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► **To cite this version:**

Kazeem A. Oshikoya, Helen M. Sammons, Imti Choonara. A systematic review of pharmacokinetics studies in children with protein-energy malnutrition. *European Journal of Clinical Pharmacology*, 2010, 66 (10), pp.1025-1035. <10.1007/s00228-010-0851-0>. <hal-00600757>

HAL Id: hal-00600757

<https://hal.science/hal-00600757v1>

Submitted on 16 Jun 2011

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HAL Authorization



A systematic review of pharmacokinetic studies in children with protein-energy malnutrition

Journal:	<i>European Journal of Clinical Pharmacology</i>
Manuscript ID:	EJCP-2010-0077.R1
Type of submission:	Original
Date Submitted by the Author:	19-May-2010
Complete List of Authors:	Oshikoya, Kazeem; University of Nottingham,, Academic Division of Child Health,; Lagos State University College of Medicine, Pharmacology Department Sammons, Helen; University of Nottingham, Academic Division of Child Health Choonara, Imti; University of Nottingham, Academic Division of Child Health

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42 **Key words:** protein-energy malnutrition, drug, absorption, distribution, protein-binding, metabolism,
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Abstract

Background: Protein-energy malnutrition (PEM) is a nutritional problem affecting many children world-wide. Its association with a wide spectrum of infections necessitates multiple drug therapies. A systematic review was performed to determine the effects of PEM on drug pharmacokinetics.

Methods: Literature search in MEDLINE and EMBASE databases (January 1960- December 2009) was performed. Malnutrition, undernutrition, underweight, protein-energy malnutrition, protein-calorie malnutrition, marasmus, marasmic-kwashiorkor or kwashiorkor was the medical subject heading (MeSH) descriptor used. Inclusion criteria were abstracts that assessed or discussed absorption, distribution, metabolism, elimination, clearance, pharmacokinetics or pharmacodynamics of drugs, except micronutrients and appetite stimulating drugs.

Results: Altogether, 41 publications were identified. A total of 34 drugs were studied. The absorption of 18 drugs was studied; the extent of absorption (AUC) was unaffected for 10 drugs. The plasma protein binding of 20 drugs was evaluated; it was significantly reduced for 12 drugs. The volume of distribution (Vd) of 13 drugs was evaluated; it was however unaffected for most of the drugs. The effect of PEM on total clearance and half-life of drugs primarily metabolised by the liver was studied for eight drugs. There was decreased total clearance and an associated increased half-life of five drugs. For two drugs (chloramphenicol and quinine), different degrees of PEM affected total clearance differently. The total clearance of six drugs primarily eliminated by the kidneys was studied; it was unaffected for four drugs but significantly decreased for two drugs (cefoxitin and penicillin).

Conclusions: Considering the proportion of children affected with PEM world-wide, there have been relatively few pharmacokinetic studies of drugs frequently used for their treatment. More studies are therefore required to establish the appropriate dose and safety of these drugs for PEM children. The studies need to recognise that PEM is a disease spectrum and should further look at the differential effects of kwashiorkor and marasmus on drug pharmacokinetics in children.

Introduction

Protein energy malnutrition (PEM), also referred to as protein calorie malnutrition (PCM), has long been recognised as a common problem, especially of children in the developing countries, whose inadequate nutritional intake is deficient for socioeconomic reasons [1]. PEM is a range of deficiency states, from mild to severe, defined as a range of pathological conditions arising from coincident deficiency of protein and calories in varying proportions, occurring most frequently in infants and young children, and commonly associated with infections [2].

PEM is responsible, directly or indirectly, for approximately half of the 10.8 million deaths per year in children under five. It also contributes to many deaths associated with infectious diseases among children in developing countries [3]. Infection is one of the major complications of PEM; malaria, bronchopneumonia and measles being the most frequently associated infections with PEM in African children [4]. HIV/AIDS and tuberculosis frequently co-exist with PEM but begin to manifest when the immunity is lowered [5]. The World Health Organization (WHO) has recommended empirical treatment of all children admitted for PEM with ampicillin and gentamicin [6], even in the absence of overt signs and symptoms of sepsis. Considering the wide range of pathophysiological derangements in children with PEM [7-9], the pharmacokinetics of many of the drugs used for their treatments is likely to be affected and this may require dose modification. This systematic review was therefore performed to determine the effects of PEM on drug pharmacokinetic parameters.

Methods

Identification of relevant literature

Articles describing drug absorption and disposition in malnourished children were searched using EMBASE and MEDLINE (January 1960- December 2009) and by reference tracking. In both methods, the search strategies involved an initial search for all relevant abstracts using the medical subject heading (MeSH) descriptor 'drug absorption' OR 'drugs absorption', limited to children between 0-17 years. Similar searches were done for drug distribution, metabolism and clearance by substituting the term 'absorption' with each of the terms 'distribution', 'pharmacokinetics', 'pharmacodynamic', 'metabolism', 'elimination' and 'clearance', respectively. Another search was made using the MeSH descriptors 'malnutrition' OR 'mal-nutrition' OR 'undernutrition' OR 'under-nutrition' OR 'underweight' OR 'under-weight' OR 'protein energy malnutrition' OR 'protein-energy

malnutrition' OR 'protein-calorie malnutrition' OR 'protein-calorie malnutrition' OR 'marasmus' OR 'marasmic-kwashiorkor' OR 'kwashiorkor'. The searches were later combined to give the desired abstracts. Abstracts that appeared in both EMBASE and MEDLINE searches were hand searched to avoid duplication and to judge whether they met the inclusion criteria.

Inclusion criteria were abstracts that assessed or discussed pharmacokinetics, pharmacodynamics, absorption, distribution, metabolism, elimination or clearance of drugs in children who are underweight, marasmic, marasmic-kwashiorkor, and/or kwashiorkor. Abstracts that assessed or discussed disposition of micronutrients and appetite stimulating drugs in malnourished children were excluded. Full articles of the relevant abstracts were then searched and retrieved. The references of the retrieved articles were searched manually in order to identify additional appropriate studies. The relevant additional articles that met the inclusion criteria were accessed.

Data abstraction

Two researchers (KAO and IC) reviewed each study independently, and using a standard form, extracted data on the number and year of studies; characteristics of the subjects and controls; types of drug studied; and the number of blood samples collected. The pharmacokinetic parameters studied (rate and extent of absorption, volume of distribution, protein-binding, metabolism, clearance and half-life) were extracted. We also extracted from each study data on the methods of PEM classification.

Results

Publications

The EMBASE search yielded 731 abstracts and MEDLINE 546 abstracts of potential use. 50 abstracts met the inclusion criteria. Most abstracts were excluded because they assessed serum macro- and micro-nutrients and serum proteins in the malnourished children. The abstracts were mainly original research (40), review articles (4) and letters to the editor (6). Both the original research articles and letters to the editor (46 publications) were included in this study. Five publications were further excluded because there were either insufficient details (no documentation of mean value of the data or the control data) or the data was published in more detail in a subsequent paper which was included in the final analysis [10-14]. Altogether, 41 publications were analysed in this study.

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3 The majority of the studies were published in 1970s (14) and 1980s (17), thereafter the
4 number progressively decreased over the next two decades (Figure 1). Thirty of the studies involved
5 one drug only. A total of 34 different drugs were studied.
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8 9 *Methodology of trials*

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11 The age range of the patients and control subjects used for the studies was three months to 16
12 years. The number of patients in individual studies varied from five to 41. Age matched, healthy
13 children were the control subjects in 25 studies. Nutritionally rehabilitated children were used as
14 additional control subjects in four studies and as the only control subjects in seven studies. Five studies
15 had no control subjects.
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19 PEM was classified in the subjects according to Wellcome Trust Party classification [8] (22
20 studies) and Gomez classification [9] (seven studies). Co-existing infections, including tuberculosis
21 (4), bacterial sepsis (3), malaria (2) and HIV with tuberculosis (1) were reported in the patients in 10
22 studies. One to 17 blood samples were collected from individual children.
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28 29 *Drug absorption*

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31 Table 1 shows the effect of PEM on absorption of 18 drugs [15-32]. The extent of absorption
32 of most of the drugs (10) was not significantly affected. Ideally, in pharmacokinetic studies, rate is
33 measured as K_a (hr^{-1}) and extent of absorption, F (%), as $\text{AUC}_{\text{oral}} \times \text{Dose}_{\text{i.v.}} / \text{AUC}_{\text{i.v.}} \times \text{Dose}_{\text{oral}}$. The extent
34 of absorption was reported in this review as AUC_{oral} or $\text{AUC}_{\text{i.m}}$ since most of the drugs were
35 administered either orally or intramuscularly. The extent of absorption of eight drugs was found to be
36 significantly increased. This was probably due to the effects of decreased clearance as all these drugs
37 were shown to have either a prolonged half-life or decreased clearance (see below). The extent of
38 absorption of aspirin [15], oral penicillin [19] and chloramphenicol [45], measured in terms of F (%),
39 was reported only in one study each. F was significantly decreased for chloramphenicol in kwashiorkor
40 by 85% compared to 44% in seven controls, $P < 0.05$ and marasmic-kwashiorkor by 85% compared to
41 30% in seven controls, $P < 0.05$ [45]. However, the difference in the F values for aspirin in both
42 malnourished children and controls (92% and 90%, respectively) was not statistically significant [15].
43 In the case of oral penicillin administered to fasted PEM children, F was decreased in underweight
44 children by 36% compared to 55% in six controls, $P < 0.05$; increased in marasmus by 66% compared
45 to 55% in six controls and in kwashiorkor by 83% compared to 55% in six controls, $P < 0.05$ [19]. The
46 statistical significance level of the decreased or increased F values for penicillin in PEM was however
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3 not reported. The decreased extents of chloramphenicol absorption reported by Eriksson et al [45] are
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5 in contrast to the increased extent of absorption in all forms of PEM reported in another study [27]. In
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7 addition, contrasting results were also documented for quinine. The extent of absorption of oral
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9 quinine was increased [30] whereas the extent of IM absorption was not significantly affected [21].
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11 K_a was reported only for chloramphenicol [45] and six other drugs (Table 1). It was
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13 significantly increased for sulphadiazine [31] and significantly decreased for sulphamethoxazole [32]
14
15 in children with PEM. In the studies involving children with different categories of PEM, the K_a of
16
17 chloramphenicol was significantly decreased in children with marasmic-kwashiorkor only [45] whereas
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19 it was significantly increased for oral penicillin in children suffering from kwashiorkor only [19].
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21 *Protein binding and distribution*

