



Dronedarone: A New Therapeutic Agent for Atrial Fibrillation

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Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias encountered in clinical practice. It is found in approximately one in 25 adults older than 60 years and one in 10 adults more than 80 years (1). The life time risk of developing atrial fibrillation after age 40 is around 26 % in males (2,3). AF is a major cause of morbidity, mortality, stroke & heart failure(4-6). The therapeutic options in the treatment of atrial fibrillation include rhythm control by restoration to sinus rhythm, rate control and reduction in the risk of thromboembolic phenomena. The benefit of one treatment option over the other (rate vs rhythm control) is not very clearly established because the effectiveness of anti arrhythmic drugs is only 50 to 70 % with the concomitant risk of proarrhythmia.(7). On the other hand using rate control as the sole treatment option allows the underlying arrhythmia to persist. AF ablation(catheter ablation) maybe appropriate as a treatment option in severely symptomatic patients or in those in whom pharmacological treatment has failed (3,8). In pharmacological treatment of AF, class IA, IC and III antiarrhythmic agents can be used to terminate acute onset AF and prevent its recurrences. No one drug is superior to the other and selection is complicated due to the risk of proarrhythmias and other adverse effects (9-11). Dronedarone, a new benzofuran derivative, resembles amiodarone in its electrophysiological profile. Yet it has different relative effects on individual ion channels and structural modifications which help to eliminate the non cardiovascular adverse effects of amiodarone (12).

Chemistry

It is a benzofuran molecule, the empirical formula is C₃₁H₄₄N₂O₅ S, HCL and has a relative molecular mass of 593.2. The iodine moieties of amiodarone considered responsible for the thyroid abnormalities caused by it are absent in dronedarone. The addition of a methyl sulphonyl group gives dronedarone less lipophilicity thereby shortening its plasma half life, reducing the risk of organ toxicity by decreasing its accumulation in body tissues.

Mechanism of Action

Dronedarone is a multi channel blocking drug which possesses properties of all four Vaughan Williams anti-arrhythmic classes (12,13). The actions include -blockade of outward potassium channels(class III effect), blockade of rapid inward Na⁺ channels(class I effect), antagonism of alpha and beta adrenergic receptors(class II effect) and blockade of slow inward calcium channels(class IV effect). The class I and III effects provide rhythm control while the class II and IV effects are responsible for the rate controlling properties of dronedarone. The other pharmacological properties include vasodilatory effects, anti-adrenergic effects and blood pressure lowering properties (14-16). The balanced inhibition of multiple outward currents may be the reason for the decrease in the incidence of proarrhythmias with dronedarone. Dronedarone also prevents the occurrence of early after depolarisations (EADs), even those induced by class III agents.

Electrophysiological Effects

Dronedarone and amiodarone have a similar electrophysiological profile as studied in animal models (12,17). Dronedarone use showed a significant prolongation of the action potential duration at 90% repolarisation (APD 90). In rabbit ventricular myocardium, oral dronedarone was shown to be more effective in prolonging ventricular action potential duration (APD) than oral amiodarone (12). Oral dronedarone has been shown to exert a dose dependent effect on PR and QTc intervals but not the heart rate in healthy human volunteers (18,19). Dronedarone does not appear to affect the circadian variation of QT intervals and heart rate. Dronedarone is also an antagonist at alpha and beta adrenoreceptors.

Pharmacokinetic Profile

Oral dronedarone is poorly absorbed in the fasting state hence its absorption is better in the fed state (18,19). Therefore, it is recommended to be taken with food. Dronedarone has non linear pharmacokinetics, it has more than dose proportional increase in mean maximum plasma concentration(C_{max}) and area under the concentration

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time curve (AUC) (18). Within 3 to 6 hours of oral administration, dronedarone and its main circulating active metabolite (N-debutyl metabolite) reaches peak plasma concentrations. A steady state is reached within 4 to 8 days of treatment after repeated administration of 400mg twice a day with the mean accumulation ratio for dronedarone ranging from 2.6 to 4.5. The in vitro plasma protein binding of dronedarone and its N-debutyl metabolite is more than 98 %, both compounds bound mainly to albumin (18). Dronedarone is widely distributed in kidneys, liver, lungs, myocardium and also crosses the blood-brain and placental barriers. The steady state pharmacokinetics are similar in healthy volunteers and in patients with atrial fibrillation (18). Dronedarone is extensively metabolised through hepatic metabolism via the CYP3A isoenzyme. The orally administered drug undergoes a first-pass effect compared to the intravenous preparation which does not. The major metabolic pathway includes N-debutylation to form the main metabolite which has a 3 to 10 times lower pharmacological activity than dronedarone. This metabolite contributes to the pharmacological activity of dronedarone in humans. Oral dronedarone is mainly (84%) excreted in faeces with approximately 6 % of the labelled dose in urine. Following intravenous administration the plasma clearance of dronedarone ranges from 130-150L/h. Dronedarone is eliminated from the plasma in a biphasic manner with an elimination half life of 13 to 19 hours, following intravenous administration.

Drug Interactions

As dronedarone is metabolised primarily by the enzyme CYP3A, drugs that inhibit this enzyme may increase the serum concentration of dronedarone. In addition, dronedarone itself is a moderate inhibitor of CYP3A and can interact with drugs which are substrates of CYP3A and CYP 2D6. CYP3A inducers like carbamazepine, phenobarbital, phenytoin and rifampicin, if used along with dronedarone, lead to reduced dronedarone exposure. Co-administration with ketoconazole which is a CYP3A inhibitor leads to a 17 fold increase in dronedarone exposure. Hence, CYP3A inhibitors like clarithromycin, ketoconazole and ritonavir should not be co-administered with dronedarone (18).

