Episodic treatment and prevention of paroxysmal atrial fibrillation

Deneer, Vera Henriëtte Marie

Publication date:
2003

Link to publication in University of Groningen/UMCG research database

Atrial Fibrillation

Atrial fibrillation is, after premature beats from the atria and ventricles, the most frequently encountered arrhythmia in ambulatory patients. The prevalence of atrial fibrillation was estimated to be 0.8% in the Netherlands in the year 2000. Furthermore, atrial fibrillation is a common complication of coronary artery bypass grafting. The arrhythmia has been reported in up to 50% of patients during the first days after the operation.

Impulses from foci, located in the pulmonary veins or at other atrial sites, can initiate atrial fibrillation if non homogeneity of conduction and atrial refractoriness is sufficient to cause re-entry. Atrial electrical remodelling occurs within a few hours after the onset of atrial fibrillation and perpetuates the arrhythmia. During atrial fibrillation the atrium is activated by multiple randomly re-entering functional circuits. It is frequently associated with a rapid, irregular ventricular response. Paroxysmal atrial, one of the patterns of the arrhythmia, is characterized by recurrent episodes of atrial fibrillation, which often terminate spontaneously. Such an attack of atrial fibrillation frequently results in hemodynamic impairment and is accompanied by symptoms such as palpitations, dizziness, chest pain, perspiration, coldness and anxiety. In ambulatory patients, paroxysmal atrial fibrillation even appears to have a negative impact on quality of life.

After a patient has experienced one or more episodes of atrial fibrillation chronic treatment with antiarrhythmic drugs is often started either to maintain sinus rhythm or to reduce ventricular rate. In patients who become aware of the arrhythmia immediately or shortly after its sudden onset, self administration of an antiarrhythmic drug to restore sinus rhythm in the outclinic situation, i.e. episodic treatment, might be a useful alternative to chronic treatment. Such episodic treatment might have advantages compared to a chronic treatment with antiarrhythmics. Patient non compliance for antiarrhythmic drugs, side effects that necessitate a change in dosage or discontinuation of the medication and the incomplete suppression of attacks of atrial fibrillation are recognized disadvantages. Furthermore, episodic treatment implies an early intervention which seems attractive since it might give an early relief of symptoms and might prevent the occurrence of electrical remodelling which promotes its perpetuation. No properly designed, controlled, prospective studies on episodic treatment of paroxysmal atrial fibrillation are found in literature.

Atrial fibrillation often occurs following coronary artery bypass grafting during the first days after the procedure. Although the arrhythmia is in general not life-threatening and often self-limiting, it can have hemodynamic consequences, increases the incidence of perioperative stroke and my lead to intolerable symptoms requiring additional drug therapy or electrical cardioversion. The development of atrial fibrillation has been associated with an increased length of hospital stay and health economic burden. Sotalol has proven to be effective in reducing the incidence of atrial fibrillation after coronary artery bypass grafting. However, side effects requiring discontinuation of the treatment are frequently observed. Therefore, the potential benefit of prevention of atrial fibrillation by treatment with antiarrhythmic drugs should not be outweighed by the occurrence of adverse events.

The objectives of the studies described in this thesis were to investigate the rationale and feasibility of formulations of antiarrhythmic drugs for self administration outside the hospital to convert atrial fibrillation, to study the efficacy and safety of a selected formulation and to study pharmacokinetic and pharmacodynamic parameters that are considered to be important as far as efficacy and safety are concerned and for future research on this treatment strategy. Furthermore, studies were initiated to investigate the pharmacokinetics and pharmacodynamics of sotalol in the direct postoperative phase of coronary artery bypass grafting and to identify risk factors for the development of supraventricular tachyarrhythmias in this category of patients.

Chapters 1, 2 and 3 are introductory chapters. Subsequently, the thesis contains three sections. Section I addresses aspects of antiarrhythmic drugs and formulations of these drugs considered to be important in episodic treatment, section II focuses on oral flecainide in patients with an episode of atrial fibrillation and section III deals with atrial fibrillation following coronary artery bypass grafting. Finally, in **chapter 13** main results are discussed and directions for future research are given.

