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Octenylsuccinic Aciduria in Children Fed Protein-Hydrolysate Formulas Containing Modified Cornstarch

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ABSTRACT. **The excretion of 2-(2′-octenyl)succinic acid (OSA) and several metabolites of OSA was studied by gas chromatography/mass spectrometry in 17 infants and children fed one of three proprietary elemental or protein-hydrolysate formulas that use OSA-modified cornstarch as an emulsifying agent. Variable but often large amounts (up to 2500 mg/g creatinine) of the fatty acid-like OSA and its metabolites were found in the urine of these children, and levels of OSA in their blood ranged from 9.5 to 57.9 μmol/L. Apparently secondary abnormalities, such as increased urinary levels of glutaric acid and 2-ketoglutaric acid, were also found in more than half of the urine specimens. The molecular weight and mass fragmentation patterns of the nine compounds associated with the excretion of OSA are consistent with the proposal that OSA is metabolized in human infants and children by a combination of ω-, ω-1-, and β-oxidation steps, similar to the metabolism of another branched-chain fatty acid, valproic acid. The urinary organic acid pattern of children fed elemental formulas containing OSA-modified starch often was dominated by OSA and its metabolites, and in several children the OSA-related changes were mistaken for a primary metabolic disease. Physicians and laboratories evaluating children for suspected metabolic diseases should be aware of the possibility of abnormal organic acid studies associated with OSA-containing formulas. (*Pediatr Res* 30: 564–569, 1991)**

Abbreviations

OSA, 2-(2′-octenyl)succinic acid
OSA-TCA, 1,2,9-non-4-enetricarboxylic acid
TMS, trimethylsilyl

Since 1987, clinical laboratories that perform urinary organic acid gas chromatography for diagnosis of inborn errors of metabolism have been finding a complex organic aciduria in children fed one of several different elemental or protein-hydrolysate infant formulas. The unusual compounds, often present in large amounts, were easily recognized as an interrelated family of fatty acid-like compounds, but only recently has the parent compound been identified with certainty by high resolution mass spectrometry as OSA (1,2,-dec-4-ene-dicarboxylic acid), a component of one form of modified cornstarch (1).

When esterified to hydrophilic starches, OSA provides hydrophobic domains that enhance the emulsifying ability of starch. As a result, OSA-modified starch improves the mixing characteristics and stability of elemental or protein-hydrolysate formulas, in which protein is absent or the natural emulsifying properties of milk or vegetable proteins have been destroyed by partial proteolysis. OSA-modified starch has been used in prepared foods such as puddings and sauces for over 20 years, but only recently has it been introduced into specialized infant formulas. Because of the unusually large amounts of OSA and its by-products found in the urine of children fed formulas containing OSA-modified starch, and because many urine specimens containing OSA and its by-products show metabolite changes that cannot be directly explained by the metabolism of OSA, our laboratory has been collecting clinical and biochemical data on patients in whose urine we have found OSA. This report describes the organic aciduria associated with OSA-modified starch and the mass spectrometric characterization of nine apparent urinary metabolites of OSA.

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MATERIALS AND METHODS

Patients were identified *1*) through urine samples submitted to the Kennedy Institute mass spectrometry laboratory for testing for possible inborn errors of metabolism, or *2*) as children who were hospitalized at the Kennedy Institute and were taking one of three formulas known to contain OSA-modified starch (Nutramigen and Pregestimil, Mead Johnson, Evansville, IL; and Vivonex T.E.N., Norwich Eaton, Norwich, NY). Random or 24-h urine specimens were collected without preservative and stored at −20°C before analysis. Heparin-anticoagulated plasma specimens (collected for diagnostic amino acid quantification) were also available for several patients and were stored frozen at −20°C until analysis. Technical information about the content of OSA-modified starch and other components of the individual formulas was provided by the manufacturers.

