

## Effects of Parenteral Nutritional Regimens on Oxidative Drug Metabolism

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To determine whether the caloric source of intravenous nutrition can influence oxidative drug metabolizing capacity, antipyrine metabolism was studied in six healthy volunteers, who were taking no food or liquid by mouth, after they had been administered an intravenous nutritional regimen of 5% dextrose, 440 kcal/day, for 4 days and after they had been switched to an essentially isocaloric intravenous nutritional regimen of amino acids (Aminosyn® 3.5%) for 1 day. The change in intravenous nutritional regimen resulted in a 21% decrease in mean half-life (range: 3-32%), a 20% decrease in mean area under the concentration-time curve (range: 4-42%), and a 24% increase in mean metabolic clearance rate (range: 2-71%) for antipyrine. These results show that the change from intravenous dextrose to intravenous amino acids for only 1 day produced in all subjects an increase in antipyrine metabolism. Interestingly, there was marked variability in the responsiveness of the different subjects to the change in intravenous caloric source. (Key words: Biotransformation (drug): antipyrine. Metabolism: antipyrine; amino acids; carbohydrate; drug.)

DIET MARKEDLY can influence human drug metabolism.<sup>1-5</sup> Dramatic changes in human drug metabolism have resulted from alterations in the protein and carbohydrate content of the diet.<sup>3-5</sup> Healthy volunteers who had been fed a low carbohydrate-high protein diet showed 63% and 46% increases in mean plasma half-lives of antipyrine and theophylline, respectively, when they were switched to an isocaloric, high carbohydrate-low protein diet.<sup>3,4</sup> Hospitalized asthmatic children receiving long-term treatment with theophylline had a 62% higher mean steady state plasma concentration of drug and nearly 50% fewer wheezing episodes when they were fed a high carbohydrate-low protein diet than when they were fed

an isocaloric, low carbohydrate-high protein diet,<sup>5</sup> indicating that the effects of protein and carbohydrate on the metabolism of drugs can indeed be clinically important.

In the hospital setting it is very common for drugs to be administered to patients who are being provided their nutrition intravenously. Intravenous nutritional regimens typically do not provide the patient with carbohydrate and protein in the ratio that would be present in a normal diet and, therefore, may produce alterations in rates of drug metabolism. Since the effects of intravenous nutritional regimens on drug metabolism never have been examined, we have carried out studies to determine whether oxidative drug metabolizing capacity would be increased by switching individuals from an intravenous nutritional regimen in which the calories were provided by dextrose to an isocaloric intravenous nutritional regimen in which the calories were provided by amino acids.

We used antipyrine elimination kinetics as an index of oxidative drug metabolizing activity. Antipyrine has been used widely as a pharmacologic tool for assessing the oxidative biotransformation capacity of humans.<sup>6</sup> It is absorbed rapidly and completely after oral doses, distributes throughout total body water, and is negligibly bound to tissue and plasma proteins.<sup>6-8</sup> It is metabolized almost completely by oxidative reactions and has a negligible renal elimination.<sup>6-8</sup> Under stable environmental conditions, antipyrine disposition is highly reproducible in a given individual.<sup>6</sup> Salivary antipyrine concentrations correspond closely to serum concentrations, obviating the need for repeated venipuncture of subjects.<sup>9</sup> At the dose selected for our studies, antipyrine can be administered multiple times at frequent intervals without altering its own metabolism.<sup>10</sup>

### Materials and Methods

Our subjects were six healthy, male, young adult volunteers who had been admitted to the Surgical Metabolism Unit of the Columbia-Presbyterian Medical Center for study of the effects of the two intravenous nutritional regimens on respiratory and metabolic parameters. No subject used any drug regularly, and no subject was a

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heavy drinker of alcohol, coffee, or tea. Informed consent was obtained from the subjects. The study was approved by the Institutional Review Board of Columbia University.