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23 The plasma protein binding of 20 drugs was evaluated by eight in vitro studies [21, 33-39].
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25 Serum or plasma of children with kwashiorkor was used for studies of protein binding of the drugs.
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27 The number of patients studied and their ages were not provided except for the study that involved
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29 quinine [21]. Fresh pooled adult serum and plasma were used as controls, except for the quinine study
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31 where plasma from healthy children was used as a control. The protein binding of 12 drugs was
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33 significantly reduced in kwashiorkor (Table 2). The plasma binding of quinine, expressed as a
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35 percentage of bound drugs, was however not significantly different in both the control group (94%) and
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37 PEM children (93%) [21].
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39 The volume of distribution (V_d) of 13 drugs was evaluated in 19 studies (Table 3) [16, 18, 19,
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41 21, 22, 40-52]. There were contrasting results for four drugs (gentamicin, quinine, streptomycin and
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43 theophylline). In the case of gentamicin, a study involving children with kwashiorkor documented
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45 decreased V_d [52]. In contrast, a study involving children who were underweight, marasmic or
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47 experiencing marasmic-kwashiorkor had an increased V_d of gentamicin [50]. In the case of
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49 theophylline, children with marasmus and kwashiorkor were found to have an increased V_d [49]
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51 whereas children who were underweight had no change in their V_d [49]. A separate study where the
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53 degree of malnutrition was undefined showed no effect of PEM on the V_d of theophylline [22]. In the
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55 case of streptomycin, children with kwashiorkor exhibited an increased V_d [48] whereas children with
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57 marasmus or underweight had a decreased V_d [48]. A decreased V_d for quinine in children with
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59 undefined PEM in one study [51] was in contrast to a separate study involving children with marasmus
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and marasmic-kwashiorkor where the V_d was unaffected [21].

Clearance and half-life

Table 4 shows the effect of PEM on the total clearance and half-life of seven drugs that are primarily metabolised in the liver. The total clearance of five drugs was significantly decreased with a correspondingly increased half-life [18, 26, 40, 42-44]. The total clearance of quinine was significantly decreased in two studies involving poorly categorised malnourished children [51] and kwashiorkor [30], but significantly increased in another study involving children with all categories of PEM except kwashiorkor [21]. Similarly, in one study, the total clearance of chloramphenicol was either significantly decreased in kwashiorkor or unaffected in marasmus and marasmic-kwashiorkor [45].

The effects of PEM on total clearance of six drugs that are primarily eliminated by the kidneys are presented in Table 5. The total CL of two drugs only was significantly decreased [19, 47, 53]. The $t_{1/2}$ of one of the drugs, cefoxitin, was not significantly increased in association with a significantly decreased CL in kwashiorkor [53]. One study documented a significant decrease in the total CL in association with a non-significant increase in $t_{1/2}$ of penicillin in all categories of PEM [19]. This was in contrast to a separate study that documented a significant decrease in the total CL and a corresponding significant increase in the $t_{1/2}$ of penicillin in children with kwashiorkor only [47]. There was no influence of PEM on the total clearance of the three aminoglycoside antibiotics studied [41, 48, 50, 52]. One of these studies involving streptomycin documented an increased plasma half-life in children with kwashiorkor but no change in children who were underweight or had marasmus only [48]. This was probably as a result of presence of oedema in kwashiorkor which enhances the volume of distribution of streptomycin.

There were 11 studies where the plasma half-life was calculated without any clearance values (Table 6) [15, 17, 20, 23, 25, 28, 29, 31, 32, 54, 55]. Five studies documented an increase in the plasma half-life of five separate drugs whereas the other studies showed no significant effect of PEM on the plasma half-life of the remaining six drugs.

Discussion

PEM is a public health problem affecting a great number of children throughout the world [1-3]. It is thought to be a contributory factor in the deaths of five million children under the age of five each year [3]. It is very surprising that, despite the global burden of PEM and treatment of the affected children with numerous medicines, there have been so few studies that looked at the effect of PEM on pharmacokinetics of drugs in children. It is also concerning that there are now fewer pharmacokinetic

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3 studies of drugs in PEM children than 20 years ago. Despite the provision of international aid and
4 support for medicines particularly used for the treatment of infectious diseases such as HIV/AIDS,
5 tuberculosis and malaria that frequently co-exist with PEM, the WHO has noted the lack of regular
6 access to essential medicines for these diseases in some parts of Asia and Africa [56]. Unfortunately,
7 Africa and Asia are two of the continents with a high burden of PEM [57]. Approximately 70% of the
8 world's malnourished children live in Asia [58]. Lack of access to essential medicines for children,
9 especially those suffering from PEM, might have contributed to the decline in the number of
10 pharmacokinetic studies of drugs in PEM children.
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19 Many of the neglected diseases in the developing world may be associated with PEM. It is
20 well recognised that there is a lack of effective, safe, and affordable medicines to control the neglected
21 diseases [59]. This may also be another contributory factor to the dearth of pharmacokinetic studies of
22 drugs in PEM. It is to be hoped that the European Union research fund for neglected diseases [60] will
23 impact positively on research on drug pharmacokinetics in PEM.
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29 The majority of the studies did not report the effect of PEM on the rate of drug absorption.
30 However, where these were studied, K_a was either unaffected [18, 28], increased [31] or decreased [32]
31 in children with PEM. Only two studies looked at the differential effects of marasmus, marasmic-
32 kwashiorkor and kwashiorkor on the rate of drug absorption [19, 45] and based on this small number of
33 studies, it is impossible to draw firm conclusions on the effects of PEM on drug absorption rate.
34 Further studies may therefore be required in this area. The extent of absorption, measured in terms of
35 AUC, was determined in most of the studies. Although, the AUC was not significantly affected for
36 most of the drugs, it was significantly decreased for two drugs and significantly increased for another
37 eight drugs, thus suggesting an altered bioavailability of oral drugs in PEM. This may be explained by
38 the pathophysiological changes in the gastrointestinal system of children with PEM [7-9].
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49 A major effect of PEM on drug disposition is decreased total clearance with an associated
50 increased plasma half-life [18, 25, 26, 30, 40, 42-45, 47, 51]. Other drugs that are primarily
51 metabolised by the liver had increased half-lives in association with PEM [28, 29, 31, 54], although
52 their clearances were not reported. This would suggest that lower doses or alternatively less frequent
53 administration of drugs in PEM may be required.
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58 PEM appears not to affect the total clearance of most drugs primarily eliminated by the
59 kidneys as their values remained almost unchanged in the subjects and controls [16, 41, 48, 50, 52].
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3 This was probably because most of these drugs are rarely metabolised as they are known to be
4 eliminated unchanged via the kidneys [61]. Decreased total clearance was, however, demonstrated for
5 two drugs [19, 47, 53] and in view of the small number of drugs studied (six), it is impossible to draw
6 firm conclusions about the effect of PEM on renal drug elimination. Further studies may therefore be
7 required.
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12 It should be recognised that PEM is not a single disease entity but rather a disease spectrum.
13 The wide range of pathophysiological changes in PEM probably explains the wide variations in the
14 findings from different researchers who have studied the same drug in different categories of PEM. The
15 presence of oedema in association with kwashiorkor or marasmic-kwashiorkor [7] is more likely to
16 result in changes in volume of distribution of drugs as observed with gentamicin [50, 52] and quinine
17 [21, 51]. Only one group of researchers (Eriksson and co-workers) [19, 45, 48, 49] have systematically
18 investigated the effects of different categories and severities of PEM on drug disposition. Their studies
19 have shown that PEM is a disease spectrum with varying effects on drug pharmacokinetics.
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25 Few antibiotics were studied relative to the wide spectrum of infections that may affect
26 children with PEM. Only two antimalarials; chloroquine [25, 39] and quinine [21, 30, 51], were
27 studied. Resistance to chloroquine has necessitated the use of artemisinin based combined therapy as
28 first line treatment for malaria in sub-Saharan African countries [62] and the WHO has recommended
29 artemether and lumefantrine combination in malaria endemic developing nations [63]. Artemether and
30 lumefantrine, like chloroquine, are metabolised by hepatic microsomal enzymes (CYP 3A4) [64, 65].
31 Given the effects of PEM on chloroquine metabolism, artemether and lumefantrine metabolism may be
32 affected by PEM; therefore the pharmacokinetics of these antimalarials may need to be studied in
33 children with PEM so as to determine their appropriate dosing and safety.
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47 The pharmacokinetics of antituberculosis drugs have been extensively studied in PEM. Their
48 rates and extents of absorption [16], protein-binding [34, 36], Vd [16, 46] and total clearance [16]
49 remain unaffected. Antiretroviral drugs, however, have not been studied in PEM and this is probably
50 due to lack of access to these drugs in developing countries in the 1980s when most of the studies were
51 performed. Additionally, antiretroviral drugs are rarely commenced in the acute phase management of
52 PEM.
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59 Lack of detailed information about the patients, using blood samples of adults as controls, and
60 limiting the studies to only kwashiorkor patients would suggest that the data on protein binding in PEM

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3 be interpreted with caution. Although information on drug protein binding in older children is lacking,
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5 a qualitative and quantitative decrease in plasma protein binding has been documented in newborns
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7 compared to adults [66]. This emphasises the significance of age and the use of appropriate controls in
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9 a study of protein binding in PEM. Many of the studies showed decreased protein binding in PEM [33-
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11 38]. Although the decreased plasma binding was statistically significant, it was felt that the clinical
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13 significance of these findings was likely to be minimal since most of the drugs studied were not highly
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15 protein bound [67]. Further research in this area may be required for only highly protein-bound drugs.
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18 Most of the studies described in this review used traditional methods of studying
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20 pharmacokinetics. These involved taking multiple blood samples from each patient. Alternative
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22 approaches that involve the use of population pharmacokinetics where a fewer number of blood
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24 samples are collected from a larger number of patients [68] or non-invasive methods such as the
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26 caffeine breath test [69, 70] may be necessary.

