premedication owing to its ability to reduce salivary secretions and prevent bradycardia prior to intubation [7]. Also, during surgery, its anti-vagal properties help to prevent attendant cholinergic effects and it reverses muscle relaxation effects of many medications. Atropine is a known antidote to anticholinesterase poisoning from ingestion of toxic agents such as muscarinic containing mushrooms, organophosphates, and carbamates [8]. Its antispasmodic functions serve in the treatment of diarrhea, irritable bowel syndrome, non-ulcer dyspepsia, and diverticular disease, and in the absence of any reversible cause of bradycardia, it is the drug of choice [8,9].

All these indications have made atropine retain its place in the list of emergency rugs that should be in any standard resuscitation box.

Systemic adverse effect affects different body systems from the Cardiovascular system (tachycardia, palpitations), GIT (dry mouth, constipation), and Skin (anhidrosis, flushing) [8,9]. Centrally, effects include altered sensorium, hallucinations, irritability, and delirium-like states. All these effects are dose related. However, atropine is contraindicated in people with hypersensitivity states.

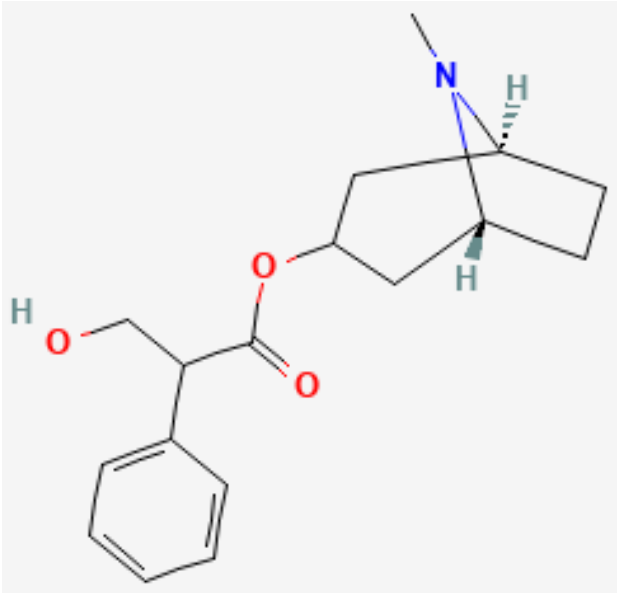

Fig. 1. Molecular Structure of atropine [3]

3. OCULAR PHARMACOLOGY

As with other parts of the body, atropine has also found used in the eyes. The human eye has all 5 muscarinic (M) receptors. These receptor subtypes are located in ocular structures at various proportions. As a result, a particular subtype of m-receptors predominates in a certain structure. In the human lens, the M1-receptors account for about 88.1% of total M-receptors [10]. In the conjunctiva, M2 and M3 receptors are predominantly involved in the muscarinic action of goblet cells that contribute to the tear film [11]. In the Iris, M3 receptors are mainly responsible for the contraction of the sphincter when stimulated and they account for 75.5% of the M-receptor population [10]. Other receptor groups are M1 (11.8%), M4 (10.4%), M5 (0.4%) and M2 (undetected). Also, the ciliary body whose circular muscle fibers are responsible for accommodative changes has predominantly M3 receptors (73.5%). Other populations are M2 (5.4%), M4 (4.9%), M5 (2.4%), and M1 (0.8%) [11,12].

The competitive binding of atropine to the M-receptors is through the M_3 receptor subpopulation. Thus, preventing contraction of the iris sphincter and circular muscles of the ciliary body.

4. OCULAR USES

Clinical Examination:

i. Cycloplegic refraction (wet retinoscopy) – the use of atropine to induce cycloplegia (a phenomenon in which mydriasis is achieved by paralyzing accommodation through ciliary muscle due to competitive inhibition of the M-receptors, mainly M_3 of the ciliary body). Atropine-induced cycloplegia has been explored in cycloplegic refraction where the refractive status of the eye is determined objectively with accommodative action completely paralyzed. Indications include proper estimation of refractive errors in children who may not be able to co-operate properly due to excess accommodation and inability to obey instructions. Also, in hyperopic adults due to excess accommodation and proper refraction in children who have accommodative esotropia.
ii. Ocular examination under anesthesia (EUA) – this is a common ophthalmic operating room procedure done when full ocular examination in the clinic is precluded due to the patient's age (especially children), level of cooperation, or developmental level. The anesthesia used in this procedure is usually general. Mahmoud et al. [13] in Ilorin, Nigeria reported congenital glaucoma (51.3%), congenital cataracts (12.8%), exotropia, microphthalmia, and megalocornea to be the most common indications for EUA in pediatric age groups. However, another single hospital study by Yip et al. [14] showed a nearly different range of indications with tuberous sclerosis complex (20%), neuro-ophthalmic causes, and neurofibromatosis (10.7%) each strabismus being the commonest indications.

