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CASE REPORTS

Seizures in a young child following mydriatic eye drops

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Abstract

Cyclopentolate, proparacaine, tropicamide and phenylephrine eye drops are frequently used for ophthalmological examinations. We report a young child who developed a generalised tonic clonic seizure on two separate occasions after ocular instillation of these four drugs with the aim of increasing the awareness of this rare but serious neurotoxic side-effect.

CASE REPORT

A 6 year old boy with brachydactyly symphlangism syndrome presented with a three minute generalized tonic clonic (GTC) seizure 45 minutes after instillation of eye drops for cycloplegic refraction during routine ophthalmological assessment. The regimen for this procedure in our centre is detailed in Table 1. The child was admitted for further evaluation of the seizure. Apart from the features of brachydactyly symphlangism syndrome[1], the physical and neurological examination was unremarkable (brachydactyly symphalangism syndrome is a condition where there is ankylosis of the proximal interphalangeal joints and carpal and tarsal bone fusion - there has been no reported association with epilepsy). He was afebrile with an ear temperature of 37.5 degrees Celsius, his heart rate was 122 beats per minute with normal sinus rhythm on 12-lead ECG, blood pressure 110/78mmHg and respiratory rate of 25 per minute. There was no evidence of concurrent acute illness and no features of an anticholinergic syndrome like tachycardia, hypertension, dry skin and mucous membranes, flushing, hyperpyrexia, hallucinations and ataxia, urinary retention or reduced gastrointestinal motility throughout the hospital stay. The following year, the child suffered another GTC seizure 44 minutes after instillation of the same eye drop regime during his next visit to the ophthalmologist. Investigations including full blood counts, serum electrolytes and glucose levels, and electro-encephalogram (EEG) on both occasions as well as cranial magnetic resonance imaging (MRI) were normal.

DISCUSSION

Cyclopentolate is an anticholinergic prepared for topical ocular use. It blocks the responses to cholinergic stimulation of the sphincter muscle of the iris and the accommodative muscle of the ciliary body to cholinergic stimulation, producing pupillary dilation (mydriasis) and paralysis of accommodation (cycloplegia). Young children have a great ability to accommodate, i.e. focus the eyes to see near objects. This gives rise to variable refraction results. Cycloplegia is often used to paralyse the accommodation reflex to derive a more accurate refraction. Cyclopentolate achieves a peak plasma level within 30 min and has a half-life of roughly 111minutes.[2] Conjunctival and nasal membranes are the sites of systemic drug absorption following ocular drug application.

Cyclopentolate has good cycloplegic effects but dilates the pupil poorly. Eyedrops like Tropicamide and Phenylephrine have less cyloclplegic effect but more dilating ability. They are added to help dilate the pupil for easier refraction by retinoscopy - an objective method of assessing refractive status in young children. Proparacaine is used as a topical local anaesthetic as the other eyedrops may produce a stinging sensation. Most systemic complications of mydriatics and cycloplegics are characterised by the anticholinergic toxidrome; *"Blind as a bat, mad as a hatter, red as a beet, hot as a hare, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone"*.[3] A distinctive feature to highlight, however, is that the seizures occurring in this case were not in association with this syndrome.

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Table 1: Mydriasis regimen for children above 3 years of age

Frequency	Eye drop
Initial	1 drop Gutt Proparacaine hydrochloride
	1 drop Gutt Tropicamide 0.5%
	1 drop Gutt Cyclopentolate 1%
Next 5 minutes	1 drop Gutt Phenylephrine 2.5%
	1 drop Gutt Cyclopentolate 1%
Next 5 minutes	1 drop Gutt Cyclopentolate 1%

Though uncommon in itself, Cyclopentolate has been reported to be associated with the side effect of seizures.[4-7] The exact mechanism of this adverse reaction is unknown but likely due to a direct-seizure causing neurotoxic effect or a systemic anticholinergic effect. Studies reporting the occurrence of seizures after eye drop instillation are summarised in Table 2.

Fitzgerald *et al.* described a case of GTC seizures associated with tachycardia and facial flushing which may have signified anticholinergic symptoms in a child with underlying cerebral palsy.[4] The seizure onset was 70 minutes after instillation of cyclopentolate 1% and there was a second seizure at 115minutes. Other studies describing cyclopentolate induced seizures are not associated with anticholinergic symptoms. Kennerdell *et al*. reported two cases, occurring 30 and 35 minutes after instillation of cyclopentolate 2% respectively.[6] These cases, as well as, ours are in keeping with the pharmacokinetics of this ocular drug which reaches the maximum systemic levels in 30 minutes and thereafter declines with a half-life of roughly 111minutes. Occasionally, a second concentration peak in plasma, probably reflecting drug absorption from the gastrointestinal tract, was

