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REVIEW ARTICLE

Clinical pharmacokinetics of drugs in cardiopulmonary associated cachexia without hepatorenal pathology: a systematic review

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ABSTRACT

Cachexia not only has a dramatically harmful impact on a patient's life, but also a poor response to therapeutic agents. The purpose of the present review is to provide updated information concerning the pharmacokinetic aspects of drugs used to treat cardiopulmonary cachexia in patients with no signs of hepatic or renal pathology. A systematic search of PubMed, the Cochrane Central Register of Control Trials, Science Direct, and Clinical Trials Registry (ClinicalTrials.gov), encompassing the period between 2000 and 2017, was conducted in accordance to PRISMA guidelines. Seven studies were identified. Collectively, these studies included a total of 196 individuals (19 healthy subjects and 177 diseased patients). This data review found no differences in bisoprolol and prothionamide absorption in cachectic patients with chronic heart failure and tuberculosis, but higher absorption of oflaxocin in the same set of patients was observed. The distribution of bisoprolol, prothionmaide, ceftazidime, and cefipirome was reduced in cardiopulmonary cachexia patients. Hepatic clearance of rifampin was equivalent in cachectic and non-cachectic patients that had normal hepatic function. Similarly in cardiopulmonary cachexia patients, renal clearance of ceftazidime was reduced by 19% but no significant differences in bisorpolol and prothionamide clearance were observed. In the case of cefipirome, both renal clearance and creatinine clearance were higher in cachectic patients with cystic fibrosis. From the limited evidence available, the main drug pharmacokinetic changes seen in cardiopulmonary cachexia patients were a reduction in the volume of distribution and impairment of clearance.

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Clinical pharmacokinetics; cardiopulmonary cachexia; hepatorenal pathology; chronic heart failure; chronic obstructive pulmonary disease

Introduction

The disorder of cachexia not only affects the patient's quality of life but also for the low response to therapy for concomitant diseases like cancer, chronic heart failure (CHF), etc. Results in the patient having poor survival. There is not a single definition of cachexia that is accepted worldwide (Aoyagi et al. 2015). This has resulted in a poor investigation of cachexia and the therapy for it (Porporato 2016).

Cachexia is mostly defined as a complicated disorder of the metabolism with underlying disease with or without loss of fatty mass, or when patients have a lean body mass index (LBMI) less than 16 kg/m^2 for males and 15 kg/m^2 for females (Schols et al. 2005; Evans et al. 2008). It is clinically assessed by the presence of underlying chronic illness, severe loss of weight, and signs of an abnormal metabolic system (Fearon et al. 2011).

Cachexia is associated with different chronic disorders like cancer, CHF, chronic obstructive pulmonary diseases (COPD), etc (Von Haehling and Anker 2014). Cardiac cachexia presents in 5–15% of CHF patients and the rate of survival is 18 m (Cicoira et al. 2011; Arthur et al. 2014). Similarly, about 25% of patients develop cachexia with chronic pulmonary diseases (Wagner 2008). The number of deaths from cardiac cachexia and pulmonary cachexia ranges from 10 to 15% and 20 to 30% per year, respectively (Von Haehling and Anker 2014).

With left ventricle dysfunction in CHF, rapid loss of weight occurs (Melenovsky et al. 2013). This severe weight loss has a negative impact on a patient's life (Younge et al. 2013). To manage the dysfunctioning of the ventricles, therapeutic drugs used are of different pharmacological classes. However, the body composition-related pharmacokinetic changes are not considered in the provision of drug-related services in patients with CHF and concomitant cachexia. Some drugs, such as carvidolol, must be supposed when body composition changes, as in the case of cachexia (Albers et al. 2008). Not only does cachexia result in fat

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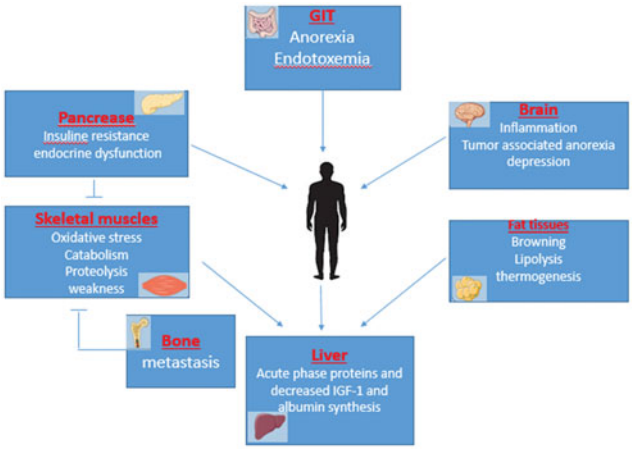

Figure 1. Effect of cachexia on functions of body systems (Porporato 2016).

wasting but alteration of the body composition also occurs. Therefore, drugs used in CHF with cachexia needs to be pharmacologically evaluated as excretion, body composition, and metabolic pathways alter in cachetic patients (Shammas and Dickstein 1988; Caldwell et al. 1995).