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28 The World Health Organization (WHO), in collaboration with UNICEF, Save the Children,
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30 Médecins Sans Frontières and the International Paediatric Association has launched a major campaign
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32 entitled "Make Medicines Child Size" [71]. This welcome initiative will result in increased research in
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34 relation to medicines for children in developing countries. It is to be hoped that this initiative will
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36 increase interest in the relationship between PEM and pharmacokinetics of drugs in children which has
37
38 been neglected in the last decade.

39 40 **Conclusion**

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42 Despite the enormous global burden of PEM and its association with a wide spectrum of
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44 infections, the pharmacokinetics of drugs used for its treatment has not been extensively studied. PEM
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46 significantly decreased total clearance and increased the half-life of many drugs primarily metabolised
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48 in the liver which may indicate a need for modifications of the doses of these drugs in acute phase
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50 management of PEM. Further pharmacokinetic studies are required to determine appropriate doses and
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52 safety of drugs used for PEM children. These studies need to recognise that PEM is a disease spectrum
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54 and should evaluate the differential effects of kwashiorkor and marasmus on drug disposition in
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56 children.

57 58 **Acknowledgement**

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3 KAO is a postgraduate research student being jointly sponsored by the Lagos State
4 Government and the Lagos State University, Ojo, Lagos, Nigeria. The authors do acknowledge these
5 sponsoring bodies.
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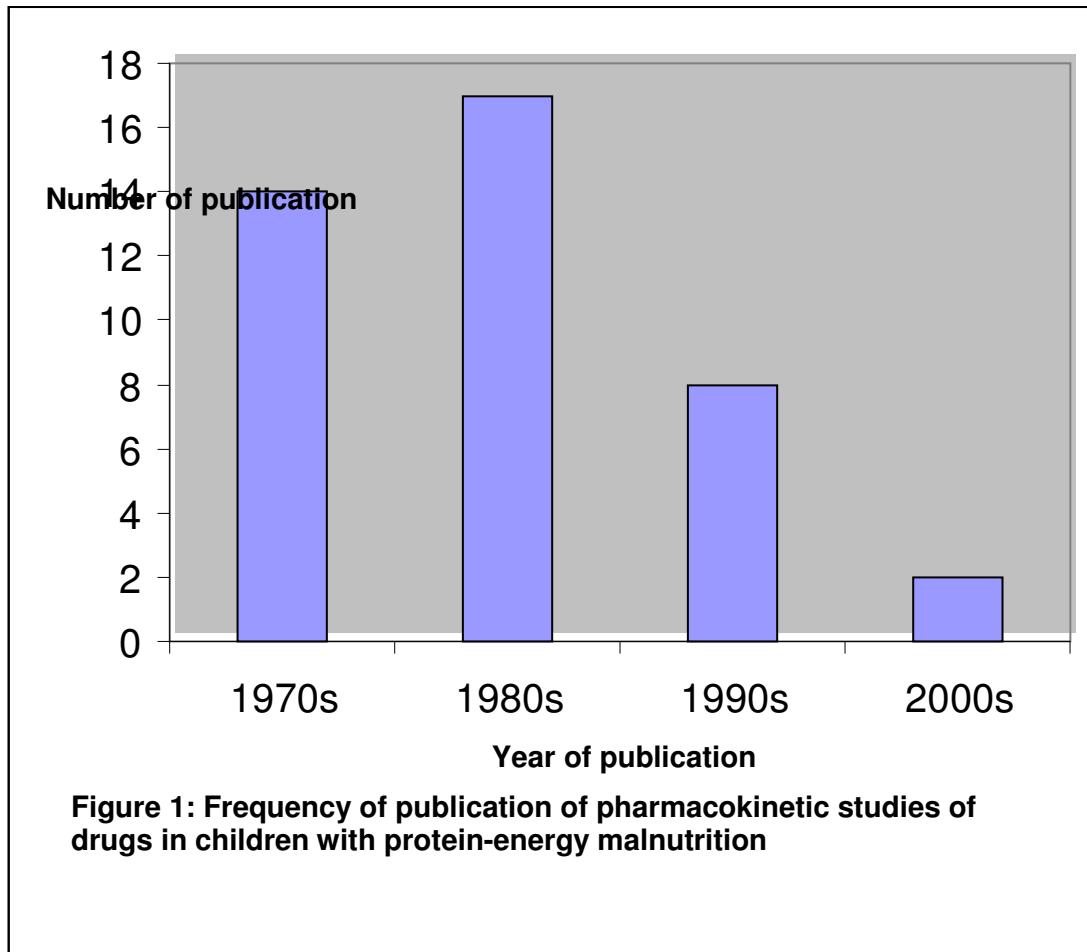
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For Peer Review



Review

Table 1 Effect of protein-energy malnutrition on drug absorption (AUC and K_a)

Drug	Route of administration	Number of PEM children	Age (years)	Degree of malnutrition	Mean AUC ($\mu\text{g/ml/hr}$)		Mean absorption rate (K_a/hr)		Controls	Reference
					Controls	PEM children	Controls	PEM children		
<i>AUC not significantly affected ($P > 0.05$)</i>										
Aspirin	Oral	5	0-2	Undefined	155	164	-	-	-	Treluyer et al [15]
Ethambutol	Oral	15	1-12	U, M	23	21	-	-	-	Graham et al [16]
Gentamicin	IM	6	4-14	Undefined	22	22	-	-	-	Samotra et al [17]
Metronidazole	Oral	10	0-4	M-K, M	142	154	0.43	0.88	R (n= 10)	Lares-Assef et al [18]
Penicillin ψ	Oral	8	0-6	U	494**	477**	10.10	9.50	NH (n= 6)	Bolme et al [19]
Phenytoin	Oral	5	7-14	Undefined	277	299	0.27	0.26	H (n= 4)	Bano et al [20]
Pyrazinamide	Oral	27	1-14	Undefined	496	337	-	-	-	Graham et al [16]
Quinine	IM	8	0-5	M, M-K	97	75	-	-	-	Treluyer et al [21]
Theophylline	Oral	11	1-16	Undefined	53	42	-	-	-	Kumar et al [22]
Tobramycin	IM	4	0-2	K	0.37*	0.43*	-	-	-	Buchanan et al [23]
<i>AUC significantly decreased ($P < 0.05$)</i>										
Carbamazepine	Oral	6	6-13	Undefined	219	72	-	-	-	Bano et al [24]
Chloroquine	Oral	5	2-4	K	9	3	-	-	-	Walker et al [25]

AUC significantly increased (P < 0.05)

Caffeine	Oral	7	1-4	K	22	67	-	-	-	Akinyinka et al [26]
Chloramphenicol	Oral	10	0-3	U, M, K, M-K	Information obtained from figure only	Information obtained from figure only	-	-	-	Mehta et al [27]
Paracetamol	Oral	11	0-6	M, M-K, K	30	66	2.87	2.73	R (n=5)	Mehta et al [28]
Penicillin ψ	Oral	6	0-6	M	494**	942**	10.10	8.40	NH (n=6)	Bolme et al [19]
	Oral	6	0-6	K	494**	975**	10.10	2.50 \dagger	NH (n=6)	Bolme et al [19]
Phenobarbitone	Oral	5	7-10	Undefined	454	607	-	-	-	Syed et al [29]
Quinine	Oral	6	1-3	K	25	37	-	-	-	Salako et al [30]
Sulphadiazine	Oral	6	0-5	M, M-K	136	284	0.74	0.52 \dagger	H (n=5)	Mehta et al [31]
Sulphamethoxazole	Oral	7	0-2	M	328	573	0.70	1.20 \dagger	NH (n=8)	Bravo et al [32]

Note: \dagger = significant difference in K_a values at $P < 0.05$; * = unit uncertain; ** = values in $\mu\text{g/ml/min}$; IM = intramuscular; U = underweight; M = marasmus; K = kwashiorkor; M-K = marasmic-kwashiorkor; Undefined = PEM not classified; ψ = drug administered to fasted patients; R = rehabilitated patients; H = healthy children with normal weight; NH = non-healthy children with normal weight.