Another common indication of EUA not mentioned above is retinoblastoma (RB) which is the most common primary intraocular malignancy of childhood. An experience in Moorefield's Hospital, London has shown RB to be a common indication of EUA which could be multiple, in the course of the therapy cycles [15].

Control of myopia: Myopia is considered to be the most common ocular disorder [16]. It is a form of refractive error in which images of light rays form in front of the retina thus causing blurred vision and is easily treated with a minus lens (spectacle or contact lens) or keratorefractive surgery without any serious cause for worry in the simple type. However, high myopia as defined by the World Health Organization (WHO) (Myopia of -5 Diopters or greater) is associated with degenerated ocular changes [17]. It is often referred to as degenerative or pathological myopia. Eyes with such changes are at a higher risk of developing complications such as retinal detachment, choroidal neovascularization, macular degeneration, foveoschisis, glaucoma, and cataract [18,19]. Recent studies have shown an alarming increase in the global prevalence of myopia, especially among young people adults in South-East Asia (80-90%) with it being the leading cause of blindness in that area [20]. A high prevalence and incidence of myopia in younger age groups are likely to result in a high burden and severity if it progresses to high myopia. The prevalence of childhood myopia varies with age and location but ranges from 1.2% in Nepal to 78.4% in China [21-30]. The lifestyle modification of children especially during

the periods of movement restriction occasioned by the COVID-19 pandemic has caused a 1.72 folds increase in a study that observed two cohorts (COVID and Pre-COVID cohort) [31].

Several studies have shown that the use of atropine in varying doses slows down the progression of myopia in children [32-34]. The primary effect of atropine appeared to be by slowing the growth of vitreous chamber depth, which in turn decelerates axial length increase [35]. Atropine has been incorporated into clinical practice, especially in Asia [19].

5. MANAGEMENT OF AMBLYOPIA

Amblyopia is defined as diminished vision as a result of an insult to the visual system during the critical period of development [36]. It is usually bilateral but can be unilateral depending on if the level of diminution of vision is out of proportion with the level expected of the underlying ocular pathology (e.g., high refractive error, anisometropia, strabismus or stimulus deprivation) which interferes with the normal cortical development). It is a fairly common condition and affects about 3-5% of children [36].

Penalization is a pharmacological or optical process of inducing blurred vision in the better eye to help stimulate the amblyopic eye to function in response to visual stimuli. Atropine is the most common pharmacological agent used for penalization, which may be a daily or weekend regimen, depending on parental preference and the practitioner's experience [36]. Evidence from a randomized trial of atropine regimens for treatment of moderate and severe amblyopia by the Paediatric Eye Disease Investigator Group shows that results with weekend dosing were similar to the daily option [37].

6. RELIEF OF ACCOMMODATIVE SPASM IN CLOSED GLOBE INJURY AND KERATITIS

Accommodative spasm is also known as accommodative excess, hyper accommodation, or ciliary spasm [38,39]. It is a result of involuntary and prolonged contraction of the ciliary muscle [40,41]. Causes could be ocular or systemic. Ocular causes include uncorrected hyperopia, prolonged near work, cholinergic drugs, uveitis, closed globe injury, and cornea ulcer. While some systemic causes include emotional stress, head injury, meningitis, migraine, and myasthenia gravis [40,42]. It is usually characterized by blurry vision, eye pain, ocular discomfort, diplopia, headache, dizziness, miosis, and excessive convergence [43-45]. Atropine serves as an adjunct to relieve the spasm while the primary cause is being investigated and treated.

In microbial keratitis, the ability of atropine to relieve pain and prevent synechiae formation by mydriasis is beneficial and in clinical use. Topical 1% preparation also has antimicrobial effects that supplement the primary antimicrobial therapy used in keratitis [46,47].

7. ADJUNCT IN TREATMENT OF ANTERIOR UVEITIS

Uveitis is the inflammation of the middle layer (tunic or coat) of the eye [48]. It is a challenging and potentially blinding condition. It is an important cause of visual impairment and negative vision-related quality of life worldwide and affects both developed and developing countries, though with varying outcomes [48]. It is classified based on the part of the uvea affected; anterior (iris- iritis), intermediate (ciliary body – cyclitis), posterior uveitis (choroid – choroiditis or chorioretinitis).

The principle of treatment is to [49];

- Treat the primary cause
- Relieve symptoms
- Minimize sequelae (e. g. synechiae)
- Prevent irreversible vision loss (e. g. cataract, with synechiae, panuveitis, ciliary shutdown, or retinal detachment)
- Prevent recurrence
- Limit side effects of medications

The cycloplegic property of atropine is applied to relieve pain. The mydriatic property helps prevent synechiae, which is a challenging sequela. Prevention of synechiae also prevents the development of complicated cataracts and also the elevation of intraocular pressure which can eventually lead to irreversible visual loss [50].

