Clinical Chemistry 48:5
708–717 (2002)

Review

Metabolic, Nutritional, Iatrogenic, and Artifactual Sources of Urinary Organic Acids: A Comprehensive Table

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Background: **The determination of organic acids and glycine conjugates in urine is key for the diagnosis and follow-up of several inborn errors of metabolism (IEM). However, clinical interpretations may still be hindered by ambiguity in the sources of some urinary organic acids and acylglycines as well as in the relationship between their excretion and IEM.**

Approach: **Relevant data have been compiled from major books and references on the topic and by exhaustive bibliographic searches through the Medline and *Current Contents* databases.**

Content: **A comprehensive table has been designed according to organic acids and conjugates. This table is intended to assist in the interpretation of organic acid profiles because, in addition to IEM, it also refers to other pathologic causes and to physiologic, nutritional, iatrogenic, and artifactual sources. Some preanalytical issues, including possible misinterpretations, are reviewed with regard to IEM.**

In the field of inborn errors of metabolism (IEM), "organic acids" are low-molecular weight (relative molecular weight less than ~300), water-soluble carboxylic acids that are intermediates or end products of amino acid, carbohydrate, lipid, or biogenic amine metabolism. Amino acids are excluded from this definition, whereas acylglycine conjugates and some decarboxylated derivatives are included because of their common clinical interest.

The analytical procedures for the determination of urinary organic acids usually include oximation, solvent extraction, and silylation followed by gas chromatography with mass detection in scan mode data acquisition. Both the retention time and the mass spectrum allow the identification of the urinary metabolites, with quantification being performed on a specific fragment abundance *(1–3)*. Analytical considerations can be found in the reports by Jellum *(4)*, Chalmers and Lawson *(1)*, Tuchman and Ulstrom *(5)*, Niwa *(6)*, Sweetman *(2)*, and Duez et al. *(3)*.

More than 250 organic acids and glycine conjugates are either typically present or may possibly be encountered in urine. More than 65 inherited metabolic abnormalities are known to yield a characteristic urinary organic acid pattern, essential for diagnosis and follow-up *(1, 2, 5, 7, 8)*. The interpretation of urinary organic acid profiles can be difficult because of the variability of the compounds excreted. Moreover, there may still be a considerable degree of ambiguity in the origin and/or significance of a given compound. To arrive at a diagnosis, organic acid data can be correlated with, or confirmed by, other analyses, including plasma amino acid determination, plasma and cerebrospinal fluid lactate and pyruvate assays, whole blood acylcarnitine profiling, enzymatic activity determinations in blood cells or other cells, and genome analysis *(7–11)*.

This report aims to compile information on the origins of the most frequently encountered urinary organic acids. In addition to IEM, our classification (Table 1) also refers to other pathologic conditions and physiologic, nutritional, iatrogenic, and artifactual causes *(1, 2, 4–8, 10–13)*. This review is intended to assist in the interpretation of organic acid profiles and the identification of some preanalytical issues. Table 1, which is classified by organic compounds, is also proposed as a handy alternative that extends previously published compilations classified by inherited metabolic disorders *(2, 5–7, 13)*.

Sampling Conditions

Urine collected over 24 h allows for variations in volume excretion during the day. The practicality of a 24-h collection is, however, such that a random specimen,

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Received November 29, 2001; accepted January 25, 2002.

Table 1. Possible origins of abnormal excretion patterns of urinary organic acids.