In chronic pulmonary disorders such as COPD, pulmonary tuberculosis and cystic fibrosis, and weight loss are considered to be the marker of a poor prognosis (Congleton 1999; Sharma et al. 2001; Muscaritoli et al. 2010; Chang et al. 2013). Cachexia associated with pulmonary diseases leads to loss of fat-free mass, specifically in the extremities. This leads to muscle fiber atrophy, and in turn correlates with other chronic diseases that make a patient prone to cachexia, such as CHF. Moreover, muscle fiber atrophy results in the whole-body metabolism being altered, ultimately affecting the pharmacokinetics of pharmaceutical agents prescribed for chronic pulmonary disorders (Sanders et al. 2016).

Cachexia has negative effects on the functioning of most organs, such as the gastro intestinal tract (GIT), liver, adipose tissues, skeletal muscles, and renal system (Figure 1) (Porporato 2016). Therefore, possible alterations in pharmacokinetics-induced pharmacodynamics due to cardiac or pulmonary cachexia can lead to dugs having an adverse or sub-therapeutic effect. These changes can result in aggravation of symptoms of chronic diseases involved. There is mounting evidence to suggest that lean body mass may be a better predictor of drug dosage than either total body weight or body surface area (Morgan and Bray 1994). Therefore, it is necessary to focus on drugs that are used for cardiac and pulmonary diseases in cachetic patients to evaluate their pharmacokinetics.

The hepatic and renal systems play an important role in the disposition of therapeutic agents. In the field of pharmaceutical and medical sciences, these two systems are usually considered of their effect on a drug's pharmacology (Poggesi et al. 2009). To establish a relation among cachexia, the renal-hepatic system, and a drug's pharmacokinetics, the liver and kidney should be assessed with respect to their physiological function.

In 2013, Trobec et al. reviewed the pharmacokinetics of drugs used in cachexia. However, they only included cachetic patients with a human immunodeficiency virus and cancer. Similarly, the hepatic and renal systems were not considered regarding their physiological function (Trobec et al. 2013). The purpose of the present review article is to update the information regarding the pharmacokinetics of drugs, specifically in patients with cardiac or pulmonary cachexia and no hepatic or renal pathology.

Materials and methods

Search strategy

A systematic electronic literature search of PubMed, the Cochrane Central Register of Control Trials, Science Direct and Clinical Trials Registry (ClinicalTrials.gov) was conducted between January 2000 and December 2017 according to PRISMA guidelines. We searched for articles published in the previous 6 m in the latest issues of related journals. The bibliographic search of the studies included, recent systematic reviews, Cochrane reviews, and meta-analyses for the relevant studies were also checked.

In PubMed, search terms describing body composition and pharmacokinetics were combined with the terms for cardiopulmonary diseases with normal hepatorenal function. In the other databases, a search was conducted using only three terms: "pharmacokinetics" AND "cardiopulmonary cachexia" but NOT "hepatorenal pathology."

We scanned all the titles and abstracts of studies identified through our searches and excluded articles that clearly did not meet selection criteria. We evaluated full-text versions of the remaining articles for their eligibility for inclusion in the review. The trials listing cardiopulmonary cachexia recorded numerical data on pharmacokinetics, and a specific description of these pharmacokinetic parameters were selected.

The keywords searched for were similar to those used in the review of pharmacokinetics in cachexia, but with some changes, and were as follows (Trobec et al. 2013):

Body wasting OR weight loss OR cachexia OR body composition OR malnutrition OR muscle wasting OR fat wasting OR fat free mass OR dexa OR dual energy x ray

absorptiometry OR dxa OR bioimpedance analysis OR low body mass index

AND

pharmacokinetic OR pharmacokinetics OR area under curve OR half-life OR Cmax OR Tmax OR drug absorption OR drug distribution OR drug metabolism OR drug clearance OR drug elimination OR dosage

AND

chronic heart failure OR heart failure OR CHF OR chronic pulmonary disorders OR chronic obstructive pulmonary disease OR COPD

NOT

renal pathology OR hepatic pathology OR renal impairment OR hepatic impairment OR hepatorenal pathology OR hepatorenal impairment.

