Influence of nutritional status on the pharmacokinetics of acetylsalicylic acid and its metabolites in children with autoimmune disease[1,2]

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ABSTRACT

Background: It is unknown whether nutritional status associated with autoimmune disease alters the pharmacokinetics of acetylsalicylic acid (ASA) and its metabolites.

Objective: We studied the effects of the nutritional status of children with autoimmune disease on the disposition of ASA and its metabolites.

Design: A prospective, open-label study was performed with 21 children aged 3–15 y who required ASA therapy. Children received 25 mg ASA/kg orally. Blood samples were drawn before and 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, and 24.0 h after ASA administration; urine samples were collected at different intervals. ASA and its metabolites were measured in plasma and urine. Nutritional status was assessed previously.

Results: The ASA maximum plasma concentration, area under the curve, and total clearance were significantly lower in underweight children than in normal-weight children. The elimination rate constants of gentisic acid (GA), salicyluric acid (SUA), and salicylic acid (SA) in plasma were slower for underweight children than for normal-weight children. The distribution volume of SUA increased significantly (r = 0.92) when the deficit percentage in weight-for-height increased. Underweight children excreted less GA and SA, but more SUA, than did normal-weight children.

Conclusions: These observations suggest a decrease in the hydrolysis and oxidative reactions of the metabolic pathway of ASA and its metabolites in underweight children. The study illustrates the need for pharmacokinetic data to establish the individual doses of drugs, particularly in conditions that alter nutritional status. *Am J Clin Nutr* 1999;69:318–24.

KEY WORDS Salicylic acid metabolism, acetylsalicylic acid, nutritional status, pharmacokinetics, children, juvenile rheumatoid arthritis, acute rheumatic fever, gentisic acid, salicyluric acid, salicylic acid

INTRODUCTION

Juvenile rheumatoid arthritis and rheumatic fever are the most common pediatric rheumatic diseases and 2 of the more common chronic diseases of childhood (1, 2). Although growth retardation was noted in the original descriptions of juvenile rheumatoid arthritis > 99 y ago (3), only recently has the nutritional status of patients with rheumatic diseases, and the possible relation between nutrition and growth, been addressed.

Nutritional impairment should not come as a surprise in children with active inflammatory diseases. Recognized impairments beginning with food allergies as a cause of chronic arthritis and extending to chronic malnutrition contribute to growth failure (4). The risk that patients with juvenile rheumatoid arthritis or rheumatic fever may develop "complicated" malnutrition—the presence of active inflammation complicated by the absence of sensitive visual cues for the clinical diagnosis of malnutrition—supports the need for routine, periodic, comprehensive nutritional assessment. The risk of nutritional depletion increases with worsening disease activity.

Protein-energy malnutrition (PEM) has been reported in 10–50% of the juvenile rheumatoid arthritis population (5, 6). In a nonrandom sample of 26 Swedish girls (aged 11–16 y) who had chronic juvenile arthritis and 28 control subjects, 19% of patients with arthritis and 0% of control subjects were malnourished (5). Preliminary results from a small, randomly selected group of American patients with juvenile rheumatoid arthritis showed PEM in 47% of 19 patients (6); similar results were detected in a group of 28 juvenile rheumatoid arthritis patients, of which 36% were identified as malnourished (7). In a study by Henderson et al (8), 70% of juvenile rheumatoid arthritis patients referred to a dietitian by a pediatric rheumatologist had PEM, as did 20% of juvenile rheumatoid arthritis patients screened by the nutritionist without referral. This finding underscores the fact that all juvenile rheumatoid arthritis patients may develop PEM in the absence of detectable clinical signs.

