National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Cardiovascular

Date: 28 October 2015

Medication: Doxazosin GITS (gastrointestinal therapeutic system)

Indication: Resistant hypertension

Executive summary: All studies show improvement with doxazosin GITS – there were no comparator drugs. The majority of studies did not report effect sizes (open-label, non-comparator studies), thus there were no statistical analysis. The length of observation was generally short (16 weeks).

Search strategy:
PubMed was searched using the following search strategy:
"Hypertension"[Mesh] AND "Doxazosin"[Majr] AND ((Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp]) AND "2005/10/29"[PDat] : "2015/10/26"[PDat] AND "humans"[MeSH Terms] AND English[lang])

Selection of studies:
This resulted in 26 studies:

- Studies not investigating doxazosin in hypertension were excluded
- Some studies were unavailable (i.e. had to be purchased) – these were excluded
- 1 'proof of concept' trial (for autonomic modulation of doxazosin) was excluded
- The ALLHAT study was excluded – this reviewed immediate release doxazosin, and looked at doxazosin as first-line therapy (in comparison to thiazide-type diuretic).

Efficacy
The ASOCIA study [1] showed a significant decrease in blood pressure with add-on doxazosin gastrointestinal therapeutic system (GITS) ($P<0.0001$) (patients on doxazosin = 3546). Patients with optimal blood pressure (<140/90mmHg) at week 4 was 39%, and 61% at end of study (week 16). It was estimated about 60% of patients required dose increase from 4mg to 8mg at their second visit (estimated because exact data not known). Patients were on ACE-inhibitors, ARBs, diuretics (mainly thiazides), calcium channel blockers, beta-blockers, and others (not mentioned). Of the cohort, 7.3% of patients had no prior antihypertensive medication at baseline. There were no significant differences between patients treated with multiple therapy, monotherapy, or no therapy at baseline in blood pressure reduction (data wasn't shown).

Of the ASCOT-BPLA study [2], doxazosin GITS was added to a mean of 2.0 other antihypertensives, as a third-line therapy (patients on doxazosin = 10 069). Mean initial dose was 4.1mg and final dose was 7.0mg. Blood pressure (BP) fell from a mean of 158.7/89.2mmHg (standard deviation 18.3/10.6mmHg) to 147.0/82.3mmHg (SD 20.4/11.5mmHg). The mean within-individual reduction was 11.7mmHg (SD 18.8mmHg, $P<0.0001$) in systolic BP and 6.9mmHg (SD 9.6; $P<0.0001$) in diastolic BP. The addition of doxazosin resulted in 29.7% of

patients reaching target BP. There appeared to be increased efficacy with greater age, and decreased efficacy in greater weight (in multivariate analysis).

The GATES study was the only placebo-controlled trial (n=272). [3] At the end of the study, patients on doxazosin GITS requiring 4mg were 30.3% and on 8mg were 67.4%. Reduction in sitting diastolic BP (primary end point) was greater in the doxazosin GITS group compared to placebo at all time points (last observation carried forward showed 9.7±1.3mmHg reduction in doxazosin GITS versus 2.5±1.3 reduction with placebo). The proportion of patients that decreased BP to <140/90mmHg was higher in the doxazosin GITS group compared with placebo (36% responders in doxazosin group, 11.6% responders placebo, P<0.001).

Safety

The ASOCIA study had 1 serious adverse event associated with doxazosin (urinary incontinence), and 1.57% of the cohort had adverse events (such as dizziness, headache, oedema, postural dizziness, hypotension, asthenia, syncope, urinary incontinence, and dry mouth). Of the cohort, 1.1% of patients withdrew due to AEs.

The ASCOT-BPLA study resulted in 7.5% of patient temporarily or permanently stopping doxazosin due to AEs (such as dizziness, fatigue, headache, vertigo, oedema). Heart failure rates between patients on doxazosin and those not were not statistically different (rate ratio 1.04; 95% CI 0.80 – 1.36; P=0.76). (This was one of the main problems associated with doxazosin in the ALLHAT study, although it was a secondary outcome.)

There were no deaths in the GATES study, with one serious AE in the doxazosin GITS group (epistaxis) and one serious AE in the placebo group (asthenia). There were 24 AEs in the treatment group, and 22 AEs in the placebo group, most frequently being dizziness, headache, asthenia, postural hypotension. Five patients in doxazosin GITS group withdrew due to AEs.

Limitations

The ASOCIA study was an open, non-comparative study. The authors did not state how they came to their sample size. Frequently data appears to be missing (as mentioned by the authors). The trial ran for only 16 weeks.

The ASCOT trial was an open, randomized trial, funded in part by Pfizer. The ASCOT-BPLA arm was not randomized, but an observational part of the main trial.

The GATES study evaluated efficacy of doxazosin as add-on therapy to patients on no more than 2 antihypertensives (i.e. third-line therapy). Method of randomization, and whether blinding was done, was not mentioned.

Evidence quality:

The evidence is not high quality. It consists of open-label, non-comparator trials.

Summary:

The trials reviewed here all indicate that doxazosin GITS is effective in decreasing blood pressure as a third-line agent. The major limitation was the lack of studies comparing doxazosin GITS as third line therapy to current South African third-line treatment options [4]. Thus the benefit of doxazosin GITS, as compared to current treatment regimens, is unknown.

Recommendation: Doxazosin GITS reduced blood pressure in ASCOT but this was an observational, open-label study where treatment was added on to patients who failed to achieve blood-pressure targets. There was no evidence of benefit in terms of hard end-points.

The available evidence that long-acting doxazosin GITS has superior safety to immediate release formulation was not considered persuasive to make a change to policy.

In the absence of a price differential it is reasonable to use doxazosin GITs formulation.

References

1. De Fernando, A, Hernandez-Presa MA, and the ASOCIA investigators. Effect of doxazosin gastrointestinal therapeutic system on patients with uncontrolled hypertension: the ASOCIA study. J Cardiovasc Pharmacol 2006;47:271-276.
2. Chapma N, Chang CL, Dahlof B, Sever PS, Wedel H, Poulter NR, and the ASCOT investigators. Effect of doxazosin gastrointestinal therapeutic system as third line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac outcoms trial. Circulation. 2008. 118:42-48.
3. Black HR, Keck M, Meredith P, Bullen K, Quinn S, Koren A. Controlled-release doxazosin as combination therapy in hypertension: the GATES study. J Clin Hypertens. 2006;8:159-166.
4. Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. Cardiovascular Journal of Africa. 2014;25:288-294.