Inclusion criteria

Studies that included human population (of both genders and any age group) were included. We did not use any language restrictions in selecting the studies. The studies selected were those that included patients with CHF or chronic pulmonary disorders, and who had been given one of three interventions.

a. Describe or compare the pharmacokinetics of a drug for cachetic patients with underlying cardiac or pulmonary diseases and non-cachetic subjects
b. Compare altered body composition with pharmacokinetics in cardiac or pulmonary diseases
c. Compare the pharmacokinetics of a drug with a severely malnourished population with underlying cardiac or pulmonary disease and well-nourished subjects.

Moreover, studies included should have data about renal function or hepatic function or both.

Exclusion criteria

We excluded studies that evaluated a drug not specifically used for cardiac or pulmonary disorders. Similarly, trials that studied pharmacokinetics of naturally occurring substances such as hormones, vitamins, etc. were also excluded.

Types of intervention

We searched for research articles that measured drug concentration in subjects' samples to compare pharmacokinetic parameters with cachetic patients with cardiac or pulmonary disease with normal renal or hepatic function.

Outcome measure

The target outcome was to check any changes in the absorption, distribution, metabolism, and excretion of a drug in relation to body composition reported by the investigator.

Data synthesis

We collected information on the study design, drug investigated, patient characteristics (underlying disease, renal function, and liver function), diagnosis of underlying disease, measurement of body composition, sampling time, analytical technique, numerical data for pharmacokinetic parameters in the control and experiment groups, pharmacokinetic model used, and conclusion of the study.

Assessment of the risk of bias

All stages of the study selection, data extraction, and quality assessment were independently assessed by both reviewers. Discrepancies were resolved after rechecking the articles and further discussion. Full consensus among authors was reached before the inclusion of any article.

Results

A total of 3412 papers were identified through a systematic search. Titles and abstracts of 1028 records were screened and 139 full-text papers were assessed for eligibility. Finally, seven papers were included in the analysis (Park et al. 2002; Lee et al. 2009; Bulitta et al. 2010; Bulitta et al. 2011; Ramachandran et al. 2013; Te Brake et al. 2015; Trobec et al. 2016).

Out of these seven studies, one study described pharmacokinetic parameters for cachectic patients with CHF (Trobec et al. 2016). Two studies correlated pharmacokinetic parameters in patients with cystic fibrosis and healthy individuals with a determined body composition (Bulitta et al. 2010; Bulitta et al. 2011). These three studies are presented in Table 1. The remaining four studies included patients with tuberculosis with wasting to examine pharmacokinetics, as presented in Table 2 (Park et al. 2002; Lee et al. 2009; Ramachandran et al. 2013; Te Brake et al. 2015).

Studies included 196 individuals, of which 19 were healthy subjects and 177 were diseased patients: CHF ($n = 46$), cystic fibrosis ($n = 20$), and tuberculosis ($n = 157$). A total of nine drugs were administered and, of these, seven were orally administered (Park et al. 2002; Lee et al. 2009; Ramachandran et al. 2013;

Table 1. Pharmacokinetics studies in cardiopulmonary associated cachetic patients with determined body composition.

Study	Trobec et al. 2016	Bulitta et al. 2010	Bulitta et al. 2011
Drug	Bisoprolol	Ceftazidime	Cefipirome
Study design	Longitudinal Study	Single-dose, single center, open, parallel group trial	Single-dose, single-center, open, parallel group trial
Drug application	Oral	Intravenous infusion	Intravenous infusion
Patient	Total of 46 patients Cachetic patients ($n = 7$) Non-cachetic patients ($n = 39$)	Total 15 volunteers Cachetic patients ($n = 8$) Healthy volunteers ($n = 7$)	Total of 24 volunteers Cachetic patients ($n = 12$) Healthy volunteers ($n = 12$)
Dosing	Daily dose of 10 mg bisoprolol in 46% of patients (Dose range, 1.25–20 mg/day)	2 g ceftazidime as intravenous infusion.	Intravenous infusion of 2 g cefpirome dissolved in 20 ml water for injection
Underlying disease	Chronic heart failure	Cystic fibrosis	Cystic fibrosis
Age (Avg)	74 y	Cachetic patients: 20 y Healthy volunteers: 22 y	Cachetic patients: 22.5 Healthy volunteers: 29
Gender (M%)	57	Cachetic patients: 50 Healthy volunteers: 57.14	Cachetic patients: 66.6 Healthy volunteers: 50
Renal function	Normally functioning as GFR: 51.8 ml/min Scr: 101 μmol/l	Normally functioning	Normally functioning as shown by creatinine clearance (ml/min) Cachetic patients: 131 Healthy volunteers: 116
Liver function	Normally functioning as AST: 0.41 μkat/l ALT: 0.32 μkat/l	–	–
Parameters of body composition	Fat mass (kg,%), Lean mass (kg,%), Body mineral content (kg), Appendicular skeletal muscle mass, and Skeletal muscle index	Total body wt (kg), Fat-free mass (kg), Lean body mass (kg), and Body mass index (kg/m^2)	Total body wt (kg), Lean body mass (kg), Fat Free Mass (kg), and Body mass index (kg/m^2)
Measured drug concentration	Prior to the morning dose and at 2, 3, and 4 h post-dose	At the start of the infusion (0 min), at the end of the infusion (5 min), and at 5, 10, 15, 20, 30, 45, 60, and 90 min and 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 h after the end of infusion	At the start of the infusion (0 min), at 5 and 10 min after the start of infusion, and at 5, 10, 15, 20, and 30 min and 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 h after the end of infusion for blood samples At the start of the infusion until 1 h after the end of infusion and at 1 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12,12 to 24,24 to 36, and 36 to 48 h after the end of infusion for urine samples
Pharmacokinetic model	One compartment model with first-order absorption and elimination	One, two, and three compartment model with linear elimination	One, two, and three compartment model with linear elimination
Findings	With lower body weight and SMI, the drug volume of distribution is reduced, which results in higher peak plasma concentrations of the drug.	A 19% lower unscaled total clearance and a 36% lower volume of distribution at steady state in cachetic patients than in healthy volunteers.	Total unscaled clearance (renal and non-renal) for cachetic patients was similar to healthy volunteers, but the volume of distribution was 6% lower for cachetic patients.