Antipyrine metabolism was studied first in the subjects while they were on their customary diets. Antipyrine, 1.0 mg/kg, was administered to the subjects orally with 200 ml of water at approximately 8:00 A.M. Breakfast was withheld for 2 h after the dose. A saliva sample was obtained just prior to the dose and at 3, 6, 9, 12, 15, and 24 h after the dose. After the last saliva sample was obtained, the subjects were not permitted to take food or liquids by mouth. They were administered then by intravenous infusion 5% dextrose in water, 440 kcal/day. At the start of the fifth day of intravenous dextrose feeding, at approximately 8:00 A.M., the subjects were again administered antipyrine orally with 200 ml of water, and saliva samples were obtained at intervals as described above. After completion of the 24-h antipyrine metabolism study, intravenous dextrose administration was continued for an additional 24 h. The subjects then were administered by intravenous infusion Aminosyn® 3.5% (crystalline amino acid solution, Abbott Laboratories, North Chicago, Illinois), 480 kcal/day, for the next 48 h. Twenty-four hours after the start of the intravenous amino acid infusion, at approximately 8:00 A.M., the subjects again were given antipyrine, 1.0 mg/kg, orally with 200 ml of water, and saliva samples were obtained at intervals as described above.

The saliva samples were analyzed for antipyrine content by the radioimmunoassay method of Chang *et al.*<sup>11</sup> Antipyrine half-lives in saliva ( $t_{1/2}$ ) were determined from the linear portion of the curve of log saliva concentration of drug against time. The areas under the saliva concentration of drug-time curves (AUC) were calculated using the trapezoidal rule. Apparent metabolic clearance rates (MCR) were calculated from the dose of drug administered divided by the AUC. Apparent volumes of distribution (aVd) were calculated by the formula  $aVd = \frac{MCR \times t_{1/2}}{0.693}$ . Results were analyzed by Student's paired  $t$  test, and differences in mean values were considered statistically significant if  $P$  values were less than 0.05. The significance of the changes that occurred in  $t_{1/2}$ , AUC, and MCR for antipyrine when the subjects were switched from the intravenous dextrose regimen to the intravenous amino acids regimen was tested by a one-tailed paired  $t$  test, since the direction of these changes had been hypothesized as a result of prior studies.<sup>3-5</sup> The significance of all other changes was tested by a two-tailed paired  $t$  test.

One subject inadvertently received a slightly too large and not precisely known dose of antipyrine for the drug metabolism study that was carried out while he was being administered the intravenous amino acid nutritional reg-

TABLE 1. Effects of Parenteral Nutritional Regimens on Antipyrine Metabolism

Subject	Saliva Half-life (h)			Area under Saliva Concentration-Time Curve ( $\mu\text{g} \cdot \text{ml}^{-1} \cdot \text{h}$ )			Metabolic Clearance Rate ( $\text{l} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$ )			Apparent Volume of Distribution ( $\text{l} \cdot \text{kg}^{-1}$ )		
	Home Diet	iv Dextrose	iv Aminosyn®	Home Diet	iv Dextrose	iv Aminosyn®	Home Diet	iv Dextrose	iv Aminosyn®	Home Diet	iv Dextrose	iv Aminosyn®
1	10.6	10.9	8.9	19.14	24.54	14.29	0.052	0.041	0.070	0.800	0.640	0.900
2	12.7	13.4	11.1	19.59	23.48	22.61	0.051	0.043	0.044	0.935	0.823	0.708
3	14.2	16.5	11.2	23.82	29.48	22.07	0.042	0.034	0.045	0.860	0.809	0.732
4	7.3	7.8	6.3	13.17	13.08	10.99	0.076	0.077	0.091	0.800	0.861	0.827
5	13.4	16.6	12.4	18.83	21.25	—	0.053	0.047	—	1.027	1.127	—
6	12.4	10.3	10.0	17.16	17.70	16.66	0.058	0.057	0.060	1.042	0.840	0.866
Six sub- jects	11.8 ± 1.0	12.6 ± 1.4	10.0 ± 0.9	18.62 ± 1.42	21.59 ± 2.33	—	0.055 ± 0.005	0.050 ± 0.006	—	0.911 ± 0.044	0.850 ± 0.064	—
$\bar{X} \pm \text{SE}$												
Five sub- jects					21.66 ± 2.85	17.32 ± 2.24		0.050 ± 0.008	0.062 ± 0.009		0.795 ± 0.040	0.807 ± 0.038
		NS	$P < 0.01$	$P < 0.05$	$P < 0.05$		$P < 0.05$	$P < 0.05$	$P < 0.05$	NS	NS	NS

