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Confirmation and Determination of Urinary Ethylmalonic Acid by Capillary Electrophoresis with Indirect UV Detection

Cansever et al. Capillary Electrophoresis for Urine EMA

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ABSTRACT

Objectives: Ethylmalonic acid (EMA) is a key urinary biomarker of ethylmalonic encephalopathy (EE), but routine gas chromatography–mass spectrometry (GC–MS) is time- and resource-intensive. This study aimed to develop and validate a simple, rapid capillary electrophoresis (CE) method with indirect ultraviolet (UV) detection for the quantitative determination of EMA in urine.

Materials and Methods: A fused-silica capillary and a background electrolyte containing 5 mmol/L 2,6-pyridinedicarboxylic acid (PDCA) and 0.1 mmol/L cetyltrimethylammonium bromide (CTAB) (pH 5.74) were used. Separation was performed at 28 kV and monitored at 200 nm. Fresh human urine was diluted 1:20, filtered, and used to prepare matrix-matched calibrators (10–750 μmol/L). Linearity, precision, sensitivity, and accuracy were assessed according to International Council for Harmonisation validation guidelines, using spiked urine samples. Electropherograms from healthy control urine, EMA-spiked urine, and urine from a patient with EE illustrated the applicability.

Results: Under optimized conditions, EMA migrated at approximately 2.0 min with baseline resolution from endogenous components. Calibration was linear between 10 and 750 μmol/L ($R^2 = 0.99920$). Within-run precision, expressed as relative standard deviation (%), was 0.17% for migration time and 0.89% for corrected peak area, while between-day precision for peak area was 1.91%. The limits of detection and quantification were 11.78 and 39.3 μmol/L, respectively. Recovery in spiked urine ranged from 96 ± 2% to 98 ± 2%.

Conclusion: The CE–UV method enables rapid, reliable quantification of urinary EMA with minimal sample preparation. Its short analysis time and modest instrumentation requirements support its use for first-line screening and monitoring of EE, with GC–MS reserved for confirmatory analyses.

Keywords: Ethylmalonic Acid, Electrophoresis, Capillary, Urine, Biomarkers, Metabolism, Inborn Errors

INTRODUCTION

Ethylmalonic encephalopathy (EE) is an autosomal recessive mitochondrial disorder caused by pathogenic variants in the *ETHE1* gene.[1] Clinically, EE is characterized by developmental delay, relapsing petechiae, orthostatic acrocyanosis, and chronic diarrhea, with a heterogeneous phenotype that can vary widely among patients.[2] The prognosis is poor. Approximately half of affected children die before the age of two due to metabolic decompensation.[3] Biochemical findings typically include persistently elevated lactate and increased butyryl- and isovalerylcarnitine in blood, together with urinary excretion of ethylmalonic acid (EMA), methylsuccinic acid, butyrylglycine, and isovalerylglycine.[1] Combined treatment with coenzyme Q10, N-acetyl cysteine, and decontamination of bowel with metronidazole results in marked neurological improvement, reduction of acrocyanosis and petechial lesions, and disappearance of diarrhea, especially in early treatment.[4]

For disorders like EE, in which urinary organic acid analysis is integral to diagnosis, gas chromatography–mass spectrometry (GC–MS) remains the reference method for comprehensive analysis.[5] However, capillary electrophoresis (CE) offers an accessible and operationally simple alternative for targeted analytes. It enables rapid separations with minimal sample preparation and instrument time.[6,7] Indirect ultraviolet (UV) detection by CE has previously been applied to biologically relevant short-chain organic acids, including EMA.[8] More recently, urinary EMA has also been determined using CE with capacitively coupled contactless conductivity detection (CE–C^4D), illustrating detector-dependent trade-offs between sensitivity and instrumentation requirements.[9] These attributes make CE an attractive option for clinical laboratories performing high-throughput screening and follow-up quantification. The objective of this study was to develop an simple, rapid, and accurate CE method to determine EMA in urine.

MATERIALS AND METHODS

Materials

EMA, cetyltrimethylammonium bromide (CTAB), and 2,6-pyridinedicarboxylic acid (PDCA) were obtained from Sigma-Aldrich, Merck (Darmstadt, Germany), and Fluka (Buchs, Switzerland), respectively. Solutions were prepared with purified, deionized water (Elgacam C114, Elga, England filtration system).

Urine samples were prepared daily by diluting fresh human urine in purified water. The dilution ratio was 1/20. EMA stock solution was dissolved in purified water and stored at +4 °C. Solutions prepared daily were filtered before analysis using a microfilter with a 0.45-µm pore size. The background electrolyte (BGE) used for separations consisted of 5 mmol/L PDCA and 0.1 mmol/L CTAB, adjusted to pH 5.74.