GFR: glomerular filtration rate; Scr: serum creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SMI: skeletol mass index.

Trobec et al. 2016) and two were intravenously administered (Bulitta et al. 2010; Bulitta et al. 2011). One drug was in the beta blocker class (Trobec et al. 2016), two were antibiotics in the cephalosporin class (Bulitta et al. 2010; Bulitta et al. 2011), and the remaining six were anti-tuberculosis drugs (Park et al. 2002; Lee et al. 2009; Ramachandran et al. 2013; Te Brake et al. 2015). Four of the seven studies examined liver function (Park et al. 2002; Lee et al. 2009; Ramachandran et al. 2013; Trobec et al. 2016), while six of the seven gave details about the functioning of kidneys (Park et al. 2002; Lee et al. 2009; Bulitta et al. 2010; Bulitta et al. 2011; Te Brake et al. 2015; Trobec et al. 2016).

Measurements of plasma concentrations and compartmental or non-compartmental pharmacokinetic models were used for pharmacokinetic analysis in the selected studies. Table 3 presents pharmacokinetic proprieties of the drugs that were investigated in the studies by comparing groups of subjects with wasting and without any wasting. Table 4 presents any changes in the absorption, distribution, metabolism, and excretion of drugs observed in cardiopulmonary associated cachexia patients with normal hepatorenal function.

The peak plasma concentration (Cmax) of a drug is affected by the extent of the absorption, volume of distribution, and clearance (Urso et al. 2002). Therefore in Figure 1, we presented a graphical comparison of the Cmax in cardiopulmonary-associated wasted patients with normal hepatorenal function and non-wasted individuals.

Table 2. Studies comparing pharmacokinetics between wasted and non-wasted tuberculosis patients.

