DRUG THERAPY IN MALNUTRITION

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The pharmacokinetics and pharmacodynamics of a drug depends upon its absorption, distribution, biotransformation and excretion. Knowledge of pharmacological principles of pediatric therapeutics(1) is essential for better understanding of these bioprocesses which are affected in protein energy malnutrition (PEM). Nutritional deficiencies may result in an altered drug response(2) requiring readjustment of drug dosages. There are limited studies on drug disposition in children with PEM(3,4). Physicians need to have practical guidelines regarding dosage and frequency of administration of the commonly prescribed drugs in malnourished children in whom reversible structural and functional changes occur. This review discusses the effect of PEM on various bioprocesses involved in drug pharamacokinetics in order to evolve guidelines in the clinical use of drugs under altered body-physiological functions.

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Drug Absorption and Bioavailability

In PEM hypochlorhydria, prolonged gastric and intestinal emptying time, villous atrophy(5), altered gut flora, motility(6) and reduced intestinal blood flow may interfere with gastrointestinal absorption. As a result, the rate of absorption assessed by the absorption rate constant (ka), is diminished(5). Pharmacokinetically, the bio-availability of a drug is represented by the area under the serum concentration-time curve (AUC). The maximum serum concentration attained and the course of concentration with time are equally important for efficacy of a drug even under altered homeostasis.

Drug Distribution

The volume of distribution (Vd) of a drug is influenced by its physicochemical properties, plasma and tissue protein binding, total body water content, body composition and blood flow through various organs. Malnutrition, by altering the total body water and reducing serum albumin and tissue binding, may lead to altered Vd of a particular drug.

Drug Metabolism (Biotransformation)

Liver is the main site of drug metabo-

lism. It involves oxidation, reduction and hydrolysis in Stage I and conjugation (glucuronidation, sulfation or acetylation) in Stage II. The peak drug levels, duration of action and inter-individual variations are all accounted for by variation in oxidative metabolism mediated by the cytochrome P-450 enzyme system(4).

We know that malnutrition and infection co-exist and have synergistic effects–one augmenting the other. Malnutrition *per se* to some extent and more recently many viral and bacterial infections, and even vaccines like BCG and hepatitis-B have been reported by Moochhala(7) to decrease drug biotransformation and elimination by inducing the formation of interferon–an immunomodulator which in itself depresses the cytochrome P-450 enzyme system.

Drug Excretion (Renal)

Renal plasma flow, glomerular filtration rate and tubular functions (excretion and reabsorption) can be markedly decreased in chronic severe malnutrition. These changes lead to delayed elimination of the drug with prolonged serum half-life which may accumulate to toxic levels.

Clinico-pharmacological Principles For Common Drugs Used in Malnutrition

1. Antibiotics

(*a*) *Chloramphenicol*

It is a broad spectrum antibiotic commonly used in the less developed countries. Oral administration of chloramphenicol in malnourished children has shown contradictory results. Mehta *et al.*(8) have observed a higher bioavailability in children especially those with PEM while Samotra *et al.*(9) reported a decreased bioavailability due to an enhanced clearance with no change in absorption rate. In malnourished children, only 35-55% of the drug was shown to be excreted in the conjugated (glucuronidated) form as compared to 75% in the controls in a study by Mehta *et al.*(10). This was more evident in cases with severe PEM. Krishnaswamy(3) showed that the rate of absorption of chloramphenicol was reduced in PEM. Despite giving a higher dosage of the drug, the peak plasma concentration and AUC were low. Hence in PEM, depending upon the extent of malnutrition, doses of chloramphenicol should be given on the lower side of the range. Therapeutically effective and safe plasma levels can be achieved with dosage of 75 mg/kg/day(4). Studies on chloramphenicol pharmacokinetics are required in normal children which must be compared to those with varying extent of malnutrition, *i. e.*, Grades I, II and III, kwashiorkor, and marasmic-kwashiorkor.