Antiarrhythmic drugs and formulations in episodic treatment of atrial fibrillation

Due to its simplicity of administration, oral loading could be an option for self administration outside the hospital. In **chapter 4** a review of studies in literature on oral loading with antiarrhythmic drugs to restore sinus rhythm in patients with an episode of atrial fibrillation is given. In all studies patients were hospitalized. The class Ic antiarrhythmic drugs propafenone and flecainide, appear to be effective in converting atrial fibrillation and seem to be safe despite having the potential of transforming atrial fibrillation into atrial flutter with 1:1 atrioventricular response. This adverse effect is rare and has also been observed in placebo treated patients. Oral sotalol, amiodarone, quinidine, digoxin and verapamil appear to be less effective. Due to the pharmacokinetics of flecainide, with low interindividual variability of absorption kinetics, no CYP2D6 genotype dependent formation of an active metabolite and a more rapid distribution to myocardial tissue based on animal experiments, flecainide seems to be a better candidate drug for episodic treatment of atrial fibrillation than propafenone. A single oral dose of 300 mg flecainide restored sinus rhythm in 59% and 68% of patients at 3 hours.

We stated that formulations of antiarrhythmic drugs to be used in episodic treatment should be easy to administer in the out clinic setting and should give a rapid and reproducible absorption profile, with high, short lasting peak concentrations. In **chapter 5** the absorption kinetics of several sotalol formulations are described. Sotalol is especially effective in converting supraventricular tachycardia e.g. AV nodal re-entry tachycardia and AV reciprocating tachycardia involving an accessory AV bypass tract, which, like atrial fibrillation, could also be treated upon the occurrence of an attack. In an open, randomized, crossover study seven healthy male subjects were given an intravenous infusion of 20 mg of sotalol, to assess bioavailability, an oral solution containing 80 mg of sotalol, an oral

solution containing both 80 mg of sotalol and 20 mg of cisapride and an 80 mg sotalol tablet which was taken sublingually. The addition of cisapride to an oral solution of sotalol decreased the median time at which maximum serum concentrations were reached from 2.79 h to 1.16 h and increased the geometric mean of the absorption rate constant from 0.49 h^{-1} to 1.26 h^{-1}. Compared to the sublingually administered tablet with a median time of maximum concentrations of 2.12 h and an absorption rate constant of 0.56 h^{-1}, the sotalol/cisapride oral solution resulted in a much faster absorption of sotalol. Based on the absorption kinetics the sotalol/cisapride oral solution might be suitable for the episodic treatment of supraventricular tachycardia. However, cisapride has been associated with the occurrence of torsade de pointes. Most cases were related to high cisapride plasma concentrations as a result of high dosages, renal insufficiency or the concomitant use of CYP3A4 inhibitors. In several countries it was recommended to avoid the concomitant use of other QTc prolonging drugs, such as sotalol, and later it even became contraindicated. However, in literature there are no reported cases of patients with long QTc or torsade de pointes, based on the combined use of sotalol and cisapride.

Oral mucosal drug delivery has the potential of a rapid onset of action of drugs. Since the sublingual administration of a conventional oral sotalol tablet did not result in a rapid absorption of sotalol, ex vivo permeation studies through porcine buccal mucosa were performed. Results are described in **chapter 6**. The transport of sotalol through porcine buccal mucosa from an aqueous solution did not improve by increasing pH from 7.4 to 9.0, at which the partition coefficient (chloroform/buffer) of sotalol is highest. Sodium glycocholate, a bile salt which has proven to enhance the permeation of several compounds through buccal mucosa, did not improve the transport of sotalol. At pH 7.4, in contrast to pH 9.0, the addition of 1.0% (w/v) sodium glycocholate even decreased the permeated amount of sotalol. Flecainide base in propylene glycol resulted ex vivo in a better transport of flecainide as compared to an aqueous solution of the more hydrophilic flecainide acetate at pH 5.8. The presence of sodium glycocholate reduced the transport of flecainide base. However, the permeated amount and flux were increased 110- and 75-fold by adding 1.0% (w/v) sodium glycocholate to a solution of flecainide acetate at pH 5.8 with the permeated amount of flecainide being 510 μg (1231 nmol). The highest permeated amount obtained for sotalol was 64 μg (235 nmol). Flecainide, rather than sotalol, seems to be a candidate drug for the development of a buccal formulation.

