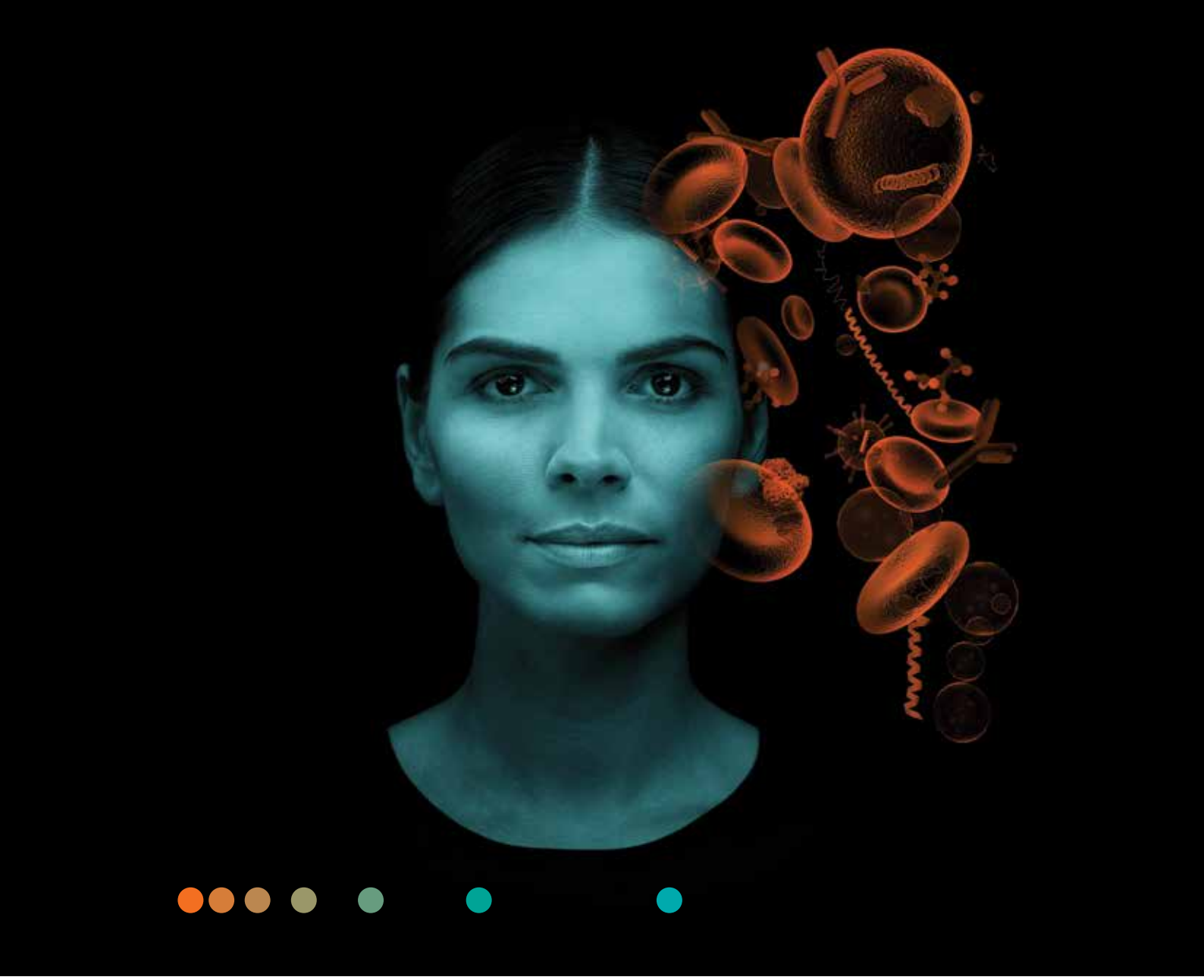

Immunoassay Monitoring of Theophylline/Caffeine Therapy for Neonatal Apnea

Syva Emit Caffeine Assay

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SIEMENS Healthineers

Protecting the lives of our most vulnerable patients—premature infants

Premature infants face many physiological challenges, including high risk of neonatal apnea—cessation of breathing for more than 20 seconds. Therapy for this life-threatening condition in newborns includes administration of theophylline or, preferably, caffeine. Regardless of which therapy is employed, continuous monitoring of serum caffeine concentration is critical to avoid accumulation of potentially toxic serum-caffeine levels.

Such therapeutic monitoring requires a highly specific and reliable diagnostic testing methodology. Certain methods such as HPLC, dioimmunoassay, and GC/MS are not an option available to—or practical for—many diagnostic laboratories.

Siemens Healthineers is committed to helping protect the lives of our most vulnerable patients. As an alternative to traditional methods, we are proud to offer the highly specific and cost-effective Syva® Emit® Caffeine Assay—an FDA-approved caffeine immunoassay that includes a neonatal testing indication.

