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EDITORIALS

Severe hypotension associated with α blocker tamsulosin

Selective action does not guarantee safety

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Benign prostatic hyperplasia is the main cause of lower urinary tract symptoms in men—voiding, storage, or post-micturition symptoms are common to several genitourinary and neurological diseases. Men with these symptoms experience decreased quality of life, depression, and loss of productivity. The prevalence of these symptoms varies from 15% to 60% of men over 40 years of age.[1]

Worldwide, population ageing is contributing to the increasing burden of benign prostatic hyperplasia. This is accompanied by increasing healthcare costs owing to the growing list of treatment options. The study by Bird and colleagues (doi:10.1136/bmj.f6320) evaluates the safety of one such treatment option—tamsulosin, a selective α adrenergic receptor antagonist (α blocker). The authors report a significant association between starting or restarting tamsulosin and hypotension severe enough to require admission to hospital.[2]

Tamsulosin was introduced in 1996 and marketed as a major innovation among α blockers because it was associated with a lower frequency of orthostatic hypotension than other drugs in this class. Tamsulosin now dominates the global drugs market for the treatment of benign prostatic hyperplasia and is the most commonly prescribed treatment for lower urinary tract symptoms worldwide. It is available in many different doses and formulations and is manufactured by a range of drug companies. Tamsulosin is available without prescription (over the counter) in the United Kingdom, thanks to its supposedly benign therapeutic profile. Selective binding of tamsulosin to prostatic receptor α1A/D instead of vascular receptor α1B receptors explains its lower rate of postural hypotension compared with other agents.[3] Concentrations of tamsulosin are higher in the prostate than the blood of men with benign prostatic hypertrophy. Importantly though, we have no comparable information about the relative concentration of other α blockers in the prostate and blood to support claims of superior tissue selectivity for tamsulosin.[4]

Evidence from systematic reviews suggests that tamsulosin is moderately effective, at best, for men with lower urinary tract symptoms.[5] Moreover, α blockers do not improve clinical outcomes of benign prostatic hypertrophy or slow down growth of the prostate. There is no clear evidence that any one α blocker is clinically better than another. Despite the availability of new treatment options for relieving lower urinary tract symptoms, the rate of presentations to emergency departments for urological diseases has remained stable, whereas costs associated with hospital admission have increased by 40%, according to one estimate from the United States.[6]

Concerns about α blockers originally emerged from hypertension trials such as ALLHAT, which was published in 2000 and reported that doxazosin was associated with inferior efficacy and worse side effects than the diuretic chlortalidone.[7] The resulting shift away from using α blockers to treat hypertension, and the belief that their side effects were caused by their non-selective effects, triggered further development and marketing of so called uroselective options. During the past decade, the uroselective α blockers, alfuzosin and silodosin, have been approved by regulatory agencies in the United States, Europe, and many other countries around the world.

The hypotensive effect of α blockers may be exacerbated by cotreatment with other vasodilating drugs including phosphodiesterase type-5 inhibitors, although evidence about clinically important interactions is conflicting. Recently, tadalafil was approved by the Food and Drug Administration (2011), European Medicines Agency (2012), and other national regulators for the treatment of men with benign prostatic hypertrophy. Fixed combinations of α blockers and a phosphodiesterase type-5 inhibitor are already being developed by some drug companies. As Bird and colleagues have shown, severe hypotension is a problem even for drugs considered to be low risk.

There is a clear need to improve postmarketing surveillance of α blockers considered to have minimal risks of orthostatic hypotension. We also need much better evidence to determine the cardiovascular safety of α blockers combined with phosphodiesterase type-5 inhibitors.

The assumption that selective agents such as tamsulosin could be combined safely with a phosphodiesterase type-5 inhibitor is based on small clinical trials with limited follow-up.[8] Publication bias may also be a problem. There are registered

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studies evaluating the combination of 5PDI and α blockers that have never been published, including two completed in 2009 that evaluated the combination of α blockers with tadalafil (NCT00848081) and vardenafil (NCT01207947).

Randomised trials have many strengths, but they are not always the best way to detect adverse drug reactions.[9] Active pharmacovigilance studies (such as cohort studies) will provide a better understanding of the cardiovascular side effects of commercially available and widely used α blockers, including tamsulosin. These studies could also explore aspects of treatment not reported by Bird and colleagues, such as drug interactions (CYP3A4 inhibitors and phosphodiesterase type-5 inhibitors), as well as the effect of different doses and different formulations of tamsulosin (such as oral controlled absorption system or modified release). In the meantime, Bird and colleagues' study should be carefully reviewed by national regulatory agencies and healthcare policy makers.

Doctors have a tendency to embrace new therapeutic options with enthusiasm, but we often forget that the history of drug development repeats itself, telling us that "new generations" of existing drugs are rarely truly novel, no matter how remarkable their pharmacokinetic and pharmacodynamic properties seem to be.

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