Subjects were administered antipyrine (1.0 mg/kg) orally after each nutritional regimen. Results were analyzed statistically by Student's paired  $t$  test.

imen. For this subject, on this occasion, we were able, therefore, to determine only  $t_{1/2}$  for antipyrine.

### Results

Intravenous administration of dextrose, 440 kcal/day, to the six subjects for 4 days resulted in a 16% increase in mean AUC for antipyrine ( $P < 0.05$ ) and a 9% decrease in mean MCR for antipyrine ( $P < 0.05$ ) as compared with the values for these parameters that were observed when the subjects were eating their customary home diet (table 1). There was no significant change in mean  $t_{1/2}$  for antipyrine. Switching the subjects from the intravenous dextrose regimen to intravenous amino acids, 480 kcal/day, for 1 day resulted in a 21% decrease in mean  $t_{1/2}$  ( $P < 0.01$ ), a 20% decrease in mean AUC ( $P < 0.05$ ), and a 24% increase in mean MCR ( $P < 0.05$ ) for antipyrine. The change from the intravenous dextrose regimen to the intravenous amino acid regimen resulted in a decrease in  $t_{1/2}$  for antipyrine in all six subjects, a decrease in AUC for antipyrine in all five subjects for whom this could be determined, and an increase in MCR for antipyrine in all five subjects for whom this could be determined. There was, however, marked individual variability in the response of the subjects to the change in the intravenous nutritional regimen. The decrease in  $t_{1/2}$  varied from 3 to 32%; the decrease in AUC varied from 4 to 42%; and the increase in MCR varied from 2 to 71%.

### Discussion

Our study demonstrates that the caloric source of intravenous nutritional regimens can influence oxidative drug metabolism in humans. Antipyrine metabolism increased, as evidenced by a decrease in  $t_{1/2}$ , a decrease in AUC and an increase in MCR for this drug in all of our subjects when they were switched from an intravenous nutritional regimen consisting of 5% dextrose to an essentially isocaloric intravenous nutritional regimen consisting of amino acids as Aminosyn® 3.5%. While the increase in antipyrine metabolism was small in some subjects, it was of considerable magnitude in others. In two prior studies<sup>1,2</sup> in which antipyrine metabolism was examined in healthy young adult volunteers on two occasions on which they were being fed a constant controlled diet, we observed a change between the two occasions of less than 3% in mean  $t_{1/2}$  for antipyrine and of less than 4% in mean MCR for antipyrine as compared with the nearly 21% change in mean  $t_{1/2}$  and the 24% change in mean MCR seen in the present study. In both prior studies, in contrast to the present study, antipyrine metabolism decreased between the two occasions in about as many subjects as it increased.

Amino acids and dextrose in equal caloric amounts are not equivalent sources of energy and, in addition to being caloric sources, have multiple, complex, and in many

ways different effects on physiologic processes and body composition. The mechanism by which intravenous dextrose and intravenous amino acids differentially affect antipyrine metabolism is not known. Clinicians should be aware that the caloric source in intravenous nutritional regimens can affect oxidative drug metabolism. A change in metabolism of the magnitude of the change in antipyrine metabolism seen in some of our subjects when they were switched from intravenous dextrose, 440 kcal/day, to intravenous Aminosyn®, 480 kcal/day, for only 1 day significantly would alter the therapeutic effect or toxicity of many drugs. It is possible that the intravenous administration of amino acids for a longer time may result in an even greater change in drug metabolism. Additional studies are needed to determine the effects of commonly used intravenous nutritional regimens on the metabolism of therapeutically important pharmacologic agents. Studies also are needed to elucidate the mechanism(s) by which intravenous nutrients influence oxidative drug metabolism.

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