Drugs that prolong QT interval like phenothiazines, cisapride and tricyclic antidepressants should not be given

concomitantly with dronedarone as they may induce torsade de pointes. Digoxin can potentiate the electrophysiological effects of dronedarone and if both need to be co-administered the dose of digoxin should be reduced by approximately 50 % (19).

Clinical Studies on Dronedarone

The therapeutic efficacy of oral dronedarone involved a series of clinical trials involving more than 7200 patients. These trials include the phase II DAFNE study and four phase III studies: ATHENA, ERATO, ADONIS and EURIDIS.

DAFNE: This trial was designed to identify the most appropriate dose of dronedarone for preventing recurrence of AF after cardioversion in patients with persistent AF (20). This was a phase II randomised prospective, double blind trial on 270 patients in 11 countries. This trial determined that oral dronedarone 400 mg twice a day was the optimal dosage in these patients with persistent AF and significantly increased the time to first recurrence of AF compared with placebo over 6 months. This dose had the lowest rate of GI related side effects.

ATHENA: is the largest single antiarrhythmic trial conducted in patients with AF whose primary end point was combined all-cause mortality and hospitalisations for cardiac causes and secondary end points included death from any cause, cardiovascular (CV) death and first hospitalisation from CV reasons (21,22). Dronedarone demonstrated a significant 24% relative risk reduction in the combined primary end point of CV hospitalisations or death from any cause. Dronedarone also significantly reduced the risk of stroke by 34% in AF patients with CV risk factors (23). CV hospitalisations were significantly reduced including hospitalisations for acute coronary syndrome and AF related CV hospitalisation (24,25) Dronedarone is the only antiarrhythmic drug to have demonstrated a morbidity/mortality benefit in AF patients, according to this trial. The median time to first AF recurrence was prolonged, the average heart rate reduced and the progression to permanent AF was reduced in patients on dronedarone.

EURIDIS & ADONIS: These were identical twelve month randomised trials to study the effectiveness of dronedarone for the maintenance of sinus rhythm in patients with AF or atrial flutter (26). Dronedarone's



efficacy in maintaining sinus rhythm and reduction in ventricular rate during AF recurrence was proved in these trials.

ERATO: This trial showed that dronedarone was significantly more effective than placebo in controlling the ventricular rate in patients with permanent AF (27).

ANDROMEDA : This trial was conducted in high risk heart failure patients and was terminated early because of higher mortality in the dronedarone group compared to placebo which was attributed to worsening heart failure (28).

Indications

Oral dronedarone is approved by FDA and European Medicines Agency (EMA) to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter (AFL), with a recent history of AF/AFL and associated cardiovascular risk factors (age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter 50 mm or left ventricular ejection fraction <40%) who are in sinus rhythm or who will be cardioverted (18).

European Society of Cardiology (ESC) 2010 new Guidelines for the Management of Atrial Fibrillation (AF) have recommend that dronedarone should be used for maintenance of sinus rhythm as a first-line treatment option in all patients with paroxysmal and persistent AF (class of recommendation I, level of evidence A) other than those with CHF NYHA class III/IV or unstable CHF NYHA class II (class of recommendation III, level of evidence B) (29).

Singh *et al*, in their recent review have recommended that dronedarone should be considered in patients of AF/AFL with hypertension and substantial left ventricular hypertrophy only if they do not tolerate amiodarone which is considered a first line drug. In patients with hypertension and no substantial left ventricular hypertrophy, dronedarone may be considered as an alternative to amiodarone which is a second line agent for this population. According to their review, dronedarone`s modest efficacy in preventing AF/ AFL recurrence or rate control as well as questions regarding its long term safety leave its role in the management of this arrhythmia uncertain (30).

Contraindications

Dronedarone is contraindicated in NYHA class IV Heart failure or NYHA class II-III heart failure with a recent decompensation, second or third degree A-V block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker), bradycardia, concomitant use of strong CYP 3A inhibitors like ketoconazole, cyclosporine, concomitant use of drugs that prolong the QT interval, pregnancy and nursing mothers.

Adverse effects

The common adverse effects include nausea, diarrhoea, abdominal pain, vomiting, asthenia, bradycardia, rash and photosensitivity. As compared to amiodarone, dronedarone has been associated with reduced risk of thyroid disorders, sleep disorders and tremors and fewer episodes of bleeding due to less drug interactions with oral anticoagulants (31). FDA is alerting healthcare professionals and patients about cases of rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant (32).

Dosage

The recommended dosage of dronedarone is 400mg twice daily, administered orally with meals (18). Dosage adjustments are not required in elderly or in patients with mild to moderate liver dysfunction or mild to moderate renal dysfunction (18).

Current Status

Oral dronedarone has been approved in the USA (FDA), European union and Canada. It is also being marketed in India for patients with AF &/or atrial flutter. In UK, NICE has issued guidelines for dronedarone to be used only as second line therapy, as mentioned above.

Conclusion

Dronedarone is an effective anti arrhythmic drug which exhibits multiple effects, rate and rhythm control and also has vasodilatory, anti adrenergic and blood pressure lowering properties. It has shown effective rate and rhythm control efficacy by prolonging time to first AF recurrence and controlling heart rate in patients with AF. It has been proven to reduce CV hospitalisations and mortality in AF patients and demonstrates a favourable safety profile. It is also patient friendly because of its easy to use fixed dose regimen.



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