The two previously described chapters mainly addressed aspects of formulations to be used in episodic treatment of paroxysmal atrial fibrillation. The rate at which the atria are loaded depends both on the rate at which the drug becomes systemically available and the rate at which the drug distributes to atrial tissue. If an antiarrhythmic drug distributes slowly to atrial tissue the impact of a more rapid absorption on the rate at which the atria are loaded might be small. The distribution of flecainide to atrial tissue was studied in patients undergoing coronary artery bypass grafting. The results of this study are described in **chapter 7**. Flecainide plasma levels and right atrial tissue levels were studied in 13 patients. Six patients received 100 mg of flecainide 2-4 hours prior to the extracorporal circulation. Seven patients received 100 mg of flecainide two times daily for two days prior to coronary artery bypass grafting and the last dose was given as in the single

dose group. Median ratios of tissue and plasma concentrations being 20.1 and 17.8 in the single dose and multiple doses group respectively, were similar. Flecainide atrial tissue concentrations correlated well with flecainide plasma concentrations. It was concluded that flecainide distributes rapidly to atrial tissue. Both QRS and QTc interval changes were not correlated with either flecainide plasma or atrial tissue concentrations. These results did not support the hypothesis that the large pharmacodynamic interindividual variability of flecainide occurs due to a highly variable disposition of flecainide in cardiac tissue.

Oral loading dosing of flecainide in patients with an episode of atrial fibrillation

A study was performed to investigate oral flecainide in converting atrial fibrillation. The results are presented in **chapters 8 and 9**. Flecainide was selected because of its high efficacy in converting atrial fibrillation and its rapid distribution to atrial tissue. Sotalol appeared to be effective in converting supraventricular tachycardia. However, atrial fibrillation is more often encountered in daily clinical practice. Therefore, it was preferred to focus on episodic treatment of atrial fibrillation instead of other supraventricular tachyarrhythmias. Patients were randomly allocated, stratified by the duration of atrial fibrillation, to receive 3 flecainide tablets of 100 mg each or an oral solution containing 300 mg of flecainide and 20 mg of cisapride. The latter formulation was chosen, because it already had proven to result in a favourable absorption profile in healthy subjects. The buccal administration of flecainide still had to be investigated in man. Data from 54 patients were analysed. In 63% of patients in the oral solution group and in 44% of patients in the tablets group cardioversion occurred. Conversion rates were not statistically different. In patients with atrial fibrillation lasting less than 24 hours, the oral solution appeared to be more effective in restoring sinus rhythm than the tablets. Conversion rates were 88% and 50% respectively. The oral solution reduced the median time of atrial fibrillation by approximately 3 hours, from 3.83 to 0.92 h. Only minor adverse effects were observed. Due to the potential QTc prolonging activity of cisapride special attention was paid to QTc intervals. Maximum measured QTc intervals during the 5 hours' observation period after ingestion of flecainide were similar in both treatment groups. A single low dose of 20 mg of cisapride in the absence of a CYP 3A4 inhibitor did not result in an increase of QTc interval in our study patients without severe cardiac disease.

The flecainide tablets gave a maximum concentration of flecainide of 0.43 mg/l at 2.37 h after ingestion. The oral solution resulted in a much faster peak concentration at 1.05 h. The maximum concentration of 0.60 mg/l obtained with the oral solution was higher as compared to the tablets. The faster absorption of the oral solution did not result in a larger interindividual variability of absorption parameters and parameters describing the relationship between QRS interval changes and concentrations. This was considered import for safety reasons. The differences in conversion rates of both formulations could not be explained by the observed differences in flecainide serum concentrations reached with the two formulations. Multivariate analysis showed that a duration of atrial fibrillation of

less than 24 hours (OR: 6.34, 95% CI: 1.70 - 23.73) and a higher absorption rate constant (OR: 1.20 per unit of 0.1 h⁻¹, 95% CI: 1.01 - 1.44) increased the probability of cardioversion. It seems that rapid loading of the effect compartment, i.e. the atria, appears to be critical to reach cardioversion. In case of both formulations, maximum flecainide serum concentrations and area under the curve could be accurately predicted by limited sampling models using 1 or 2 measured concentrations. For safety reasons it has been advised to start episodic treatment in a patient after an initial conversion in hospital. During the in hospital verification the limited sampling models are useful to check whether the maximum flecainide concentration is below a, for safety reasons, initially determined upper limit. These limited sampling models can also be used in assessing the relationship between drug exposure and the occurrence of side effects, when data from more patients become available.

