Ibopamine in heart failure. Efficacy and safety in clinical and experimental studies.

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SUMMARY AND CONCLUSIONS

The aim of this thesis was to assess the role of ibopamine, in the treatment of patients with heart failure. Ibopamine is an orally active dopamine agonist which has beneficial hemodynamic and neurohumoral effects. In the 10 Appendices both clinical and experimental studies are reported that were designed to examine the efficacy and safety of ibopamine. The clinical studies, which constitute Appendices 1-7, were conducted in patients with mild, moderate and severe heart failure. In these studies, we evaluated the influence of ibopamine on hemodynamics (Appendices 3,4,6), renal function (Appendices 5,6), neurohumoral parameters (Appendices 1,2,3), arrhythmias and electrophysiology (Appendices 1,3), exercise tolerance (Appendices 1,2), signs and symptoms of heart failure and side-effects (Appendices 1,5,7).

The experimental studies, which constitute Appendices 8-10, were performed in rats who underwent coronary ligation, thereby creating a model of myocardial infarction and heart failure. We first studied the effects of ibopamine when administered late (6 weeks) after myocardial infarction (Appendix 8). Subsequent studies were undertaken to investigate the effect of the drug when given early after myocardial infarction. Accordingly, we evaluated the effects of ibopamine on ventricular remodeling (Appendix 9) and ß-adrenoceptor density (Appendix 10).

The studies can be summarized as follows:

In **Appendix 1**, The Dutch Ibopamine Multicenter Trial (DIMT) is reported. This double-blind, placebo-controlled trial was performed in 161 patients with mild to moderate heart failure (80% of patients in NYHA class II and 20% in class III), who had background treatment of low dose diuretics or no medication. Patients were randomized to treatment with ibopamine (n=53), digoxin (n=55) or placebo (n=53) and follow-up was 6 months. Of the 161 patients, 128 (80%) completed the study. Compared to placebo, digoxin prevented a decrease in exercise time after 6 months ($p=0.008$ on intention-to-treat analysis), but ibopamine did not. In a subgroup of patients with a relatively preserved left ventricular function, ibopamine significantly increased exercise time. However, in patients with more advanced disease, more patients dropped out of the study for progression of heart failure on ibopamine than on digoxin, but the design of the study (patients were allowed to have 0-80 mg furosemide at entry to the study, but if more than 80 mg was required, they were considered a treatment failure), did not allow definite conclusions to be drawn from this finding. On the neurohumoral level, ibopamine and digoxin favorably affected plasma norepinephrine and plasma renin, but did not influence plasma aldosterone concentrations. With regard to safety, no proarrhythmia was observed with ibopamine and total mortality was similar between the treatment groups. Ibopamine was well tolerated and caused less side-effects than digoxin

in this study.

In Appendices 2 and 3, the effects of ibopamine in patients with moderate to severe heart failure are reported. In these 2 studies, ibopamine was given as adjunct to maximal, conventional treatment, including ACE-inhibitors. In **Appendix 2**, the effect of ibopamine on peak oxygen consumption (peak VO2) and plasma catecholamines (at rest and during exercise) was studied in 11 patients with moderately severe heart failure. After 6 weeks, peak VO2 was not significantly increased, but plasma norepinephrine was significantly reduced, both at rest (-23%) and during exercise (-41%). This blunting of sympathetic drive confirmed results from previous studies. As it has been suggested that neurohumoral inhibition implies a beneficial long-term effect, it might therefore also be true for ibopamine.

In **Appendix 3**, the electrophysiological profile of ibopamine was analyzed, both invasively (programmed electrical stimulation) and noninvasively (Holter monitoring) in 12 patients with heart failure and documented ventricular tachycardia, who were also treated with amiodarone. Invasive electrophysiologic measurements were performed at baseline and after 1 tablet of 100 mg ibopamine. Ambulatory arrhythmias on 24 hour Holter recordings were compared before and after 1 weeks ibopamine (3x 100 mg) treatment. Electrophysiologic effects of ibopamine were related to changes in hemodynamics and plasma catecholamines. Ibopamine did not significantly affect the induction of ventricular tachyarrhythmias and the effective refractory period during programmed electrical stimulation. Ambulatory arrhythmias on 24 hour Holter monitoring were also unchanged. It is suggested that the favorable effect of ibopamine on hemodynamics and plasma norepinephrine concentrations counteracts possible adverse electrophysiologic effects of the drug, or that ibopamine lacks such electrophysiologic effects.