Urinary organic acids were quantified as their TMS ether/esters essentially as described by Tanaka *et al.* (2). Before acidification and ethyl acetate extraction, the urine was incubated at pH 11 in the presence of 20 mg/mL methoxylamine to convert ketoacids to their methoximes and to hydrolyze organic acid esters (principally carnitine and glucuronide esters). To prepare methyl-TMS derivatives, the organic acid extracts were methylated with 10% (vol/vol) acetyl chloride in methanol at 70°C for 1 h before silylation. For gas chromatographic analysis, 1-μL portions of the organic acid derivative mix, equivalent to 1 μg of urinary creatinine, were injected into dual HP-5890A gas chromatograph spitless injectors leading to matched 0.2 mm × 25 m methylsilicone (0.25-μm liquid phase) capillary columns (Ultra 1; Hewlett-Packard Co., Palo Alto, CA). The gas chromatographic oven was programmed from 60 to 290°C at 4°/min with an initial dwell time of 4 min. Quantification of organic acids was performed by flame ionization relative to the internal stand-

ard, undecanedioic acid (250 mg/g creatinine). Because metabolites of OSA are not commercially available, more accurate quantification using specific response curves for each compound was not possible. Although organic acid concentrations are therefore reported without correction for extraction efficiency and detector response, the extraction efficiencies of most of the metabolites of OSA should be high. Studies with the parent compound, OSA, showed that extraction from urine under these conditions was essentially quantitative.

Organic acid peak identity and purity were determined by mass spectrometry using a Hewlett-Packard 5970A mass selective detector. The mass selective detector was operated in the electron impact mode with source temperature of 200°C and electron energy of 70 eV. Organic acids, other than OSA and its metabolites, were identified by comparison of the peak retention times and mass spectra with those of authentic standards. Racemic 2-(2′-octenyl)succinic anhydride was provided by the Humphrey Chemical Company, North Haven, CT, and converted to the free acid (OSA) by alkaline hydrolysis. By gas chromatography, 87% of the free acid was in the *trans*-configuration under these conditions of analysis.

Plasma FFA and organic acids were quantified as described by Ng *et al.* (3), using the same instrumentation and chromatographic system as described above for urinary organic acid analysis. Aliquots (200 μL) of two prepared formulas, Nutramigen and Pregestimil, were analyzed for organic acid and fatty acid content by the same methods.

RESULTS

Data were collected on 17 children fed proprietary formulas containing OSA-modified starch, as summarized in Table 1. The children ranged in age from 3 mo to 6 y. Most were receiving the formulas for poorly defined recurrent vomiting. Only patients 5 and 15 had well-documented milk-protein intolerance. For all children except patient 3, the formula provided at least 75% of calories. Compared with all children who are fed OSA-containing formulas, our patient sample contains a higher proportion of children with neurologic problems and a smaller proportion of patients with simple milk-protein intolerance or intestinal malabsorption, two of the principal indications for use of protein-hydrolysate formulas. However, at least four patients (nos. 12 and 14–16) were being fed elemental formulas for exclusively gastrointestinal problems and were taking no medications other than multivitamins.

Figure 1 shows a portion of a typical gas chromatogram of urinary organic acids from a patient fed Nutramigen, a protein-hydrolysate formula containing casein hydrolysate, corn oil, corn syrup solids, and OSA-modified cornstarch (2.2 g/100 kcal) as major components. The principal compounds in Figure 1 that are associated with the ingestion of OSA-modified cornstarch (Table 2) are: tricarballylate (peak A); OSA (peaks B and C); a tentatively identified tricarboxylic acid ω-oxidation product of OSA, OSA-TCA (peaks J and K); an apparent structural homolog of OSA-TCA weighing two methylene units less (peaks D and E); and two pairs of compounds weighing 460 D, tentatively identified by TMS/methyl ester analysis as monohydroxylated forms of OSA (peaks F and G, H and I). In a few urine specimens, there were trace amounts of a pair of compounds with apparent molecular weights of 418 and gas chromatography/mass spectrometry characteristics suggesting the structure of 1,4,5-pent-1-enetricarboxylic acid, equivalent to OSA-TCA shortened by four methylene units. Except for tricarballylate, all OSA-related compounds chromatographed as pairs presumed to correspond to the minor *cis*- and major *trans*-isomers of OSA. However, the relative areas of the smaller, paired, OSA-related peaks, D,E and F,G in Figure 1, varied somewhat from sample to sample because of small amounts of coeluting compounds.