Table 2 Effect of kwashiorkor on drug protein binding or free unbound drug (f_u)

Drug	Drug
<i>Decreased protein binding (Increased f_u)</i>	<i>Increased protein binding (Decreased f_u)</i>
Chloramphenicol [33, 34]	Chloroquine [39]
Cloxacillin [34]	
Digoxin [34, 35]	<i>Unaffected protein binding (Unaffected f_u)</i>
Ethionamide [34, 36]	Dicumarol [34]
Flucloxacillin [34]	Ethambutol [34, 36]
Para-amino salicylic acid [34, 36]	Gentamicin [34]
Penicillin [34]	Isoniazid [33, 34]
Phenobarbitone [34]	Rifampicin [34, 36]
Salicylate [37]	Phenytoin [34]
Streptomycin [34, 36]	Quinine [21]
Sulphamethoxazole [34]	
Thiopentone [34, 38]	

Table 3 Effect of protein-energy malnutrition on drug distribution (Vd)

Drug	Number of PEM children	Age (years)	Degree of malnutrition	Mean Vd (L/kg)		Controls	Reference
				Controls	PEM children		
<i>Vd not significantly affected (P>0.05)</i>							
Acetanilide	5	0-2	K	6.26	5.28	R (n=5)	Buchanan et al [40]
Amikacin	10	1-4	K	<1.00*	0.35	H (controls, adults from another study)	Hendricks et al [41]
Antipyrine	5	0-5	M, K	0.64	0.70	R/H (n=5)	Narang et al [42]
	15	0-2	K	4.70	4.40	R (n=15)	Buchanan et al [43]
	8	9-13	Undefined	25.00	21.70	R (n=8)	Homeida et al [44]
Aspirin	5	0-2	Undefined	0.30	0.30	H (n=6)	Treluyer et al [15]
Chloramphenicol¶	8	0-6	M	1.86	2.10	NH (n=8)	Eriksson et al [45]
	9	0-6	M-K	1.86	1.46	NH (n=8)	Eriksson et al [45]
	8	0-6	K	1.86	1.33	NH (n=8)	Eriksson et al [45]
Ethambutol	6	1-12	U, M	510.6§	300§	NH (n=7)	Graham et al [16]
Isoniazid	7	0-3	K	14.20	9.70	R (n=7)	Buchanan et al [46]
Metronidazole	10	0-4	M-K, M	1.60	1.47	R (n=10)	Lares-Assef et al [18]
Penicillin¶	7	0-6	U	1.39	0.91	NH (n=6)	Bolme et al [19]
	8	0-6	M	1.39	1.50	NH (n=6)	Bolme et al [19]
	8	0-6	M-K	1.39	1.18	NH (n=6)	Bolme et al [19]
	8	0-6	K	1.39	0.93	NH (n=6)	Bolme et al [19]
	8	0-2	K	1.40	1.60	R (n=9)	Buchanan et al [47]
Quinine	8	0-5	not K	1.70	2.00	NH (n=7)	Treluyer et al [21]
Streptomycin	11	0-12	U	0.29	0.32	NH (n=4)	Bolme et al [48]
	12	0-12	M	0.29	0.32	NH (n=4)	Bolme et al [48]
Theophylline	11	1-16	Undefined	0.68	1.04	H (n=10)	Kumar et al [22]
	6	1-3	U	0.05	0.53	H (n=12)	Eriksson et al [49]
<i>Increased Vd (P<0.05)</i>							
Gentamicin¶	11	0-1	U, M, M-K	0.39	0.46	H (n=7)	Bravo et al [50]

Streptomycin	5	0-12	K	0.29	0.37	NH (n=4)	Bolme et al [48]
Theophylline	8	1-8	M	0.50	0.68	NH (n=12)	Eriksson et al [49]
	5	1-8	K	0.50	0.72	NH (n=12)	Eriksson et al [49]

Decreased Vd (P <0.05)

Quinine¶	10	2-6	Undefined	1.63	0.56	H (n=10)	Pussard et al [51]
Gentamicin¶	6	1-3	K	4.53§	3.90§	R (n=6)	Buchanan et al [52]

Note: *= values for adult reference; U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; ¶= drug administered intravenously; §= values in litres; R- rehabilitated patients; H= healthy children with normal weight; NH= non-healthy children with normal weight.

Table 4 Effect of protein-energy malnutrition on total clearance (CL) and half-life ($t_{1/2}$) of drugs primarily metabolised by the liver

Drug	Number of PEM children	Age (years)	Degree of malnutrition	Mean CL (ml/min/kg)		Mean $t_{1/2}$ (hr)		Reference
				Controls	PEM children	Controls	PEM children	
<i>Decreased CL and increased $t_{1/2}$ ($P < 0.05$)</i>								
Acetanilide	5	0-2	K	2.45]	0.92]	1.76	4.78s	Buchanan et al [40]
Antipyrine	10	0-5	M, M-K, K	70.10]]	4.72]]	6.30	10.40	Narang et al [42]
	15	0-2	K	15.50]]]]	8.40]]]]	4.30	7.90	Buchanan et al [43]
	8	9-12	Undefined	32.00]]]]]	19.50]]]]]	9.90	14.80	Homeida et al [44]
Caffeine	7	1-4	K	4.50	1.60	3.70	13.10	Akinyinka et al [26]
Chloramphenicol]	8	0-6	K	7.53	4.16	2.85	3.76	Eriksson et al [45]
Isoniazid	7	0-3	K	329.40]]]]	125.70]]]]	0.73	1.03	Buchanan et al [47]
Metronidazole	10	0-4	M-K, M	0.17+]	0.08+]	5.09+	10.21+	Lares-Assef et al [18]
Quinine	6	1-2	K	108.50]]]]]]	37.50]]]]]]	8.00	15.0	Salako et al [30]
Quinine]]	20	2-4	Undefined	4.00	1.70	5.10	7.20	Pussard et al [51]
<i>Increased CL and decreased $t_{1/2}$ ($P < 0.05$)</i>								
Quinine	8	0-5	not K	2.30	4.40	10.10	6.30	Treluyer et al

[21]

CL and t_{1/2} not significantly affected (P>0.05)

Chloramphenicol [¶]	17	0-6	M	7.53	8.16	2.85	2.88	Eriksson et al [45]
	8	0-6	M-K	7.53	5.39	2.85	3.20	Eriksson et al [45]
Theophylline	11	1-16	Undefined	129.00 ^{¶¶}	170.70 ^{¶¶}	4.10	5.21	Kumar et al [22]
	6	1-8	U	1.22 ^{¶*}	1.09 ^{¶*}	4.93	5.25	Eriksson et al [49]
	8	1-8	M	1.22 ^{¶*}	1.45 ^{¶*}	4.93	5.38	Eriksson et al [49]
	5	1-8	K	1.22 ^{¶*}	1.49 ^{¶*}	4.93	5.61	Eriksson et al [49]

Note: U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; [¶]= drug administered intravenously; †= median value; [¶]= value in l/hr; ^{¶¶}= value in ml/hr/kg; ^{¶*}= value in ml/min/kg; ^{¶¶}= value in ml/min; ^{¶¶¶}= unit of the value was not given; ^{¶¶¶¶}= value in mg/min; ^{¶¶¶¶¶}= value in L/kg/hr.

Table 5 Effect of protein-energy malnutrition on total clearance (CL) and half-life ($t_{1/2}$) of drugs primarily eliminated by the kidneys

Drug	Number PEM of children	Age (years)	Degree of malnutrition	Mean CL in (ml/min/kg)		Mean $t_{1/2}$ (hr)		Reference
				Controls	PEM children	Controls	PEM children	
<i>Decreased CL (P<0.05)</i>								
Cefoxitin	6	1-4	K	70.60[[[50.70[[[0.47	0.49	Buchanan et al [53]
Penicillin¶	7	0-6	U	22.20	15.10	0.72	1.13	Bolme et al [19]
	8	0-6	M	22.20	14.00	0.72	0.75	Bolme et al [19]
	8	0-6	M-K	22.20	16.90	0.72	0.75	Bolme et al [19]
	8	0-6	K	22.20	11.60	0.72	0.93	Bolme et al [19]
	8	0-2	K	286.30[[[183.40[[[0.53*	0.95*	Buchanan et al [47]
<i>CL not significantly affected (P>0.05)</i>								
Gentamicin	11	0-1	U, M, M-K	3.57	3.99	0.01	0.01	Bravo et al [50]
Gentamicin¶	6	1-3	K	28.70[[[13.60[[[2.98	3.82	Buchanan et al [52]
Amikacin	10	1-4	K	<0.50**[[[[[[0.11[[[[[[<0.50**	2.11	Hendricks et al [41]
Ethambutol	6	1-12	U, M	33.60§§	67.00§§	9.70	7.40	Graham et al [16]
Streptomycin	11	0-12	U	67.00	74.00	2.58	2.14	Bolme et al [48]
	12	0-12	M	67.00	91.00	2.58	2.27	Bolme et al [48]
	5	0-12	K	67.00	49.00	2.58*	9.69*	Bolme et al [48]

Note: *= significant difference in $t_{1/2}$ values; **= values for adult reference; ¶= drugs administered intravenously; U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; [[[[= value in ml/min; [[[[[[[[= value in L/kg/hr; §§= value in litres/hr.

Table 6 Effect of protein-energy malnutrition on drug half-life ($t_{1/2}$)

Drug	Number of PEM children	Age (years)	Degree of malnutrition	Mean $t_{1/2}$ (hr)		Reference
				Controls	PEM children	
<i>Increased $t_{1/2}$ ($P < 0.05$)</i>						
Chloramphenicol	8	0-5	Undefined	12.00	≥ 30.00	Mehta et al [54]
Paracetamol	11	0-6	U, M, M-K, K	4.33	8.15	Mehta et al [28]
Phenobarbitone	5	7-10	M-K, K	30.15	58.90	Syed et al [29]
Sulphadiazine	6	0-5	Undefined	21.27	31.78	Mehta et al [31]
Sulphamethoxazole [†]	7	0-2	M	4.90	9.60	Bravo et al [32]
<i>$t_{1/2}$ not significantly affected ($P > 0.05$)</i>						
Aspirin	5	0-2	Undefined	4.00	5.60	Treluyer [15]
Chloroquine	5	2-3	K	195.00	180.00	Walker et al [25]
Gentamicin	6	4-14	Undefined	3.31	6.21	Samotra et al [17]
Isoniazid	13	0-7	U	1.82	1.78	Seifart et al [55]
Phenytoin	5	7-13	Undefined	0.04	0.03	Bano et al [20]
Tobramycin	4	0-2	K	1.12	0.84	Buchanan et al [23]

Note: U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified

[†] Clearance and half-life of the drug were provided in the study, clearance was apparently decreased in PEM but the level of significance was not provided when compared with normal control children.