Apparatus and Operating Condition

Agilent CE system (Germany) equipped with a diode-array detector was used for EMA seperations. Agilent ChemStation software was used for data processing. 75-µm i.d. fused-silica capillaries for the separation experiment were purchased from Agilent. The total lengths of the capillary and the detector were 57 cm and 49 cm, respectively. The separations were performed at 28 kV with a wavelength set at 200 nm in indirect-UV mode.

The new fused-silica capillary adjustment was performed by rinsing with 1 mol/L NaOH for 30 min, followed by purified water for 10 min. The capillary was rinsed with 0.1 mmol/L NaOH and water for 3 min each, and was buffered for 3 min on each working day. A three-min flush with buffer was performed between runs. Injections were administered at 5 × 10−3 MPa for 5 s.

pH measurements were performed using Metrohm 654 Digital pH Meter (Metrohm, Switzerland) equipped with a pH glass electrode. The Addition of CTAB provided a positively charged inner surface, slowing or reversing electroosmotic flow (EOF) toward the anode, so that anionic analytes co-migrated with the bulk flow under the applied field.

Sample Preparation

Fresh urine was diluted 1/20 (urine/water), mixed, and filtered (0.45 µm) immediately prior to analysis. The 1:20 dilution was selected to minimize urine matrix effects (e.g., high ionic strength or conductivity and viscosity), which can compromise peak shape, current stability, and the migration-time repeatability in CE, while still enabling reliable detection and quantification of EMA within the validated range. This sample-handling approach is consistent with prior CE methods for urinary organic acids, where urine is commonly analyzed after centrifugation, with dilution as needed; a 1:20 final dilution has been reported for urine matrices in CE–based organic acid profiling.[10] Matrix-matched calibrators and recovery samples were prepared by spiking aliquots of 1/20-diluted pooled urine with EMA at specified concentrations (see Sections 2.4–2.5).

Calibration and Linearity

Method validation was performed according to the International Council for Harmonisation (ICH) Q2 (R2) guideline.[11] Linearity was evaluated in 1:20-diluted human urine over the range 10–750 µmol/L EMA using matrix-matched external calibration. Calibration points across this range were injected (n ≥ 3 per level), and peak quantification was performed using corrected peak areas (A/t). The calibration model was fitted using ordinary least squares linear regression.

Precision

Within-run precision was assessed by six successive injections (n = 6) of a 50 µmol/L EMA standard in urine diluted 1:20; precision was expressed as relative standard deviation (RSD%) for migration time and the corrected peak area (A/t). Between-day precision was determined as RSD% of peak areas from measurements obtained on three different days (n = 3).

Sensitivity Limit of Detection/Limit of Quantification (LOD/LOQ)

The LOD was defined as the EMA concentration producing a signal with peak height three times the baseline noise (S/N ≈ 3), and the LOQ as the concentration corresponding to S/N ≈ 10.

Accuracy (Recovery)

Accuracy was assessed by recovery experiments in urine diluted 1/20 at three EMA concentrations (25, 50, and 100 µmol/L). Each level was measured six times (n = 6), and recoveries were calculated as (measured/added) × 100%.

Data Processing

Electropherograms were integrated using ChemStation. Quantification employed corrected peak areas (A/t) to minimize run-to-run variability associated with migration time shifts. Quality metrics (linearity, precision, recovery, LOD/LOQ) were summarized according to ICH-style analytical validation conventions.

RESULTS

Validation Results

Method performance characteristics are summarized in Table 1. Linearity was demonstrated over 10–750 µmol/L using matrix-matched calibration in 1:20-diluted urine; the regression equation was $y = 2.25045 \times 10^{-3} x + 1.59091 \times 10^{-2}$ with $R^2 = 0.99920$ (Figure 1). Within-run precision, expressed as RSD%, was 0.17 RSD% for migration time and 0.89 RSD% for the corrected peak area (A/t) (n = 6). Between-day precision for corrected peak area was 1.91% RSD (three different days).

Sensitivity, assessed using signal-to-noise criteria, yielded an LOD of 11.78 μmol/L and an LOQ of 39.3 μmol/L. Accuracy assessed by recovery experiments at 25, 50, and 100 μmol/L (n = 6 each) showed recoveries ranging from 96 ± 2% to 98 ± 2% (Table 1).