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Nutrition is becoming more widely recognized in the medical community as an essential component of chronic illness in children. There is some uncertainty about whether drug dosages based on studies in well-nourished persons are appropriate for malnourished patients. High doses of acetylsalicylic acid (ASA) are used widely in the treatment of rheumatic disease. In humans, ASA is rapidly hydrolyzed to salicylic acid (SA) by nonspecific esterases found in many tissues. SA is eliminated from the body by renal excretion and by hepatic biotransformation to salicyluric acid (SUA) and gentisic acid (GA). ASA dosage is determined by the accumulation of the metabolite SA, which has a much longer half-life than ASA and consequently accumulates more in the blood. The rate of formation of SUA is inducible, but continued induction of SUA contributes to the clearance of SA (9). This study was conducted to acquire a better understanding of the effects of the nutritional status of children with autoimmune disease on the pharmacokinetics of ASA and its metabolites.

SUBJECTS AND METHODS

Subjects

Pediatric patients with autoimmune disease and in whom ASA treatment was indicated were included in the study. All children had normal results on tests of liver and kidney function. Children were excluded from the study if they had an active opportunistic infection or were receiving chronic immunosuppressive therapy that might affect compliance with the study protocol. Subjects were hospitalized in the internal medicine service of the Instituto Nacional de Pediatría and in the rheumatology service of the Hospital de Pediatría del Centro Médico Nacional Siglo XXI del IMSS in Mexico City. Eleven children with juvenile rheumatoid arthritis and 10 with rheumatic fever participated in the investigation; their ages ranged from 3 to 15 y and their weights ranged from 13.2 to 74.0 kg. Nutritional status characteristics of the 21 children are shown in **Table 1**. Informed consent was obtained from the children's parents and the study protocol was approved by the ethics committee of the Instituto Nacional de Pediatría.

Protocol

Anthropometric measurements and classification of nutritional status

The following measurements were taken: *1*) body weight to the nearest 0.01 kg, by using a scale with a range of 0.100–140 kg that was calibrated daily (model 20/140; Braunker Aut DGN 679, Mexico City), and *2*) body height to the nearest 0.1 cm, on upright stadiometers (MC, Mexico City) (10, 11). All anthropometric measurements were performed by the same observer after the measurement techniques were standardized.

Weight-for-age and weight-for-height, an index of present nutritional status, were calculated as percentages of median Mexican reference values (12). The children were classified as to their nutritional status by both weight-for-height as in the Waterlow (13) classification and weight-for-age as in the Gómez (14) classification. Children who fell into the categories of first- and second-degree malnutrition according to the Gómez classification (14) were placed in the underweight group. On the other hand, children were placed in the normal-weight group if they

TABLE 1
Nutritional status characteristics of the studied patients

Patient no. and sex	Age	Actual weight	Reference median weight	Reference median weight[1]	Actual height	Reference median height	Reference median height[1]
	mo	*kg*	*kg*	*%*	*cm*	*cm*	*%*
Underweight patients (n = 11)							
1, F	84	15.9	23.33	68.2[2]	119.5	119.5	0.00
2, M	119	27.0	32.46	83.2[2]	132.0	135.0	2.22
3, M	120	25.0	32.46	77.0[2]	131.0	135.5	3.32
4, F	120	23.5	32.78	71.7[2]	122.5	135.9	9.22
5, F	132	30.1	38.43	78.3[2]	142.0	142.8	0.56
6, M	144	31.0	40.66	76.2[2]	141.0	146.0	3.42
7, F	156	42.3	49.70	85.1[2]	144.0	154.9	7.03
8, M	168	35.0	52.25	67.0[2]	150.0	160.0	6.25
9, M	168	38.0	52.25	72.7[2]	149.0	160.0	6.88
10, M	168	40.0	52.25	76.6[2]	150.0	160.0	6.25
11, M	180	46.4	58.19	79.7[2]	160.0	166.0	3.61
Normal-weight patients (n = 10)							
12, M	31	13.2	14.56	90.7	88.0	95.1	7.46
13, F	84	23.1	23.33	99.0	118.0	119.5	1.25
14, F	108	26.8	29.05	92.2	126.0	130.1	3.15
15, F	132	43.8	38.42	114.0	142.0	142.8	0.56
16, F	144	48.0	44.01	109.1	149.0	148.5	0.33
17, M	161	49.0	49.13	99.7	154.0	155.6	1.28
18, F	168	48.0	53.10	90.4	154.0	158.0	2.53
19, F	168	52.0	53.10	98.0	154.2	158.0	2.40
20, M	180	74.0	58.19	127.2[3]	172.0	166.0	3.61[4]
21, F	180	74.0	55.51	133.3[3]	165.0	158.8	3.90[4]