Figure 2 shows the mass spectra of the major *trans*-isomers of OSA and its apparent tricarboxylic acid (OSA-TCA), which are major organic acid peaks in the urine of children excreting OSA and its by-products. Spectral data for OSA and its nine associated metabolites are also listed in Table 3. Although one of the apparently OSA-related components, tricarballylate (1,2,3-propanetricarboxylate), also occurs as a by-product of beet-sugar and maple-sugar refining, its presence in all patients fed OSA-modified starch whom we studied, but rare presence in only trace amounts in the urine of other formula-fed infants, suggests that it is produced from OSA by ω-oxidation followed by three complete cycles of β-oxidation, as indicated in the proposed scheme of OSA metabolism (Fig. 3). The tentative identifications of the other metabolites of OSA are based on interpretations of

Table 1. *Clinical and laboratory data*

Patient	Age	Diagnosis	Formula	Urine collection	Urinary metabolites (mg/g creatinine) OSA	OSA metabolites	Glutarate	2-Keto-glutarate	Plasma OSA level (μmol/L)	Plasma carnitine level (F/T)* (μmol/L)
1	2 mo	Hypotonia, dev delay	Nutramigen	Random	1353	497	7.0	560		
2	16 mo	Cerebral palsy	Nutramigen	24-h	221	211	18.1	97	17.3	36/53
3	3 y	Mult cong anomalies	Nutramigen	24-h	121	73	3.6	45		
4	10 mo	Cerebral palsy	Nutramigen	Random	297	420	19.0	258		
5	6 y	Myopathy	Vivonex T.E.N.	24-h	199	508	9.8	56		15/16
6	10 mo	46,XX,8p+	Nutramigen	24-h	507	158	15.6	168	57.9	40/53
7	9 mo	Werdnig-Hoffmann disease	Pregestimil	Random	465	2168	31.7	677	16.9	
8	2 y	Mental retardation	Pregestimil	Random	167	523	29.0	78	48.7	15/31
9	3 mo	Prematurity	Pregestimil	Random	130	625	6.0	40		44/59
10	6 y	Cerebral palsy	Nutramigen	24-h	187	598	10.9	140	9.5	
11	5 y	Hydrocephalus	Pregestimil	Random	291	253	15.6	48		
12	5 mo	Recurrent diarrhea	Pregestimil	Random	566	527	13.6	284		
13	5 mo	Seizure disorder	Nutramigen	Random	527	403	70.8	300		
14	5 mo	Milk allergy	Pregestimil	Random	175	522	11.3	44		
15	4 mo	Recurrent diarrhea	Pregestimil	Random	326	197	18.4	276		
16	3 mo	Prematurity	Pregestimil	24-h	439	901	23.2	286		
17	2 mo	Zellweger syndrome	Pregestimil	Random	138	591	8.4	281		
Normal range										
3 mo–1 y							1–12	30–200		20–60/25–80
1–6 y							1–8	25–120		20–60/25–80

* F/T, free/total.