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3 **A systematic review of pharmacokinetic studies in children with protein-energy**
4 **malnutrition**
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41
42 **Key words:** protein-energy malnutrition, drug, absorption, distribution, protein-binding, metabolism,
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44 children
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Abstract

Background: Protein-energy malnutrition (PEM) is a nutritional problem affecting many children world-wide. Its association with a wide spectrum of infections necessitates multiple drug therapies. A systematic review was performed to determine the effects of PEM on drug **pharmacokinetics**.

Methods: Literature search in MEDLINE and EMBASE databases (January 1960- December 2009) was performed. Malnutrition, undernutrition, underweight, protein-energy malnutrition, protein-calorie malnutrition, marasmus, marasmic-kwashiorkor or kwashiorkor was the medical subject heading (MeSH) descriptor used. Inclusion criteria were abstracts that assessed or discussed absorption, distribution, metabolism, elimination, clearance, pharmacokinetics or pharmacodynamics of drugs, except micronutrients and appetite stimulating drugs.

Results: Altogether, 41 publications were identified. A total of 34 drugs were studied. The absorption of 18 drugs was studied; **the extent of absorption (AUC)** was unaffected for 10 drugs. The plasma protein binding of **20** drugs was evaluated; it was significantly reduced for 12 drugs. The volume of distribution (Vd) of **13** drugs was evaluated; it was however unaffected for most of the drugs. **The effect of PEM on total clearance and half-life of drugs primarily metabolised by the liver was studied for eight drugs.** There was decreased total clearance and an associated increased half-life of five drugs. For two drugs (chloramphenicol and quinine), different degrees of PEM affected total clearance differently. The total clearance of six drugs primarily eliminated by the kidneys was studied; it was unaffected for four drugs but significantly decreased for two drugs (cefoxitin and penicillin).

Conclusions: Considering the proportion of children affected with PEM world-wide, there have been relatively **few pharmacokinetic studies of drugs frequently used for their treatment**. More studies are therefore required to establish the appropriate dose and safety of these drugs for PEM children. The studies need to recognise that PEM is a disease spectrum and **should further look** at the differential effects of kwashiorkor and marasmus on drug **pharmacokinetics** in children.

Introduction

Protein energy malnutrition (PEM), also referred to as protein calorie malnutrition (PCM), has long been recognised as a common problem, especially of children in the developing countries, whose inadequate nutritional intake is deficient for socioeconomic reasons [1]. PEM is a range of deficiency states, from mild to severe, defined as a range of pathological conditions arising from coincident deficiency of protein and calories in varying proportions, occurring most frequently in infants and young children, and commonly associated with infections [2].

PEM is responsible, directly or indirectly, for approximately half of the 10.8 million deaths per year in children under five. It also contributes to many deaths associated with infectious diseases among children in developing countries [3]. Infection is one of the major complications of PEM; malaria, bronchopneumonia and measles being the most frequently associated infections with PEM in African children [4]. HIV/AIDS and tuberculosis frequently co-exist with PEM but begin to manifest when the immunity is lowered [5]. The World Health Organization (WHO) has recommended empirical treatment of all children admitted for PEM with ampicillin and gentamicin [6], even in the absence of overt signs and symptoms of sepsis. Considering the wide range of pathophysiological derangements in children with PEM [7-9], the pharmacokinetics of many of the drugs used for their treatments is likely to be affected and this may require dose modification. This systematic review was therefore performed to determine the effects of PEM on drug **pharmacokinetic parameters**.

Methods

Identification of relevant literature

Articles describing drug absorption and disposition in malnourished children were searched using EMBASE and MEDLINE (January 1960- December 2009) and by reference tracking. In both methods, the search strategies involved an initial search for all relevant abstracts using the medical subject heading (MeSH) descriptor 'drug absorption' OR 'drugs absorption', limited to children between 0-17 years. Similar searches were done for drug distribution, metabolism and clearance by substituting the term 'absorption' with each of the terms 'distribution', 'pharmacokinetics', 'pharmacodynamic', 'metabolism', 'elimination' and 'clearance', respectively. Another search was made using the MeSH descriptors 'malnutrition' OR 'mal-nutrition' OR 'undernutrition' OR 'under-nutrition' OR 'underweight' OR 'under-weight' OR 'protein energy malnutrition' OR 'protein-energy

malnutrition' OR 'protein-calorie malnutrition' OR 'protein-calorie malnutrition' OR 'marasmus' OR 'marasmic-kwashiorkor' OR 'kwashiorkor'. The searches were later combined to give the desired abstracts. Abstracts that appeared in both EMBASE and MEDLINE searches were hand searched to avoid duplication and to judge whether they met the inclusion criteria.

Inclusion criteria were abstracts that assessed or discussed pharmacokinetics, pharmacodynamics, absorption, distribution, metabolism, elimination or clearance of drugs in children who are underweight, marasmic, marasmic-kwashiorkor, and/or kwashiorkor. Abstracts that assessed or discussed disposition of micronutrients and appetite stimulating drugs in malnourished children were excluded. Full articles of the relevant abstracts were then searched and retrieved. The references of the retrieved articles were searched manually in order to identify additional appropriate studies. The relevant additional articles that met the inclusion criteria were accessed.

Data abstraction

Two researchers (KAO and IC) reviewed each study independently, and using a standard form, extracted data on the number and year of studies; characteristics of the subjects and controls; types of drug studied; and the number of blood samples collected. The pharmacokinetic parameters studied (rate and extent of absorption, volume of distribution, protein-binding, metabolism, clearance and half-life) were extracted. We also extracted from each study data on the methods of PEM classification.

Results

Publications

The EMBASE search yielded 731 abstracts and MEDLINE 546 abstracts of potential use. 50 abstracts met the inclusion criteria. Most abstracts were excluded because they assessed serum macro- and micro-nutrients and serum proteins in the malnourished children. The abstracts were mainly original research (40), review articles (4) and letters to the editor (6). Both the original research articles and letters to the editor (46 publications) were included in this study. Five publications were further excluded because there were either insufficient details (no documentation of mean value of the data or the control data) or the data was published in more detail in a subsequent paper which was included in the final analysis [10-14]. Altogether, 41 publications were analysed in this study.

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3 The majority of the studies were published in 1970s (14) and 1980s (17), thereafter the
4 number progressively decreased over the next two decades (Figure 1). Thirty of the studies involved
5 one drug only. A total of 34 different drugs were studied.
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8 9 *Methodology of trials*

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11 The age range of the patients and control subjects used for the studies was three months to 16
12 years. The number of patients in individual studies varied from five to 41. Age matched, healthy
13 children were the control subjects in 25 studies. Nutritionally rehabilitated children were used as
14 additional control subjects in four studies and as the only control subjects in seven studies. Five studies
15 had no control subjects.
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19 PEM was classified in the subjects according to Wellcome Trust Party classification [8] (22
20 studies) and Gomez classification [9] (seven studies). Co-existing infections, including tuberculosis
21 (4), bacterial sepsis (3), malaria (2) and HIV with tuberculosis (1) were reported in the patients in 10
22 studies. One to 17 blood samples were collected from individual children.
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28 29 *Drug absorption*

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31 Table 1 shows the effect of PEM on absorption of 18 drugs [15-32]. **The extent of absorption**
32 **of most of the drugs (10) was not significantly affected. Ideally, in pharmacokinetic studies, rate is**
33 **measured as K_a (hr^{-1}) and extent of absorption, F (%), as $\text{AUC}_{\text{oral}} \times \text{Dose}_{\text{i.v.}} / \text{AUC}_{\text{i.v.}} \times \text{Dose}_{\text{oral}}$. The extent**
34 **of absorption was reported in this review as AUC_{oral} or $\text{AUC}_{\text{i.m}}$ since most of the drugs were**
35 **administered either orally or intramuscularly. The extent of absorption of eight drugs was found to be**
36 **significantly increased. This was probably due to the effects of decreased clearance as all these drugs**
37 **were shown to have either a prolonged half-life or decreased clearance (see below). The extent of**
38 **absorption of aspirin [15], oral penicillin [19] and chloramphenicol [45], measured in terms of F (%),**
39 **was reported only in one study each. F was significantly decreased for chloramphenicol in kwashiorkor**
40 **by 85% compared to 44% in seven controls, $P < 0.05$ and marasmic-kwashiorkor by 85% compared to**
41 **30% in seven controls, $P < 0.05$ [45]. However, the difference in the F values for aspirin in both**
42 **malnourished children and controls (92% and 90%, respectively) was not statistically significant [15].**
43 **In the case of oral penicillin administered to fasted PEM children, F was decreased in underweight**
44 **children by 36% compared to 55% in six controls, $P < 0.05$; increased in marasmus by 66% compared**
45 **to 55% in six controls and in kwashiorkor by 83% compared to 55% in six controls, $P < 0.05$ [19]. The**
46 **statistical significance level of the decreased or increased F values for penicillin in PEM was however**
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3 not reported. The decreased extents of chloramphenicol absorption reported by Eriksson et al [45] are
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5 in contrast to the increased extent of absorption in all forms of PEM reported in another study [27]. In
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7 addition, contrasting results were also documented for quinine. The extent of absorption of oral
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9 quinine was increased [30] whereas the extent of IM absorption was not significantly affected [21].
10