(*b*) *Penicillins and Aminoglycosides*

Children suffering from PEM have a diminished muscle mass and edema of lower limbs. Repeated injections may be difficult to administer and edema may interfere with absorption of drugs. Severe malnutrition can lead to reduction in glomerular filtration rate, tubular functions and renal plasma flow. The serum levels of penicillins and aminoglycosides which are not metabolised in the liver but eliminated through glomerular filtration or tubular excretion, may thus be altered. Buchanan *et al.*(11) studied the pharmacokinetics of penicillin and Mitchell and Jollow(12) of gentamicin in children with kwashiorkor. They found an increase in the plasma half-lives and reduced renal clearance of both drugs which, after nutritional rehabilitation returned to normal. It is suggested that children with kwashiorkor should initially receive penicillin and gentamicin at less

frequent intervals compared to normally nourished ones(4). Once dietary therapy is initiated and the child becomes edema-free, the dosage schedule may be revised appropriately.

2. Antitubercular drugs

As tuberculosis and malnutrition often co-exist, the knowledge of kinetics of rifampicin and isoniazid in the malnourished patients is important for successful therapy. Seth *et al.*(13,14), in their pharmacokinetic studies on isoniazid and rifampicin in relation to the nutritional status in children with pulmonary tuberculosis, have shown higher peak serum concentations (C_{max}) of both the drugs in undernourished (Grade I + II) and malnourished (Grade III + IV) patients (*Table I*). The serum half-life (T½) of isoniazid and bioavailability (AUC) of both isoniazid and rifampicin were higher in undernourished and malnourished patients when compared to the normally nourished ones. Polasa *et al.*(15), and Polasa and Krishnaswami(16) have also reported higher C_{max}, T½ and AUC values for rifampicin in adults with undernutrition.

In kwashiorkor and marasmic-kwashiorkor patients on antitubercular therapy, the potential hepatotoxic drugs like isoniazid and hepatic enzyme-inducer rifampicin should be given on their lower side of the range, *i.e.,* 5-10 and 10 mg/kg/day respectively as there is involvement of liver with fatty infiltration. In tuberculous meningitis where severe malnutrition is often an accompanying feature, the liver is exposed to incessant insults by malnutrition, disseminated disease and a battery of hepatotoxic antitubercular drugs. Here drug doses and regimens should be judiciously chosen. Udani(17) has suggested that in tuberculous malnourished children on therapy with evidence of rifampicin-induced-hepatotoxicity, rifampicin should be discontinued, or alternatively, it should be given in a dose of 12 mg/kg on alternate days for initial 3-4 months followed by twice a week for 4-6 months. In severe

TABLE I— *Pharmacokinetic Parameters of Rifampicin and Isoniazid in Pulmonary Tuberculosis in Relation to Nutritional Status*

Nutritional grade	Drug	No. of patients	Pharmacokinetic parameters				
			C_{max} (μg/ml)	T_{max} (hr)	$T_{½}$ (hr)	AUC (μg/ml.hr)	Ke (h^{-1})
Normal	RIF	15	3.0	2.0	2.4	20.53	0.29
	INH	20	3.42	1.0	3.77	25.51	0.19
I + II (Under-nourished)	RIF	30	3.25	2.0	2.05	24.58	0.195
	INH	30	4.72	1.0	4.5	35.98	0.154
III + IV (Malnourished)	RIF	10	3.39	2.0	2.35	22.06	0.295
	INH	10	4.51	1.0	4.47	34.93	0.155

RIF = rifampicin; INH = isoniazid; C_{max} = peak serum concentration; T_{max} = time to peak concentration; $T_{½}$ = terminal half-life; AUC = area under the serum concentration-time curve; Ke = elimination rate constant; Doses of RIF = 12 mg and INH = 10 mg/kg of body weight/day.

tuberculous cases streptomycin, isoniazid and ethambutol, and in less severe cases isoniazid and ethambutol should form the effective therapy. In case of isoniazid-induced-hepatotoxicity in malnourished patients, we advocated its substitution by ethambutol or streptomycin for 1 to 2 months and then reintroduction of isoniazid in lower dose with gradual increments.

3. Anticonvulsants

Absorption of carbamazepine is also reported to be diminished in PEM. The bioavailability of this drug is almost one-third in cases with PEM as compared to normally nourished controls(18). Therefore, a higher daily dosage of carbamazepine may be required to maintain plasma levels within the therapeutic range in TBM and CNS tuberculoma.