Effects on invasive hemodynamics are often the first parameters studied, when a new drug like ibopamine is introduced. This was indeed the first work which we conducted in patients with heart failure (**Appendix 4**). The hemodynamic effects of ibopamine were studied again later in relation to the electrophysiologic (Appendix 3) and renal effects (Appendix 6). The effects of one tablet of 100 mg ibopamine were investigated both in the presence and in the absence of concomitant medication (including ACE-inhibitors) in 27 patients with moderate to severe heart failure. A significant increase in cardiac index was observed, which was mainly attributed to a fall in vascular resistance. Heart rate was not affected, and blood pressure slightly increased after 30 minutes, only in patients in whom other medication was continued, and was

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In **Appendix 5**, the cardiac and renal effects of the most commonly used dopaminergic agents (intravenous: dopamine and dopexamine, oral: levodopa, fenoldopam and ibopamine) were compared, and data of studies in normal men, and in patients with heart failure were reviewed. Intravenous dopamine is a valuable compound in the intensive care setting. With regard to dopexamine, questions remain concerning its additive value. Levodopa has a beneficial hemodynamic profile and induces no tolerance. Because of the high incidence of side-effects that are observed in the doses required for patients with heart failure, the drug can however, not be recommended for clinical use. Fenoldopam is a potent vasodilator, but it increases neurohumoral activity, which limits its long-term efficacy. As a result, it is not being used anymore for heart failure. Perhaps the drug may earn a place in the treatment of acute hypertensive crises. Ibopamine appears to have the most favorable profile of the dopaminergic agents, at least with respect to the long-term treatment of patients with heart failure.

The effects of ibopamine on renal parameters in relation to its cardiovascular profile are reported in **Appendix 6**. Ten patients with mild to moderate heart failure, who were clinically stable on digoxin and low-dose diuretics, underwent renal function studies before and after 1 tablet of 100 mg ibopamine, while invasive hemodynamics were monitored simultaneously. Ibopamine caused a 10% increase in effective renal plasma flow and a 10% increase in glomerular filtration rate (both $p < 0.05$), while filtration fraction and sodium excretion were unaffected. Cardiac output showed a similar increase, without an effect on heart rate and blood pressure. The data therefore suggest, that although ibopamine elicits favorable effects on renal function, this influence appears to be secondary to systemic hemodynamic changes, but not because of a selective renal effect.

In **Appendix 7** the clinical data on ibopamine were reviewed, particularly the long-term efficacy and safety. In most of the long-term trials that are discussed, large groups of patients were studied, who were using open label (=not placebo-controlled) ibopamine. One study that was performed earlier in our institution, is discussed, in which 25 patients with severe heart failure (NYHA class IV) were treated long-term with ibopamine 100 mg tid. The one-year mortality that was found in this study (38%) is in

agreement with data from other groups. Not included in this review are subsequent studies of which the results were not yet available at that time, particularly the DIMT study (Appendix 1). Also, our animal experiments had not yet been concluded at that time. Finally, some indications for the use of ibopamine in patients with heart failure are provided.

The experimental work with ibopamine (Appendices 8-10), conducted at the Department of Pharmacology and Clinical Pharmacology, was initiated to evaluate the effects of ibopamine in a rat model of myocardial infarction and heart failure. This model is currently the most widely used experimental heart failure model. Our aim was to study the neurohumoral and hemodynamic effects of ibopamine when given in the early and late phase after myocardial infarction. At the time we started these studies (1990), it had become clear, that early intervention after myocardial infarction with ACE-inhibitors was beneficial. Since the rat myocardium is endowed with predominantly α-adrenoceptors (in contrast to man), there was initially some concern, however, whether or not this model might be suitable to evaluate the effects of ibopamine.

We started therefore by giving ibopamine in the chronic phase (6 weeks) after myocardial infarction (**Appendix 8**). The principal findings of this study were, that after 3 weeks treatment, ibopamine significantly reduced the elevated plasma norepinephrine levels and cardiac (tissue) ACE-activity in rats with myocardial infarction. In contrast, other plasma neurohumoral parameters and hemodynamics were not different between infarcted and normal rats, and were also not affected by ibopamine. These findings suggested, that ibopamine acted as a selective sympathetic antagonist in rats with heart failure after myocardial infarction.

High levels of circulating catecholamines have been associated with:

1): ventricular hypertrophy and remodeling after myocardial infarction, because of growth-stimulating effects on the cardiac myocyte, and

2): down-regulation of myocardial ß-adrenoceptor density, with loss of contractile force and hemodynamic impairment.

Since ibopamine was shown to lower plasma norepinephrine levels in the first (pilot-) study (and also to reduce cardiac ACE), we hypothesized, that ibopamine a) might have a beneficial effect on ventricular remodeling and b) as a result, myocardial ß-adrenoceptor density might increase.