Study	Te Brake et al. 2015	Ramachandran et al. 2013	Park et al. 2002	Lee et al. 2009
Drug	Rifampin	Rifampicin, Isoniazid, Pyrazinamide	Oflaxocin	Prothionamide
Drug application	Oral	Oral	Oral	Oral
Subjects (*n*)	Total 36 Patients BMI of $<16.0\,kg/m^2$ as severely malnourished ($n=7$) BMI of $<18.5\,kg/m^2$ as malnourished (n = 4) BMI of $\geq 18.5 kg/m^2$ as well nourished ($n=25$)	Total 84 children Stunting ($n=22$) Underweight ($n=31$) Wasting ($n=16$) Well nourished ($n=15$)	Total of 20 patients Group A $18.5 \leq$ BMI <23 ($n=12$) Group B BMI <18.5 ($n=8$)	Total of 17 patients Group A $18.5 \leq$ BMI <23 ($n=11$) Group B BMI <18.5 ($n=6$)
Dosing	Severe Malnourished received the dose of 12.4 mg/kg Malnourished received the dose of 11.4 mg/kg Well nourished received the dose of 9.6 mg/kg	According to RNTCP (India's Revised National TB Control Programme) guidelines for at least 2 w, that is, total six doses of each drug	300 mg twice a day (600 mg/day) for all patients	Multiple oral doses of 375 mg or 250 mg twice daily for at least 2 w
Disease	Pulmonary-TB	Pulmonary and extra pulmonary TB	MDR-TB	MDR-TB
Age (Years)	35 ($\bar{x}$)	1–12 (Range)	Group A = 35.5 ($\bar{x}$) Group B = 36.8 ($\bar{x}$)	Group A = 37.4 ($\bar{x}$) Group B = 39.2 ($\bar{x}$)
Gender (% Male)	39	40	Group A = 83.3 Group B = 75	Group A = 90.9 Group B = 100
Renal function	Normally functioning	–	Normally functioning as BUN (mg/dl) A = 12, B = 11.5 SCr (mg/dl) A = 0.8, B = 0.8	Normally functioning as BUN (mg/dl) A = 12.4, B = 14.8 SCr (mg/dl) A = 1.0, B = 1.0
Liver function	Normally functioning	–	Normally functioning as AST (μ/ml) A = 29.2, B = 27.4 ALT (μ/ml) A = 21.8, B = 22.4	Normally functioning as AST (U/ml) A = 22.9, B = 19.2 ALT (U/ml) A = 10.7, B = 9.2
Parameters of body composition	BMI	Z score and Nutritional anthropometry	BMI	BMI
Measured drug concentration	At 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hrs after drug intake	At pre-dosing, 2, 4, 6 and 8 hr after drug intake	At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after the ingestion of drug	At before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after the ingestion of drug
PK model	Non-compartment model	None	Non- compartment model	Non-compartment model
Findings	No significant correlation between BMI and rifampin (total and unbound) pharmacokinetics	Nutritional status (stunting and underweight) could influence plasma level of drug	The emaciation have an influence on the pharmacokinetics of ofloxacin	The extent of emaciation did not influence the pharmacokinetics of prothionamide

BMI: body mass index; TB: Tuberculosis; MDR-TB: multi-drug-resistant tuberculosis; BUN: blood urea nitrogen; Scr: serum creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Discussion

The disorder of cachexia is normally associated with severe weight loss (Deans and Wigmore 2005), and other factors. A drop in body weight is the main factor that has a bad impact on all organs and body systems. Almost all the organs of the body can be affected by cachexia, but the main consequences are changes in the gastrointestinal tract, abnormalities in cardiac and respiratory functions, acidification, and reduced concentration of the urine (Porporato 2016).

The pathophysiology of cachexia arises due to the tumor necrosis factor and systemic inflammation. This mechanism is common in all forms of cachexia or wasting, like cancer cachexia, human immunodeficiency virus wasting, or cardiopulmonary cachexia (Loncar et al. 2016; Rahman et al. 2016; Sanders et al. 2016).

While studying pharmacokinetics in cardiopulmonary cachexia, two main dependent factors are involved, that is, cachexia and underling diseases such as CHF or chronic pulmonary disorder (Shammas and Dickstein 1988; Taburet et al. 1990; Trobec et al. 2013). Therefore, we will discuss pharmacokinetic parameters in cardiopulmonary cachexia with respect to these factors.

Table 3. Pharmacokinetic properties of drugs in cardiopulmonary associated cachetic patients with normal hepatorenal functions and non-wasted individuals.

Study	Te Brake et al. 2015		Park et al. 2002		Lee et al. 2009		Bulitta et al. 2010		Bulitta et al. 2011		Trobec et al. 2016	
Drug	Rifampin		Oflaxocin		Prothionamide		Ceftazidime		Cefipirome		Bisoprolol	
Application	Oral		Oral		Oral		Intravenous		Intravenous		Oral	
Subject group	BMI <18.5	BMI ≥ 18.5	18.5 ≤ BMI <23	BMI <18.5	18.5 ≤ BMI <23	BMI <18.5	CF	Healthy	CF	Healthy	Low SMI	Normal SMI
Ka (l/hr)											2.14	2.14
C_{max}	10.9 mg/l	10.9 mg/l	4.37 ug/l	5.21 ug/l	2.5 ug/ml	1.8 ug/ml	445 mg/l	210 mg/l	221 mg/l	206 mg/l		
T_{max} (h)	2.0	2.5	2.88	2.56	3.4	3.9						
V/F or Vdss/F	25.1 L	23.7 L	1.2 l/kg	1.1 l/kg	2.6 l/kg	2.3 l/kg	9.14 L	14.3 L	14.4 L	15.3 L	156 L	270 L
AUC	54.8 h mg/l	54.6 h mg/l	24.05 ug/mlhr	31.43 ug/mlhr	11.3 ughr/hr	10.4 ughr/hr						
Half life (hr)	2.1	2	5.26	5.67	3	2.2	1.48	1.94	2.07	2.17		
CL/F	8.2 l/hr	8.2 l/hr	0.16 l/hr/kg	0.14 l/hr/kg	0.6 l/hr/kg	0.7 l/hr/kg	5.37 l/h	6.59 l/h	6.52 l/h	6.64 l/h	10.4 l/h	10.4 l/h
Cl_R (l/hr)			7.95	7.88								
Ke					0.2	0.3/h						
Mean residence time (hr)			6.99	7.17			1.54	2.10	2.16	2.33		
Unchanged urine (%)									84.4	87		

