
Foreword

Diuretics in heart failure

Heart failure is a complex pathophysiological syndrome of diverse aetiology that is now assuming epidemic proportions worldwide. Some of the reasons for this are obscure—for example, the cardiomyopathies—but others are more obvious. Undoubtedly the increasing age of the population, which includes survivors of other lethal conditions, is the major reason for the increasing incidence of the syndrome. Treatment of hypertension, increasing salvage from acute myocardial infarction, and perhaps other preventive measures are also adding to the numbers of survivors of these primary pathological syndromes who live to develop heart failure. The syndrome of heart failure is increasingly replacing hypertension as the most frequent cardiovascular condition facing the physician; and the relative ease with which high blood pressure is pharmacologically controlled contrasts with the pharmacotherapeutic problems of the patient with heart failure. Moreover, once heart failure has become symptomatic it is imminently lethal. Pharmacotherapy can do nothing more than postpone by a few weeks and months the ultimate outcome. This may explain why there is currently no evidence in any developed country of a significant decline in deaths from heart failure.

Advances have been made in basic science and in clinical investigation, and there is a continuous unravelling of the increasingly complex pathophysiological features of the syndrome at all its stages. Despite major efforts in drug development, the gulf continues to widen between what is known of the biological processes and how to correct or modulate the progress of the disease by pharmacotherapeutic means. Fortunately, currently available drugs do much to lessen the suffering of patients in the congestive phase of the syndrome.

Diuretics indisputably remain the drugs of first choice in the treatment of congestive heart failure, irrespective of aetiology, age, sex, and the individual characteristics of the patient. Compared with other drug groups used in the treatment of heart failure, the pharmaceutical development of new diuretics has been in abeyance because of the efficacy of many of the earlier compounds. Their direct clinical investigation has also been inhibited by their success as the first-line drug of choice in patients with congestive heart failure. Many clinicians would probably consider it unethical to withhold them. The diuretics have widespread and potentially beneficial haemodynamic activities in congestive heart failure, both direct and indirect, because of their renal excretory activity. The reduction of pulmonary congestion and oedema relieves breathlessness and the consequent reductions in peripheral oedema, hepatic distension, and intestinal oedema also improve the patient's well-being. The diuretics are well tolerated and give rise to few adverse

side effects. This array of clinical benefits explains their pre-eminent role in the treatment of patients with congestive heart failure irrespective of its aetiology.

Their widely accepted efficacy has, however, tended to cloud many issues related to their use, including their impact on the patient at different stages of heart failure. The impact of different diuretic groups on the neuroendocrine profile and accurate information on their dose-response effects are unclear. The prognostic implications of such effects are unknown and the full implications of the partial or complete suppression of diuretic-induced neuroendocrine activation by other drugs used to treat heart failure, such as the ACE-inhibitors and β adrenoceptor antagonists, is equally obscure. Are diuretics responsible for the waning of the angiotensin suppressor effects of ACE inhibitors in some patients when both groups of drugs are given long term? Considerable clinical debate continues regarding their potential ability to aggravate or even precipitate cardiac arrhythmias (particularly in the presence of digitalis glycosides) through their influence on potassium and magnesium excretion. This controversy has been fuelled by the lack of pharmacologically precise studies. Their influence on lipid metabolism and uric acid mobilisation in heart failure has attracted little investigative attention. Although the impact of such a metabolic side effect on prognosis is unlikely to be substantial in the later stages of heart failure, it could be considerable in the earlier phases of the syndrome. Fortunately, the low doses of diuretics, which may be used in all but the terminal stages of heart failure, induce few if any measurable metabolic disorders.

A practical dilemma which frequently confronts the physician is the apparent development of diuretic resistance in patients with severe heart failure. It is now clear, however, that a combination of diuretics with different sites of action in the renal tubule overcomes this resistance and can relieve symptoms in the diuretic-resistant patient. This new knowledge should assist in correcting the unfounded prejudice of many physicians against using more than one diuretic at a time to treat patients with severe congestive heart failure.

Diuretics are universally accepted in the treatment of heart failure once it has entered the congestive phase, with symptoms of breathlessness, fatigue, and peripheral oedema; but how useful are they in preventing progression to this terminal phase? Their impact on outcome when they are started at the onset of the cardiac damage is a question increasingly mooted. At present there is no answer.

The diuretics used to treat congestive heart failure predominantly exert their activity in the loop of Henle. Most of these have the therapeutic drawbacks of high peak

plasma concentrations and a transient effect, which leads to a need for several doses a day. The future for diuretic therapy may lie in developing drugs with a longer duration of action that allow once a day administration.

The seminar reported in this supplement was designed to review many of the crucial clinical considerations related to the use of diuretics in heart failure. It was an opportunity to review new knowledge, many aspects of the practical treatment of heart failure, and also the formal clinical trials—both published and underway. It was outstanding in detailing many aspects of the

excretory role of the diuretics. The seminar was conducted under the auspices of the Drug Therapy in Cardiology Working Group of the European Society of Cardiology. Publication of this supplement is made possible by an educational grant from Boehringer Mannheim, Germany.

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