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Effect of malnutrition on chloramphenicol kinetics in Indian children

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ABSTRACT Pharmacokinetics of chloramphenicol was studied in 8 malnourished and 4 normal children. After an oral dose of chloramphenicol 50 mg/kg, malnutrition reduced the elimination half-life and the area under the time-concentration curve. But malnutrition exerted no effect on absorption kinetics, C_{max} and t_{max}.

KEY WORDS chloramphenicol; child; nutrition disorders; pharmacokinetics

Protein malnutrition is the most widespread disorder affecting the children of less developed and less affluent societies[1]. Extensive pathophysiological abnormalities are known to occur in this nutritional deficiency[2]. Experimental evidences point towards an altered drug handling by liver in animals[3]. Handling of drugs may be altered in malnutrition in consequence to altered physiology. Reports of altered antimicrobial kinetics in protein energy malnutrition (PEM) have appeared in the literature[4-8]. Chloramphenicol, having a broad spectrum and being inexpensive, is widely used in many countries for enteric fever and other serious infectious diseases. The emergence of ampicillin-resistant *Haemophilus* microorganisms has further increased its utility. In contrast to the data available for chloramphenicol kinetics in adults, the studies in children have been few. Accordingly it was thought worthwhile to investigate the kinetics of chloramphenicol in protein energy malnutrition.

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METHODS

Eight malnourished (3 M, 5 F; 5.5-10.5 yr) children and 4 normal boys (4-14 yr) were admitted in this study. The degree of nutrition was determined by the norms suggested in Harvard scale[9]. A voluntary consent was obtained from the subjects or their parents. Chloramphenicol palmitate was given in a dose of 50 mg/kg on an empty stomach at 7 AM and food was withheld for 1 h thereafter.

Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 12 and 18 h after medication and stored in 4℃ till assay. The chloramphenicol in serum was estimated by the method of Hughes and Diamond (1964) at 430 nm.

The pharmacokinetic parameters were calculated by plotting serum concentration against time on a semi-logarithmic scale. Elimination half-life was read directly from the graph and elimination rate constant (K_{el}) was computed by the formula $K_{el} = 0.693/t_{0.5el}$.

The method of residuals ($Ae^{-K_a t} = Ae^{-Kt} - C$) was used to determine the absorption profile of chloramphenicol.

Absorption rate constant was obtained by determining the slope and multiplying that by -2.303. Absorption half-life was obtained by the formula $t_{0.5ab} = 0.693/K_a$.

The time taken for the concentration to reach the peak was obtained by the

formula $t_{max} = [2.303/(K_a - K_{el})] \log(K_a/K_{el})$.

The area under time-concentration curve (AUC) 0–18 h was calculated by trapezoidal method[10].

The values of the 2 groups were compared by t test.

RESULTS

The serum concentration after 0.5 h in the control group was 8.1 ± SD 2.9 μg/ml. It continued to rise for 2 h and then declined. At 18 h the levels were 4.7±0.3 μg/ml. The malnourished group differed in that the downhill part of the curve was much steeper. These data are summarized in Tab 1.

Tab 1. Pharmacokinetic data of chloramphenicol (single oral dose of 50 mg/kg) in 4 normal and 8 malnourished children. $\bar{x}$±**SD.** *$p>0.05$, ***$p<0.01$

	Volunteers	Malnourished
Plasma albumin (g/l)	42.5±0.4	22.7±0.3*
$t_{\frac{1}{2}ab}$(h)	0.8±0.4	0.74±0.20*
K_a(h^{-1})	1.1±0.6	1.0±0.4*
$t_{\frac{1}{2}el}$(h)	7.0±1.9	3.4±0.7***
K_e(h^{-1})	0.10±0.04	0.20±0.04***
C_0(μg/ml)	29±13	31±15*
C_{max}(μg/ml)	24±6	18±7*
t_{max}(h)	2.7±0.8	2.1±0.4*
AUC(μg/ml/h)	252±45	128±45***

There was no significant difference between the 2 groups as far as the absorption kinetics were concerned. In malnourished group the elimination half-life was reduced and rate increased. There was no difference in the maximal concentrations or times taken to achieve maximal concentrations in 2 groups. The AUC was much smaller in malnourished children.

DISCUSSION

The reports on pharmacokinetic parameters in children vary from study to study primarily because of differing age groups used by different authors and different methods of estimation. Malnutrition causes gross abnormalities in absorption processes of gastrointestinal tract[11]. In the present study no difference was found in the absorption of chloramphenicol between normal and malnourished children. It is likely that alterations in gastrointestinal physiology in malnutrition are not of a magnitude as to hinder the passage of chloramphenicol from the gut to the central compartment.

The observations of the present study, however, suggest an enhanced clearance of chloramphenicol in PEM About 50–60% of the drug is known to be protein-bound. Malnutrition is accompanied by a reduction in the albumin fraction of blood. As a consequence more of free chloramphenicol is expected to be available for degradation in these patients. It is therefore reasonable to assume that hypoalbuminemia associated with malnutrition may be a contributing factor for enhanced clearance of chloramphenicol. Another factor for enhanced clearance of the antibiotic could be due to alterations in metabolic mechanisms. There are several experimental evidences which suggest enhanced hepatic metabolic activity in undernourished animals.

The reduced bioavailability of the antibiotic in malnutrition as suggested by lowered AUC is also likely to be a reflection of enhanced clearance of the antibiotic in these patients. Considering the said results a modified dosage schedule comprising of more frequent drug administration may be needed.

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营养不良对印度儿童氯霉素动力学的影响

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摘要　本文研究了 8 例营养不良和 4 例正常印度儿童的氯霉素药物动力学。口服剂量 50 mg/kg 后，营养不良能缩短药物消除的半衰期，并减少时间-浓度曲线内面积。但是，营养不良对吸收动力学参数 C_{max} 和 t_{max} 的影响不大。

关键词　氯霉素；　儿童；　营养障碍；　药物动力学