ka: absorption rate constant; Cmax: maximal concentration; Tmax: time of maximal concentration; V/F: apparent volume of distribution; Vdss/F: apparent volume of distribution at steady state; CL/F: clearance divided by bioavailability; AUC: area under concentration time curve; Cl_R: rate of clearance; ke: elimination rate constant. In case of Brake et al total Rifampin (protein bound and unbound) was considered.

Absorption

Cachexia affects the functioning of the gut, irrespective of the concomitant disease. This can lead to the absorption of orally administered drugs being altered (Kumar et al. 1987). The effect of cachexia on absorption depends on the drug's characteristics and the associated disease. Therefore, cachexia or malnutrition could increase or decrease, or sometimes have no effect on drug absorption (Kazeem et al. 2010). A reduction in a drug's action could occur when its absorption decreases due to weight loss (Peloquin et al. 1993; Bento et al. 2010). Many researchers have studied the kinetics of absorption in cachetic patients. For instance, in 1979 Semple et al. concluded that there were no changes in the absorption of iron, vitamin B12, and folate in cachetic pulmonary patients (Semple et al. 1979). However, data specifically for the absorption of drugs in patients with cardiopulmonary cachexia are very limited (Trobec et al. 2013).

CHF, the cause of cardiac cachexia, is a multisystem disorder. It reduces the flow of blood toward the intestine and alters the morphology and permeability of the intestine. However, intestinal drug absorption shows a very mild dependence on blood flow toward the intestine. It means that the absorption of a drug is unaffected by small changes in blood flow and a very large drop in blood flow is required (Carlton et al. 1996). In general, however, CHF can slow the rate or extent of the absorption or both, which could prolong the action of the drug (Sica 2003; Sandek et al. 2007). Trobec et al. in their study measured the absorption rate constant for bisoprolol. According to results, the rate of absorption of bisoprolol was the same for both cachetic and non-cachetic CHF patients (2.14 l/hr vs 2.14 l/hr). It was concluded that cachexia does not affect the rate of the absorption of the drug under study (Trobec et al. 2016).

Lung function is reduced in several chronic pulmonary disorders, which in turn increases intestinal barrier permeability. In the case of COPD, the gastrointestinal tract is the main site that is affected by the reduced capacity of the lungs (Fricker et al. 2018). Chronic pulmonary disorders alter the absorption of drugs in the same manner as CHF (Taburet et al. 1990).

In patients with multi-drug-resistant tuberculosis, the oral clearance of oflaxocine was significantly lower with a high value of area under the curve in severely malnourished patients. This shows that the absorption of the drug was increased in such patients (Park et al. 2002). On the other hand, a study by Lee et al. reported no significant difference in oral clearance and in the area under the curve for prothionamide, in spite of the

Table 4. Pharmacokinetics in cardiopulmonary associated cachetic patients with normal hepatorenal functions.

Drug	Rifampin	Oflaxocin	Prothionamide	Ceftazidime	Cefipirome	Bisoprolol
Route	Oral	Oral	Oral	IV	IV	Oral
Absorption		↓	=			=
Distribution	=	↓	↓	↓	↓	↓
Metabolism	=					
Excretion			=	↓	↓	=

patients having the same disease, that is, tuberculosis (Lee et al. 2009).

Besides the oral route, other routes for drug administration are also used for patients with COPD and CHF. Of these, the inhalation route is the most common route for pulmonary disorders (Simon et al. 2012). It is not clear whether pathological changes in the endothelium of the lungs in respiratory disorders alter the absorption of drugs or not. Some studies have reported that drug absorption through the inhalational route is not impaired in patients with COPD (Taburet et al. 1990). We did not find any article that could be used to draw a conclusion about possible changes in the inhalational route with absorption in cachetic pulmonary patients.

The changes that occur in GIT due to cachexia are not significant in mild-to-moderate cases of the underlying disease in affecting drug absorption. Therefore, it can be concluded that the effect of cardiopulmonary cachexia on the absorption of drugs occurs in severe stages of the underlying disease.

