Antipyrine pharmacokinetics and D-glucaric excretion in kwashiorkor

N. Buchanan, F.C.P., Ph.D., C. Eyberg, B.Sc., and M. D. Davis, F.C.P.

ABSTRACT

Hepatic microsomal oxidation and glucuronidation were studied in 15 children with kwashiorkor on admission to the hospital and again after 3 weeks of nutritional rehabilitation. Microsomal oxidation as measured by antipyrine half-life and clearance was shown to be depressed in the acute phase of malnutrition ($T_1/2 = 7.9 \pm 5.0 \text{ hr}$, clearance $= 8.4 \pm 5.1 \text{ ml/min}$) improving with nutritional rehabilitation ($T_1/2 = 4.3 \pm 2.3 \text{ hr}$, clearance $= 15.5 \pm 8.7 \text{ ml/min}$). Urinary D-glucaric acid excretion increased from $60.6 \pm 42.2 \mu\text{moles/24 hr}$ to $121.8 \pm 105.0 \mu\text{moles/24 hr}$ over the same time period. Evidence is thus presented that both hepatic microsomal oxidation and glucuronidation are depressed in the acute phase of kwashiorkor but recover with nutritional rehabilitation.

The activity of hepatic drug metabolizing enzymes has been shown in animals to be affected by nutritional status (1). More recently, hepatic microsomal oxidative function has been demonstrated to be reduced in both malnourished children and adults (2, 3). The present study sought to confirm and expand these observations by measuring antipyrine half-life (hepatic microsomal oxidation) and D-glucaric acid excretion (an indirect index of hepatic microsomal activity) (4) in 15 children with kwashiorkor before and after nutritional rehabilitation.

Patients studied and methods used

Fifteen children with kwashiorkor as judged by the Wellcome classification (5) (mean age $15.6 \pm 7.5$ months) were studied at the time of admission to hospital and again 21 days later when they had been rehabilitated (serum albumin $>3 \text{ g/lOO ml}$). The patients received no drugs during the study periods except an oral potassium supplement.

Initially the children were placed on metabolic beds for a 24-hr urine collection for D-glucaric acid which was measured by the method of Simmons et al. (6). The next day, after a 4-hr fast, during which hourly Dextrostix measurements were carried out, $18 \text{ mg/kg}$ antipyrine was administered by nasogastric tube. Blood samples were collected at 1, 2, 3, and 6 hr and analyzed for antipyrine (7). Serum albumin and $\gamma$-glutamyltransferase were analyzed on the first sample collected.

Antipyrine half-life ($T_1/2$) and extrapolated zero time plasma concentration were determined by log-linear regression. The apparent volume of distribution was obtained by dividing the dose of antipyrine received by each patient by zero time plasma concentration. Antipyrine clearance was calculated from the formula: clearance $= 0.693 \times \text{volume distribution}/T_1/2$, where $0.693/T_1/2$ is the overall elimination rate constant.

Statistical analysis used standard linear regression procedures and the paired $t$ test.

Results

The results obtained from the 15 patients are shown in Table 1. Body weight on admission was $8.1 \pm 1.6 \text{ kg}$ rising to $8.75 \pm 1.9 \text{ kg}$, 21 days later. The serum albumin concentration was $2.1 \pm 0.4 \text{ g/lOO ml}$ on admission and $3.7 \pm 0.3 \text{ g/lOO ml}$ on recovery. Serum $\gamma$-glutamyltransferase was $19.7 \pm 4.9 \text{ IU/liter}$ on admission and $17.9 \pm 6.1 \text{ IU/liter}$ on recovery.

Antipyrine $T_1/2$ (Fig. 1, Table 1) was $7.0 \pm 5.0 \text{ hr}$ on admission shortening significantly to $4.3 \pm 2.3 \text{ hr}$ on recovery. This was associated with marked increase in plasma antipyrine clearance from $8.4 \pm 5.1$ to $15.5 \pm 8.7 \text{ ml/min}$, but no significant change in Vd.

The urinary D-glucaric acid observations were similar (Table 1, Fig. 2) with an excretion of $60.6 \pm 44.2 \mu\text{moles}/24 \text{ hr}$ on admission increasing significantly to $121.8 \pm 105.0 \mu\text{moles}/24 \text{ hr}$ on recovery.
FIG. 1. Antipyrine T½ (hours) on admission to hospital and on recovery 3 weeks later.

