

## Drug metabolism in malnourished children: a study with antipyrine

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**SUMMARY** The effect of malnutrition on hepatic drug-metabolising enzymes was investigated in 8 Sudanese children aged between 9 and 12·5 years using as a model the drug antipyrine. Antipyrine half-life and clearance were measured in the malnourished state and after 3 or 4 weeks of good nutrition. Associated with the improvement in nutritional state was a shortening of antipyrine half-life and an increase in its clearance. There was also a rise in serum triiodothyronine. It is concluded that poor nutrition is associated with impairment of drug metabolic capacity and that many factors are responsible.

Primary malnutrition is the most common medical problem in children in underdeveloped countries (National Institute of Child Health and Human Development, 1971) and is often associated with diseases requiring treatment with drugs. Deficiencies of essential nutrients have been shown to affect the activity of hepatic enzyme systems responsible for drug metabolism. In animal studies dietary withdrawals of protein, vitamin A, thiamine, riboflavin, vitamin C, and minerals have been found to decrease the activity of the mixed function oxidase system of enzymes in the liver and thus to depress the metabolism of certain drugs (Dixon *et al.*, 1960; Kato, 1967; Campbell and Hayes, 1974). Studies in humans deprived of at least one essential nutrient for variable periods have also demonstrated prolonged plasma disappearance of drugs (Conney *et al.*, 1977). In developing countries malnutrition comprises a chronic deficiency of macronutrients and micronutrients, and it is commonly associated with hormone deficiencies (Chopra and Smith, 1975) which in turn can influence hepatic drug metabolism. Alteration in body composition, particularly the presence of nutritional oedema, can also influence plasma disappearance of drugs by changing their volume of distribution.

This study was designed to investigate the effect of established protein-calorie malnutrition on drug

metabolism in children and the effect of its treatment. The possible contribution of change in thyroid function to alteration in drug metabolism in malnutrition was also investigated.

Antipyrine was chosen for the study as it is rapidly and completely absorbed after oral administration, is extensively hydroxylated in the liver, is only 10% bound to plasma proteins, and is distributed in body water (Brodie and Axelrod, 1950). Plasma kinetics of antipyrine have been used widely as an indicator of hepatic drug metabolism (Stevenson, 1977).

### Patients and methods

Eight children aged between 9 and 12·5 years were studied. In each child protein-calorie malnutrition was established at the beginning of the study. Selection of patients was based on the presence of all the following criteria: history of dietary inadequacy, weight <75% of the standard using the Wellcome Trust classification (*Lancet*, 1970); Hb <10 g/dl, serum albumin <35 g/l (3·5 g/100 ml) in the absence of other causes of anaemia or hypoproteinaemia; presence of signs suggesting vitamin deficiency—for example, angular stomatitis or dry flaky skin. No patient had peripheral oedema or ascites. In 6 patients investigations showed no concurrent disease and there was no recent drug administration. One patient had had malaria which had been treated before the start of the study, and one patient was found to have typhoid fever which was treated with chloramphenicol in the latter part of the study.

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Patients were studied on admission to hospital and again after 3 or 4 weeks on a high-protein, high-calorie diet. The diet contained 5 g protein/kg in the form of meat, fish, and eggs, and adequate amounts of carbohydrates, vegetables, and fresh fruits. Vitamin supplement of the B-group was added with iron in the form of ferrous sulphate.

The following measurements were made: Hb, serum albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase, serum thyroxine (T4), free thyroxine index (FTI), and triiodothyronine (T3). Plasma antipyrine kinetics were performed before and after treatment using the following procedure: after an overnight fast and withdrawal of blood for blank plasma, 600 mg antipyrine as a freshly prepared solution was given orally. Venous samples were drawn at 3, 6, 9, and 24 hours after the dose. Plasma was separated and stored at  $-20^{\circ}\text{C}$  for future analysis. Plasma was sent frozen to Bristol for the assay of antipyrine levels using the method of Brodie *et al.* (1949).

Antipyrine plasma half-life ( $t_{1/2}$ ) was calculated from linear regression analysis of the log plasma concentration-time profile. Volume of distribution (Vd) of antipyrine was calculated as dose/plasma concentration antipyrine, extrapolated back to the time of administration. Clearance of antipyrine was calculated as  $\text{Vd} \times 693 \div t_{1/2}$ .

Statistical analysis was carried out using Student's paired *t* test.

## Results

The clinical condition of each patient improved during the study period. There were significant increases in weight, Hb, and serum albumin, although mean Hb and mean serum albumin did not reach normal levels (Table 1).

The mean baseline plasma T4 and FTI were normal and the change in these parameters after treatment was not significant (Table 1). However, T3 levels were low at the beginning of the study and rose to normal after treatment.

There were no abnormalities or changes in the levels of alkaline phosphate, bilirubin, or aspartate aminotransferase.

Antipyrine plasma kinetics are shown in Table 2. The mean volume of distribution of antipyrine was higher after treatment, but the difference was not significant and disappeared when corrected for change in body weight. There was a significant 33% shortening of antipyrine plasma half-life, and a significant 64% increase in plasma clearance after treatment for malnutrition.

## Discussion

This study showed that drug metabolism is impaired in malnourished children and that impairment can be reversed within a month of starting an improved diet. Such a finding has not been previously reported.