Distribution

The main symptom of cachexia is diminution of the body composition. The reduction in both total body fat and lean body mass (80 and 13%, respectively), leads to the volume of distribution of the drugs being altered, as the distribution depends on a drug's characteristics, like lipophilicity or hydrophilicity (Fearon and Preston 1990; Mangoni et al. 2009). Therefore, the distribution of both types of drugs is equally affected. Similarly, hypoalbuminemia may occur in cachexia, which could have an effect on the protein binding of a drug (47 Pichard and Kyle 1998).

In CHF, the volume of distribution reduces by up to 40% of the initial volume, which could result in a high level of a drug in the plasma (Woosley 1987). A significant difference in the distribution of bisoprolol between cachetic and non-cachetic CHF patients (156 L vs 270L) has been observed (Trobec et al. 2016). As bisoprolol is equally lipophilic and hydrophilic, its distribution, therefore, in both fatty and lean body mass is equally reduced (Leopold et al. 1986).

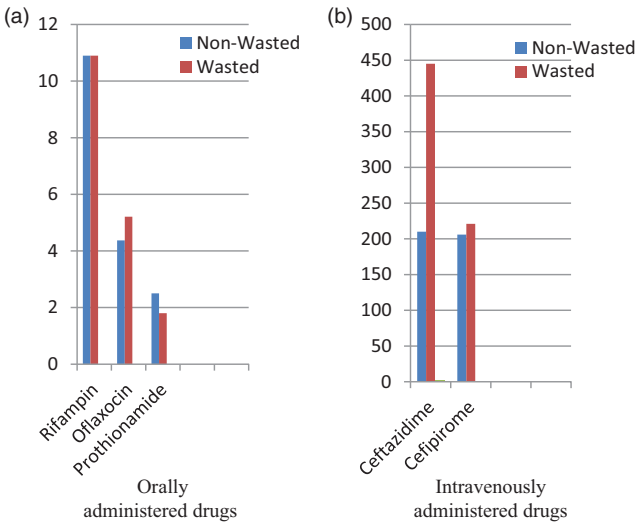

Figure 2. Comparison of peak plasma conc (Cmax) of drugs in cardiopulmonary associated cachetic patients with normal hepatorenal functions and non-cachetic individuals.

On the other hand, relevant data for distribution changes in chronic pulmonary disorders that can be used to draw a conclusion about the distribution of drugs are not available (Taburet et al. 1990).

Buileta et al. conducted studies on two antibiotics in the cephalosporin class, which were cefipirome, a poorly lipophilic drug, and ceftazidime, a hydrophilic antibiotic (Nix et al. 1992; Pea et al. 2005). They concluded that there were reductions of 36% and 6% in the volume of distribution for both ceftazidime and cefipirome, respectively, in cachetic patients with cystic fibrosis (Bulitta et al. 2010; Bulitta et al. 2011). This leads to a high concentration of the drug in the plasma (Figure 2). Similarly, there was a reduced volume of distribution for prothionamide in wasted tuberculosis patients compared with non-wasted tuberculosis patients but the difference was not statistically significant.

Brake et al. conducted a study on both protein-bound and unbound rifampicin pharmacokinetics. No numerical data were presented for the concentration of bound and unbound drugs in wasted and non-wasted patients. Thus, we were unable to draw a conclusion regarding the effect of pulmonary cachexia on protein binding (Te Brake et al. 2015).

Drug distribution is the main parameter affected by cachexia irrespective of the underlying cause, and could result in a low volume of distribution and high plasma concentration being associated with a drug.

Metabolism

Cytochromes are the main system of enzymes responsible for drug metabolism in the body (Tanaka 1998). Cachexia is shown to reduce the production of cytochromes in the human liver. This can alter the half-life of a drug and may require a reassessment of the dosage regimen for the patients (George et al. 1996).

In CHF, due to a reduced blood flow, the ability of the liver to metabolize the drugs is also reduced. Up to 80% of CHF patients present with some form of liver pathology (Woosley 1987). The same mechanism associated with blood flow reduction occurs at other metabolizing sites as well, such as the intestinal wall. These changes could increase the bioavailability of a drug at the target site by reducing the first pass effect (Darwich et al. 2010).

Similarly, chronic pulmonary disorders also lead to reduced cardiac output and ultimately decrease hepatic blood flow (Burrows et al. 1972). The hypoxia at the metabolizing sites due to decreased lung function can negatively affect the metabolizing function of the organs. Therefore, these factors, that is, decreased cardiac output, reduced hepatic blood flow, and hypoxia in chronic pulmonary patients could result in an increase in the plasma concentration of drugs (Taburet et al. 1990).