Patients of PEM receiving isoniazid and phenobarbitone together, also show increased plasma half-life and reduced renal clearance. Hence, phenobarbitone should be given in decreased dose. Children receiving isoniazid show reduced metabolism of phenytoin leading to the higher risk of neurotoxicity. Hence, phenytoin should be given in the lower range of drug dose. Following dietary therapy, most of these parameters return to normal and therefore dosages should be readjusted accordingly.

4. Bronchodilators

Theophylline

Eriksson *et al.*(9) have shown that in children with marasmus and kwashiorkor there was an increase in volume of distribution reflected in increased biological half-life along with a slight but not significant increase in clearance of theophylline. The pharmacokinetic changes in clearance and volume of distribution found in malnutrition counteract each other. Hence, from clinical point of view theophylline can be given in standard dosage regardless of the nutritional status. Kumar *et al.*(20) also found no effect of malnutrition on the pharmacokinetic parameters of theophylline. However, recently Moochhala(7) has shown that in infections by adenovirus, influenza virus and *S. pneumoniae* which are commonly seen in malnourished children, the elimination of theophylline is impaired. Its clinical implications should be further studied.

5. Miscellaneous

Antipyrine is rapidly absorbed when given orally, almost completely metabolised by the hepatic microsomal system (mixed function oxidases) and excreted in urine. Its metabolism is a reliable indicator of the hepatic microsomal function. In PEM, the plasma half-life of antipyrine is significantly prolonged and associated with a low clearance(21,22). With nutritional rehabilitation, however, both these changes are normalised, indicating that the effect of malnutrition is reversible.

Paracetamol (acetaminophen) is considered to be an extremely safe drug, having negligible binding to plasma proteins. It is normally metabolised in the liver to the glucuronide and sulfate conjugates. However, at plasma concentrations higher than 120 μg/ml, the above pathways get saturated and an alternate pathway is utilized resulting in formation of hepatotoxic acetaminophen mercapturate. In malnourished patients with reduced capacity for biotransformation, the normal conjugation pathway may become saturated even at lower plasma concentration with a higher risk of hepatotoxicity(4). Hence, it is necessary to

investigate paracetamol further before considering it a safe drug in children with malnutrition.

Sulfadiazine is conjugated by the N-acetyl transferase in the reticuloendothelial cells of the liver. Patients with PEM show decrease in excretion of the acetylated drug, with a corresponding increase in plasma half-life and AUC(12). Hence, dose of sulfadiazine should be adjusted according to the severity of PEM.

Ciprofloxacin is a newer fluoroquinolone derivative, is being increasingly used in pediatric patients. Even though recent studies like that of Schaad *et al.*(23) have shown safer use of it in children (no arthropathogenicity shown) its clinical and pharmacokinetic evaluations are most needed in malnourished infants and children where it is going to be extensively used in countries like India.

Moochhala(17) has reported decreased cytochrome P-450 mediated biotransformation and elimination of drugs in many viral and other infections which are commonly seen in malnourished infants and young children. Reduced biotransformation and elimination of theophylline was demonstrated in infections with influenza-A and B virus, rhinovirus, adenovirus, herpes simplex virus, *S. pneumoniae, H. influenzae* and in BCG and influenza vaccinated individuals. Acetaminophen and phenytoin metabolism was reported to be decreased in infectious mononucleosis while that of quinine in malaria.

These observations, showing loss of drug metabolism from the effect of interferon, have important clinical consequences as they are likely to cause problems in the use of standard drug dosages in malnourished children with infections, those who are vaccinated or in patients with cancer who are receiving interferon or immunoactive drugs like tumor necrosis factor. Presently, information regarding drug disposition in PEM is limited and not sufficient to provide precise therapeutic recommendations. Carefully designed clinical, pharmacokinetic and pharmacodynamic studies are required to provide a better understanding of drug disposition in malnutrition. It will enable the practitioners in making more rational use of the drugs and altering the dosage schedules accordingly.