The main observation is the shortening of antipyrine half-life and the increase in its clearance which occurred between measurements in the malnourished and treated states. In most patients the only treatment was dietary replacement. Two patients were receiving treatment for malaria and typhoid which might have influenced antipyrine kinetics. However, if these patients are excluded the change in antipyrine half-life is still significant. It is reasonable to conclude that the change in antipyrine kinetics

Table 2 *Antipyrine disposition in 8 children with malnutrition before and after treatment*

Case	Treatment	Sex	Volume of distribution (l)	Half life (hours)	Clearance
1	Before	M	20.8	27	9
	After		27.3	13.5	23.3
2*	Before	M	15.8	16.5	11.1
	After		35.3	12	33
3	Before	F	11.5	15	9
	After		14.3	14	11.8
4	Before	F	21.4	7.8	31.7
	After		15	5.4	32.1
5	Before	M	27	18.6	17
	After		24	13.5	20.7
6**	Before	M	21	9.1	26.7
	After		25.6	6.7	44
7	Before	M	18.8	9	24
	After		20	6.8	44
8	Before	M	36.6	15.4	27.4
	After		38.7	7.6	58
Mean $\pm$ SEM	Before		21.7 $\pm$ 2.7	14.8 $\pm$ 2.1†	19.5 $\pm$ 3.2†
	After		25 $\pm$ 3.1	9.9 $\pm$ 1.3	32 $\pm$ 5.1

† $P < 0.05$

\*Patient with typhoid, \*\*patient with malaria.

Table 1 *Comparative clinical and biochemical data on 8 children with malnutrition before and after treatment*

	Weight (kg)	Hb (g/dl)	Serum albumin (g/l)	T4 (nmol/l)	FTI	T3 (nmol/l)
Before treatment (mean $\pm$ SEM)	24.7 $\pm$ 1.4*	7.3 $\pm$ 0.2*	28.3 $\pm$ 3.0†	117 $\pm$ 7.8	121 $\pm$ 6.6	0.69 $\pm$ 0.1†
After treatment (mean $\pm$ SEM)	29.5 $\pm$ 1.8	10 $\pm$ 0.4	33.9 $\pm$ 3.3	130 $\pm$ 11.4	129 $\pm$ 10.9	1.96 $\pm$ 0.2

\* $P = 0.001$ , † $P < 0.05$ .

Conversion: SI to traditional units—T4: 1 nmol/l  $\approx$  0.078  $\mu\text{g}/100\text{ ml}$ ; T3: 1 nmol/l  $\approx$  0.65  $\mu\text{g}/\text{ml}$ .

during the study period was related to altered nutritional state and that the results obtained at the beginning of the study reflected abnormally depressed drug metabolism due to nutritional deficiency. Evidence of an improvement in nutritional state is provided by the changes in bodyweight, Hb, and serum albumin levels.

The results of this study differ from those of Krishnaswamy and Naidu (1977) who compared groups of normal and malnourished adults. In their study the antipyrine half-life was normal in undernourished patients and was prolonged only in patients with nutritional oedema, possibly due to altered volume of distribution. However, exposure to environmental enzyme-inducing factors could not be excluded. In the present study the within-patient comparison excludes all such environmental factors. Furthermore the absence of change in volume of distribution, and the pronounced increase in plasma clearance of antipyrine with nutritional replacement, support the concept that malnutrition decreases the drug-metabolising capacity of the liver.

It is not possible to say which factor in the malnourished children was most responsible for the decreased drug metabolism, and it is likely that they were deficient of many of the essential nutrients which have been shown to affect hepatic enzyme systems. The reduced serum albumin provides evidence of protein malnutrition which may cause a reduction in total amount of microsomal enzymes. In the rhesus monkey, protein deprivation resulted in loss of liver weight with an associated decrease in concentration and activity of microsomal enzymes (Rumack *et al.*, 1973), and in rats protein deficiency induced fatty infiltration of the liver with reductions in the number of functioning cells and in total microsomal protein content (Campbell, 1977). Protein deficiency has also been shown to decrease *in vitro* microsomal oxidation of strychnine, aminopyrine, and ethyl morphine, and to reduce cytochrome P450 content (Campbell and Hayes, 1974).

The children in the present study received supplements of vitamin B, vitamin C-rich fruits, and oral iron. Drug-metabolising enzyme systems have been shown to be highly dependent on vitamin C status in animals (Campbell and Hayes, 1974). Supplementation of the diet of normal individuals with vitamin C has resulted in a substantial increase in antipyrine clearance (Houston, 1977), and vitamin C deficiency is partly responsible for the retardation of drug clearance in elderly people (Smithard and Langman, 1977), and in patients with liver disease (Beattie and Sherlock, 1976). It is possible that the vitamin supplements in this study accounted for some of the observed improvement in antipyrine clearance. As there is evidence that iron deficiency enhances drug

metabolism (Langman and Smithard, 1977), the iron supplements are unlikely to have contributed to the change.

The findings of low T3 levels in the face of normal T4 and FTI in the malnourished children is in agreement with the results of other workers (Pimstone *et al.*, 1973; Chopra and Smith, 1975). It has been suggested that the low serum T3 level is due to a reversible defect in the extra-thyroidal conversion of T4 to T3 (Chopra and Smith, 1975). Similar results have been observed in patients with anorexia nervosa when the biotransformation of labelled testosterone and oestradiol was impaired in all patients studied. Drug metabolism was restored to normality by the administration of T3 and by reversion of thyroid function tests to normal after good nutrition (Fishman *et al.*, 1977). It is possible therefore that the low T3 levels in the present study could be a factor in the prolongation of antipyrine half-life.

The present study has shown a reduction in the metabolism of antipyrine in malnourished children which is reversible by proper nutrition. Many factors may have contributed to this finding. Dose requirements of drugs metabolised by microsomal hydroxylation in the liver in children are dependent on nutritional status.

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