EMA Electropherograms and Urinary EMA Levels

Under the separation conditions described above, EMA migrated at approximately 2.0 min. Electropherograms of a healthy control urine sample, a control urine sample spiked with EMA, and a urine sample from a patient diagnosed with EE are shown in Figure 2A–C, respectively. In the healthy control urine (Figure 1A), no distinct peak was observed at the EMA migration time, indicating that EMA < LOQ (39.3 μmol/L) under the applied conditions. In the matrix-matched spiked urine (Figure 2B), pooled urine (1:20 dilution) fortified with EMA at 50 μmol/L produced a well-defined peak at the same migration time, confirming the peak identity and demonstrating baseline resolution from endogenous components. In the patient sample (Figure 2C), a prominent peak at ≈2.0 min was detected and quantified as 78.4 μmol/L EMA in the analyzed (1:20 diluted) urine, which is above the LOQ. Because indirect UV detection yields negative peaks, electropherograms were displayed after polarity inversion to facilitate visualization and integration. Urinary EMA levels for the illustrative samples are summarized in Table 2.

DISCUSSION

This study optimized a CE–UV method for the rapid quantification of urinary EMA. The method achieved a migration time of ~2 minutes in urine diluted 1:20, demonstrated excellent linearity across 10–750 μmol/L (r = 0.99920), exhibited tight intra- and interday precision, and showed high recovery. The LOD and LOQ were 11.78 and 39.3 μmol/L, respectively. EMA is a clinically significant urinary biomarker in EE and may be elevated in short-chain acyl-CoA dehydrogenase deficiency. Therefore, fast, reproducible first-line quantification of EMA has practical value for triage and monitoring.[1,12]

Traditionally, urine organic acid analysis is performed by GC–MS, which remains the confirmatory reference method. However, GC–MS requires derivatization and extraction as well as batch processing, which together extend turnaround times and increase resource use.[13] Faster preliminary results are clinically useful in disorders where EMA abnormalities inform acute and longitudinal management. This enables earlier decision-making while MS confirmation proceeds.[1] In this context, our CE–UV assay shortens the analytical step to minutes while maintaining the quantitative performance necessary for routine screening and monitoring. This enables a more efficient workflow in which cases that are clearly abnormal or ambiguous proceed to MS confirmation.[14]

The separation strategy employed in this study established principles for the separation of anionic analytes. Cationic surfactants, such as CTAB, dynamically modify the capillary wall, thereby reversing EOF. This promotes the rapid and reproducible migration of anions to the detector.[15,16] Because EMA lacks a strong native UV absorbance, indirect UV detection is appropriate. A Prior study has demonstrated indirect CE–UV of biologically relevant short-chain organic acids, including EMA, by using UV-absorbing co-ions and mobility matching.[8] The use of PDCA as the absorbing co-ion in the background electrolyte during method implementations further supports robust indirect UV detection of carboxylic acids.[17] Our data expand upon existing literature by demonstrating the quantification of short-term EMA directly from minimally processed urine using a widely available UV/diode-array detector platform. Alternative CE implementations, such as CE–C^{4}D, have also achieved sensitive EMA detection, albeit with different detector trade-offs.[9]

Two methodological aspects merit emphasis. First, stable approximately 2-minute separations are achieved using low-level CTAB (0.1 mmol/L) with PDCA (5 mmol/L), a balanced EOF control, and indirect UV detection.[15] Second, our LOQ of 39.3 μmol/L is adequate for routine urine EMA screening within a reflex workflow, while CE–C^{4}D and MS methods achieve lower limits—an LOQ of ~3–4 μmol/L and an LOD of ~1 μmol/L—reflecting a trade-off between accessibility and sensitivity.[9] Given that EMA elevations in EE and related phenotypes are typically above normal, borderline results can be reflexed to MS for confirmation.[1]

From an interpretive standpoint, the method's analytical limitations should be considered when reporting results for healthy subjects and patients. In the healthy control (Figure 1A), the absence of a distinct EMA peak at ≈2.0 min should be interpreted as EMA < LOQ (39.3 μmol/L) rather than complete absence. By contrast, the EE patient sample (Figure 1C) showed an EMA concentration of 78.4 μmol/L in 1:20-diluted urine, which was readily quantifiable by CE–UV. Compared with indirect UV detection, CE–C^{4}D generally provides lower limits of detection for small ionic acids, which can improve interpretation of low-level or borderline EMA elevations (9).Therefore, samples near the LOQ or with strong clinical suspicion should be reflexed to CE–C^{4}D or MS-based confirmatory testing

This study has limitations. Indirect UV lacks the molecular specificity of MS; therefore, rare co-migrating matrix anions could interfere. This warrants orthogonal confirmation when measurements are near the LOQ or resolution is suboptimal. Also, the absolute concentrations in spot urine were reported without creatinine normalization.. Laboratories that adopt this method should validate reporting in μmol/L with paired creatinine measurement or in mmol/mol creatinine, according to local practice standards. Finally, a head-to-head comparison against GC–MS and LC–MS in the same cohort was not performed to establish clinical concordance and decision thresholds for reflex testing.