[1] To specific age.
[2] Deficit of reference median weight.
[3] Excess of reference median weight.
[4] Excess of reference median height.

were 1 SD above Mexican reference values (weight-for-age: 1.49–7.6 kg; weight-for-height: 3.4–7.4 kg).

Study design

An initial dose of 25 mg ASA/kg with 200 mL water was given to children in both the underweight and normal-weight groups. ASA was provided as conventional tablets; children fasted the night before receiving the dose and for 3 h afterward. None of the children had received ASA before the start of the study. A plastic cannula was inserted in a forearm vein and blood samples were drawn immediately before the administration of ASA and 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, and 24.0 h after. Blood samples (2 mL each) were collected in tubes containing heparin. Plasma was separated within 30 min. Urine samples were collected at intervals of 0–1 h, 1–2 h, 2–4 h, 4–8 h, 8–12 h, and 12–24 h. The volume and pH of the plasma and urine samples were measured immediately after collection. Samples were then placed in chilled tubes containing potassium fluoride to prevent rapid hydrolysis and stored at −20°C until analyzed. Children continued to receive 25 mg ASA/kg every 6 h for 3 wk. Creatinine, serum urea nitrogen, sedimentation rate, hemoglobin, hematocrit, albumin, and total protein were monitored on the day of the study.

Laboratory analysis

Plasma concentrations of salicylates were measured with a modified version of Buskin et al's method (15, 16). The chromatographic system consisted of a solvent delivery system (model 510; Waters Associates, Milford, MA), a variable-wavelength detector (model 490 E; Waters), a 20-μL loop injector (Rheodyne, Cotati, CA), and a Servogor recorder (Norma Goerz Instruments GmbH, Neudorf, Austria). Analyses were carried out on a 300 × 3.9–mm internal diameter μBondapak C_{18} column with a 5-μm particle size (Waters).

Methylparaben (used as an internal standard), ASA, SA, GA, and SUA were purchased from Sigma Chemical Co (St Louis). The assay was calibrated by adding known amounts of ASA, its metabolites, and the internal standard. Samples used for calibration contained ASA, SA, SUA, and GA in concentrations ranging from 0.512 to 362.0 mmol/L in plasma and from 1.024 to 362.0 mmol/L in urine; the internal standard was used at a fixed concentration of 13.14 mmol/L. Calibration curves were constructed by plotting the ratio of the peak height of ASA and its metabolites to that of the internal standard (*y* axis) as a function of the concentration of ASA and its metabolites in the sample (*x* axis). The accuracy and precision of the method were evaluated by adding known amounts of the drug to duplicated plasma samples over the concentration range used for calibration. Percentage recovery of ASA and its metabolites ranged from 92.0% to 98.0% in plasma and from 88.0% to 93.0% in urine. A linear relation between the peak height of ASA and its metabolites and that of the internal standard was found (r = 0.998–0.999 in plasma and urine). Precision was satisfactory; the intraassay CV was always <5%. Day-to-day precision of the assay was evaluated over 5 wk (n = 6). The detection limit for ASA and its metabolites in plasma was 0.256–1.448 mmol/L; in urine, the detection limit ranged from 0.512 to 2.17 mmol/L.

