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S5: CARDIOVASCULAR AND SMOOTH MUSCLE PHARMACOLOGY

S5-1
NEW DRUGS IN THE TREATMENT OF ACUTE HEART FAILURE: HOPE OR HYPE?

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Acute heart failure (AHF), defined by a rapid or gradual onset of signs and symptoms of HF requiring urgent therapy, is a heterogeneous, multifactorial and progressive syndrome presenting a wide spectrum of phenotypes often associated with multiple comorbidities. AHF represents a major health problem due to its high prevalence, morbidity, mortality and significant healthcare costs, and a therapeutic challenge for the clinician. In the last 25 years, multiple potential therapeutic targets involved in the genesis/progression of AHF have been identified and many promising new drugs were investigated. However, the treatment of AHF has not changed much over this time as new drugs improved signs and symptoms, but failed to improve HF outcomes when compared to placebo or conventional therapies. These considerations provide the stimulus for the development of new drugs that target the underlying pathophysiological processes leading to progressive myocardial dysfunction and unfavourable remodelling and improve long-term outcomes of patients with AHF. The development of new safer and more effective drugs for AHF should be based on well-supported hypotheses, robust preclinical data and well-designed randomized controlled trials. Interestingly, a repeated finding in AHF treatment has been the discrepancy between the positive results found in preclinical studies and the lack of efficacy and safety in phase II and III clinical trials. In this presentation the mechanisms of action, efficacy and safety of new drugs under development for the treatment of AHF (inotropes, vasodilators, hormones, atrial natriuretic peptides and NO-independent stimulators and activators of soluble guanylate cyclase, ß-arrestin-biased AT1R ligands) and the possible explanations for the discrepancy between preclinal and phase II-III trials will be analyzed. A better understanding of AHF triggers and pathophysiology will allow to identify new targets and develop novel therapeutic approaches that might prevent the progression of myocardial dysfunction and improve outcomes.

S5-2
NOVEL MEDIATORS OF INFLAMMATION IN VASCULAR DAMAGE IN HYPERTENSION

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Hypertension is a global burden that significantly contributes to target organ damage and is a major risk factor for cardiovascular diseases. Despite this knowledge recent evidence suggest that over the past 25 years, the number of individuals with prehypertension or established hypertension has increased substantially and this is associated with the estimated number of deaths. Different factors and mechanisms are involved in hypertension development and maintenance but at vascular level specific alterations are found in both patients and hypertension models. In general, endothelial dysfunction, vascular remodeling and increased vascular stiffness are key hallmarks of hypertensive vascular disease and they predict target organ damage and the development of future cardiovascular disease. Different factors and mechanisms have been involved in the vascular alterations observed in hypertension and it is now well accepted that low-grade inflammation triggered by several components of the innate and adaptive immune systems plays a key role in promoting a misbalance between vasoconstrictor/growth promoter and vasodilator/growth inhibitor factors in hypertension. Proinflammatory cytokines, oxidative stress derived from novel sources such as lysyl oxidase, prostanoids from the inducible isoform of the microsomal prostaglandin E synthase-1 and other mediators seem to have a role in vascular alterations in hypertension through their effects in NO availability, vascular smooth muscle cells proliferation or extracellular matrix deposition.

Key words: Hypertension; inflammation; endothelial dysfunction; vascular remodeling.

S5-3
DRUGS FOR PULMONARY HYPERTENSION: OLD STORIES OF PARTIAL SUCCESS, PARTIAL FAILURE AND NEW PERSPECTIVES

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Pulmonary arterial hypertension is a rare life-threatening progressive disease characterized by vasoconstriction, vascular remodeling and thrombosis. Over the last 20 years we have witnessed the introduction of an unprecedented large number of drugs belonging to different classes which are directed mainly to reduce the vasoconstrictor component. They restore endothelial function by mimicking or inhibiting endothelial derived factors: NO (inhaled NO, phosphodiesterase 5 inhibitors and soluble guanylyl cyclase stimulators) prostacyclin (epoprostenol and its analogues), and endothelin-1 (endothelin-1 receptor antagonists). Unfortunately, there are no approved specific therapies for the most common "non-arterial" forms of PH: PH due left heart disease (group 2) and associated to lung diseases and hypoxia. Current therapies improve symptoms and prolong survival but the disease remains fatal. Vasodilators are limited by several factors. First, they lack pulmonary selectivity, thus their systemic effects leading to hypotension often preclude the use of effective doses. Second, despite most approved drugs show antiproliferative effects to some extent, aggressive proliferative phenotypes are often drug-resistant. However, attempts to directly address proliferation with kinase inhibitors have failed in clinical trials. Third, vasodilators are often unable to induce effective vasodilation depending on the underlying vasoconstrictor mechanism. Finally, they may uncouple ventilation-perfusion ratio. Hypoxic pulmonary vasoconstriction (HPV) represents a crucial protective mechanism that redistributes blood flow away from diseased (hypoxic) lung tissue to the best oxygenated alveoli at the expense of elevated pulmonary pressure. Vasodilators, by inhibiting HPV, may also increase blood flow to poorly-ventilated areas of the lung decreasing arterial oxygenation.

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Aims and Scope

Basic & Clinical Pharmacology & Toxicology is an independent journal, publishing original scientific research in all fields of toxicology, basic and clinical pharmacology. This includes experimental animal pharmacology and toxicology and molecular (-genetic), biochemical and cellular pharmacology and toxicology. It also includes all aspects of clinical pharmacology: pharmacokinetics, pharmacodynamics, therapeutic drug monitoring, drug/drug interactions, pharmacogenetics/-genomics, pharmacoepidemiology, pharmacovigilance, pharmacoeconomics, randomized controlled clinical trials and rational pharmacotherapy. For all compounds used in the studies, the chemical constitution and composition should be known, also for natural compounds.

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