8. BREAKING OF SYNECHIAE

When uveitis is complicated by posterior synechiae, it can predispose to cataract with synechiae from fibrotic membranes, pupil block, and secondary angle closure. Most times, under such conditions, atropine alone will not help as its cycloplegic property only causes ciliary

muscle paralysis and mydriasis. Results from unopposed action of the radial muscle fibers [51], which is insufficient to break the fibrotic membrane.

In the early phase, a combination of steroids, topical application of atropine, and a sympathomimetic (e. g. 2.5% or 10% phenylephrine) are sufficient to break the membrane.

Atropine is also a component of mydriacaine (Numbers 1 and 2). It is a combination of 0.12mg adrenaline, 1mg atropine, and 6 mg procaine. It can be administered as a cotton pledget in the fornices. Also, a subconjunctival injection is effective. Any of these application routes is sufficient to break fresh posterior synechiae. However, injections have been associated with cardiovascular events such as sinus tachycardia [52].

9. ATROPINE IN POST TRABE-CULECTOMY CARE

An important application of the cycloplegic and mydriatic effect of atropine is in the deepening of the anterior chamber as a result of flattening and posterior movement of the lens and increasing distance between the ciliary body and the lens following paralysis of the ciliary muscle [52-53]. Orengo et al. [54] in 2000 reported a statistically significant deepening of the central and peripheral anterior chamber in a randomized controlled clinical trial that involved two groups of post trabeculectomy patients in which one group received atropine and the other did not. Atropine may not prevent postoperative complications in routine use after trabeculectomy but has been found to be especially useful in a shallow anterior chamber where it helps in deepening it.

One percent atropine is also used in the treatment of malignant glaucoma, which is a challenging complication of trabeculectomy [52]. Atropine is also useful in the management of choroidal effusion and detachment [55]. Outside trabeculectomy, 1% atropine is used in the medical treatment of pseudoexfoliative glaucoma [56].

10. INTRAOPERATIVE FLOPPY IRIS SYNDROME (IFIS)

As the name implies, it is an intraoperative complication of cataract surgery due to poor pupillary dilation. It is characterized by flaccid iris stroma in response to intraocular fluid currents, and progressive pupillary constriction with the attendant risk of posterior capsular rupture [57]. Other potential complications include iris injury, iridodialysis, hyphemia, wound dehiscence, nuclear drop, and wound dehiscence.

Table 1. Shows ocular preparations of atropine, indications, and side effects

Preparation	Concentration	Indication	Ocular side effects
Eye drop	0.1%, 0.3%, 0.5%	Myopia	Ocular irritation Contact dermatitis on lid skin Elevation intraocular pressure Risk of angle closure
	1%	Cycloplegia in amblyopia Keratitis Shallow Anterior chamber Cycloplegic refraction Uveitis	
	2%	Uveitis	
Ointment	1%	Ciliary spasm Cycloplegic refraction EUA in pediatric glaucoma, strabismus, retinoblastoma, retinopathy of prematurity, and other causes of leukocoria	
Conjunctival injections and pledgets	Mydriacaine No 1 and 2 (1% atropine, 1mg adrenaline and 6mg procaine)	Posterior synechiae	

It is important to note that miosis of IFIS is characterized by an elastic iris that does not dilate with mechanical stretching compared to other causes of intraoperative miosis like diabetes [57]. A high index of suspicion is needed to make a diagnosis of IFIS. Of particular note are patients on tamsulosin, finasteride, alfuzosin, doxazosin, prazosin, silodosin, losartan, benzodiazepines, duloxetine and a host of others. Also, antipsychotics like quetiapine, chlorpromazine, zuclopenthixol, aripiprazole, and risperidone [58-62].

In such patients, especially those on alpha-adrenergic agonists for benign prostatic hyperplasia, preoperative pupillary dilation was implemented.

Floppy iris syndrome is one example of why extensive atropine is used with or without epinephrine to prevent this unwanted on the operating table [8,63,64]. There appears to be no consensus as to the preferred concentration but the use of 1% is common. A review of drug history is important in the preoperative evaluation of cataract patients.

11. AVAILABLE OPHTHALMIC PREPARATION OF ATROPINE

The different ophthalmic indications may demand different dosages and preparations. Atropine sulfate formulations are commercially available as 0.3%, 0.5%, 1%, and 2% preparations as topical eye drops while the ointment is available as a 1% formulation as shown in the Table 1 [8,46,47,52].

12. CONCLUSION

Atropine has various diagnostic and therapeutic uses in Ophthalmology. The safety profile is excellent, and the side effects are usually dose-dependent with no long-term sequelae.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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