DRUG & THERAPEUTICS LETTER

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Should beta blockers remain first-line drugs for hypertension?

The antihypertensive drugs are mainly diuretics, beta-blockers, calcium channel blockers and antagonists of the renin angiotensin aldosterone system.

A meta-analysis has found that, compared to placebo, beta blockers are effective drugs and are associated with a 19% lower relative risk of stroke. Compared to other antihypertensive drugs, there were no differences for all cause mortality or for myocardial infarction, but beta-blockers did not reduce stroke to the same extent. This was reported as a 16% higher relative risk of stroke.

The majority of trials in the meta-analysis studied atenolol. When the analysis was restricted to other beta-blockers, no significant differences were found in comparison with other antihypertensive drugs. However, this restricted analysis contained only a few trials, with a low number of adverse events, so it was most likely underpowered to detect a difference. The authors of the meta-analysis concluded that all beta-blockers are less effective than other antihypertensives and should not be used as first-line drugs in hypertension. However, the major differences observed between beta-blockers and other antihypertensive are largely due to the influence of two trials.

The recently published guidelines of the UK National Institute for Clinical Excellence (NICE) no longer include beta-blockers in their routine treatment algorithm for hypertension, citing concerns of lower effectiveness and a greater risk of diabetes especially in combination with thiazide diuretics. They also state

that prospective trials with newer (more selective) beta-blockers are needed.

Epidemiological studies consistently show that the majority of strokes are directly attributable to high blood pressure. An overview of reviews highlighted that the association of blood pressure and the risk of stroke is log linear. This means that for any given absolute decrease in blood pressure from a baseline level, there is a similar relative risk reduction of stroke. The difference in blood pressure reductions achieved by different drugs was often less than 1 mmHg, implying minimal difference between the drug classes.

A collaborative trial of blood pressure-lowering treatment observed a greater risk reduction for stroke with regimens based on calcium channel blockers compared with those based on diuretics or beta-blockers, but the results were of borderline statistical significance. The mean age of these patients was 65 years and there was no overall significant difference in major cardiovascular events between the drugs.

Another analysis based on 61 prospective trials (12.7 million person-years at risk) concluded that throughout middle and old age, a person's usual blood pressure is strongly and directly related to vascular and overall mortality, without any evidence of a threshold down to at least 115/75 mmHg. stroke is much more common in older age than in middle age and, given the continuous relationship observed between blood pressure and the risk of death from vascular disease, the absolute benefits of a lower blood pressure are likely to be greatest for those at greatest absolute risk of vascular disease.

These large reviews suggest that reducing blood pressure is more important than the drug used. Achieving a lower blood pressure will result in a reduction in the risk of major adverse events.

There are different types of beta-blockers. They vary in their lipophilicity, receptor specificity, mode of elimination, half-life, primary indications and cost.

The exact mechanism by which beta blockers exert their antihypertensive effect is uncertain. Possible actions include a reduction of cardiac output (negative inotropic and negative chronotropic effect), an effect on vascular resistance, as well as an inhibitory effect on the release of renin (which is stimulated by the sympathetic nervous system) and central effects that may be influenced by the hydro-or lipophilicity of the beta-blocker.

Many patients taking beta-blocker in clinical trials required combination therapy, especially with thiazide diuretics, to achieve their target blood pressures. This has raised as evidence that beta blockers have a

weak antihypertensive effect. However, the need for combination therapy is not unique to beta-blockers and many trials show better blood pressure control with combination therapy rather than single drug therapy, largely irrespective of the initial drug class used.

Conclusion

It is unlikely there will ever be a single ideal first-line drug for hypertenson and most patents will eventually need multiple drugs to control their blood pressure. Treatment needs to be individualised for all patients.

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Brief Information

Drug Information Unit (DIU), TUTH

The DIU under the Department of Clinical Pharmacology has provided following services during the period January – June 2007.

-*Publication of Drug and Therapeutics Letter* - two issues

-*Adverse Drug Reactions (ADR) monitoring* - 14 cases of reactions have been reported from the OPDs and wards of TUTH.

TUTH is one of the two ADR regional centers in the county and is affiliated through the national centre (Department of Drug Administration) to the Uppsala Monitoring Centre in Sweden, a WHO Collaborating Centre for International Drug Monitoring.

-*Question answering services* questions related to drug treatment, monitoring of the treatment and prognosis etc.

Thiazolidinediones and reduced bone density

Thiazolidinediones include rosiglitazone and piglitazone These medicines act to increase insulin sensitivity and are widely prescribed to

treat type II diabetes mellitus. Recent evidence suggests thiazolidinediones are associated with an increased risk of peripheral fractures in post-menopausal women.

The incidence of fractures in women taking rosiglitazone was 9.3% (2.7 patients per 100 patient years), compared with 5.1% (1.5 patients per 100 patient years) in those taking metformin and 3.5% (1.3 per 100 patient years) in those taking glibenclamide. The majority of fractures in these patients were in the humerus, hand, or foot. The incidence of fractures of the hip or spine in women and the incidence of fractures in males were similar among the 3 treatment groups.

The mechanism for increased fracture risk was examined in a 14 week study in 50 healthy postmenopausal women in New Zealand.This study showed reductions in markers of bone formation in women taking rosiglitazone 8 mg/day compared with placebo. These changes were evident after 4 weeks and persisted for the duration of the study. There were also small reductions in hip and lumbar spine bone density in women taking rosiglitazone.

Pharmacovigilance in Nepal is growing

Anna Celen, Uppsala Monitoring Centre writes,

at DDA, Pradeep Gyawali and Professor Kumud Kumar Kafle from Tribhuvan University Teaching Hospital (TUTH) presented an ADR study performed at their hospital. They showed that dermatological reactions caused by antibiotics accounted for the majority of ADRs in the study. The Director of DDA, Bhupendra Bahadur Thapa, made a request to include TUTH as a regional centre in the Pharmacovigilance Programme and Professor Kafle agreed to this.

During my stay in Nepal, I was also invited to the following hospitals in Kathmandu: TUTH, Shahid Gangalal National Heart Centre, Man Mohan Memorial Hospital, Kathmandu Model Hospital and Patan Hospital.

"Drug and Therapeutics Letter" is also available now in the following websites:http://www.teachinghospital.org.np/diu.html,http://www.iom.edu.np/diu.html.

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