11 K_a was reported only for chloramphenicol [45] and six other drugs (Table 1). It was
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13 significantly increased for sulphadiazine [31] and significantly decreased for sulphamethoxazole [32]
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15 in children with PEM. In the studies involving children with different categories of PEM, the K_a of
16
17 chloramphenicol was significantly decreased in children with marasmic-kwashiorkor only [45] whereas
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19 it was significantly increased for oral penicillin in children suffering from kwashiorkor only [19].
20

21 *Protein binding and distribution*

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23 The plasma protein binding of 20 drugs was evaluated by eight in vitro studies [21, 33-39].
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25 Serum or plasma of children with kwashiorkor was used for studies of protein binding of the drugs.
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27 The number of patients studied and their ages were not provided except for the study that involved
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29 quinine [21]. Fresh pooled adult serum and plasma were used as controls, except for the quinine study
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31 where plasma from healthy children was used as a control. The protein binding of 12 drugs was
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33 significantly reduced in kwashiorkor (Table 2). The plasma binding of quinine, expressed as a
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35 percentage of bound drugs, was however not significantly different in both the control group (94%) and
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37 PEM children (93%) [21].
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39 The volume of distribution (Vd) of 13 drugs was evaluated in 19 studies (Table 3) [16, 18, 19,
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41 21, 22, 40-52]. There were contrasting results for four drugs (gentamicin, quinine, streptomycin and
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43 theophylline). In the case of gentamicin, a study involving children with kwashiorkor documented
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45 decreased Vd [52]. In contrast, a study involving children who were underweight, marasmic or
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47 experiencing marasmic-kwashiorkor had an increased Vd of gentamicin [50]. In the case of
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49 theophylline, children with marasmus and kwashiorkor were found to have an increased Vd [49]
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51 whereas children who were underweight had no change in their Vd [49]. A separate study where the
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53 degree of malnutrition was undefined showed no effect of PEM on the Vd of theophylline [22]. In the
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55 case of streptomycin, children with kwashiorkor exhibited an increased Vd [48] whereas children with
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57 marasmus or underweight had a decreased Vd [48]. A decreased Vd for quinine in children with
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59 undefined PEM in one study [51] was in contrast to a separate study involving children with marasmus
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and marasmic-kwashiorkor where the Vd was unaffected [21].

Clearance and half-life

Table 4 shows the effect of PEM on the total clearance and half-life of seven drugs that are primarily metabolised in the liver. The total clearance of five drugs was significantly decreased with a correspondingly increased half-life [18, 26, 40, 42-44]. The total clearance of quinine was significantly decreased in two studies involving poorly categorised malnourished children [51] and kwashiorkor [30], but significantly increased in another study involving children with all categories of PEM except kwashiorkor [21]. Similarly, in one study, the total clearance of chloramphenicol was either significantly decreased in kwashiorkor or unaffected in marasmus and marasmic-kwashiorkor [45].

The effects of PEM on total clearance of six drugs that are primarily eliminated by the kidneys are presented in Table 5. The total CL of two drugs only was significantly decreased [19, 47, 53]. The $t_{1/2}$ of one of the drugs, cefoxitin, was not significantly increased in association with a significantly decreased CL in kwashiorkor [53]. One study documented a significant decrease in the total CL in association with a non-significant increase in $t_{1/2}$ of penicillin in all categories of PEM [19]. This was in contrast to a separate study that documented a significant decrease in the total CL and a corresponding significant increase in the $t_{1/2}$ of penicillin in children with kwashiorkor only [47]. There was no influence of PEM on the total clearance of the three aminoglycoside antibiotics studied [41, 48, 50, 52]. One of these studies involving streptomycin documented an increased plasma half-life in children with kwashiorkor but no change in children who were underweight or had marasmus only [48]. This was probably as a result of presence of oedema in kwashiorkor which enhances the volume of distribution of streptomycin.

There were 11 studies where the plasma half-life was calculated without any clearance values (Table 6) [15, 17, 20, 23, 25, 28, 29, 31, 32, 54, 55]. Five studies documented an increase in the plasma half-life of five separate drugs whereas the other studies showed no significant effect of PEM on the plasma half-life of the remaining six drugs.

Discussion

PEM is a public health problem affecting a great number of children throughout the world [1-3]. It is thought to be a contributory factor in the deaths of five million children under the age of five each year [3]. It is very surprising that, despite the global burden of PEM and treatment of the affected children with numerous medicines, there have been so few studies that looked at the effect of PEM on pharmacokinetics of drugs in children. It is also concerning that there are now fewer pharmacokinetic

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3 **studies of drugs** in PEM children than 20 years ago. Despite the provision of international aid and
4 support for medicines particularly used for the treatment of infectious diseases such as HIV/AIDS,
5 tuberculosis and malaria that frequently co-exist with PEM, the WHO has noted the lack of regular
6 access to essential medicines for these diseases in some parts of Asia and Africa [56]. Unfortunately,
7 Africa and Asia are two of the continents with a high burden of PEM [57]. Approximately 70% of the
8 world's malnourished children live in Asia [58]. Lack of access to essential medicines for children,
9 especially those suffering from PEM, might have contributed to the decline in the number of
10 pharmacokinetic **studies** of drugs in PEM children.
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19 Many of the neglected diseases in the developing world may be associated with PEM. It is
20 well recognised that there is a lack of effective, safe, and affordable medicines to control the neglected
21 diseases [59]. This may also be another contributory factor to the dearth of **pharmacokinetic studies** of
22 drugs in PEM. It is to be hoped that the European Union research fund for neglected diseases [60] will
23 impact positively on research on **drug pharmacokinetics** in PEM.
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29 **The majority of the studies did not report the effect of PEM on the rate of drug absorption.**
30 **However, where these were studied, K_a was either unaffected [18, 28], increased [31] or decreased [32]**
31 **in children with PEM. Only two studies looked at the differential effects of marasmus, marasmic-**
32 **kwashiorkor and kwashiorkor on the rate of drug absorption [19, 45] and based on this small number of**
33 **studies, it is impossible to draw firm conclusions on the effects of PEM on drug absorption rate.**
34 **Further studies may therefore be required in this area. The extent of absorption, measured in terms of**
35 **AUC, was determined in most of the studies. Although, the AUC was not significantly affected for**
36 **most of the drugs, it was significantly decreased for two drugs and significantly increased for another**
37 **eight drugs, thus suggesting an altered bioavailability of oral drugs in PEM. This may be explained by**
38 **the pathophysiological changes in the gastrointestinal system of children with PEM [7-9].**
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49 **A major effect of PEM on drug disposition is decreased total clearance with an associated**
50 **increased plasma half-life [18, 25, 26, 30, 40, 42-45, 47, 51]. Other drugs that are primarily**
51 **metabolised by the liver had increased half-lives in association with PEM [28, 29, 31, 54], although**
52 **their clearances were not reported. This would suggest that lower doses or alternatively less frequent**
53 **administration of drugs in PEM may be required.**
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58 PEM appears not to affect the **total** clearance of most drugs **primarily eliminated by the**
59 **kidneys as their values remained almost unchanged in the subjects and controls [16, 41, 48, 50, 52].**
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3 This was probably because most of these drugs are rarely metabolised as they are known to be
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5 eliminated unchanged via the kidneys [61]. Decreased total clearance was, however, demonstrated for
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7 two drugs [19, 47, 53] and in view of the small number of drugs studied (six), it is impossible to draw
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9 firm conclusions about the effect of PEM on renal drug elimination. Further studies may therefore be
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11 required.

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13 It should be recognised that PEM is not a single disease entity but rather a disease spectrum.
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15 The wide range of pathophysiological changes in PEM probably explains the wide variations in the
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17 findings from different researchers who have studied the same drug in different categories of PEM. The
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19 presence of oedema in association with kwashiorkor or marasmic-kwashiorkor [7] is more likely to
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21 result in changes in volume of distribution of drugs as observed with gentamicin [50, 52] and quinine
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23 [21, 51]. Only one group of researchers (Eriksson and co-workers) [19, 45, 48, 49] have systematically
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25 investigated the effects of different categories and severities of PEM on drug disposition. Their studies
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27 have shown that PEM is a disease spectrum with varying effects on drug pharmacokinetics.

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29 Few antibiotics were studied relative to the wide spectrum of infections that may affect
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31 children with PEM. Only two antimalarials; chloroquine [25, 39] and quinine [21, 30, 51], were
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33 studied. Resistance to chloroquine has necessitated the use of artemisinin based combined therapy as
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35 first line treatment for malaria in sub-Saharan African countries [62] and the WHO has recommended
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37 artemether and lumefantrine combination in malaria endemic developing nations [63]. Artemether and
38
39 lumefantrine, like chloroquine, are metabolised by hepatic microsomal enzymes (CYP 3A4) [64, 65].
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41 Given the effects of PEM on chloroquine metabolism, artemether and lumefantrine metabolism may be
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43 affected by PEM; therefore the pharmacokinetics of these antimalarials may need to be studied in
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45 children with PEM so as to determine their appropriate dosing and safety.

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47 The pharmacokinetics of antituberculosis drugs have been extensively studied in PEM. Their
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49 rates and extents of absorption [16], protein-binding [34, 36], Vd [16, 46] and total clearance [16]
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51 remain unaffected. Antiretroviral drugs, however, have not been studied in PEM and this is probably
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53 due to lack of access to these drugs in developing countries in the 1980s when most of the studies were
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55 performed. Additionally, antiretroviral drugs are rarely commenced in the acute phase management of
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57 PEM.