In **Appendix 9**, the effects of ibopamine on ventricular remodeling was studied, and compared to the effects of captopril. Drug treatment was started within 24 hours after myocardial infarction and the measurements were made 8 weeks later. Since

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receptor activation is related to the dose of ibopamine, both a high and a low dose was used. These regimens were compared with a standard dose of captopril and with a control (=no drug treatment) group. Ibopamine, particularly the higher dose, was found to significantly reduce infarct size and ventricular dilatation, compared to untreated infarcted rats. In the chronic phase, both ibopamine and captopril treated rats had a higher blood pressure than untreated infarcted rats. In addition, a significant reduction of the elevated plasma norepinephrine levels was caused by both ibopamine and captopril, compared to untreated infarcted rats. It should be noted, that although infarcted rats were again found to have significantly higher plasma norepinephrine levels than controls, and also that ibopamine treatment significantly reduced these levels, the values found in Appendix 9 (and 10) were markedly higher than in Appendix 8. This difference may be explained by a different method of blood sampling. The conclusion of Appendix 9 is, that both ibopamine and captopril favorably affect ventricular remodeling after myocardial infarction. Since previous studies have indicated that ibopamine has no vasodilating effects in the rat, it seems that the reduction in plasma norepinephrine levels may play an important role in this beneficial effect. Moreover, these findings confirmed the first part of our (aforementioned) hypothesis.

In **Appendix 10**, the influence of ibopamine on ß-adrenoceptor density and distribution ($ß_1$:$ß_2$) was investigated and this was related to possible changes in contractile function. In this study we compared 3 treatment regimens: ibopamine, ibopamine plus captopril, and no treatment (=control group). At the end of the study (after 8 weeks treatment), untreated infarcted rats had a significant impairment of baseline hemodynamics, compared to untreated normal rats. However, ß-adrenoceptor density (B_{max}) was unaffected, as well as the distribution of $ß_1$ vs $ß_2$ adrenoceptors. In rats with myocardial infarction though, a significant increase in B_{max} was observed with ibopamine plus captopril compared to untreated animals ($p=0.03$), while ibopamine alone did not induce a significant increase. It was concluded, that in this model of myocardial infarction and heart failure, there is a dissociation between ß-adrenoceptor density and left ventricular function. Further, it was found that although there was no decrease in B_{max} (=down-regulation) in untreated infarcted rats, an increase in ß-adrenoceptors was found in infarcted rats treated with ibopamine plus captopril. Although these findings do not fully confirm the second part of our hypothesis, a treatment effect of ibopamine appears to be present, and these promising results support further research with ibopamine in this model.

CONCLUSIONS

The following conclusions can be drawn from these studies:

- The hemodynamic effect of ibopamine, an increase in cardiac output, is mainly caused by peripheral vasodilation, although a mild positive inotropic effect could possibly be present. Heart rate and blood pressure are not affected.
- The renal effects of ibopamine are a (mild) increase in renal blood flow and glomerular filtration rate, and are mainly secondary to the systemic hemodynamic effect of the drug. The degree in which ibopamine exerts this renal effect depends on the clinical situation in which these parameters are studied. This holds also true for its stimulating effect on sodium excretion.
- Ibopamine inhibits neurohumoral activation in patients with heart failure. Plasma norepinephrine levels are reduced, both at rest and during exercise. Although the drug does not directly affect the renin-angiotensin system, plasma aldosterone, plasma renin and in experimental studies also cardiac (tissue) ACE may be lowered under special circumstances, depending on the degree of neurohumoral activation.
- The electrophysiologic effects of ibopamine are mild and neither invasive nor noninvasive studies indicate clinically significant proarrhythmic effects.
- Small, but significant increases in exercise tolerance have been reported when given alone or in combination with low-dose diuretics in mild heart failure. When ibopamine is given as adjunct to maximal medication in more advanced disease, this effect appears to be also present.
- The effects of ibopamine on signs and symptoms of heart failure were also beneficial when the drug was administered to the same patients groups.
- Ibopamine is well tolerated and in general a low incidence of side-effects is reported; gastrointestinal complaints are the most common.

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THE PLACE OF IBOPAMINE IN HEART FAILURE

The results of these studies are supported by other studies, which have been summarized in Chapter 3. During the time when these studies were performed, the treatment of heart failure has changed fundamentally due to new insights in its pathophysiology, as well as results of recently published major trials with old and new drugs. This is discussed in Chapter 2. When this is all put together, conclusions can be drawn with regard to the role of ibopamine in the treatment of heart failure. This is done in Chapter 4.

At the present time, the use of ibopamine can already be prescribed to all patients who have chronic manifest heart failure, despite treatment with ACE-inhibitors and diuretics, or as an alternative for ACE-inhibitors in patients who are intolerant for these agents, with the primary aim to improve symptomatology and quality of life. In patients with mild heart failure, ibopamine may be considered as monotherapy or in combination with diuretics. Furthermore, because of its neurohumoral modulating properties and the absence of proarrhythmia, one may even postulate a beneficial effect on the chain of events that will lead to manifest heart failure. This means, early pharmacologic intervention at a stage when only left ventricular dysfunction is present, without symptoms of heart failure. Results of impending studies on survival and on remodeling following myocardial infarction have to be awaited before definite conclusions can be drawn on this issue. Nevertheless, ibopamine offers a new approach to the treatment of patients with heart failure with promising perspectives.