Increased risk for preterm births

According to World Health Organization (WHO) statistics, the current global preterm birth rate is 1 in 10 births, and this rate is projected to increase. The mortality rate for preterm births is 1 million children per year.

Premature infants are subject to serious physiological issues. In addition to neonatal apnea, other short-term impacts include low birth weight and lung immaturity. Potential long-term medical effects include higher incidences of cerebral palsy and learning disability.[1] Preterm births also have significant economic consequences, including long stays in the neonatal unit and the ongoing high cost of medical care.[1]

Prevalence of neonatal apnea

Apnea—the cessation of breathing for more than 20 seconds—is most frequently seen in premature infants and is a significant contributor to the morbidity of low-birth-weight infants. Apnea occurs in approximately 25% of infants weighing less than 2500 grams and in 85% of infants weighing less than 1000 grams at birth.[2]

Therapies for neonatal apnea

Therapy for neonatal apnea may include methylxanthine drugs, particularly theophylline, and assisted ventilation therapy. Methylxanthines are used to both control and prevent neonatal apnea.[3,4] The respirogenic action of methylxanthines is due to their ability to stimulate the central nervous system.[4]

As an alternative to methylxanthine drugs such as theophylline, caffeine is also administered to treat neonatal apnea.[4,5,6]

Theophylline and caffeine therapies are both are administered intravenously and must be monitored continuously to prevent caffeine toxicity. These therapies may have possible side effects, including tachycardia and cardiac dysrhythmias, feeding intolerance, and, occasionally, seizures.

However, toxicity and side effects are more common with theophylline, and caffeine therapy is therefore the preferred treatment due to fewer side effects.[7]

Worldwide premature birth rate

10%

Approximately 1 in 10 births are premature.
Source: WHO

Incidence of Neonatal Apnea[2]

25%

Infants weighing less than 2.5 kg

85%

Infants weighing less than 1 kg

Caffeine therapy: improved care, reduced cost[1,8]

- Reduction in apneotic attacks
- Possible avoidance of intubation/ventilation
- Reduced rate of death before 18–24 months
- Decreased incidence of cerebral palsy
- Reduced cost of NICU care

Better patient care: the benefits of caffeine therapy
Caffeine therapy has short-term, long-term, and economic benefits. Clinicians have observed a significant reduction in apneoic attacks within 8 hours after administration of higher doses of caffeine.[8] Another short-term benefit is possible avoidance of intubation for ventilation.[8]

In the longer term, caffeine therapy has been associated with a reduced rate of death before 18–20 months and a decrease in the incidence of cerebral palsy.[1]

Studies have also shown a decrease in the cost of NICU care for premature infants receiving caffeine therapy compared to those in a placebo group.[1]

Serum theophylline and caffeine levels
Caffeine is a pharmacologically active metabolite of theophylline. Premature infants receiving theophylline have significant levels of caffeine in their blood because they metabolize theophylline to caffeine.[3]

Theophylline concentration is a poor indicator of serum caffeine level. Therefore, both caffeine and theophylline concentrations should be measured in premature infants receiving theophylline. By doing so, the total methylxanthine level can be assessed, thus avoiding toxicity.[9,10,11]

Risks of caffeine's extended half-life
Caffeine has a long half-life and is therefore easily accumulated in premature infants receiving either theophylline or caffeine therapy.[12] Caffeine half-life in infants varies from 30 to 200 hours. The wide range seen in premature infants is due to individual variations in caffeine metabolism.[5]

As the metabolism of premature infants matures during the first 3–6 months of life, their caffeine half-life reaches adult rates of 4–6 hours.[2]

Therefore, multiple dosing of theophylline and its subsequent metabolization into caffeine, or similar multiple dosing of caffeine as an alternative therapy, may result in over dosage. Thus, clinicians may opt to closely monitor caffeine levels in neonates receiving therapy for apnea.

Therapeutic monitoring methods for caffeine
While the critical need for continuous monitoring of serum caffeine levels in neonates is well-established, today's hospital laboratories may have few in-house options for cost-efficient and timely testing methods.

The methods historically used to measure serum levels of caffeine are high-performance liquid chromatography (HPLC),[5] radioimmunoassay,[13] and gas chromatography/mass spectrometry (GC/MS).[14]

These traditional testing methods, while specific and reliable, may be time- and cost-prohibitive for laboratories that do not currently have investment in or access to this expensive instrumentation.

The Syva Emit Caffeine Assay
Siemens Healthineers offers the Syva Emit Caffeine Assay as a reliable, cost-effective alternative to traditional caffeine-testing methods.

The Syva Emit Caffeine Assay is a highly specific immunoassay intended for use in the quantitative analysis of caffeine levels in human serum in subjects undergoing therapy with theophylline or caffeine, especially in cases of neonatal apnea. The Emit Caffeine Assay is an FDA-approved caffeine immunoassay with a neonatal testing indication, making it an innovative alternative to traditional testing methods.