Kinetic analysis

After salicylates were measured in both plasma and urine, the values were used to build profiles that described the kinetics of ASA, GA, SUA, and SA by the minimum residual square method (17). The maximum plasma concentration (C_{max}) of ASA and its metabolites and the time of peak plasma concentration (t_{max}) for each subject were derived directly from the original measured values. The terminal log-linear phases of the concentration-time curves of ASA and its metabolites in plasma and urine were identified visually for each subject. The elimination rate constant (k_e) was determined by linear regression analysis of the plot of the natural logarithm of the plasma or urine concentration versus time. Areas under the curve (AUCs) were calculated by using the trapezoidal rule with extrapolation to infinity by dividing the last measured concentration (at 24 h) by k_e (17). The values were determined to follow first-order kinetics by using an independent model (18). The amount of ASA and of each metabolite excreted in urine was also calculated.

Statistics

Results are reported as median values (with ranges) unless indicated otherwise. Significance of differences was estimated by using the Mann-Whitney *U* test or the Kolmogorov-Smirnov test. The level of significance was $P \leq 0.05$. Pearson's correlation coefficients were used to quantify the univariate association between the distribution volume of ASA and its metabolites and the percentage deficit in weight-for-height. Linear regression analyses were also performed. Statistical analyses were performed with PAQUEST (version 1.0; Biomedical Software Development, Mexico).

RESULTS

The nutritional status characteristics of the children studied are shown in Table 1. Eleven children were classified as being underweight. The percentage deficit in weight-for-age in this group varied from 67.0% to 85.1%, with a median of 77.0%. Ten children were classified as having normal weights. The reference median weight in this group ranged from 90.4% to 133.3%, with a median of 99.4%. As shown in **Table 2**, all children had normal values for creatinine, serum urea nitrogen, sedimentation rate, hemoglobin, hematocrit, albumin, and total protein.

The time course of the cumulative urinary excretion of ASA and its metabolites in underweight and normal-weight children is shown in **Figure 1**. In general, underweight children excreted less SA and GA than did normal-weight children (P = 0.01), but excreted more SUA (P = 0.01).

Some differences in the kinetics of ASA and its metabolites in plasma between normal-weight and underweight children are

TABLE 2
Laboratory data[1]

Variable	
Age (mo)	138.81 ± 38.71
Creatinine (μmol/L)	67.77 ± 16.62
Serum urea nitrogen (mmol/L)	4.36 ± 1.18
Sedimentation rate (mm/h)	9.38 ± 1.96
Hemoglobin (g/L)	130.67 ± 12.50
Hematocrit	0.40 ± 0.03
Albumin (g/L)	43.09 ± 3.38
Total protein (g/L)	69.33 ± 7.02

[1] $\bar{x}$ ± SD; n = 10 F, 11 M. Laboratory reference ranges were as follows: creatinine, 26.52–88.40 μmol/L; serum urea nitrogen, 2.5–6.42 mmol/L; sedimentation rate, 0.0–12.0 mm/h; hemoglobin, 95.0–148.0 g/L; hematocrit, 0.32–0.44; serum albumin, 39.0–53.0 g/L; total protein, 61.0–82.0 g/L.