Table 2: Summary of studies reporting seizures after instillation of eye drops

Study	Age (years)	Gender	Comorbidities	Eye drops	Time delay (min)	Type of seizure
Demayo[2]	2	Male	None	6 drops of 1% cyclopentolate and 10% phenylephrine	45	GTC (status)
Fitzgerald[3]	4	Male	Cerebral palsy	1% cyclopentolate	70, 115	GTC
Kennerdell[4]	1	Male	None	2 drops of 2% cyclopentolate	35	GTC
	2	Male	Epilepsy	2 drops of 2% cyclopentolate	30	GTC
Mwanza[5]	12	Female	Epilepsy	4-6 drops of 2% cyclopentolate	30-45	GTC (two separate occasions)
Cydulka[6]	28	Female	None	0.5% proparacaine hydrochloride	3	GTC
Brunner[7]	62	Male	None	12 drops 0.5% tropicamide	Not stated	GTC

GTC – generalised tonic clonic
*MEDLINE search from 1963-April 2013 (Appendix A)

seen after 2 hours.[2] The case of generalised status epilepticus after cyclopentolate and phenylephrine eye drops reported by Demayo *et al*. may have been confounded by a number of factors including trauma and severe electrolyte disturbances.[7]

Mwanza *et al.* is the only other report which described seizures occurring on two separate occasions after instillation of cyclopentolate 2% eye drops in an epileptic girl.[5] Along with our report, this provides a strong association between the cyclopentolate eye drops and the seizure event – Naranjo score indicating probable adverse drug reaction.[8]

Cydulka *et al.* reported seizures that occurred rapidly within 3 minutes after instillation of 0.5% proparacaine hydrochloride in a 28 year old epileptic woman and proposed a hypersensitivity mechanism.[9] The reaction described by Brunner *et al*. approximated a severe anticholinergic reaction (dilated pupils, dry mouth, flushed skin, tachycardia) with two GTC seizures followed by coma and respiratory arrest in a 68 year old man .[10] This was supported by the fact that the dose of Tropicamide given was high - almost 1g and that the reaction was reversed by physostigmine. There were no reports of either proparacaine or tropicamide causing seizures in children. The only report associating topical ocular phenylephrine with seizures is the study by Demayo *et al*. (described above), which also involved cyclopentolate.[7] Other possible mechanisms we considered were vagal stimulation as a result of eye ball stimulation, breath holding and photosensitivity – however, the seizures occurred in our patient at rest and sometime after the eye examination had been completed.

From the information presented and the time course for the development of GTC seizures for our patient, it would seem that cyclopentolate has the strongest association. The clinical presentation of a young child, especially one with an underlying neurological predisposition, who develops seizures 30-60 minutes after instillation of cyclopentolate, should prompt a physician to suspect an adverse drug reaction. Nevertheless, it is also vital to appreciate that this is a diagnosis of exclusion and other important and more common conditions like infections of the central nervous system and epilepsy be considered first. A limitation in our hypothesis is that there are no reports describing the transport of cyclopentolate across the blood-brain-barrier. However, given that cyclopentolate hydrochloride demonstrates well-known neurotoxic effects like cerebellar dysfunction and psychosis, one can assume some amount of the drug or its metabolites are able to enter the central nervous system.

In our centre, this is the first occurrence of mydriatic eye drop associated seizures in a young child. While we cannot exclude the possibility that the pre-morbid condition of the child could have predisposed him to seizures, it is safer to recommend precautions on the future use of mydriatic eye drops. Cyclopentolate in particular, should be used with caution in children with underlying neurological conditions or who have a history of seizures. This means a careful history and punctal occlusion (which reduces drug penetration through the nasal mucosa) should be implemented for all such cases. For those who do not tolerate cyclopentolate, 0.5% atropine eye drops may be used instead.[5]

DISCLOSURE

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Disclosures: none

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Appendix A

MEDLINE search from 1963- April 2013

Search (((((((neonatal convulsions) OR infantile convulsions) OR convulsion) OR convulsion children)) OR ((((((((((((((((((((neonatal seizures) OR epileptic seizures) OR partial seizures) OR seizures) OR seizures children) OR seizure) OR nonepileptic seizures) OR absence seizures) OR seizure disorder) OR seizure epilepsy) OR seizure eeg) OR induced fit) OR generalised seizures) OR generalised epilepsy) OR tonic clonic) OR tonic clonic seizures) OR tonic seizures) OR clonic seizures) OR generalized tonic clonic seizures))) AND ((((((((((((eye drop) OR atropine eye drops) OR phenylephrine eye drops) OR ocular drug) OR ocular drug delivery) OR topical ocular drug delivery) OR topical ocular delivery) OR cyclopentolate) OR proparacaine eye drops) OR cyclopentolate eye) OR tropicamide) OR cycloplegic) OR mydriatic) OR mydriatic eyedrops)