Association, Risk and Causation - Examining the Role of Systemic Medications in the Onset of Acute Angle-Closure Episodes

Authors:
Paul J Foster PhD FRCS(Ed). 1,2
Robert Luben PhD. 1,2
Anthony P Khawaja PhD FRCOphth. 1,2

Affiliation:

1. Ocular Informatics Group
   Population and Data Sciences Research Department
   UCL Institute of Ophthalmology
   Bath Street
   London EC1V 9EL, United Kingdom

2. Translational Data Sciences Theme
   National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology
   Moorfields Eye Hospital
   City Road
   London EC1V 2PD, United Kingdom

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Corresponding author:
Prof Paul J Foster PhD FRCS(Ed)
Population and Data Sciences Research Department
UCL Institute of Ophthalmology
Bath Street
London EC1V 9EL, United Kingdom

Albert Einstein is credited with the quotation that "As our circle of knowledge expands, so does the circumference of darkness that surrounds it", implying that the more we know, the more we recognise that we do not know. If we consider carefully the study by Na & Park in JAMA Ophthalmology this month, we find that this large study, drawing on data from three South Korean compulsory national health insurance schemes covering 53 million people, spanning 9 years and 19 million relevant claims, may raise more questions than it answers, and highlights some of the challenges in using large sets of routinely collected data.[1]

Foremost among these is the accurate ascertainment of cases. Most researchers carrying out prospective studies, and also smaller retrospective studies, will carefully exclude false positives, and attempt to identify false negative cases. The use of insurance claims data in angle-closure research presents particular challenges. The 2002 ISGEO (International Society for Geographical and Epidemiological Ophthalmology) diagnostic framework draws a clear division between primary angle-closure (closed drainage angles with elevated intraocular pressure and/or peripheral anterior synechiae, but no glaucomatous optic neuropathy) and primary angle-closure glaucoma (closed angles together with glaucomatous disc damage and reproducible visual field loss). However, while this classification predominates in international peer-reviewed research, it has penetrated mainstream clinical care less widely. Clinicians differ in their adherence to diagnostic classification systems. In some cases, a diagnosis of “glaucoma” is required for reimbursement. It is relevant here that the authors have chosen an inclusive approach in their specification of diagnostic codes to identify cases.

The association between acute angle closure (AAC) and the use of topical ophthalmic drugs used to achieve mydriasis is uncontroversial. The mode of action of these drugs fits well with our understanding of the mechanical processes within the anterior segment that lead to the onset of AAC.[2] Associations between some non-ophthalmic medications and the onset of AAC have been widely reported, and can be divided into two groups; those drugs with a (presumed) effect on pupillary size or dynamics, and "idiosyncratic" effects, exemplified by the supra-ciliary effusions and consequent rotation of the ciliary body. Among the former, widely-documented associations include many antidepressant medications, smooth muscle relaxants, nasal decongestants, urological medications and both inhaled and nebulised bronchodilators.[3] While many of these associations are biologically plausible and have strong temporal relationships with exposure directly preceding onset, the concepts of association and causation are widely conflated by authors.

Na & Park add to the list of associated medications. Some are plausible causes of AAC, some less so. One additional finding in this study is the proportion of AAC sufferers exposed to polypharmacy. Of 13,531 people experiencing AAC (mean age: 66.8 ± 10.6 years), 37% (4,951) were on at least 1 of 61 systemic medications. Of those receiving medication, 47% (2,325) were prescribed 3 or more medications, and 9% (463), 6 or more medications. This indicates a high proportion of multiple systemic morbidity in AAC patients, and in turn, complicates the interpretation of results. Some systemic conditions have been proposed as a potential cause of angle-closure, diabetes mellitus being one example. The proposed mechanism is through increased plasma osmotic potential resulting from hyperglycaemia, which causes swelling of the

crystalline lens. This concept raises the possibility that at least part of the observed associations between medications and AAC may not be the direct result of the medication.

Na & Park's strongest identified association, a link between AAC and sumatriptan (OR: 12.60 [95% confidence interval (95% CI), 4.13–38.44]), is explicable on the basis of a direct increase in risk of AAC as a consequence of administration of the drug (sumatriptan is a selective serotonin receptor agonist). However, it may be more likely that patients with intermittent AAC prodrome will present with a unilateral headache which may be mis-diagnosed as migraine. Notable absences from the list published by Na & Park include inhaled or nebulised bronchodilators used to treat asthma or other chronic upper airways diseases. Bronchodilators are an interesting omission, as studies have shown (limited) evidence of a dose response relationship, an important feature when weighing the evidence for an association showing features suggesting causal relationship.Their absence may relate to local availability of medications and prescribing patterns.

When drawing practical conclusions from this publication, the magnitude of risk is highly relevant. The recent ZAP trial carried out in southern China, studying the highest-risk population on Earth, has calculated the risk of suffering AAC in somebody with an anatomically predisposed anterior chamber angle is less than 1/1,000 over one year.[4] Considering the general adult population, the Rotterdam Eye Study and the Baltimore Eye Study recorded 2/6,760 episodes of AAC and 0/4,870 among study participants undergoing pupil dilation for examination, respectively.[5,6] Pharmacological dilation is probably the single strongest stimulus for the onset of AAC in a predisposed individual. Not withstanding the uncertainty around causation, and in light of the bulk of OR's in Na & Park's study being around 2, the absolute risk of members of the general population suffering AAC will be extremely small, possibly in the region of 1/500 over one year among primary angle-closure suspects (i.e. those who are anatomically predisposed) who receive a medication which doubles their risk of AAC. We do not know if the risk of multiple medications which elevate the risk does so in an additive or multiplicative manner, or if it behaves as a different mathematical relationship.

Patients suffering supraciliary effusions from topiramate, and less often from other drugs, clearly should have this medication withdrawn. However, many drugs with recognised associations with AAC offer important and potent benefits for patients. To deprive patients access to these medications because of a likely very small AAC risk is probably a disproportionate response, erring too far towards the avoidance of small risks and unlikely to outweigh the benefits offered by the medication. Peripheral iridotomy (PI) is effective in preventing "primary" AAC, although its benefits in controlling drug "induced" AAC are less clear. Clear lens extraction is likely more efficacious than PI in most drug associated AAC cases, but again, this is unproven. The management of those suspected to be at increased risk will differ according to a variety of factors including access to and cost of ophthalmological care, geography, ophthalmic and systemic co-morbidity. In the context of low overall risk of drug induced AAC, we suggest clinicians and patients should not be alarmed about the possible risks of a new medication precipitating AAC. A pragmatic approach would be for the prescribing physician to warn of the very small possibility of AAC, to explain the symptoms, and to instruct the patient to seek urgent

ophthalmological care if these occur. Nonetheless, some patients are more vulnerable than others, and may deserve a more proactive approach. A recent UK Royal College of Ophthalmologists Guidelines document on angle-closure glaucoma codified these people and proposed that, in the UK's relatively resource-constrained National Health Service, the group of primary angle-closure suspect individuals, designated "PACS PLUS" should be offered prophylactic PI.[7] Finally, in all industrialized nations, all adults should be encouraged to avail themselves of the benefits of a regular ophthalmic examination by an eye care professional.

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