Acid/Metabolite	Non-IEM *(4, 12, 15, 16, 22)*	IEM
Aromatic amino acid metabolism *(23)*		
2-Hydroxyphenylacetate	Uremia	PKU; BH4[a] deficiency
4-Hydroxyphenylacetate *(24, 25)*	Bacterial gut metabolism and bacterial contamination (from tyrosine); short bowel syndrome; liver diseases	Tyrosinemia; PKU; hawkinsinuria
4-Hydroxyphenyllactate *(24–27)*	Bacterial gut metabolism; short bowel syndrome; liver diseases (e.g., secondary to PA, galactosemia, fructosemia); scurvy; lactic acidosis	Tyrosinemia; PKU; Zellweger; hawkinsinuria; lactic acidosis
4-Hydroxyphenylpyruvate	VPA; liver diseases (e.g., secondary to PA, galactosemia, fructosemia)	Tyrosinemia; hawkinsinuria
Homogentisate		Alcaptonuria
Mandelate *(28)*	Preservative in albumin solution for intravenous perfusion; methenamine mandelale; gastrointestinal malabsorption diseases	PKU
N-Acetyltyrosine	Some parenteral solutions	Tyrosinemia
Phenylacetate	Intestinal bacterial origin (from phenylalanine)	PKU; BH4 deficiency
Phenylacetylglutamine	Bacterial metabolism (from phenylacetate); hyperammonemia treated with phenylbutyrate or phenylacetate; uremia	PKU
Phenyllactate *(29)*	Bacterial gut metabolism (D-form); liver diseases	PKU; tyrosinemia (L-form); BH4 deficiency
Phenylpyruvate	Bacterial gut metabolism; liver diseases	PKU; BH4 deficiency
Succinylacetoacetate		Tyrosinemia type I
Succinylacetone		Tyrosinemia type I
Branched-chain amino acid metabolism		
2-Hydroxy-3-methylvalerate		MSUD; dihydrolipoyl DH (E3) deficiency
2-Hydroxyisocaproate *(23)*	Short bowel syndrome (D-form)	MSUD; dihydrolipoyl DH (E3) deficiency
2-Hydroxyisovalerate	Ketosis; lactic acidosis	MSUD; dihydrolipoyl DH (E3) deficiency; MAD deficiency; lactic acidosis
2-Keto-3-methylvalerate	Lactic acidosis; ketosis	MSUD; dihydrolipoyl DH (E3) deficiency; lactic acidosis
2-Ketoisocaproate	Lactic acidosis; ketosis	MSUD; dihydrolipoyl DH (E3) deficiency; lactic acidosis
2-Ketoisovalerate	Lactic acidosis; ketosis	MSUD; dihydrolipoyl DH (E3) deficiency; lactic acidosis
2-Methyl-acetoacetate *(30)*		Mitochondrial acetoacetyl-CoA-thiolase deficiency
2-Methylglutaconate		PA; MMA (?)[b]; β-ketothiolase deficiency
3-Hydroxy-2-ethylglutarate		PA
3-Hydroxy-2-ethylpropionate *(31, 32)*	Ketosis	3-Methylglutaconic aciduria (type II); methylmalonic semialdehyde DH deficiency[c]; respiratory chain defects (complex I and II)
3-Hydroxy-2-methylbutyrate *(30, 33–35)*	Ketosis	Mitochondrial acetoacetyl-CoA-thiolase deficiency; 2-methyl-3-hydroxybutyryl-CoA DH deficiency; PA; Pearson syndrome
3-Hydroxy-3-methylglutarate	Ketosis	HMG-CoA lyase deficiency
3-Hydroxyisovalerate *(30, 34)*	Reye & Reye-like syndromes; VPA; ketosis	IVA; multicarboxylase deficiency; HMG-CoA lyase deficiency; 3-methylcrotonyl-CoA carboxylase deficiency; 3-methylglutaconyl-CoA hydratase deficiency; succinyl-CoA:3-oxoacid-CoA transferase deficiency; MAD deficiency
3-Hydroxypropionate (hydracrylate) *(33, 34, 36)*	Bacterial metabolism and contamination; short bowel syndrome; lactic acidosis	PA; MMA; multiple carboxylase deficiency; succinic semialdehyde DH deficiency; methylmalonic semialdehyde DH deficiency[c]; lactic acidosis (with pyruvate carboxylase deficiency)
3-Keto-2-methylbutyrate *(33)*		PA; MMA (?); β-ketothiolase deficiency

Table 1. Continued.

