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Review

Pharmacokinetics and pharmacodynamics of cardiovascular drugs in chronic heart failure

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ABSTRACT

Pharmacotherapy in chronic heart failure (HF) is challenging, due to the diverse neuroendocrine, inflammatory, metabolic and immunological mechanisms involved in its pathogenesis, the presence of co-morbidities and use of multiple therapies. Further, physiological parameters influencing drug pharmacokinetics (PKs) and pharmacodynamics (PDs) may be altered in patients with HF.

There is growing evidence that the disease-induced physiological changes may influence the PKs and PDs of all drugs used in patients with HF. Therapeutic approaches should consider all factors that might influence the response to treatment and dosage should be tailored to individual patients. Hence, further studies are required to understand the PK and PD differences between chronic HF patients and healthy subjects. Because PK is difficult to be assessed in the individual patient with HF, PD effects should be used to tailor therapy in patients with HF.

1. Introduction

Heart failure (HF) is a growing cardiovascular disease affecting 1–2% of the population in developed countries [1]. It is a syndrome with high mortality and morbidity and it is often associated to other co-morbidities, above all in elderly patients, that may influence drug pharmacokinetics (PKs) and pharmacodynamics (PDs) used for the treatment of HF [2–4]. The pathogenesis of HF is complex and multifactorial, involving neuroendocrine, inflammatory, metabolic and immunological mechanisms [5].

Different classes of drugs are available for the treatment of patients with HF [6]. The aim of the pharmacological approach of patients with chronic HF is to improve survival and to reduce hospitalizations. However, in the acute phase the treatment is primarily aimed to improve symptoms and hemodynamics, while in the chronic phase it is aimed at improving long-term prognosis. According to the European Society of Cardiology guidelines [6], ACE-inhibitors (ACEIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor blockers (ARBs) (in patients intolerant to ACEIs) and diuretics are all indicated for the treatment of chronic HF. In addition, other pharmacological therapies, such as ivabradine and digitalis should be used in selected patient populations (with sinus rhythm and atrial fibrillation respectively) to improve prognosis. More recently, LCZ696 has shown mortality benefits in patients with heart failure and it will likely be a mainstay of treatment of heart failure once approved by the Regulatory Agencies. Finally, other drugs, such as trimetazidine (TMZ), ranolazine, antiarrhythmics, antihypertensive agents and inotropes, may be used to treat complications and/or co-morbid conditions.

Given the key role of both the renin angiotensin aldosterone system and the nervous autonomic tone in the pathogenesis and progression of HF, the neurohormonal antagonists (ACEIs, beta-blockers, MRAs and ARBs) are fundamental to modify the progression of systolic dysfunction in chronic HF, and are commonly used in combination with a diuretic to relieve symptoms and signs of congestion.

Since HF with reduced ejection fraction (HFrEF) is a systemic low-perfusion syndrome that can alter physiological parameters, the PKs and PDs of these drugs are often altered in patients with this condition [7]. Furthermore, also patients with HF and preserved ejection fraction often present with impaired renal and liver function that can alter the PK/PD properties of most cardiovascular drugs.

Whatever the etiology, the PK properties (absorption, distribution, metabolism, and elimination) of cardiovascular drugs may be altered in

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chronic HF. Furthermore, being HFrEF a chronic disease, body wasting and cachexia may develop [8], inducing additional changes in PK properties of a drug [9]. Understanding PDs in chronic HF is challenging as well, due to the high heterogeneity in the therapeutic responses to drugs.

The aim of this review is to summarize the state-of-the-art on PKs and PDs of established drugs used for treatment of chronic HF: ACEIs, beta-blockers, MRAs, ARBs, ivabradine, digitalis and diuretics. Further, we will review available literature on PKs and PDs of TMZ, the latter as a relatively novel agent with prognostic benefit in chronic HF [10].

2. Pharmacokinetics and pharmacodynamics of drugs in chronic HF: general considerations

Several factors influence the PKs of drugs in HF (Fig. 1). Gut wall dysfunction may lead to impaired absorption, which is also influenced by reduction of blood flow to the gastrointestinal tract [11], contributing to both chronic inflammation and malnutrition. On the other hand, increased gut permeability in HF patients could enhance transition of drugs from gastrointestinal tract to portal blood [12]. Blood flow reduction to central organs and peripheral tissue may lead to altered drug distribution in HF. Further, due to the marked increases in extracellular volume, differences in body composition may have an effect on drug distribution [13,14]. Plasma protein binding of drugs may also be altered in patients with HF, particularly after acute myocardial infarction in elderly and in patients with cachexia [7].

Besides absorption and distribution, hypoperfusion of organs typical of chronic HF may also influence drug elimination either by the liver or kidneys [7]. Impaired liver function causes slower drug metabolism and renal insufficiency slows elimination of drugs and their metabolites [11]. The frequent coexistence of renal and liver failure in patients with HF may result in decreased clearance of various drugs.