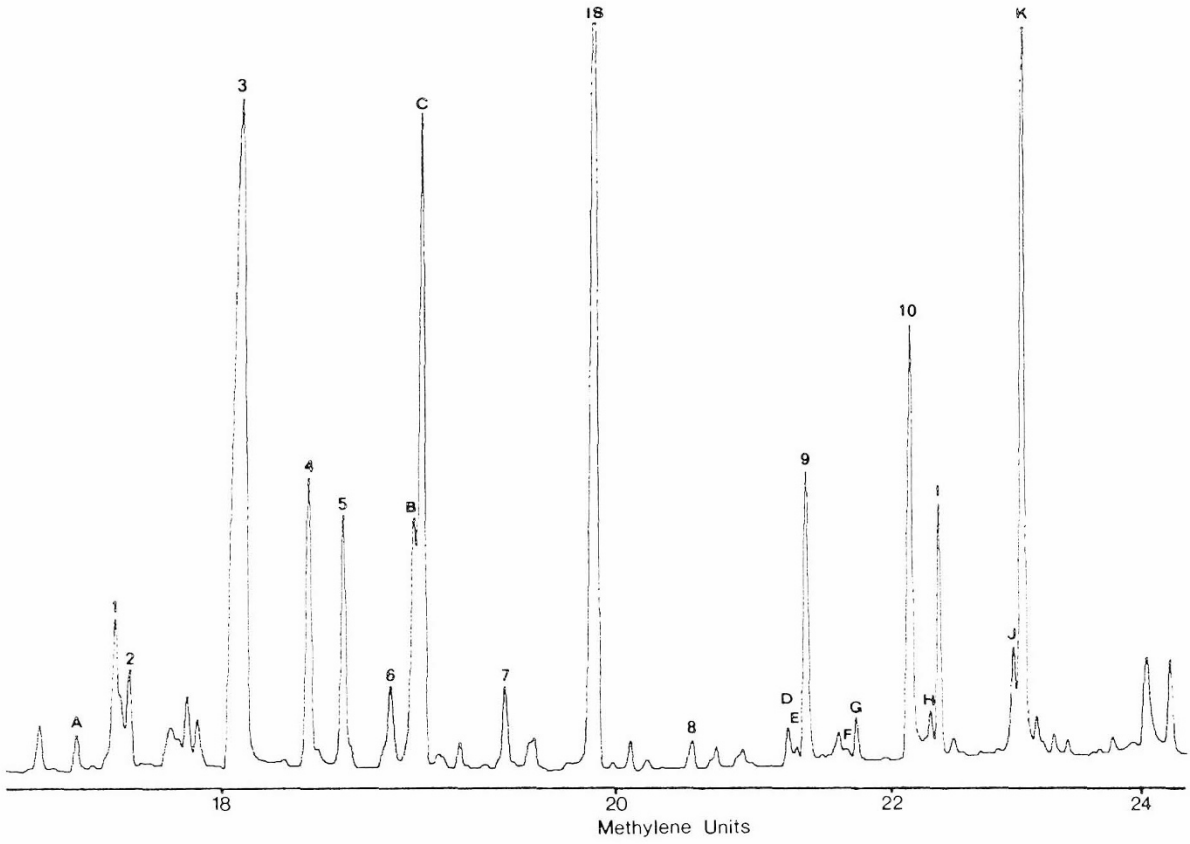

Fig. 1. Expanded region from 19 to 24 methylene units of a flame ionization gas chromatogram of urinary organic acid TMS ester/ethers from an infant fed Nutramigen. Known compounds related to OSA are tricarballylate (*A*) and *cis*- and *trans*-2-octenylsuccinic acid (*B,C*). Other tentatively identified OSA-related compounds are *cis*- and *trans*-1,2,7-hept-4-enetricarboxylic acid (*D,E*); *cis*- and *trans*-7-hydroxy-OSA (*F,G*), *cis*- and *trans*-8(?)-hydroxy-OSA (*H,I*), and *cis*- and *trans*-OSA-TCA (*J,K*). Compounds A through K are further described in Tables 2 and 3. Other organic acids identified here for purposes of comparison are: aconitate (*1*), homovanillate (*2*), hippurate-diTMS (*3*), citrate (*4*), 3-OH-phenylhydracrylate (*5*), vanillylmandelate (*6*), indole-3-acetate (*7*), internal standard (undecanedioate) (*IS*), palmitate (*8*), 3-OH-hippurate-diTMS (*9*), and 4-OH-hippurate-diTMS (*10*).

Table 2. *Octenylsuccinate and related metabolites*

Peak in Figure 1	Proposed organic acid structure (as TMS derivative)	Molecular weight	Methylene units*	Proposed biosynthesis from octenylsuccinate	Proposed structure in Figure 2
A	Tricarballylate†	392	17.35	ω-oxidation + 3 cycles β-oxidation	V†
B	*c*-2-octenylsuccinate†	372	18.99	Parent compound	I†
C	*t*-2-octenylsuccinate†	372	19.03	Parent compound	I†
D	*c*-1,2,7-hept-4-enetricarboxylate	446	21.17	ω-oxidation + 1 cycle β-oxidation	IV
E	*t*-1,2,7-hept-4-enetricarboxylate	446	21.23	ω-oxidation + 1 cycle β-oxidation	IV
F	*c*-7-hydroxyoctenylsuccinate	460	21.75	ω-1 hydroxylation	VII
G	*t*-7-hydroxyoctenylsuccinate	460	21.81	ω-1 hydroxylation	VII
H	*c*-hydroxyoctenylsuccinate	460	22.28	? ω-hydroxylation	?II
I	*t*-hydroxyoctenylsuccinate	460	22.35	? ω-hydroxylation	?II
J	*c*-1,2,9-non-4-enetricarboxylate	474	22.95	ω-oxidation	III
K	*t*-1,2,9-non-4-enetricarboxylate	474	23.03	ω-oxidation	III

* On OV-1 methylsilicone capillary column.