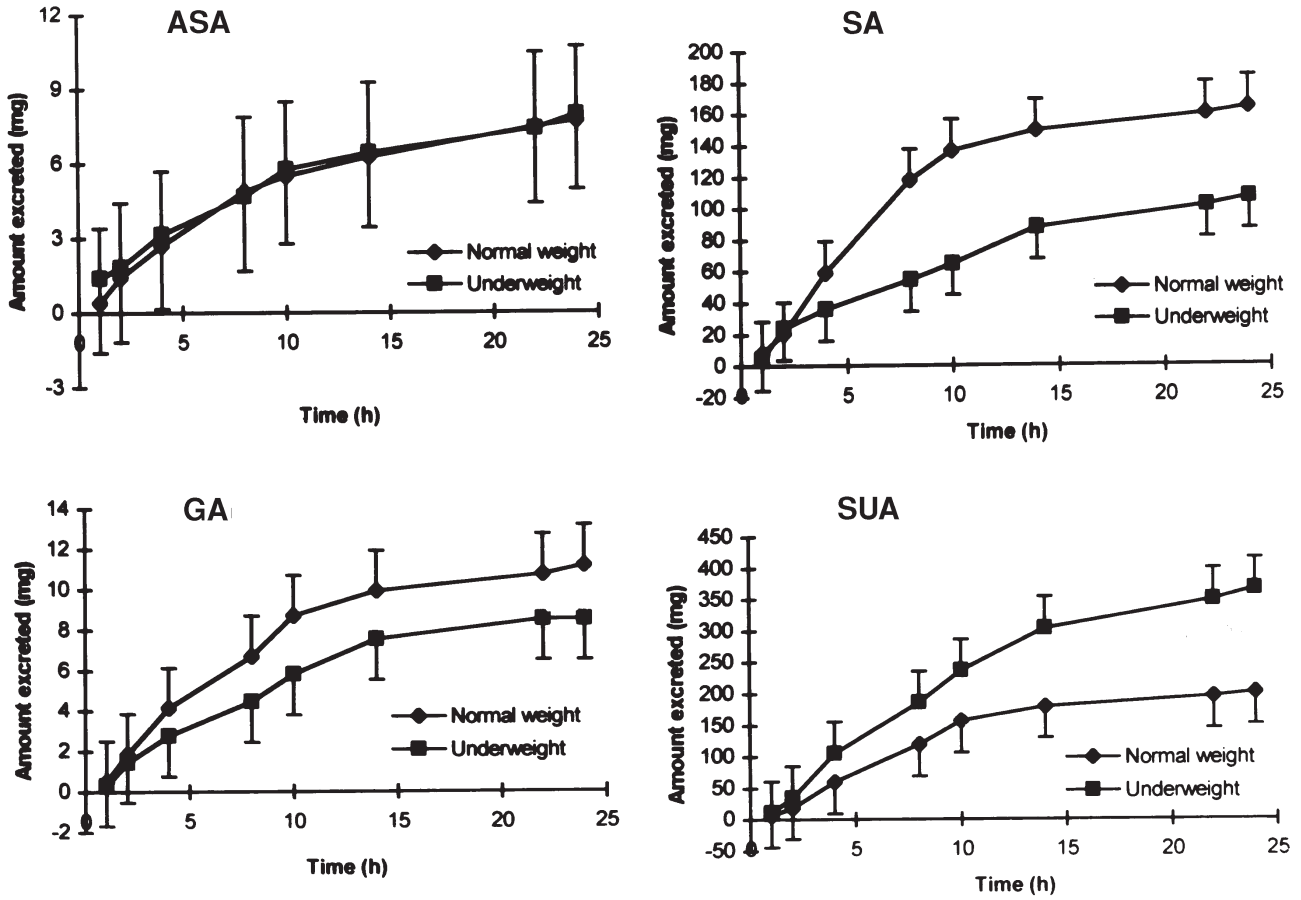

FIGURE 1. Time course of mean (±SD) urinary excretion of acetylsalicylic acid (ASA) and its metabolites salicylic acid (SA), gentisic acid (GA), and salicyluric acid (SUA) in normal-weight (n = 10) and underweight (n = 11) children. Excretion of SA and GA was significantly lower and that of SUA was significantly higher in underweight children than in normal-weight children, P = 0.01 (Kolmogorov-Smirnov test).

shown in **Table 3**. For ASA, the C_{max} was significantly lower in underweight children than in normal-weight children, and the k_e was significantly higher in underweight children. The total clearance and AUC of ASA were significantly lower in underweight children than in normal-weight children. The k_e values of GA and SUA were significantly slower in underweight children than in normal-weight children. The k_e of SA was also significantly slower in underweight children than in normal-weight children; in addition, the AUC of SA was significantly lower in normal-weight children than in underweight children.

