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Drug Information Unit (DIU), TUTH

The DIU has provided following services during the period October 2009 to September 2011.

Publication of Drug and Therapeutics Letter

Eight issues have been published.

Adverse Drug Reaction (ADR) monitoring

Forty five cases of ADR have been reported from the Dermatology OPD and Internal Medicine and Dermatology wards of TUTH.

Question Answering service

It included answers to questions regarding

- Composition of salbair - I.
- Trade name for combination of Levosalbutamol sulphate and Ipratropium bromide powder for inhalation and its availability in Nepal.
- Significance of Cholinesterase level at 440U/l on second day of OP poisoning inspite of atropinization with dose of 30 ampoules per day.
- Clinical significance of Monteleukast and Sitagliptine.
- Prophylaxis and treatment of abdominal migraine.
- Use of Sucralfate in cholilithiasis to protect gall bladder.
- Features of aluminum toxicity.

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

Chief Editor :
Prof. Kumud Kumar Kafle
Editors:
Dr. Sanu Maiya Shakya, Dr. Sangha Ratna Bajracharya, Dr. Satish Deo,
Dr. Naba Raj Simkhada, Dr. Pradip Gyanwali.
Department of Clinical Pharmacology, Drug information Unit, Room Number: 1-85
Doctors' Room Block, TU Teaching Hospital, P.O.Box: 3578, Maharajgunj, Kathmandu

Phone No.: 4412404 Extn 1093, **E-mail:** diu@iom.edu.np

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Department of Clinical Pharmacology
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Current management of atrial fibrillation

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, occurring in 1–2% of the population of the developed world. It may occur in isolation or secondary to structural heart disease, hypertension, myocardial ischaemia and infarction, hyperthyroidism, obesity and sleep apnoea. It can also develop following cardiac surgery or excess consumption of alcohol.

Atrial fibrillation may be categorised according to its presentation (initial, paroxysmal or recurrent, persistent) and duration. Its management depends on the assessment of thromboembolic risk and control of symptoms. In general, a decision is made to pursue either a rhythm or rate control strategy. With rhythm control the aim is to maintain the patient in sinus rhythm, while with rate control the aim is to control the ventricular rate with medication and accept permanent atrial fibrillation.

Assessing stroke risk

Atrial fibrillation carries the risk of cerebral thromboembolism and may be responsible for one in five of all strokes. Systemic thromboembolism, leading to stroke, transient ischaemic attacks or embolisation to other sites, is the most dreaded complication of atrial fibrillation. Anticoagulant therapy reduces this risk. The decision to use anticoagulant or antiplatelet therapy is dictated by the patient's risk of these events.Those with mitral valve disease should always be considered for anticoagulant therapy. The $CHADS_2$ {C-Congestive heart failure, H-Hypertension, A-Age ≥ 75years, D-Diabetes, S-Systemic embolism, including Stroke(previous episode)} score has been commonly used to stratify risk of patients with atrial fibrillation. The score for C-1 point, H-1 point, A-1 point, D-1 point, S_2-2 points. A score of 2 or more is generally taken to indicate a risk of thromboembolism which may warrant warfarin therapy, depending on the patient's haemorrhagic risk, although even those with only one risk factor ($CHADS_2$ score of 1) may benefit from oral anticoagulants .

Drug therapies for preventing stroke

For low-risk patients with atrial fibrillation, aspirin, or no treatment, may be sufficient. For higher-risk patients, treatment options include warfarin, aspirin and clopidogrel. Several studies have compared the efficacy of antiplatelet regimens to warfarin. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that warfarin (target INR 2–3) was superior to aspirin 75 mg daily. The ACTIVE-W trial showed that clopidogrel plus aspirin was associated with a 45% increase in the risk of stroke, non-central nervous system embolism, myocardial infarction or vascular death compared to oral anticoagulation. In summary, warfarin is more effective in preventing cerebrovascular events than dual antiplatelet therapy, although the danger of major bleeding is similar.

The INR is usually maintained between 2 and 3, but a higher range may be appropriate in patients with prosthetic heart valves or rheumatic mitral valve disease. In patients

unable to take warfarin, adding clopidogrel to aspirin reduces the risk of major vascular events by 11%, particularly stroke, but increases the risk of major haemorrhage by 57%.