Acid/Metabolite	Non-IEM *(4, 12, 15, 16, 22)*	IEM
3-Keto-2-methylvalerate *(33)*		PA; MMA (?); β-ketothiolase deficiency
3-Methylcrotonylglycine	Reye & Reye-like syndromes	3-Methylcrotonyl-CoA carboxylase deficiency; multiple carboxylase deficiency; HMG-CoA lyase deficiency
3-Methylglutaconate *(37–42)*	Uremia; acquired HMG-CoA lyase deficiency; other biochemical origin still unknown; pregnancy	3-Methylglutaconyl-CoA hydratase deficiency (methylglutaconic aciduria type I); HMG-CoA lyase deficiency; 3-methylglutaconic aciduria (other than type I); respiratory chain defects (e.g., Pearson syndrome or mitochondrial ATP synthase deficiency); Smith–Lemli–Opitz syndrome; carbamyl phosphate synthetase deficiency
3-Methylglutarate		As 3-methylglutaconate
4-Hydroxyisovalerate		IVA
Isovalerylglycine *(34)*	VPA	IVA; MAD deficiency; EMA aciduria (short-branched chain acyl-CoA DH deficiency; muscle COX deficiency[c])
Methylcitrate *(33, 34, 43)*	Malnutrition	PA; MMA; multiple carboxylase deficiency
Methylmalonate *(27, 34, 43–49)*	B_{12} vitamin deficiency, pernicious anemia; bacterial gut metabolism; gastroenteritis in very young infants; short bowel syndrome; apnea; "benign" MMA; decreased GFR (in plasma); malnutrition	MMA; transcobalamine II deficiency; malonic aciduria
Propionylglycine *(33, 34)*		PA; MMA
Tiglylglycine *(30, 31, 33–35, 50)*	Reye & Reye-like syndromes; VPA	PA; 2-methyl-3-hydroxybutyryl-CoA DH deficiency; mitochondrial acetoacetyl-CoA-thiolase deficiency; multiple carboxylase deficiency; respiratory chain defects (e.g., complex I)
Fatty acid oxidation *(16, 51–55)*		
DCA (even, saturated): adipate, suberate, sebacate *(17, 26, 43, 56–59)*	Seriously ill states: infection, malnutrition, fever, seizures, liver diseases, pulmonary stenosis; MCT administration; ketosis; VPA or acetaminophen; lactic acidosis; hypoglycemia; Reye & Reye-like syndromes; Jamaican vomiting sickness	β-Oxidation defects (MAD, MCAD, SCAD, VLCAD, SCHAD, LCHAD/TFP); HMG-CoA lyase deficiency; systemic carnitine deficiency; succinic semialdehyde DH deficiency; CPT II deficiency; peroxisomal diseases; glycogen storage disorders I & II; lactic acidosis; fructose intolerance
Odd DCA *(57, 58)*	As even DCA; from plastic containers; uremia	Peroxisomal diseases
Unsaturated DCA *(59)*	Ketosis	VLCAD deficiency; CPT II deficiency
3-Hydroxy DCA *(60)*	MCT administration; fasting; ketosis; celiac disease	LCHAD/TFP deficiency; VLCAD deficiency
2-Hydroxysebacate *(58)*		Peroxisomal diseases
2-Methylbutyrylglycine	VPA	MAD deficiency; EMA aciduria (short-branched chain acyl-CoA DH deficiency; muscle COX deficiency[c])
3-Hydroxyadipic (lactone)	See 3-hydroxy DCA	See 3-hydroxy DCA
3-Hydroxydo-/tetradecanedioate *(61)*	Hepatocellular disease; ketosis; acetaminophen intoxication	LCHAD/TFP deficiency
3-Hydroxysebacate *(31, 62)*	See 3-hydroxy DCA; progressive liver disease; acetaminophen	See 3-hydroxy DCA; MCAD deficiency; glycogen storage disorders I & II; secondary to respiratory chain defects
3-Hydroxysuberate	See 3-hydroxy DCA	See 3-hydroxy DCA
4-Octenedioate	Jamaican vomiting sickness; neonates on fasting	MCAD deficiency; MAD deficiency; VLCAD deficiency; LCHAD/TFP deficiency; nonketotic dicarboxyluria; systemic carnitine deficiency; peroxisomal diseases
5-Hydroxyhexanoate *(59)*	MCT administration; VPA; Reye & Reye-like syndromes; ketosis	MAD deficiency; MCAD deficiency; nonketotic dicarboxyluria
5-Hydroxysebacate		Peroxisomal diseases
7-Hydroxyoctanoate *(59)*	MCT administration; VPA	MCAD deficiency

Table 1. Continued.