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59 Lack of detailed information about the patients, using blood samples of adults as controls, and
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limiting the studies to only kwashiorkor patients would suggest that the data on protein binding in PEM

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3 be interpreted with caution. Although information on drug protein binding in older children is lacking,
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5 a qualitative and quantitative decrease in plasma protein binding has been documented in newborns
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7 compared to adults [66]. This emphasises the significance of age and the use of appropriate controls in
8
9 a study of protein binding in PEM. Many of the studies showed decreased protein binding in PEM [33-
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11 38]. Although the decreased plasma binding was statistically significant, it was felt that the clinical
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13 significance of these findings was likely to be minimal since most of the drugs studied were not highly
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15 protein bound [67]. Further research in this area may be required for only highly protein-bound drugs.
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18 Most of the studies described in this review used traditional methods of studying
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20 pharmacokinetics. These involved taking multiple blood samples from each patient. Alternative
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22 approaches that involve the use of population pharmacokinetics where a fewer number of blood
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24 samples are collected from a larger number of patients [68] or non-invasive methods such as the
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26 caffeine breath test [69, 70] may be necessary.

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28 The World Health Organization (WHO), in collaboration with UNICEF, Save the Children,
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30 Médecins Sans Frontières and the International Paediatric Association has launched a major campaign
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32 entitled “Make Medicines Child Size” [71]. This welcome initiative will result in increased research in
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34 relation to medicines for children in developing countries. It is to be hoped that this initiative will
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36 increase interest in the relationship between PEM and pharmacokinetics of drugs in children which has
37
38 been neglected in the last decade.

39 Conclusion

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41 Despite the enormous global burden of PEM and its association with a wide spectrum of
42
43 infections, the pharmacokinetics of drugs used for its treatment has not been extensively studied. PEM
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45 significantly decreased total clearance and increased the half-life of many drugs primarily metabolised
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47 in the liver which may indicate a need for modifications of the doses of these drugs in acute phase
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49 management of PEM. Further pharmacokinetic studies are required to determine appropriate doses and
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51 safety of drugs used for PEM children. These studies need to recognise that PEM is a disease spectrum
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53 and should evaluate the differential effects of kwashiorkor and marasmus on drug disposition in
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55 children.

56 Acknowledgement

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3 KAO is a postgraduate research student being jointly sponsored by the Lagos State
4 Government and the Lagos State University, Ojo, Lagos, Nigeria. The authors do acknowledge these
5 sponsoring bodies.
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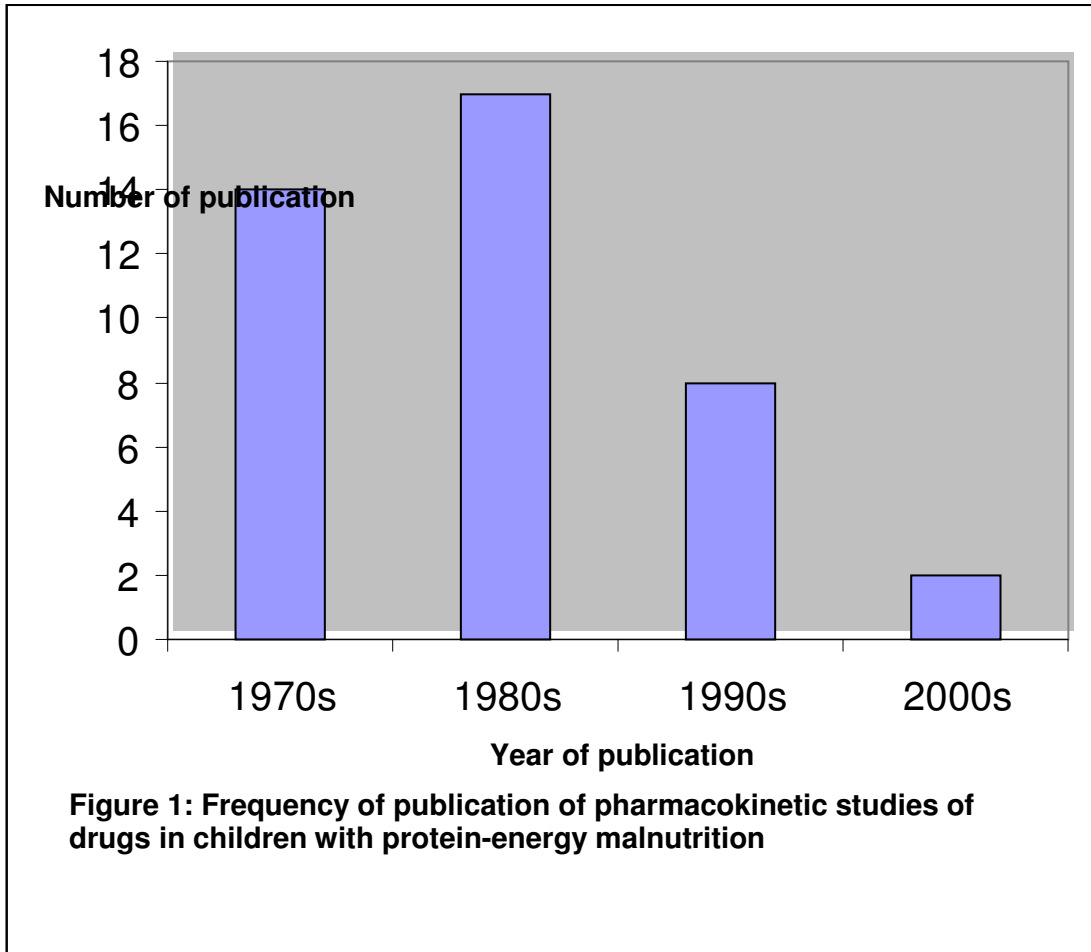
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For Peer Review



Review

Table 1 Effect of protein-energy malnutrition on drug absorption (AUC and K_a)

Drug	Route of administration	Number of PEM children	Age (years)	Degree of malnutrition	Mean AUC ($\mu\text{g/ml/hr}$)		Mean absorption rate (K_a/hr)		Controls	Reference
					Controls	PEM children	Controls	PEM children		
<i>AUC not significantly affected ($P > 0.05$)</i>										
Aspirin	Oral	5	0-2	Undefined	155	164	-	-	-	Treluyer et al [15]
Ethambutol	Oral	15	1-12	U, M	23	21	-	-	-	Graham et al [16]
Gentamicin	IM	6	4-14	Undefined	22	22	-	-	-	Samotra et al [17]
Metronidazole	Oral	10	0-4	M-K, M	142	154	0.43	0.88	R (n= 10)	Lares-Assef et al [18]
Penicillin ψ	Oral	8	0-6	U	494**	477**	10.10	9.50	NH (n= 6)	Bolme et al [19]
Phenytoin	Oral	5	7-14	Undefined	277	299	0.27	0.26	H (n= 4)	Bano et al [20]
Pyrazinamide	Oral	27	1-14	Undefined	496	337	-	-	-	Graham et al [16]
Quinine	IM	8	0-5	M, M-K	97	75	-	-	-	Treluyer et al [21]
Theophylline	Oral	11	1-16	Undefined	53	42	-	-	-	Kumar et al [22]
Tobramycin	IM	4	0-2	K	0.37*	0.43*	-	-	-	Buchanan et al [23]
<i>AUC significantly decreased ($P < 0.05$)</i>										
Carbamazepine	Oral	6	6-13	Undefined	219	72	-	-	-	Bano et al [24]
Chloroquine	Oral	5	2-4	K	9	3	-	-	-	Walker et al [25]

AUC significantly increased (P< 0.05)

Caffeine	Oral	7	1-4	K	22	67	-	-	-	Akinyinka et al [26]
Chloramphenicol	Oral	10	0-3	U, M, K, M-K	Information obtained from figure only	Information obtained from figure only	-	-	-	Mehta et al [27]
Paracetamol	Oral	11	0-6	M, M-K, K	30	66	2.87	2.73	R (n=5)	Mehta et al [28]
Penicillin ψ	Oral	6	0-6	M	494**	942**	10.10	8.40	NH (n=6)	Bolme et al [19]
	Oral	6	0-6	K	494**	975**	10.10	2.50†	NH (n=6)	Bolme et al [19]
Phenobarbitone	Oral	5	7-10	Undefined	454	607	-	-	-	Syed et al [29]
Quinine	Oral	6	1-3	K	25	37	-	-	-	Salako et al [30]
Sulphadiazine	Oral	6	0-5	M, M-K	136	284	0.74	0.52†	H (n=5)	Mehta et al [31]
Sulphamethoxazole	Oral	7	0-2	M	328	573	0.70	1.20†	NH (n=8)	Bravo et al [32]

Note: †= significant difference in K_a values at $P<0.05$ *= unit uncertain; **= values in $\mu\text{g/ml/min}$; IM = intramuscular; U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; ψ = drug administered to fasted patients; R- rehabilitated patients; H= healthy children with normal weight; NH= non-healthy children with normal weight.