† Identity confirmed by gas chromatography/mass spectrometry of authentic standard.

the mass spectra of their TMS and methyl-TMS derivatives and on the relative retention times of the derivatives on methylsilicone capillary columns. For example, the mass spectra of the methyl-TMS derivatives of isomers F and G had prominent fragments at m/e = 117, characteristics of ω-1-hydroxy compounds, and apparent molecular weights of 344, consistent with a methyl-TMS derivative of monohydroxy OSA. The reconstructed ion currents of several urine specimens were also searched by selected ion analysis for possible keto-derivatives of OSA, but none in amounts greater than 5 mg/g creatinine could be identified with certainty. Other compounds that appear to be associated with ingestion of OSA-containing formulas, and which may also be metabolites of OSA, were found in some urine specimens, but their identities are less certain.

The mean concentration of tricarballylate, the apparent product of microsomal ω-oxidation of OSA to OSA-TCA followed

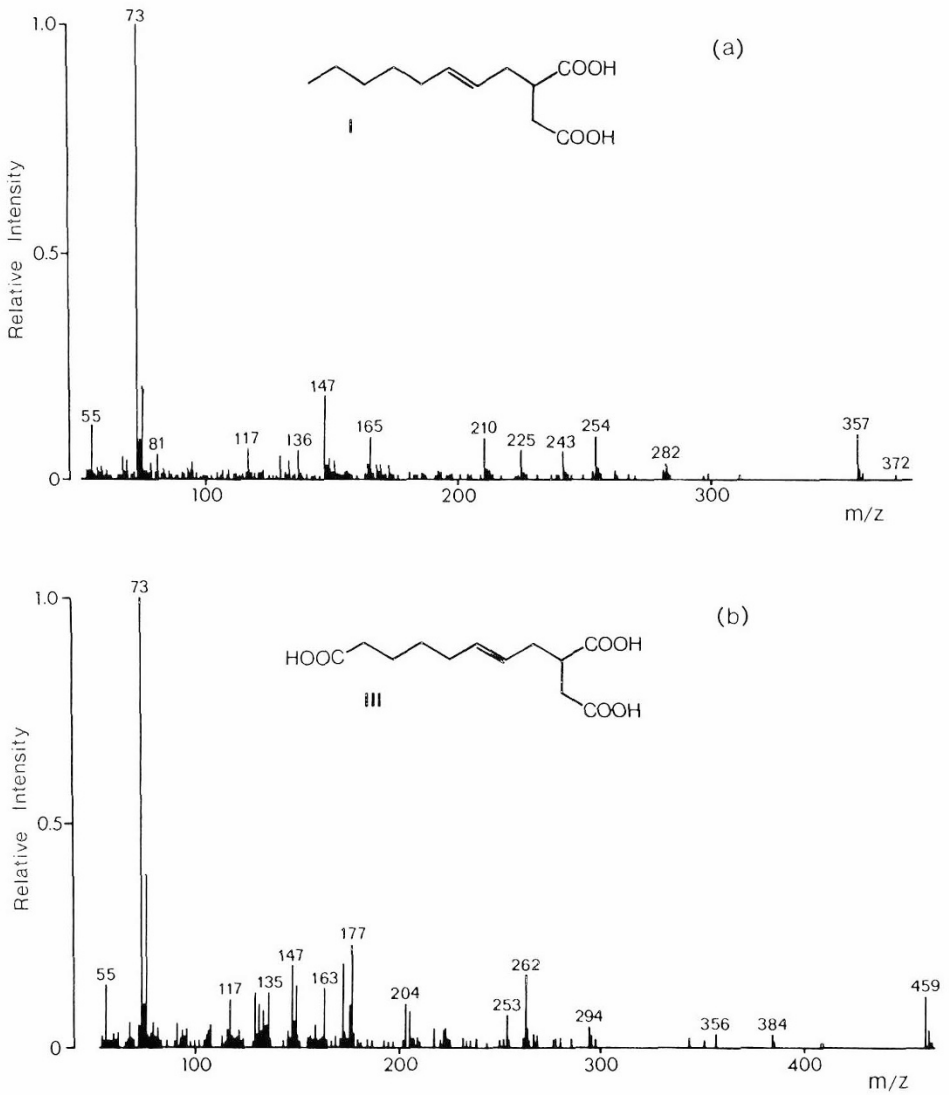

Fig. 2. Electron impact mass spectra from the chromatogram shown in Figure 1: *a*, *trans*-2(2′-octenyl)succinate; and *b*, a compound consistent with the tricarboxylic acid ω-oxidation product of *a*, *trans*-1,2,9-non-4-enetricarboxylate (compound III, Fig. 3).

by three cycles of β-oxidation, was 31.4 mg/g creatinine (range 6.0 to 91.5 mg/g creatinine). In most patients the urinary concentration of tricarballylic acid was 5–10% of the concentration of OSA-TCA. However, the urine of the patient with Zellweger syndrome (no. 17), a generalized disorder of peroxisomal function including peroxisomal β-oxidation, contained no tricarballylate despite a urinary level of the presumed precursor, OSA-TCA, of 440 mg/g creatinine. Peaks D and E, corresponding to compounds consistent with OSA-TCA shortened by one cycle of β-oxidation, also were absent from this patient's urine.