REFERENCES

1. Seth SD, Seth V, Beotra A. Pharmacological principles of Pediatric therapeutics. Part I and II. World Pediatr Child Care 1985, 1: 51-65; 2: 87-105.
2. Rumack BH, Holtzman J, Chase HP. Hepatic drug metabolism and protein malnutrition. J Pharmacol Exp Ther 1973, 186: 441-444.
3. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnutrition. Trends Pharmacol Sci 1983, 4: 295-299.
4. Mehta S. Nutrition and drug disposition. Indian J Pediatr 1986, 53: 163-171.
5. Reddy V, Mammi MVI. Intestinal function in malnourished children. J Trop Pediatr Environ Child Health 1976, 22: 3-4.
6. Mata LJ, Jimenez F, Gordon M, *et al.* Gastrointestinal flora of children with PEM. Am J Clin Nutr 1972, 25: 1118-1126.
7. Moochhala SM. Alteration of drug biotransformation by interferon and host defence mechanism. Ann Acad Med Singapore 1991, 20: 13-18.
8. Mehta S, Nath CK, Sharma B, Mathur VS. Steady state of Chloramphenicol in malnourished children. Indian J Med Res 1981, 73: 538-541.
9. Samotra K, Gupta S, Raina RK. Effect of malnutrition on chloramphenicol

kinetic in Indian children. Acta Pharmacol Sinica 1986, 7: 162-164.

10. Mehta S, Kalsi HK, Jayaraman S, Mathur VS. Chloramphenicol metabolism in children with protein calorie malnutrition. Am J Clin Nutr 1975, 28: 977-981.

11. Buchanan N, Robinson R, Koornhof HJ, Eyberg C. Penicillin pharmacokinetics in kwashiorkor. Am J Clin Nutr 1979, 32: 2233-2236.

12. Mitchell JR, Jollows JJ. Metabolic activation of drug to toxic substances. Gastroenterol 1975, 68: 392-410.

13. Seth V, Seth SD, Beotra A, Semwal OP, Mukhopadhyaya S. Absorption kinetics of isoniazid and rifampicin in tuberculosis in children in relation to nutritional status. (Communicated).

14. Seth V, Seth SD, Beotra A, Semwal OP, Mukhopadhyaya S. Monitoring of isoniazid and rifampin in childhood tuberculosis. Am Rev Respir Dis 1990, 141: A337.

15. Polasa K, Murthy KR, Krishnaswamy K. Rifampicin kinetics in undernutrition. Br J Clin Pharmacol 1984, 17: 481-484.

16. Polasa K, Krishnaswamy K. Rifampicin kinetics in undernourished. Indian J Med Res 1986, 83: 175-178.

17. Udani PM. Tuberculosis. *In:* Text Book of Pediatrics (Vol 1), 1st edn. New Delhi, Jaypee Brothers, 1991, p 1174.

18. Bano G, Raina RK, Sharma DS. Pharmacokinetics of carbamazepine in protein calorie malnutrition. Pharmacol 1986, 32: 232-236.

19. Erikasson M, Paulzow L, Bolme P, Mariam TW. Pharmacokinetics of theophylline in Ethiopian children of different nutritional status. Eur J Clin Pharmacol 1983, 24: 89-92.

20. Kumar L, Garg SK, Singh S, Lal R, Shukla VK. Theophylline pharmacokinetics in well-nourished and malnourished asthmatic children. Int J Clin Pharmacol Ther Toxicol 1989, 27: 888-892.

21. Tranvouez JL, Lerebours E, Chretien P, Fouin Firtunet H, Colin R. Hepatic antipyrine metabolism in malnourished patients; influence of the type of malnutrition and course after nutritional rehabilitation. Am J Clin Nutr 1985, 41: 1257-1264.

22. Homeida M, Karrar ZA, Roberts CJ. Drug metabolism in malnourished children: a study with antipyrine. Arch Dis Child 1979, 54: 299-302.

23. Schaad UB, Stoupis C, Wedgwood J, Tschaeppeler H, Vock P. Clinical, radiological and magnetic resonance monitoring for skeletal toxicity in pediatric patients with cystic fibrosis receiving a three-month course of ciprofloxacin. Pediatr Infect Dis J 1991, 10: 723-729.