Felodipine in congestive heart failure pharmacokinetic, pharmacodynamics, hemodynamic and clinical aspects
Dunselman, Peter Henricus Johannes Marie

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Summary

Chapter 1 offers an introduction in which the place of vasodilator therapy in heart failure is described. A review of the relevant studies with vasodilating drugs is presented. In the second part, the methodological problems in heart failure research are analyzed. In the third part the results of published studies with felodipine in congestive heart failure are discussed, together with the results of studies in other circulatory diseases. The aims of the study published in this book are outlined in the last part of the chapter.

Chapter 2 evaluates the necessity of an objective measurement to assess the severity of congestive heart failure. It is demonstrated that the subjective appraisal of patients' complaints, the New York Heart Association (NYHA) Classification separates patients with a mild to moderate impairment of functional capacity very well from patients with a moderate to severe impairment of functional capacity, but it also shows that about one third of the patients with congestive heart failure, eligible for research protocols by their history and documented left ventricular dysfunction, will be wrongly classified when an objective assessment of heart failure, the measurement of maximal oxygen uptake during a cardio pulmonary exercise test, is not performed. It is therefore concluded, that an objective assessment of patients' performance at exercise is necessary for a proper selection procedure of patients for heart failure studies.

Chapter 3 describes the pharmacokinetics of felodipine after acute intravenous and chronic oral treatment, and the relationship between flow and pharmacokinetics. The data of congestive heart failure patients are compared with data from young healthy individuals and hypertensive patients. Significant correlations were found between cardiac output before therapy and felodipine absorption characteristics after therapy. An increase in flow during chronic oral therapy induced by felodipine itself may lead to an increase in bioavailability of the drug, and thereby to higher plasma levels. The pharmacokinetics of felodipine in congestive heart failure patients are almost equal to those in elderly hypertensives. Compared with young healthy individuals, oral clearance is reduced by 50%, and terminal half life is increased in the same order. It is concluded that felodipine treatment should be initiated at a low dosage in patients with congestive heart failure, that an individual dose titration is necessary, and that special attention should be given to the possibility that the pharmacokinetic characteristics of a vasodilating drug may change during therapy, as a result from changes in liver blood flow, induced by the drug itself.

Chapter 4 analyzes the pharmacodynamics of felodipine intravenously in patients with congestive heart failure. Analysis of the changes in hemodynamic variables over time demonstrated a clockwise hysteresis in heart rate, cardiac output and systemic vascular resistance, but not in mean arterial pressure. This de-
monstrates that a physiological adjustment occurs after massive vasodilation, resulting in a mean arterial pressure that remains closely related \((r = 0.97, P < 0.001)\) to felodipine plasma levels over a wide range. It is concluded that the observed hysteresis does not reflect the onset of early tolerance, and that in pharmacodynamic studies with vasodilating drugs pressure variables are more important than flow and resistance variables.

In Chapter 5 an analysis is made of the possibility to predict oral pharmacokinetics of felodipine at steady state after 8 weeks chronic treatment from intravenous slow bolus pharmacokinetics before oral treatment. In patients whose intravenous data resulted in well predictable oral pharmacokinetic data, predictability was significantly correlated with half life, plasma clearance and distribution volume of the intravenous study. Analysis of the data after 8 weeks chronic oral treatment revealed that no differences could be detected between the oral pharmacokinetics of predictable and unpredictable patients. This gave way to the conclusion that felodipine kinetics indeed change during, and, most likely, as a result from felodipine treatment itself.

Chapter 6 analyzes whether an interaction exists between felodipine and digoxin. Between group comparison of patients demonstrated a modest, non significant increase \((+15\%)\) in peak serum digoxin levels in the felodipine group, without differences in the trough and 6 hours post dose levels. Further analysis revealed a clear bimodal distribution of the observed difference in serum digoxin levels. A significant increase in serum digoxin levels \((P < 0.001)\) was observed only in patients with high felodipine plasma levels. The lack of differences at trough and 6 hours post dose levels resulted in the conclusion that these differences were caused by changes in absorption of digoxin at high felodipine plasma levels. The observed increase in serum digoxin levels warrants monitoring of trough and peak levels of digoxin in patients with congestive heart failure, concomitantly treated with felodipine.

The beneficial clinical and hemodynamic effects of felodipine in congestive heart failure are described in Chapter 7. The results of a double blind, placebo controlled, randomized, parallel study during a treatment period of 8 weeks are presented. Between group analysis of difference in changes revealed that felodipine increased cardiac output, decreased systemic vascular resistance while heart rate remained unchanged. Exercise duration increased significantly, without significant changes in maximal oxygen uptake. Side effects were minor and appeared to be dose related.

In Chapter 8 the results of cardio pulmonary exercise tests with measurement of oxygen uptake at rest, during submaximal and maximal exercise, exercise duration and hemodynamic variables are compared in two patient groups, before and after long term (> 16 weeks) treatment with felodipine and enalapril respectively. Enalapril treatment resulted in an increase of both exercise duration and
assive vasodilation, related ($r = 0.97,$ $P < 0.001$) concluded that the ob-

Artery dilating properties, lead to essential different results in cardio pulmonary exercise tests, making a direct comparison of their overall clinical efficacy in congestive heart failure even more interesting.

Chapter 9 discusses the necessity of further research with felodipine, in acute and chronic heart failure.

maximal oxygen uptake, but heart rate, mean arterial pressure and rate pressure product remained unchanged at every exercise level. Felodipine treatment gave a consistent reduction in all hemodynamic variables at all exercise levels, but no significant differences in exercise duration and oxygen uptake were observed between the groups. It is concluded that the arterial vasodilating calcium antagonist felodipine and the ACE-inhibitor enalapril, with both venodilating and arterial dilating properties, lead to essential different results in cardio pulmonary exercise tests, making a direct comparison of their overall clinical efficacy in congestive heart failure even more interesting.

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