In addition to OSA and its metabolites, many urine samples showed significant increases in the levels of glutarate and 2-ketoglutarate (Table 1). Children fed Pregestimil, which contains medium-chain triglycerides, also excreted large amounts of medium-chain fatty acid metabolites: octanoate, adipate, suberate, sebacate, 5-hydroxyhexanoate, and 7-hydroxyoctanoate. In some cases, the increased levels of glutarate were substantial, and a primary diagnosis of glutaric aciduria often was entertained. However, in five patients (nos. 2, 5, 6, 10, and 11) urinary levels of glutarate and 2-ketoglutarate were found to be normal after changing to a standard infant formula or protein-hydrolysate formula not containing OSA. The excretion of 2-ketoglutarate had a relatively high correlation with the total excretion of OSA and its metabolites ($r = 0.88$), but a much weaker correlation existed between glutarate and OSA + OSA metabolites ($r = 0.22$). Extraction of organic acids and fatty acids from two OSA-containing formulas (Nutramigen and Pregestimil), both before and after alkaline hydrolysis, showed the expected presence of OSA and FFA (from triglycerides) but no measurable amount of glutarate, 2-ketoglutarate, or any of the nine OSA-associated metabolites found in urine. We do not know at this time if the increased urinary levels of glutarate and 2-ketoglutarate reflect increased plasma levels of these compounds, increased renal secretion, or decreased tubular reabsorption caused by OSA, OSA-metabolites, or other formula components. Although two patients were also found to have mildly to moderately depressed plasma free and total carnitine levels (Table 1), there was no apparent correlation between levels of free or total carnitine and the levels of OSA, its metabolites, or other organic acids.

In addition to large amounts of OSA and its metabolites in urine, measurable levels of OSA were found in the plasma of the several children for whom both urine and plasma samples were available (Table 1). The highest level found was 57.9 μmol/L in a child fed Nutramigen. No other metabolites of OSA, all of which should be more readily excreted than OSA, were detected in plasma at levels greater than 1 μg/mL. For comparison, typical levels of palmitate, one of the major FFA in nonfasting plasma, range from 30 to 150 μmol/L in our laboratory.