Brake et al. conducted a study on rifampicin, which is mainly cleared through hepatic metabolism (Burman et al. 2001). The patients included in the study had normal hepatic function. It was concluded that there was no significant difference in the clearance and half-life of rifampicin for wasted and non-wasted tuberculosis patients (Te Brake et al. 2015).

As liver is the main site for drug metabolism (Almazroo et al. 2017), the effect of cardiopulmonary cachexia on the metabolism of a drug, therefore, totally relies on the liver functioning normally. However, due to the fact that significant data were not available, we were unable to specify the effect of weight loss in cardiac or pulmonary diseases on drug metabolism.

Excretion

In the development of a dosage regimen for drugs that undergo significant excretion through glomerular filtration, weight loss should be considered as one of the factors, because severe loss of weight effects the excretion of such types of drugs (Johnston et al. 2014).

The renal system is affected in the same manner in patients with CHF as the hepatic system is; that is, drug excretion declines due to reduced blood flow (Woosley 1987; Cicoira et al. 2011). It has been reported that 7% of CHF patients have a normal kidney function, while most patients present with mild-to-moderate impairment in their glomerular filtration rate (De Silva et al. 2006). Trobec et al. in their study reported that cachexia has no significant effect on the clearance of bisorpolol in the cachetic group with CHF (Trobec et al. 2016). The literature shows that hepatic impairment or moderate renal impairment can lead to bisoprolol pharmacokinetics being altered (McGavin and Keating 2002). Therefore, the normal renal function of the patients can be one of the factors for the non-alteration in bisoprolol clearance.

The physiology of the renal system is also affected by changes in blood oxygen, carbon dioxide levels, and reduced blood flow. In chronic pulmonary patients, these factors are responsible for altering the function of kidneys (Sharkey et al. 1999; Gjerde et al. 2012).

Regarding cefipirome intravenous route, approximately 80% of the dose is unchanged, when it is eliminated in the urine. Elimination appears to be primarily due to glomerular filtration as the total clearance of cefpirome is approximately equal to creatinine clearance (Strenkoski and Nix 1993). It means that the excretion of cefipirome totally depends on the creatinine clearance of the patient (Lipman et al. 2003). Builleta et al. concluded in their study that both renal clearance of cefipirome and creatinine clearance were higher in cystic fibrosis cachetic patients when compared with healthy volunteers, that is, 5.59 l/hr vs 5.51 l/hr and 131 ml/min vs 116 ml/min. Therefore, creatinine clearance could be a major factor in the high renal clearance of cefipirome in cachetic patients (Bulitta et al. 2011).

Ceftazidime is a broad-spectrum cephalosporin antibiotic. The elimination of ceftazidime depends totally on renal excretion (Welage et al. 1984). It has been reported that there is a 19% lower clearance of ceftazidime in cachetic patients compared with healthy volunteers (6.59 l/hr vs 5.37 l/hr). The renal function of subjects in both groups was normal, but no numerical data were provided that can be compared with the excretion of the drug (Bulitta et al. 2010).

Prothioanamide is used as a second-line drug for tuberculosis, and the main site of its excretion is the renal system (Coyne et al. 2009). Lee et al. showed that there was no significant difference in the rate of elimination (Ke) of prothianamide in wasted and non-wasted

tuberculosis patients with normal renal function. They concluded that weight loss has no effect on the excretion of prothionamide (Lee et al. 2009). Subjects of both the groups had normal renal function, which could be one of the reasons why there were similar rates of excretion (Table 2).

In summary, the renal clearance of drugs in cardiopulmonary cachexia reduces in a direct relation with renal function. However, the elimination half-life is generally not affected due to the reduced volume of distribution on the other hand.

Limitations

Due to the lack of data, the number of studies of cardiac cachexia in particular was found to be small in number. Moreover, the articles that looked at tuberculosis patients did not provide any information regarding the number of patients, specifically with pulmonary tuberculosis (Park et al. 2002; Lee et al. 2009; Ramachandran et al. 2013; Te Brake et al. 2015). Instead, they included all the patients in one group.

Conclusion

The main changes in drug pharmacokinetics seen in cardiopulmonary cachexia are a reduction in the volume of distribution and impairment in clearance. Similarly, drug absorption is only affected in severe cases of cardiopulmonary cachexia, while the metabolism of drugs depends on the functioning of the liver and other metabolizing sites that could be affected by cachexia and underlying diseases. Due to the limited evidence available, further research regarding pharmacokinetics in cardiopulmonary cachexia is warranted.

Disclosure statement

No potential conflict of interest was reported by the authors.

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