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Sinus node inhibitors

A new concept in angina pectoris

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Foreword

Although surgical and catheter-based revascularization techniques have substantially improved today's therapeutic potential in ischemic heart disease, in the majority of patients treatment will be conservative for a number of reasons, the cost-effectiveness of non-pharmacological approaches being of major importance. During the last two decades, drug development for ischemic heart disease has been impressive and many new compounds have been added to our therapeutic armamentarium. Nevertheless, where mode of action is concerned, it is interesting to note that, despite all these efforts, we are still confined to three categories of drugs. Antithrombotics and platelet-active agents aside, these concern nitrates, betablocking drugs and calcium antagonists, agents which reduce ischemia by diminishing cardiac work or wall stress, thereby affecting myocardial oxygen demand and/or by improving coronary blood flow. Alone or in combination, these agents have proved to be efficacious in the treatment of angina pectoris or other symptoms of ischemic heart disease in a number of patients, but certainly not in all. Moreover, as side-effects are often a problem with current antianginal compounds, the physician may find himself restricted in his therapeutic capabilities and in need of new and, preferably, alternative forms of pharmacological treatment.

This has been recognized by pharmaceutical companies and has led to several interesting new developments. Although often in their initial stages, novel, but promising concepts in antiischemic pharmacological therapy include calmodulin antagonists, potassium channel modulators, intracellular-acting antioxidants, and agents which have direct myocardial metabolic effects, such as carnitine derivatives. Moreover, for certain conditions, modulation of ischemia-induced neurohumoral activation by converting-enzyme inhibitors may be of therapeutic value.

A different novel concept in antiischemic therapy, sinus node inhibition, is addressed in this volume. Reduction of heart rate as a mechanism to limit myocardial oxygen demand is, of course, not a new concept, this being one of the major effects of betablocking drugs and certain calcium antagonists. However, specific slowing of heart rhythm through a selective reduction of the spontaneous diastolic depolarization rate of the sinus node without concomitant effects on the heart is certainly a novel approach. Sinus node inhibitors (also referred to as "specific bradycardic agents") which have been developed up to now include the clonidine-derivative alinidine, falipamil – a modification of verapamil – and the benzazepinone derivative ULFS 49 CL. It is the latter which, through its specificity, appears to be the agent of choice in this class.

Consequently, this volume mainly concerns animal and clinical research with ULFS 49 CL. In both, the potential of the drug to limit or prevent myocardial ischemia through a modulating effect on heart rate during exercise without other apparent activities is clearly demonstrated. It is striking that, in the clinical studies presented in this volume, the antiischemic properties of ULFS 49 CL appear rather pronounced in relation to the moderate reductions in heart rate, both at rest and

during exercise. This suggests that different, as yet unknown, mechanisms of action may still be present.

Moreover, it indicates that this challenging and promising new concept in the treatment of myocardial ischemia needs to be investigated further. Besides mechanisms of action, the place of ULFS 49 CL in the treatment of myocardial ischemia as first-line therapy or added to currently available medication should be explored, as well as its potential usefulness in other areas of cardiovascular medicine.

W. J. Remme

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