DISCUSSION

The organic aciduria associated with OSA-modified cornstarch is formally similar to the organic aciduria caused by the anticon-

Table 3. *Mass spectral ions of octenylsuccinic acid and associated organic acids*

Organic acid	Peak in Figure 1	Molecular weight	Ten most abundant ions*									
Tricarballylic acid-triTMS	A	392	73	147	377	75	185	217	55	149	184	69
			100	70	56	35	28	21	18	17	12	11
c-2-(2′-octenyl)succinic acid diTMS	B	372	73	75	147	357	55	165	254	210	117	225
			100	24	21	14	13	12	12	10	8	5
t-2-(2′-octenyl)succinic acid diTMS	C	372	73	75	147	357	55	254	165	74	210	282
			100	22	20	19	13	11	10	9	9	4
c-1,2,7-hept-4-enetricarboxylic acid-triTMS	D	446	73	75	149	147	204	177	328	55	431	266
			100	42	26	20	19	12	12	11	9	8
t-1,2,7-hept-4-enetricarboxylic acid-triTMS	E	446	73	75	149	204	147	328	431	55	266	225
			100	35	31	24	23	17	14	12	10	9
c-7-hydroxyoctenylsuccinic acid-triTMS	F	460	73	75	147	117	262	55	210	163	172	445
			100	42	21	20	15	10	10	9	9	4
t-7-hydroxyoctenylsuccinic acid-triTMS	G	460	73	75	147	117	262	163	210	172	55	445
			100	31	23	23	21	11	11	11	10	6
c-8-hydroxyoctenylsuccinic acid-triTMS (?)	H	460	73	75	262	147	149	172	163	55	445	329
			100	39	24	21	18	18	16	10	5	3
t-8-hydroxyoctenylsuccinic acid-triTMS (?)	I	460	73	75	262	147	172	149	163	55	129	445
			100	35	28	23	18	18	15	12	10	6
c-1,2,9-non-4-enetricarboxylic acid-triTMS	J	474	73	75	177	147	262	459	172	55	163	149
			100	36	21	19	17	17	16	13	12	12
t-1,2,9-non-4-enetricarboxylic acid-triTMS	K	474	73	75	147	262	172	177	163	149	129	459
			100	40	22	21	20	20	15	14	14	11

* The numbers in the top row of each pair of rows are the individual fragment sizes (m/e), and the numbers in the bottom row are the % base peak.

vulsant valproate (4). Both OSA and valproate (2-propylpentanoate) are medium-length, branched-chain organic acids that appear in the urine together with variable amounts of by-products produced by a combination of microsomal ω- and ω-1-oxidation and mitochondrial or peroxisomal β-oxidation. Moreover, both valproate and OSA-containing formulas appear to have secondary effects on the metabolism of patients receiving them. Medication with valproate increases urinary levels of medium-chain dicarboxylic acids and 3-hydroxyisovalerate, a metabolite of leucine, whereas OSA-containing formulas were associated in our patients with increased urinary levels of both glutarate and 2-ketoglutarate.

OSA in OSA-modified cornstarch is chemically bound in ester-linkages to carbohydrate hydroxyl groups, but appears to be at least partially liberated from the starch, possibly by intestinal esterases, and absorbed. OSA-modified starch typically contains approximately 2.7% OSA by weight and constitutes from 2.0 to 2.6 g/100 kcal of the most frequently used formulas known to contain OSA-modified starch. At a formula intake of 100 kcal/kg/d, the average amount of OSA ingested is approximately 50–70 mg/kg/d. Our measurements indicate that at least 10 to 25% of ingested OSA was absorbed and ultimately excreted in the urine of the patients we studied. At this time, however, we have no information about other possible metabolic or excretory fates of ingested OSA.

Because complete medication information was available for only about half of the children, we were not able to identify possible effects of specific medications on the excretion of OSA and its metabolites. Theoretically, however, the large variation in the apparent proportion of OSA that was metabolized could be influenced by medications, such as anticonvulsants, that induce or otherwise modify the activity of microsomal oxidases or other pathways of xenobiotic metabolism. Substantial intrinsic variation in individual absorption and metabolism of OSA may occur, and the possibility that some or all of the metabolites are produced by the action of intestinal bacteria and then absorbed must also be considered.