Atrial fibrillation following coronary artery bypass grafting

During and after coronary artery bypass grafting patients receive multiple drugs and blood loss can be considerable. For pharmacokinetic and pharmacodynamic studies in this group of patients a selective assay for the determination of sotalol serum concentrations, requiring a low volume blood sample, has to be available. A method with a limit of detection and a limit of quantification of 0.04 mg/l and 0.06 mg/l respectively, when 0.5 ml was used, is described in **chapter 10**. The intra-assay precision and inter-assay precision were 1.1% and 11%. There was no interference in the chromatography from drugs which are commonly used in the immediate postoperative phase.

In **chapter 11** an observational study to identify risk factors for the occurrence of supraventricular tachyarrhythmias following coronary artery bypass grafting is presented. Patients received sotalol, diltiazem or digoxin. The data from 348 patients were analysed. None of the treatments was associated with a lower risk for the development of the arrhythmia. Supraventricular tachyarrhythmias, mainly atrial fibrillation, occurred in 28% of patients. Independent risk factors were: a history of the arrhythmia (OR: 25.31, 95% CI: 5.44 - 117.73), higher age (OR per year of age 1.05, 95% CI: 1.02 - 1.08), postoperative need for a temporary pacemaker (OR: 2.29, 95% CI: 1.01 - 5.17), preoperative treatment with digoxin (OR: 5.42, 95% CI: 1.24 - 23.63) and preoperative treatment with an ACE inhibitor (OR: 1.86, 95% CI: 1.03 - 3.36). In the majority of patients who received an ACE inhibitor preoperatively, this agent was discontinued for at least 30 hours or definitely. This suggest than the renin angiotensin system might play a role in the development of the arrhythmia postoperatively.

In **chapter 12** the pharmacokinetics and pharmacodynamics of sotalol immediately following coronary artery bypass grafting are described. Patients routinely received a fixed dose of 40 mg 4 times daily, with the first dose given within 8 hours after the end of the operation. Data of 221 patients were analysed. Arrhythmia occurred in 25% of patients and 34% of patients developed side effects leading to a temporary or definite discontinuation of the treatment. Most side effects developed on the first postoperative

day. Interindividual variability of sotalol serum concentrations on the first postoperative day was large with a coefficient of variance of 144%, which indicates that the absorption immediately following the operation is variable.

Concentrations of patients whose data were included in a validation data set could be accurately predicted. Therefore, the population pharmacokinetic model could be used to predict missing concentrations. Sotalol serum concentrations were not associated with the occurrence of supraventricular tachyarrhythmias. Age with an OR of 1.06 (1.02 - 1.09) per year of age was identified as independent risk factor for the development of sotalol associated side effects. The probability of developing side effects on the second postoperative day at a concentration of 1.92 mg/l was 0.5. In patients older than 70 years the probability of side effects was 0.5 at concentrations of 0.56 mg/l and 1.33 mg/l on the first and second postoperative day respectively. Considering all these aspects, a sotalol dosage regimen starting on the first postoperative day with a low starting dose seems to be more suitable.

Perspectives

Episodic treatment of paroxysmal atrial fibrillation seems an attractive alternative for chronic treatment with antiarrhythmic drugs. The efficacy appears to be dependent on the absorption profile of the pharmaceutical formulation. It seems worthwhile to investigate the combination of flecainide and a β-blocker or a calcium channel antagonist, which should prevent the occurrence of 1:1 AV conduction. In addition to efficacy and safety, quality of life scores and health care cost should be end points of future studies on episodic treatment.

Future research on prophylactic treatment with antiarrhythmic drugs should focus on high risk patients. The balance between benefit and risk of prophylactic treatment with antiarrhythmic drugs might change with increasing age. Despite a plethora of reports on atrial following coronary artery bypass grafting the mechanism is still incompletely understood. The molecular and genetic basis has hardly been studied so far. From the observational study the hypothesis was generated that the renin angiotensin system might be involved in the development of the arrhythmias postoperatively. This opens new questions for further research.