As shown in **Figure 2**, in underweight children, when the percentage deficit in weight-for-height increased, the distribution volume of SUA in plasma increased significantly (r = 0.92). The amount of each salicylate excreted in urine over 24 h is shown in **Figure 3**. Data are presented as amount and as percentage of dose excreted. More SA was excreted in normal-weight children than in underweight children ($P \leq 0.05$). The maximal portion of the salicylates excreted was SUA and significantly more SUA was excreted in underweight children than in normal-weight children ($P \leq 0.05$).

DISCUSSION

Early recognition of children with significant nutritional problems requires careful and frequent screening during hospitalization and follow-up. Patients identified as being at high nutritional risk should undergo a complete nutritional assessment. Nutrition has also taken on a new perspective in light of secondary nutrient deficiencies in chronic childhood diseases such as inflammatory bowel disease (19).

The functional disturbances leading to abnormal body composition in chronic, severe infantile PEM are well known (20). Some studies indicate that the hepatic elimination of salicylates may be altered by disorders of nutritional state. The half-life of total salicylate was reported to be prolonged in marasmic Chilean children after the intravenous administration of ASA (21). In India, Shastri reported (22) that the steady state plasma SA concentrations of undernourished adults were not significantly different from those of control groups after repeated oral doses of 30, 50, and 100 mg ASA $\cdot$ kg^{-1} $\cdot$ d^{-1}. Serum protein binding values of ≈57% were found in both groups at the highest doses, despite significantly lower serum albumin concentrations in the undernourished group (23). A significant decrease in serum protein binding of SA and SUA in a kwashiorkor subgroup was found by Ashton et al (24). No effect of nutritional status on plasma salicylate concentrations was observed after oral administration of aspirin in a small study of African children (23).

A study of the disposition of SA in 57 malnourished Ethiopian children after administration of either a high or low single oral dose showed that the plasma half-lives and predicted half-lives of the unbound drug after the high dose were slightly longer in

TABLE 3
Comparison of the pharmacokinetic parameters of the metabolic pathway of acetylsalicylic acid and its metabolites in plasma[1]

	Underweight children (n = 11)	Normal-weight children (n = 10)
C_{max} (mmol/L)		
ASA	1.06 (0.12–1.66)	2.01 (0.46–54.07)[2]
SA	124.75 (30.84–242.17)	49.35 (65.16–254.34)
GA	3.98 (0.40–12.07)	3.91 (0.96–25.91)
SUA	13.01 (0.46–31.60)	8.45 (0.84–50.38)
k_e (h^{-1})		
ASA	0.227 (0.142–0.276)	0.195 (0.065–0.855)[2]
SA	0.206 (0.099–0.342)	0.294 (0.017–0.427)[2]
GA	0.149 (0.035–0.624)	0.193 (0.039–0.939)[2]
SUA	0.111 (0.061–0.343)	0.171 (0.008–1.970)[2]
Cl_T (L · kg/h)		
ASA	0.280 (0.092–0.841)	0.842 (0.213–1.970)[2]
SA	0.319 (0.052–0.813)	0.475 (0.039–1.073)
GA	0.913 (0.037–1.1721)	0.412 (0.057–2.400)
SUA	0.473 (0.069–1.171)	0.210 (0.017–1.900)
AUC (mmol · h/L)		
ASA	14.51 (9.26–19.81)	28.95 (19.66–30.65)[2]
SA	1226.40 (888.88–1343.11)	723.06 (477.63–982.63)[2]
GA	42.19 (27.34–48.94)	48.93 (31.96–59.77)
SUA	130.72 (89.72–220.78)	128.97 (91.85–164.45)

[1] Median; range in parentheses. ASA, acetylsalicylic acid; SA, salicylic acid; GA, gentisic acid; SUA, salicyluric acid; C_{max}, maximum concentration; k_e, elimination rate constant; Cl_T, total clearance; AUC, area under the curve.