Acid/Metabolite	Non-IEM *(4, 12, 15, 16, 22)*	IEM
Adipate	See DCA; food additive (Jello®); lithium; neonates on fasting	See DCA
Butyrylglycine	MCT administration; ketosis; Jamaican vomiting sickness	SCAD deficiency; MAD deficiency; EMA aciduria (short-branched chain acyl-CoA DH deficiency; muscle COX deficiency[c])
Decenedioate		MCAD deficiency; VLCAD deficiency; LCHAD/TFP deficiency
Do-/Tetradecanedioate *(63)*	Ketosis	VLCAD deficiency; LCHAD/TFP deficiency; MAD deficiency; CPT II deficiency
Ethylmalonate *(11, 64–67)*	Jamaican vomiting sickness; neonates on fasting; diet (?)	SCAD deficiency; MAD deficiency (severe form); MAD deficiency (mild form); acetyl-CoA carboxylase deficiency; EMA aciduria (short-branched chain acyl-CoA DH deficiency; muscle COX deficiency[c]); respiratory chain defects
Hexanoylglycine *(20, 59)*	VPA; MCT administration; Jamaican vomiting sickness	MCAD deficiency; MAD deficiency; SCAD deficiency
Isobutyrylglycine		MAD deficiency; EMA aciduria (short-branched chain acyl-CoA DH deficiency, muscle COX deficiency[c])
Methylsuccinate		As EMA
Octanoate *(59)*	MCT administration	MCAD deficiency
Phenylpropionylglycine *(20)*	Bacterial gut metabolism and bacterial contamination	In MCAD deficiency (from phenylalanine bacterial metabolism or after load)
Suberylglycine *(20, 59)*	MCT administration; ketosis; Reye & Reye-like syndromes	MCAD deficiency; MAD deficiency
Tetradecanedioate		VLCAD deficiency; LCHAD/TFP deficiency; MAD deficiency
Krebs cycle/respiratory chain *(68–71)*		
2-Ketoglutarate *(38, 72)*	Bacterial contamination; lithium; uremia; increase with younger age	As malate; 2-ketoglutaric DH deficiency; GA I; 2-amino/2-ketoadipate acidemia; dihydrolipoyl DH (E3) deficiency; glycogen storage disorder I; 2-hydroxyglutaric aciduria (D-form); fumarase deficiency
Aconitate		Respiratory chain defects (e.g., complex I); Pearson syndrome
Citrate, isocitrate	High carbohydrate intake; parathyroid extract; saturnism; citrate intake; fruit juice added to urine; hyperparathyroidism; increase with younger age	Dihydrolipoyl DH (E3) deficiency; fumarase deficiency; pyruvate carboxylase deficiency; Pearson syndrome
Fumarate	Lithium; renal tubular reabsorption defect (fumaric aciduria); increase with younger age	As malate; fumarase deficiency
Malate *(73–75)*	Lithium; uremia; increase with younger age	Respiratory chain defects; pyruvate carboxylase deficiency; PDH complex (E1, E3) deficiency; Pearson syndrome
Succinate *(72, 76)*	Bacterial (on storage); 2-ketoglutarate degradation; lithium; ketosis; tissue ischemia; increase with younger age	As malate; malonic aciduria; fumarase deficiency
Lactic acid, ketone bodies *(30, 71, 77)*		
2-Hydroxybutyrate	Ketosis; lactic acidosis	Lactic acidosis; GA I; respiratory chain defects
2-Hydroxyisobutyrate	Lactic acidosis	Lactic aciduria
3-Hydroxybutyrate *(32, 49, 77–79)*	Ketosis (e.g., vomiting, prolonged fasting, diabetic ketoacidosis); B_{12} vitamin deficiency; Reye & Reye-like syndromes; pulmonary infections; viral gastroenteritis; von Gierke disease; hyperthyroidism; pregnancy; heat stroke; ethanol; protein malnutrition; high-fat diet	Gluconeogenesis; PHD complex deficiency; respiratory chain defects; IVA; PA; MMA; multiple carboxylase deficiency; 3-methylcrotonyl-CoA carboxylase deficiency; glyceroluria; MSUD; GA I; MAD deficiency; β-ketothiolase deficiencies; 2-amino/2-ketoadipic acidemia; mitochondrial SCHAD; fatty acids oxidation deficiency (inappropriate ketosis)
Acetoacetate *(78)*	As 3-hydroxybutyrate; acetylsalicylate	As 3-hydroxybutyrate