Alternative oral anticoagulants

Several effective substitutes for warfarin are used for stroke prevention in North America and Europe. These include the direct thrombin antagonist dabigatran and factor Xa inhibitors such as rivaroxaban, apixaban, betrixaban and edoxaban.

Dabigatran is the first drug to show non-inferiority to warfarin for stroke prevention in atrial fibrillation. 150 mg twice-daily dose was superior to warfarin in efficacy with a similar risk of major bleeding whereas 110 mg twice daily was non-inferior for efficacy with a reduced risk of major bleeding.The risk of intracranial haemorrhage was less with both doses of dabigatran than with warfarin. Rivaroxaban is also an effective anticoagulant. The main advantage of rivaroxaban and dabigatran over warfarin is they have more predictable pharmacokinetics, and routine anticoagulation monitoring is not needed. No interaction between cytochrome P450 enzymes and dabigatran has been observed, although P-glycoprotein inhibitors such as amiodarone and verapamil may increase plasma concentrations of dabigatran and lead to an increased bleeding risk. There is also a risk of dabigatran accumulation in renal impairment.There is no antidote if bleeding occurs with dabigatran and rivaroxaban.

These drugs may replace warfarin for thromboembolic prophylaxis in atrial fibrillation if their cost-effectiveness can be shown. However, for a condition that requires long-term prophylaxis there are no long-term data to suggest that they will be safe and effective alternatives.

Device-based strategies for preventing stroke

Medical prophylaxis of stroke in patients with atrial fibrillation has been plagued by a high risk of bleeding complications, frequent drug interactions and a narrow therapeutic range of the drugs and hence poor compliance. Alternative approaches have been sought and a number of device-based treatments are becoming available or being evaluated.

Rate control

Most patients with atrial fibrillation are managed by controlling the ventricular rate. In patients with minimal symptoms, aggressive attempts to maintain sinus rhythm have not been shown to reduce mortality, improve quality of life, or prevent heart failure or thromboembolic complications. The ventricular rate may be controlled using beta blockers, non-dihydropyridine calcium channel blockers (for example verapamil) or digoxin. However, beta blockers should be avoided in patients with asthma, and digoxin and calcium channel blockers should be avoided in those with pre-excitation. Lenient control (resting heart rate less than 110 beats/minute) is as effective as strict rate control and is easier to achieve. Anticoagulation should be continued in these patients.

Rhythm control

The severity of symptoms usually drives the decision to pursue a rhythm control strategy. In symptomatic patients it may be reasonable to attempt to restore sinus rhythm. For those without structural heart disease who present within 48 hours of the onset of atrial fibrillation, immediate cardioversion (electrical or drug) may be attempted under cover of unfractionated or low molecular weight heparin. Those who present later should be presumed to have left atrial thrombus (unless this has been excluded with a trans-oesophageal echocardiogram) and cardioversion should be deferred until they have been effectively anticoagulated for at least three weeks. Anticoagulants should be continued for at least four weeks after successful cardioversion even if transoesophageal echo has excluded left atrial thrombus.

Although amiodarone is the most effective antiarrhythmic drug for maintenance of sinus rhythm its long-term value is limited by adverse effects.

Dronedarone cannot be recommended as a

first-line drug. Although it may not have the pulmonary and thyroid toxicity of amiodarone and is more effective than placebo in maintaining sinus rhythm and reducing the ventricular rate during recurrent atrial fibrillation, its use has been associated with worsening heart failure and increased mortality in patients with severe left ventricular systolic dysfunction.

Conclusion

The burden of atrial fibrillation will grow further as populations age. The major adverse outcome is embolic stroke. Newer antithrombotic regimens offer an alternative to warfarin as do techniques for left atrial appendage occlusion.

If the management of atrial fibrillation is directed towards restoring and maintaining sinus rhythm, percutaneous (catheter directed) creation of lesions within the left atrium may be warranted, but for most patients with permanent atrial fibrillation controlling the ventricular rate is the most practical strategy.

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