Table 2 Effect of kwashiorkor on drug protein binding or free unbound drug (f_u)

Drug	Drug
<i>Decreased protein binding (Increased f_u)</i>	<i>Increased protein binding (Decreased f_u)</i>
Chloramphenicol [33, 34]	Chloroquine [39]
Cloxacillin [34]	
Digoxin [34, 35]	<i>Unaffected protein binding (Unaffected f_u)</i>
Ethionamide [34, 36]	Dicumarol [34]
Flucloxacillin [34]	Ethambutol [34, 36]
Para-amino salicylic acid [34, 36]	Gentamicin [34]
Penicillin [34]	Isoniazid [33, 34]
Phenobarbitone [34]	Rifampicin [34, 36]
Salicylate [37]	Phenytoin [34]
Streptomycin [34, 36]	Quinine [21]
Sulphamethoxazole [34]	
Thiopentone [34, 38]	

Table 3 Effect of protein-energy malnutrition on drug distribution (Vd)

Drug	Number of PEM children	Age (years)	Degree of malnutrition	Mean Vd (L/kg)		Controls	Reference
				Controls	PEM children		
<i>Vd not significantly affected (P>0.05)</i>							
Acetanilide	5	0-2	K	6.26	5.28	R (n=5)	Buchanan et al [40]
Amikacin	10	1-4	K	<1.00*	0.35	H (controls, adults from another study)	Hendricks et al [41]
Antipyrine	5	0-5	M, K	0.64	0.70	R/H (n=5)	Narang et al [42]
	15	0-2	K	4.70	4.40	R (n=15)	Buchanan et al [43]
	8	9-13	Undefined	25.00	21.70	R (n=8)	Homeida et al [44]
Aspirin	5	0-2	Undefined	0.30	0.30	H (n=6)	Treluyer et al [15]
Chloramphenicol¶	8	0-6	M	1.86	2.10	NH (n=8)	Eriksson et al [45]
	9	0-6	M-K	1.86	1.46	NH (n=8)	Eriksson et al [45]
	8	0-6	K	1.86	1.33	NH (n=8)	Eriksson et al [45]
Ethambutol	6	1-12	U, M	510.6§	300§	NH (n=7)	Graham et al [16]
Isoniazid	7	0-3	K	14.20	9.70	R (n=7)	Buchanan et al [46]
Metronidazole	10	0-4	M-K, M	1.60	1.47	R (n=10)	Lares-Assef et al [18]
Penicillin¶	7	0-6	U	1.39	0.91	NH (n=6)	Bolme et al [19]
	8	0-6	M	1.39	1.50	NH (n=6)	Bolme et al [19]
	8	0-6	M-K	1.39	1.18	NH (n=6)	Bolme et al [19]
	8	0-6	K	1.39	0.93	NH (n=6)	Bolme et al [19]
	8	0-2	K	1.40	1.60	R (n=9)	Buchanan et al [47]
Quinine	8	0-5	not K	1.70	2.00	NH (n=7)	Treluyer et al [21]
Streptomycin	11	0-12	U	0.29	0.32	NH (n=4)	Bolme et al [48]
	12	0-12	M	0.29	0.32	NH (n=4)	Bolme et al [48]
Theophylline	11	1-16	Undefined	0.68	1.04	H (n=10)	Kumar et al [22]
	6	1-3	U	0.05	0.53	H (n=12)	Eriksson et al [49]
<i>Increased Vd (P<0.05)</i>							
Gentamicin¶	11	0-1	U, M, M-K	0.39	0.46	H (n=7)	Bravo et al [50]

Streptomycin	5	0-12	K	0.29	0.37	NH (n=4)	Bolme et al [48]
Theophylline	8	1-8	M	0.50	0.68	NH (n=12)	Eriksson et al [49]
	5	1-8	K	0.50	0.72	NH (n=12)	Eriksson et al [49]

Decreased Vd (P <0.05)

Quinine¶	10	2-6	Undefined	1.63	0.56	H (n=10)	Pussard et al [51]
Gentamicin¶	6	1-3	K	4.53§	3.90§	R (n=6)	Buchanan et al [52]

Note: *= values for adult reference; U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; ¶= drug administered intravenously; §= values in litres; R- rehabilitated patients; H= healthy children with normal weight; NH= non-healthy children with normal weight.

Table 4 Effect of protein-energy malnutrition on total clearance (CL) and half-life ($t_{1/2}$) of drugs primarily metabolised by the liver

Drug	Number of PEM children	Age (years)	Degree of malnutrition	Mean CL (ml/min/kg)		Mean $t_{1/2}$ (hr)		Reference
				Controls	PEM children	Controls	PEM children	
<i>Decreased CL and increased $t_{1/2}$ ($P < 0.05$)</i>								
Acetanilide	5	0-2	K	2.45]	0.92]	1.76	4.78s	Buchanan et al [40]
Antipyrine	10	0-5	M, M-K, K	70.10]]	4.72]]	6.30	10.40	Narang et al [42]
	15	0-2	K	15.50]]]]	8.40]]]]	4.30	7.90	Buchanan et al [43]
	8	9-12	Undefined	32.00]]]]]	19.50]]]]]	9.90	14.80	Homeida et al [44]
Caffeine	7	1-4	K	4.50	1.60	3.70	13.10	Akinyinka et al [26]
Chloramphenicol]]	8	0-6	K	7.53	4.16	2.85	3.76	Eriksson et al [45]
Isoniazid	7	0-3	K	329.40]]]]	125.70]]]]	0.73	1.03	Buchanan et al [47]
Metronidazole	10	0-4	M-K, M	0.17+]]	0.08+]]	5.09+]]	10.21+]]	Lares-Assef et al [18]
Quinine	6	1-2	K	108.50]]]]]]	37.50]]]]]]	8.00	15.0	Salako et al [30]
Quinine]]	20	2-4	Undefined	4.00	1.70	5.10	7.20	Pussard et al [51]
<i>Increased CL and decreased $t_{1/2}$ ($P < 0.05$)</i>								
Quinine	8	0-5	not K	2.30	4.40	10.10	6.30	Treluyer et al

[21]

CL and t_{1/2} not significantly affected (P>0.05)

Chloramphenicol	17	0-6	M	7.53	8.16	2.85	2.88	Eriksson et al [45]
	8	0-6	M-K	7.53	5.39	2.85	3.20	Eriksson et al [45]
Theophylline	11	1-16	Undefined	129.00]]	170.70]]	4.10	5.21	Kumar et al [22]
	6	1-8	U	1.22]]*	1.09]]*	4.93	5.25	Eriksson et al [49]
	8	1-8	M	1.22]]*	1.45]]*	4.93	5.38	Eriksson et al [49]
	5	1-8	K	1.22]]*	1.49]]*	4.93	5.61	Eriksson et al [49]

Note: U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; ¶= drug administered intravenously; †= median value;]= value in l/hr;]]= value in ml/hr/kg;]]*= value in ml/min/kg;]]]= value in ml/min;]]]]= unit of the value was not given;]]]]]= value in mg/min;]]]]]]= value in L/kg/hr.

Table 5 Effect of protein-energy malnutrition on total clearance (CL) and half-life ($t_{1/2}$) of drugs primarily eliminated by the kidneys

Drug	Number PEM of children	Age (years)	Degree of malnutrition	Mean CL in (ml/min/kg)		Mean $t_{1/2}$ (hr)		Reference
				Controls	PEM children	Controls	PEM children	
<i>Decreased CL (P<0.05)</i>								
Cefoxitin	6	1-4	K	70.60[[[50.70[[[0.47	0.49	Buchanan et al [53]
Penicillin¶	7	0-6	U	22.20	15.10	0.72	1.13	Bolme et al [19]
	8	0-6	M	22.20	14.00	0.72	0.75	Bolme et al [19]
	8	0-6	M-K	22.20	16.90	0.72	0.75	Bolme et al [19]
	8	0-6	K	22.20	11.60	0.72	0.93	Bolme et al [19]
	8	0-2	K	286.30[[[183.40[[[0.53*	0.95*	Buchanan et al [47]
<i>CL not significantly affected (P>0.05)</i>								
Gentamicin	11	0-1	U, M, M-K	3.57	3.99	0.01	0.01	Bravo et al [50]
Gentamicin¶	6	1-3	K	28.70[[[13.60[[[2.98	3.82	Buchanan et al [52]
Amikacin	10	1-4	K	<0.50**[[[[[[0.11[[[[[[<0.50**	2.11	Hendricks et al [41]
Ethambutol	6	1-12	U, M	33.60§§	67.00§§	9.70	7.40	Graham et al [16]
Streptomycin	11	0-12	U	67.00	74.00	2.58	2.14	Bolme et al [48]
	12	0-12	M	67.00	91.00	2.58	2.27	Bolme et al [48]
	5	0-12	K	67.00	49.00	2.58*	9.69*	Bolme et al [48]

Note: *= significant difference in $t_{1/2}$ values; **= values for adult reference; ¶= drugs administered intravenously; U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified; [[[[= value in ml/min; [[[[[[[[= value in L/kg/hr; §§= value in litres/hr.

Table 6 Effect of protein-energy malnutrition on drug half-life ($t_{1/2}$)

Drug	Number of PEM children	Age (years)	Degree of malnutrition	Mean $t_{1/2}$ (hr)		Reference
				Controls	PEM children	
<i>Increased $t_{1/2}$ ($P < 0.05$)</i>						
Chloramphenicol	8	0-5	Undefined	12.00	≥ 30.00	Mehta et al [54]
Paracetamol	11	0-6	U, M, M-K, K	4.33	8.15	Mehta et al [28]
Phenobarbitone	5	7-10	M-K, K	30.15	58.90	Syed et al [29]
Sulphadiazine	6	0-5	Undefined	21.27	31.78	Mehta et al [31]
Sulphamethoxazole†	7	0-2	M	4.90	9.60	Bravo et al [32]
<i>$t_{1/2}$ not significantly affected ($P > 0.05$)</i>						
Aspirin	5	0-2	Undefined	4.00	5.60	Treluyer [15]
Chloroquine	5	2-3	K	195.00	180.00	Walker et al [25]
Gentamicin	6	4-14	Undefined	3.31	6.21	Samotra et al [17]
Isoniazid	13	0-7	U	1.82	1.78	Seifart et al [55]
Phenytoin	5	7-13	Undefined	0.04	0.03	Bano et al [20]
Tobramycin	4	0-2	K	1.12	0.84	Buchanan et al [23]

Note: U= underweight; M= marasmus; K= kwashiorkor; M-K= marasmic-kwashiorkor; Undefined= PEM not classified

† Clearance and half-life of the drug were provided in the study, clearance was apparently decreased in PEM but the level of significance was not provided when compared with normal control children.