Table 1. Continued.

Acid/Metabolite	Non-IEM *(4, 12, 15, 16, 22)*	IEM
Lactate and pyruvate *(29, 78, 80–82)*	Gut bacteria and bacterial contamination (D-lactate); short bowel syndrome (D-lactate); secondary lactic acidosis (e.g., apnea, septicemia, seizures, respiratory or cardiac insufficiency); diabetic ketoacidosis; Reye & Reye-like syndromes; increase with younger age; saccharose, fructose, lactose; drugs inducing hyperlactemia; dialysis bath; MCT administration	Primary lactic acidosis; PDH complex (E1, E2, E3) deficiency; oxidative phosphorylation and respiratory chain defects (e.g., MERRF, MELAS, Kearns-Sayre), Krebs acid cycle defects, gluconeogenesis defects (e.g., pyruvate carboxylase, fructose-1, 6-diphosphatase, glycogen storage I disorder); (short-branched chain acyl-CoA DH deficiency; muscle COX deficiency[c]); MAD deficiency (severe form); VLCAD deficiency; GA I; multiple carboxylase deficiency; some other organic aciduria (MMA, PA, IVA); citrullinemia, glycerol kinase deficiency; HMG-CoA lyase deficiency; EMA aciduria
Lysine, glycine, serine metabolism		
Glutaconate		GA I
Glycerate	Uremia; increase with younger age	D-Glyceric aciduria; hyperoxaluria type II (L-form); succinic semialdehyde DH deficiency
Glycolate *(83, 84)*	Ethylene glycol poisoning	Hyperoxaluria type I; succinic semialdehyde DH deficiency; isolated glycolic aciduria[c]
Glyoxylate		Hyperoxaluria type I
2-Hydroxyadipate *(85)*		2-Amino/2-Ketoadipic aciduria
3-Hydroxyglutarate *(85)*		GA I
2-Ketoadipate *(85)*		2-Amino/2-Ketoadipic aciduria
Glutarate *(18, 19, 85–87)*	2-Ketoglutarate degradation; bacterial gut metabolism; uremia; ethylene glycol poisoning; lithium	GA I; MAD deficiency (severe form); MAD deficiency (mild form); 2-amino/2-ketoadipic aciduria; malonic aciduria; other mitochondrial dysfunctions
Oxalate *(83, 88–90)*	Enteric malabsorption (regional enteritis or ileitis, celiac sprue disease, resection of ileum, Crohn disease); idiopathic stone disease; pyridoxine deficiency; increase with younger age; diet (e.g., beans, leafy vegetables, rhubarb, spinach, tomatoes, strawberries, tea, chocolate); infant formula; ascorbic acid; xylitol; ethylene glycol; methoxyflurane	Hyperoxaluria type I and II; hyperoxaluria without known enzyme deficit
Other acids and metabolites		
2-Hydroxyglutarate *(82, 85)*	Bacterial contamination (D-form); lithium; uremia; increase with younger age; 2-ketoglutarate degradation	2-Hydroxyglutaric aciduria (L- and D-forms); MAD deficiency, severe (D-form); MAD deficiency, mild (D-form); 2-amino/2-ketoadipic aciduria; malonic aciduria
3,4-Dihydroxybutyrate (2-deoxytetronate)	Diet	Succinic semialdehyde DH deficiency
3-Hydroxyisobutyrate *(32)*	Ketosis	3-Hydroxyisobutyric DH deficiency and/or methylmalonic semialdehyde DH deficiency[c]
4,5-Dihydroxyhexanoate		Succinic semialdehyde DH deficiency
4-Hydroxybutyrate	Ketosis (?)	Succinic semialdehyde DH deficiency
4-Hydroxycyclohexylacetate *(91)*	Bacterial gut metabolism (?)	Hawkinsinuria
Glycerol	Contamination (suppository, emollients); uremia	Gylcerol kinase deficiency; fructose-1,6-phosphatase deficiency
Malonate *(92)*		Malonyl-CoA-decarboxylase deficiency; malonic aciduria with normal malonyl-CoA-decarboxylase activity
Mevalonate and/or its lactone		Mevalonate kinase deficiency
N-Acetylaspartate		Canavan disease
Orotate *(93–95)*	Allopurinol treatment; azauridine; high cell turnover (tissue breakdown, menstruation); folate malabsorption	Argininemia; orotic aciduria; citrullinemia; OCT deficiency; hyperornithinemia-hyperammonemia-homocitrullinuria syndrome; lysinuric protein intolerance; purine nucleoside phosphorylase deficiency; Lesh–Nyhan disease