Although it has been suggested that most drugs exhibit lower volume of distribution (Vd) in HF [9], this depends on the degree of intravascular volume, in turn related to the use of diuretics, to the protein binding capability and degree of ionization. Also, given the same physiological condition (intravascular volume, renal and kidney function, protein content) completely different behaviors may occur for drugs that are uni-compartmentally distributed and those that are two-compartmentally distributed. All these conditions also may greatly vary within the same patient according to the clinical condition.

Plasma concentrations of drugs are therefore highly variable in patients with HF compared to healthy subjects. Due to decreased clearance of drugs, longer time is needed to achieve a steady state leading to a slower titration of drugs in patients with HF [15]. Similarly, PK of intravenously administered drugs in patients with severe HF is commonly altered because of the presence of renal and liver impairment and the altered Vd that may vary considerably within days or hours [16–18].

Thus, considering the disease-induced physiological changes that may influence the PK properties of drugs, given dose must be individualized in acute and chronic HF patients. Given that most of the drugs used in HF have a clear PD effect on cardiovascular physiological parameters the PD effects may be more appropriate to individualize treatment.

This patient centered approach is in disagreement with almost all trial designs that have aimed at target doses of a given drug. However, even in trials where forced titration has been pursued only a minority of patients achieved target therapeutic dose [19]. In trials that have demonstrated clinical efficacy of key drugs for chronic HF, patients with advanced disease, severe liver and/or renal impairment in whom PK and PD parameters could be different, were mostly excluded. Studies that primarily focused on most severe patients [20–22] report clinical benefit but the proportions of patients treated with target daily dose and average daily dose were not ideal. Furthermore, side effect profile was dose dependent in CONSENSUS trial [20]. It is therefore not well established whether guideline recommended target daily doses are equally effective and safe over all clinical stages of chronic HF or do we need to adjust pharmacological therapy as HF progresses.

Finally, PDs of drugs commonly used in chronic HF is further complicated by age-related differences in cardiovascular function [23]. Older patients with chronic HF may show impaired sinus node activity, altered baro-reflex sensitivity and an increase in systemic vascular resistance that may further alter drug response.

3. Angiotensin converting enzyme inhibitors

ACEIs are considered first-line therapeutic agents for the treatment of patients with stable chronic HF. Their mechanism of action is a

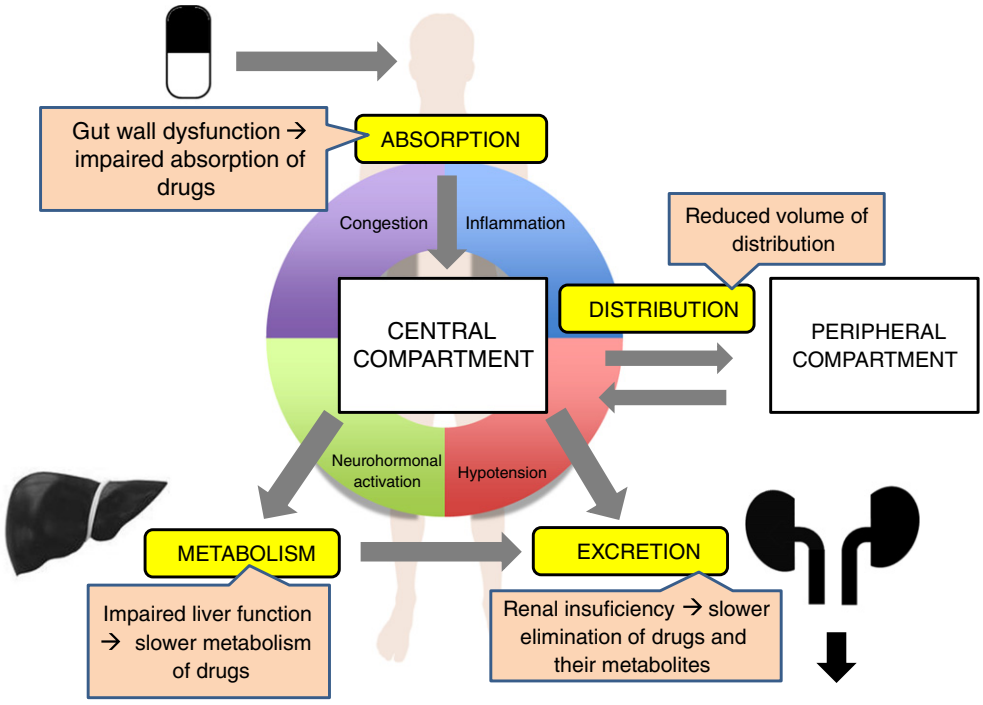

Fig. 1. Pharmacokinetics of drugs in heart failure.