μmoles/24 hr on recovery. There was a poor correlation by linear regression between antipyrine T½ and urinary D-glucaric acid excretion ($r = -0.18$).

In summary there was a consistent shortening of antipyrine T½ associated with an increase of plasma clearance of the drug over a 21-day period of nutritional rehabilitation. There was also an increase in urinary D-glucaric acid excretion over the same period.

Discussion

The present observations confirm and extend those of Narang et al. (2) and Krishnaswamy et al. (3) that hepatic drug oxidative function is depressed in protein-energy malnutrition (PEM) and recovers with nutritional rehabilitation.

D-Glucaric acid excretion has been used as a moderately nonspecific index of microsomal enzyme function. It has been shown, for example, to be increased by exposure to pesticides (8) and decreased by antiemetic drugs, especially phenothiazines (9). In addition, D-glucaric acid excretion has been shown to be enhanced in pregnancy, probably as a result of induction due to increased endogenous hormone production (10); however, Sorrell et al. (11) have expressed doubts as to the reliability of this particular index of

<table>
<thead>
<tr>
<th>Weight</th>
<th>Serum Albumin</th>
<th>Antipyrine</th>
<th>D-Glucaric Acid</th>
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<tr>
<td>kg</td>
<td>g/100ml</td>
<td>VD</td>
<td>Plasma clearance</td>
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<tr>
<td>Admission</td>
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<td>2.1</td>
<td>4.4</td>
</tr>
<tr>
<td>SD</td>
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<tr>
<td>Recovery</td>
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<tr>
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<td>$P$</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&gt;0.25</td>
</tr>
</tbody>
</table>

FIG. 2. Urinary D-glucaric acid excretion on admission to hospital and on recovery 3 weeks later.
microsomal enzyme induction. In the context of the present report, the increased excretion of D-glucaric acid with nutritional rehabilitation is seen solely as a pointer to a generalized amelioration of hepatic microsomal enzyme function.

Antipyrine metabolism is, however, a reliable index of hepatic microsomal oxidation and has been extensively studied both in normal populations and in a variety of disease states. The present data show, as did that of Narang et al. (2), that antipyrine $T_{1/2}$ decreased and clearance increased with nutritional rehabilitation. The antipyrine $T_{1/2}$ of 4.3 ± 2.3 hr on recovery is extremely rapid compared with adult values (11.2 hr) (3), but it is known that in children, with the exception of low birth weight infants (12), that $T_{1/2}$ is considerably shorter than in adults (2, 13).

Patients with PEM are known to have hepatic dysfunction (14), and antipyrine clearance has been shown to be reduced both in acute viral hepatitis (15) and chronic liver disease (16). In addition, Obel and Vere (17) have demonstrated a slowing of metabolism of both antipyrine and propanolol in undernourished African patients. In normal volunteers, Conney et al. (18) showed that 14 days of a high-carbohydrate, low-protein diet had no effect on antipyrine $T_{1/2}$, while a high-protein, low-carbohydrate diet reduced antipyrine $T_{1/2}$ from control values of 16.2 ± 1.6 to 9.6 ± 0.4 hr. It would thus appear that, as with our patients, the introduction of protein induced antipyrine metabolism. More recently Bakke et al. (19) have not been able to demonstrate any change in antipyrine metabolism in patients suffering from anorexia nervosa. Although the effects of starvation and restricted feeding are complex both in animals and in man (20), it would appear from the present study and others in malnourished patients (2, 3), that hepatic microsomal function is adversely affected.

From a clinical point of view, the present findings suggest that, at least as measured by antipyrine, hepatic microsomal oxidation is depressed in PEM. Unfortunately, however, it is difficult to extrapolate from a model drug such as antipyrine to actual therapeutic compounds. For example, Smith and Rawlins (21) have shown low order correlations between antipyrine $T_{1/2}$ and those of phenylbutazone and warfarin. Thus it seems likely that the use of a model drug is only valid if it is metabolized in the same pathway as that followed by the therapeutic compound. Further studies in PEM should thus be directed to the kinetics of commonly used therapeutic compounds. Such studies are in progress in a variety of centers.

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References
14. KINNEAR, A. A., AND P. J. PRETORIUS. Liver function