Table 1. Continued.

Acid/Metabolite	Non-IEM *(4, 12, 15, 16, 22)*	IEM
Pyroglutamate (L- or D-5-oxoproline) *(82, 91, 96–102)*	From glutamine of hydrolyzed proteins (infant formula); acetaminophen; vigabatrin; fludoxacillin, netilmicin (?); glutamine degradation (in hyperammonemia, urea cycle defects); vegetarian or low-protein diets, undernutrition; iron oxoprolinate; Steven–Johnson syndrome; burns; premature newborns; transitory (?); glycine deficiency; increase with younger age; renal insufficiency; pregnancy (increased metabolic demand for glycine)	Glutathione synthetase deficiency; 5-oxoprolinase deficiency; nephropathic cystinosis; hawkinsinuria; homocystinuria; OCT deficiency; PA
Thymine	Caffeine (?)	Dihydropyrimidine DH deficiency
Uracil	Caffeine (?)	Dihydropyrimidine DH deficiency; OCT deficiency; citrullinemia
Vanillactate *(103)*	Catecholamine-containing foodstuff (e.g., bananas); L-dopa decarboxylase inhibitors; neuroblastoma	L-Amino acid decarboxylase deficiency
Nutritional, exogenous, or artifactual compounds *(6)*		
2,5-Furane dicarboxylate and 5-hydroxymethyl-2-furanoate	Heated furanoic sugars (chocolates, fruit juice, intravenous perfusion)	
2-Furoylglycine	Chocolate; heated fruit juice or parenteral solution; uremia	
3-(3-Hydroxyphenyl)-hydracrylate	From nutrition	
4-Hydroxycyclohexane-1-carboxylate *(104)*	Diet; bacterial gut metabolism (from tyrosine)	
4-Hydroxyhippurate	Bacterial gut metabolism	
Benzoate *(61, 105)*	Bacterial metabolism (gut, urinary tract) from hippurate or from aromatic amino acids; benzoate treatment; food additive; ethylene glycol poisoning; toluene; hyperammonemia	
Hippurate *(106)*	As benzoate; uremia	
Maleate	Fluvoxamine maleate	
Palmitate	Soap; Jamaican vomiting sickness	
p-Cresol	Bacterial metabolism from tyrosine; toluene; uremia	
Phenol	Bacterial metabolism from tyrosine; exposure to benzene or phenol; malabsorption; uremia	
Pivalate	Pivampicillin or pivmecillinam	
Tartarate	Food additive; uremia	