In summary, we present a fast, precise, and accessible CE–UV assay for urinary EMA that can separate samples in approximately two minutes each with excellent linearity, low imprecision, and high recovery. In a reflex workflow, CE–UV can be used for same-day screening. Samples with borderline concentrations can then be referred to GC–MS for confirmation or further analysis. This strategy could reduce turnaround time, allow GC–MS resources to focus on cases requiring greater specificity, reduce workload, and support longitudinal monitoring in EE.

CONCLUSION

A rapid and accessible CE–UV method for urinary EMA quantification was developed and validated. The assay provides an approximately 2-minute separation and demonstrates excellent linearity, low imprecision, and high recovery in urine diluted 1:20. This approach can support same-day screening and follow-up, with reflex MS confirmation recommended for borderline concentrations or when analytical specificity is required.

Ethics

Ethics Committee Approval: This study involved the development of analytical methods using de-identified urine samples and did not include any identifiable personal data. The Local Ethics Committee reviewed the study and determined that formal ethics committee approval was not required.
Informed Consent: All urine specimens were de-identified residual samples obtained during routine laboratory procedures, and no identifiable patient information was accessed. Therefore, informed consent was waived by the Local Ethics Committee.

Footnotes
Authorship Contributions
Concept: M.Ş.C., E.K., T.Z., A.Ç.A.Z., F.B.E.B., Design: M.Ş.C., E.K., T.Z., A.Ç.A.Z., F.B.E.B., Data Collection or Processing: M.Ş.C., K.Ç., E.K., T.Z., A.Ç.A.Z., F.B.E.B., Analysis or Interpretation: M.Ş.C., K.Ç., E.K., T.Z., A.Ç.A.Z., F.B.E.B., Literature Search: M.Ş.C., K.Ç., E.K., T.Z., A.Ç.A.Z., F.B.E.B., Writing: M.Ş.C., K.Ç., E.K., T.Z., A.Ç.A.Z., F.B.E.B.
Conflict of Interest: One author of this article, Ertuğrul Kıykım, is a member of the editorial board of the Inherited Metabolic Disorders and Nutrition. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.
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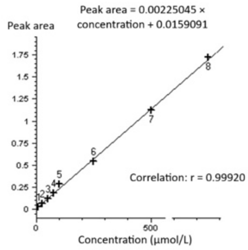

Figure 1. Calibration curve for EMA ethylmalonic acid.
EMA, ethylmalonic acid.

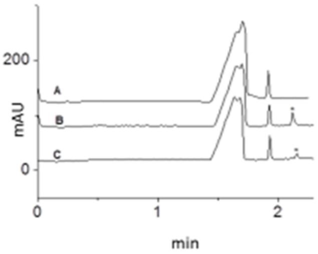

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Figure 2. (a) Shows the electropherogram of healthy urine; (b) shows the electropherogram of a healthy urine spiked with EMA; (c) shows the electropherogram of a patient diagnosed with EE.
EE, ethylmalonic encephalopathy; EMA, ethylmalonic acid.

Table 1. Validation values.

	Parameter	**Result**
Precision	Within-run precision (corrected peak area, A/t), RSD% (n = 6)	0.89
	Within-run precision (migration time), RSD% (n = 6)	0.17
	Between-day precision (corrected peak area, A/t), RSD% (n = 3 days)	1.91
Sensitivity	LOD (µmol/L)	11.78
	LOQ (µmol/L)	39.30
Accuracy (recovery)	EMA-spiked urine samples (25 µmol/L), recovery (%)	96 ± 2
	EMA-spiked urine samples (50 µmol/L), recovery (%)	96 ± 2
	EMA-spiked urine samples (100 µmol/L), recovery (%)	98 ± 2

EMA, ethylmalonic acid; LOD, limit of detection; LOQ, limit of quantification; RSD, relative standard deviation.

Table 2. Urinary EMA levels in illustrative human urine samples analyzed by CE–UV.

Sample	**Matrix/dilution**	**EMA status**	**Reported urinary EMA (µmol/L)**	**Interpretation**
Healthy control (Figure 1A)	Urine, 1:20 diluted	Unspiked	<LOQ (39.3)*	Not quantifiable under conditions
Spiked control (Figure 1B)	Pooled urine, 1:20 diluted	Spiked	50	Peak identity confirmed at ≈2.0 min
EE patient (Figure 1C)	Urine, 1:20 diluted	Clinical sample	78.4	Quantifiable; above LOQ

*LOQ, 39.3 µmol/L. For the spiked sample, the concentration indicates the nominal added EMA level.
CE, capillary electrophoresis; CTAB, cetyltrimethylammonium bromide; EE, ethylmalonic encephalopathy; EMA, ethylmalonic acid; LOQ, limit of quantification; PDCA, 2,6-pyridinedicarboxylic acid; UV, ultraviolet.