[2] Significantly different from underweight children, $P < 0.05$ (Mann-Whitney U test).

the kwashiorkor group than in the control group, whereas the reverse was true after the low dose (both $P \leq 0.05$) (25). The AUC of SUA did not differ significantly with nutritional status or increment of dose. The percentage of the dose recovered as the original drug or as its metabolites in urine after 23–24 h (n = 53) varied greatly, with median values of 61% (range: 27–87%) in the control group, 54% (29–79%) in marasmic children, and 49% (26–66%) in children with kwashiorkor. In children with kwashiorkor receiving the low dose (12.5 mg/kg), there was a lower relative excretion of SUA and a higher fractional excretion of salicylic glucuronides. A lower intrinsic clearance in kwashiorkor patients was indicated by greater AUC values for the unbound drug. The observed difference in fractional salicyl glucuronide excretion in kwashiorkor patients reflects a diminished formation of SUA and is not an indication of metabolic capacity for salicylate glucuronidation (25).

Salicylic acid is eliminated from the body by biotransformation to SUA, salicyl acyl and phenolic glucuronides, and GA and by renal excretion of unmetabolized drug. Two of these parallel pathways (the formation of SUA and salicyl phenolic glucuronide) are of limited capacity in humans and exhibit Michaelis-Menten kinetics (26). Because of the capacity-limited kinetics of salicylate, its clearance from the body decreases with increasing concentration or dose (27).

Our results make clear that secondary malnourishment affects the biotransformation of ASA and its metabolites because the k_e values of SA and GA as well as the total clearance of ASA were significantly diminished in underweight children with chronic inflammatory disease compared with normal-weight children. On the basis of differences in the pharmacokinetics in plasma of ASA and its metabolites between normal-weight and underweight children (Table 3), as well as differences in the time course of cumulative excretion (Figure 1) and the percentages of ASA and its metabolites excreted in urine (Figure 3), the most affected metabolic pathways of biotransformation in underweight patients were a diminution in the hydrolysis reaction from ASA to SA and in the oxidative reaction from SA to GA. This suggests that the most affected biotransformation pathway in cases of malnourishment is the oxidative one. This was shown previously by Lares-Asseff et al (28) in a study in which alterations in the oxidative mechanism in phase 1 were described in

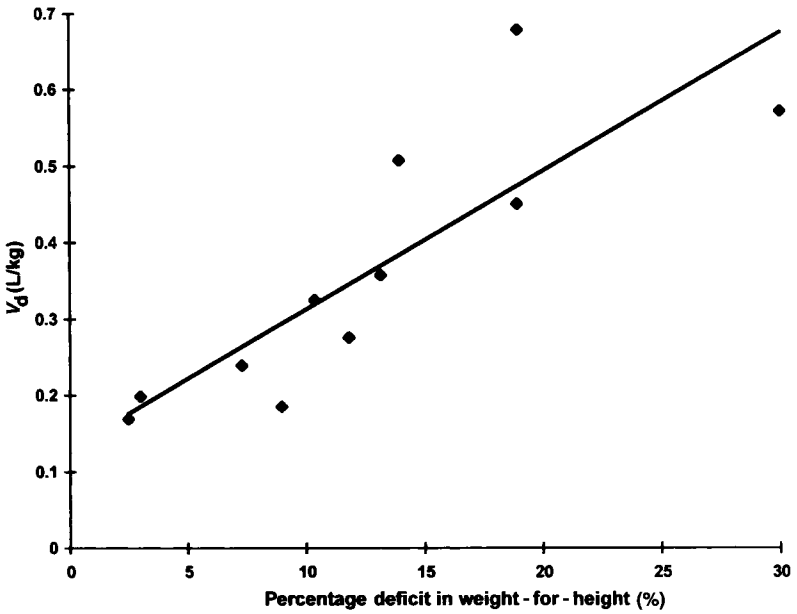

FIGURE 2. Simple linear regression analysis of the relation between percentage deficit in weight-for-height and the distribution volume (V_d) of salicyluric acid in 11 underweight children. $R^2 = 0.84$, $P \leq 0.05$.