[a] PKU, phenylketonuria; BH4, tetrahydrobiopterin; PA, propionic acidemia; VPA, valproate; MSUD, maple syrup urine disease; DH, dehydrogenase; MMA, methylmalonic acidemia; HMG, 3-hydroxy-3-methylglutarate; IVA, isovaleric acidemia; MAD, multiple acyl-CoA dehydrogenase; EMA, ethylmalonate; COX, cytochrome *c* oxidase; GFR, glomerular filtration rate; DCA, dicarboxylic acid; MCT, medium-chain triglyceride; MCAD, medium-chain acyl-CoA dehydrogenase; SCAD, short-chain acyl-CoA dehydrogenase; VLCAD, very long-chain acyl-CoA dehydrogenase; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase; LCHAD/TFP, long-chain 3-hydroxyacyl-CoA dehydrogenase/trifunctional protein; CPT, carnitine palmitoyltransferase; GA I, glutaric aciduria type I; PDH, pyruvate dehydrogenase; OCT, ornithine carbamoyltransferase.

[b] (?) indicates that this information remains to be confirmed.

[c] Enzymatic confirmation not yet established.

preferably the first morning voiding, is an acceptable alternative. This specimen usually consists of at least 2 mL and is stored until analysis at below −18 °C without the use of any preservative.

Intraindividual variations will occur with respect to the time of sampling, the patient's clinical status, eventual diet management, and whether the sample is collected when the patient is fasted or fed. Sampling during fasting or metabolic decompensation is often considered to be most valuable because, in most cases, metabolites of interest are then excreted selectively or at a higher concentration. On the other hand, metabolic decompensation, such as lactic acidosis, ketosis, or liver failure, gives rise to an abnormal excretion of organic acids (α-keto branched, dicarboxylic, or aromatic acids, respectively) that are otherwise involved in particular IEM; this sometimes renders interpretation even more difficult.

Poor preservation of samples will lead to nonenzymatic conversion of all keto acids to the respective hydroxyacid; for example, acetoacetate is converted to 3-hydroxybutyrate, and 2-ketoglutarate is converted to 2-hydroxyglutarate.

Abnormal Excretion Patterns Not Attributable to IEM

An increase in excretion may be nonspecific because some metabolites are reported to be abnormally excreted in conditions not attributable to IEM (drug therapy, diet, non-IEM diseases, or physiologic conditions), as indicated in Table 1.

Two frequent abnormal excretions not necessarily related to IEM are lactic aciduria and ketonuria. Whatever its origin, lactic aciduria is generally accompanied by other compounds; the greater the lactate excretion, the more likely the extent of the excretion of pyruvate, *p*-hydroxyphenyllactate, 2-hydroxyisovalerate, 2-hydroxybutyrate, and to a lesser extent, branched-chain 2-ketoacids. The abnormal excretion of these branched compounds implies the need for differentiation from dihydrolipoyl dehydrogenase deficiency.

Ketonuria (3-hydroxybutyrate and acetoacetate) is often accompanied by 3-hydroxyisobutyrate, 3-hydroxyisovalerate, 2-hydroxybutyrate, and dicarboxylic acids, particularly their 3-hydroxy derivatives with chain lengths up to C14. In this latter case, the pattern could mimic a long-chain 3-hydroxyacyl-CoA dehydrogenase or a trifunctional protein deficiency profile, except for the very high excretion of ketone bodies [in fatty acid oxidation defects, ketone bodies may appear increased in urine during fasting, but the ketosis remains at an inappropriately low level and the ratio of urinary adipate to 3-hydroxybutyrate is >0.5 *(14)*].

Another common misinterpretation may arise from bacterial metabolism. Of possible endogenous origin (e.g., intestinal infection) is the abnormal excretion of D-lactate (not chromatographically separated from L-lactate), methylmalonate, *p*-hydroxyphenylacetate, *p*-hydroxyphenyllactate, phenylacetylglutamine, phenylpropionylglycine, glutarate, benzoate, and hippurate. Of possible exogenous origin (bacterial growth in urine) are D-lactate, 2-ketoglutarate, D-2-hydroxyglutarate, succinate, 3-hydroxypropionate, and phenol derivatives (phenol, *p*-cresol, hippurate) *(15)*.