The causes of the apparently formula-dependent increased levels of glutarate and 2-ketoglutarate found in the urine of many of our patients are unclear. The increased 2-ketoglutarate levels, which correlated with total OSA levels and possibly formula intake, may be related to other formula components such as citrate, which is a major component (0.5 g/100 kcal) of Nutramigen and Pregestimil and a precursor of 2-ketoglutarate in the citric acid cycle. The more variably increased levels of glutarate may be an idiosyncratic response to OSA or other formula components. Of note, also, is the apparent complete absence of β-oxidation metabolites of OSA-TCA in a child with Zellweger syndrome, which suggests that β-oxidation of OSA-TCA occurs in the peroxisome. However, more detailed studies will be required to establish the sequence and sites of metabolism of OSA.

OSA-modified starch is currently approved by the United States Food and Drug Administration as a food additive. Before the use of OSA-modified cornstarch in infant formulas, toxicity

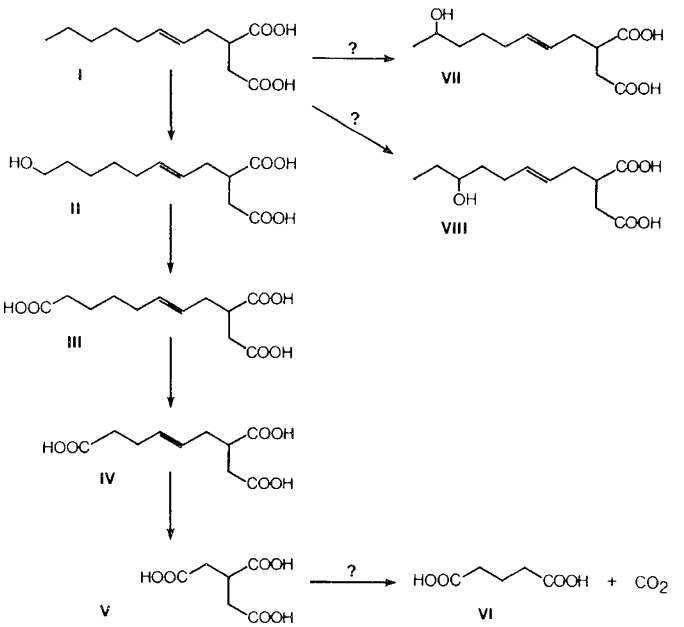

Fig. 3. Proposed metabolism of 2-octenylsuccinate (compound I). The conversions of compounds I to II and II to III would be expected to occur by microsomal ω-oxidation activity, whereas the conversions of compounds III to IV and IV to V are proposed to occur by cycles of mitochondrial or peroxisomal β-oxidation after formation of a terminal coenzyme A ester. Compounds VII and VIII are other possible products of microsomal oxidase action on 2-(2′-octenyl)succinate. Table 2 gives additional information about the chemical and chromatographic characteristics of the urinary compounds shown or tentatively assigned to these structures. Note that a different labeling system (I–VIII) is used in this figure to differentiate the experimental peaks (A–K) of Figure 1 from compounds in the above theoretical metabolic scheme. Both are included in Table 2.

testing of the additive had apparently been limited to several studies in rats, one of which has been published (5). Although no adverse effects specific to OSA-starch were identified in that study, to our knowledge, there have been no published studies on the pharmacokinetics of free OSA in man nor on the effects of free OSA on the growth and development of young animals. Because, as shown here, substantial blood levels of free OSA can accumulate in some children, our laboratory is continuing to evaluate the pharmacokinetics of OSA, individual variation in the handling of this material, and possible secondary metabolic effects.

In summary, a complex pattern of organic acids has been identified in the urine of children fed formulas containing OSA-modified cornstarch and further characterized by gas chromatography/mass spectrometry. The major components of the organic aciduria include unmodified OSA, at least nine metabolites that appear to arise from OSA by a combination of microsomal and mitochondrial or peroxisomal oxidative processes, and apparently secondary increases in the levels of glutarate and 2-ketoglutarate. Because this acquired organic aciduria can be mistaken for a primary metabolic disease and has led to unnecessary and expensive additional testing in some children, it is important that physicians requesting urinary organic acid quantification and laboratories performing these studies be aware of the effects of OSA-modified starch on urinary organic acid profiles. Furthermore, because OSA is a xenobiotic compound and appears to undergo absorption and metabolism similar to valproate and other drugs, the possibility of drug interactions or other adverse clinical effects should be considered.

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