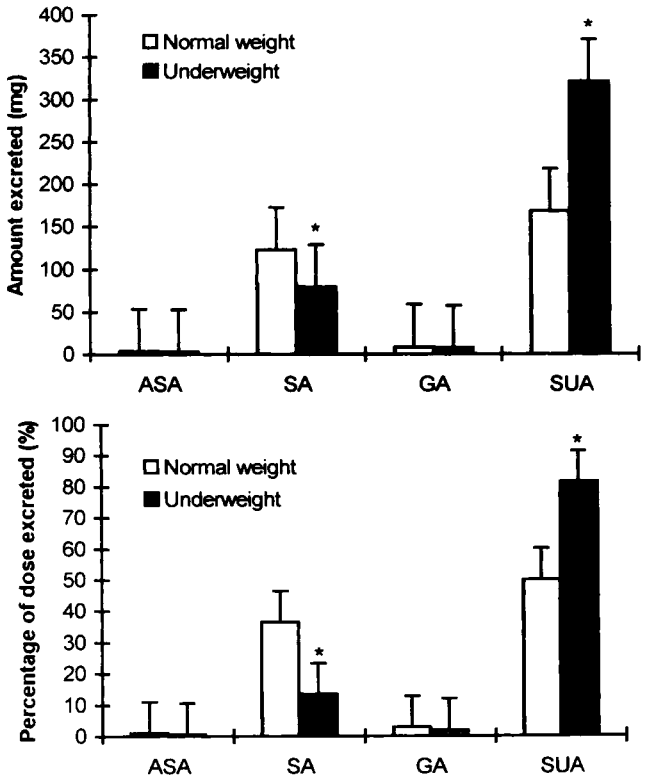

FIGURE 3. Mean (±SD) amount of acetylsalicylic acid (ASA) and its metabolites salicylic acid (SA), gentisic acid (GA), and salicyluric acid (SUA) excreted in urine in 24 h in normal-weight (n = 10) and underweight (n = 11) children. *Significantly different from normal-weight children, $P \leq 0.05$ (Mann-Whitney U test).

relation to the pharmacokinetics of metronidazol, which is modified as a result of severe malnourishment.

The observed changes in our patients, characterized by a larger volume of distribution of SUA when the percentage deficit in weight-for-height increased, can be explained by a reduction in binding between the ASA metabolites and the plasma proteins, resulting in a higher unbound plasma fraction that was susceptible to wide distribution throughout the body. As a result of this wider distribution, maximal plasma ASA concentrations were lower in malnourished children than in normal-weight children: 1.06 compared with 2.01 mmol/L, respectively. We used a single dose of ASA because the usual approach to the prediction of multiple-dose plasma concentrations as a function of time and dose is to first generate the pharmacokinetic parameters that describe a plasma concentration-time curve after a single dose (17).

Knowledge of the pharmacokinetic principles of pediatric therapeutics is essential for a better understanding of the processes that are affected in PEM. Physicians should have practical guidelines regarding dose and frequency of administration of commonly prescribed drugs in malnourished children, who have biological and biochemical alterations that can modify physiologic characteristics of the body.

As a consequence of secondary malnourishment, we observed a reduction in the biotransformation of ASA with a rise in its distribution volume, as well as an increase in the interval of administration of ASA with an increase in loading dose (as shown by the decreased AUC of ASA in underweight children). Individualization of drug therapy is necessary for optimum results. Evaluation of drug kinetics and metabolism in malnutrition will enable us to design more rational approaches and will aid in optimizing the therapeutic management of patients with minimum side effects.

Our study suggests that a substantial percentage of malnourished patients may be relatively slow eliminators of salicylate. It is also likely that certain pathophysiologic perturbations that affect salicylate kinetics are more frequent or become more severe with old age because of diminished hepatic and renal function. These considerations indicate a special need for clinical and kinetic monitoring of salicylate therapy in both malnourished and obese patients because of the association between weight and drug dose. Our results suggests that nutritional status (normal weight or underweight) should be used to calculate ASA dosages in patients with autoimmune diseases.

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