The drug valproic acid may lead to increased excretion of 3-hydroxyisovalerate, 5-hydroxyhexanoate, 7-hydroxyoctanoate, *p*-hydroxyphenylpyruvate, dicarboxylic acids, and to a lesser extent, hexanoylglycine, tiglylglycine, and isovalerylglycine. The metabolites of this anticonvulsant drug are an important clue to the analyst, however.

The administration of medium-chain triglycerides may yield a pattern resembling fatty acid β-oxidation defects, with increased saturated even-numbered dicarboxylic acids, mainly sebacate, as well as increased 5-hydroxyhexanoate and 7-hydroxyoctanoate, and the presence of octanoate but the absence or low excretion of glycine derivatives *(16, 17)*.

Misleading Normal or Near-Normal Excretion

The excretion of organic acids in pathologic conditions may be characterized by large variability and thus casts doubt on the clinical sensitivity of the results. Interindividual variations are also possible because, for some diseases, urinary biochemical features may depend on what have been called "excretory" and "non-excretory" patients. Indeed, compounds typically excreted in large amounts may also appear at only slightly increased or even normal concentrations in some IEM. This is particularly true when a patient is clinically well (not in a state of metabolic decompensation) or under suitable dietary control. Among these inborn errors are glutaric aciduria type I *(18, 19)* (glutarate concentrations may be within reference values, whereas 3-hydroxyglutarate is present); medium-chain acyl-CoA dehydrogenase deficiency (adipate, suberate, and sebacate concentrations may be within reference values, but the presence of suberylglycine and hexanoylglycine will reveal the disorder) *(20)*; multiple acyl-CoA dehydrogenase deficiency, particularly in its mild forms (metabolites suggesting such a disease, including ethylmalonate and glutarate, are quite variable); and 2-ketoglutarate dehydrogenase deficiency (2-ketoglutarate excretion ranges from within reference values to 10 times higher than the upper limit of the reference interval).

Respiratory chain defects give an unpredictable organic acid pattern, but nearly always with marked lactic aciduria; Krebs cycle acids, ethylmalonate, 3-methylglutaconate, and 3-methylglutarate may also be excreted in varying quantities. Urinary orotate may be high but possibly borderline in citrullinemia, ornithine carbamoyltransferase deficiency, lysinuric protein intolerance, and the hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, all disorders for which the biochemical diagnosis, however, is based on plasma ammonium and plasma and urinary amino acid profiles.

Interpretation and Misinterpretations *(7, 8, 10, 11)*

The relevance of the abnormal excretion of some characteristic metabolites in the diagnosis of IEM has to be emphasized. For example, the presence of succinylacetone and succinylacetoacetate is pathognomonic of tyrosinemia type I (fumarylacetoacetate hydrolase deficiency). Other compounds may also be quite specific, including 3-hydroxyglutarate for glutaric aciduria type I, mevalonic acid for mevalonic aciduria, *N*-acetylaspartate for Canavan disease, 4-hydroxycyclohexylacetate for hawkinsinuria, and 2-ketoadipate and 2-hydroxyadipate for 2-amino/2-ketoadipate aciduria.

Cooperation between clinical chemists and clinicians is essential for the interpretation of the results. On the one hand, information on diet, drug intake, and clinical symptoms and signs may often be required by the clinical chemist to refine his or her interpretation. The clinical chemist can inform the clinician of pitfalls, the possible origins of abnormal results, and further analyses that can be performed *(21)*. On the other hand, a final diagnosis can be established only in terms of the patient's history and clinical picture, in addition to results from biochemical and medical examinations.

CONCLUSION

As a practical consequence of possible misinterpretations, urinary organic acid patterns must be interpreted in the context of the complete clinical picture. In this context, both an abnormal organic acid pattern in the urine from an asymptomatic individual and a normal profile from a patient suspected of IEM must be considered as indications for repeated sampling: in the former circumstance, more information on possible drug therapy, diet, non-IEM pathology, and physiologic conditions is mandatory, whereas in the latter case, a period of illness would be preferred for resampling.

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