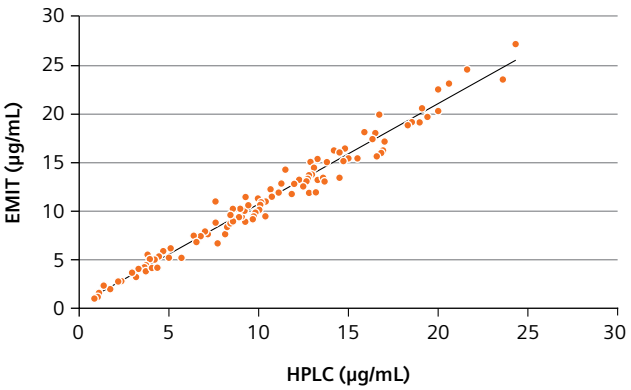
The Emit Caffeine Assay combines the convenience of an immunoassay with the specificity of HPLC testing, as shown in the following tables:

Table 1 — Comparative Analysis

	Study 1	Study 2*	Study 3
Slope	1.06	1.06	1.04
Intercept (µg/mL)	0.36	-0.24	0.44
Mean (µg/mL)			
Emit	4.3	7.8	11.45
HPLC	3.7	7.6	10.61
Standard Error of the Estimate (µg/mL)	0.30	0.71	0.90
Correlation Coefficient	0.99	0.99	0.99
Number of Samples	40	49	110

**To demonstrate performance over the full assay range, Study 2 added caffeine to 12 samples known to contain less than 10 µg/mL caffeine.*

Comparative Analysis of Emit Caffeine Assay vs. HPLC



Slope:	1.04	**Samples**	
Intercept (µg/mL):	0.44	Caffeine:	79
Std. error (µg/mL):	0.90	Theophylline:	31
Corr. coefficient (R):	0.99	Total:	110

Accuracy
Samples from neonates receiving theophylline were analyzed by the Emit Caffeine Assay and by HPLC. A comparative analysis of the results is shown in Table 5 (Study 1 and Study 2).

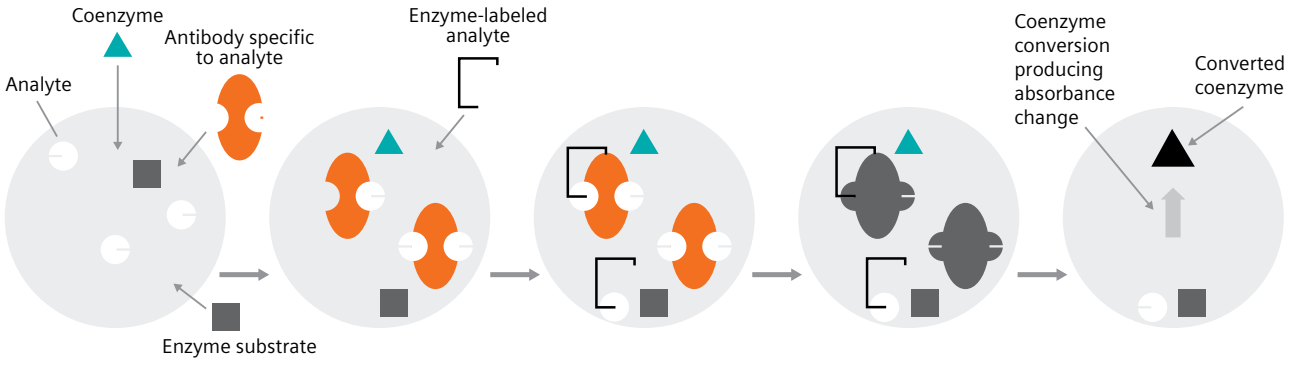
In a third study, samples from neonates dosed with theophylline (n=31) or caffeine (n=79) were analyzed by the Emit Caffeine Assay and HPLC. A comparative analysis of the results is shown in Table 1 (Study 3).

Proven Emit technology
The Emit Caffeine Assay employs proven Emit assay technology used to measure trace amounts of drugs and drug metabolites in human biological fluids. Emit assays combine the specificity and sensitivity of immunoassay with the convenience, speed, and reproducibility of enzyme measurements to deliver efficiency and utility in routine analytical determinations.

	Emit Caffeine Assay	HPLC†
Sample	Serum	Serum
Sample preparation	None	Extraction or mixing with internal standard
Instrumentation	Routine chemistry analyzers and specialty drug testing systems	Specialized HPLC instrumentation
STAT capabilities	Yes	No
Random access	Can be run with other chemistry tests	Batch mode

†Letter to the Editor: HPLC determination of caffeine and theophylline by direct serum injection. Clinical Chemistry. 1993;39(6)

Enzyme-multiplied Immunoassay Technique



DRUG-G6PDH (active)

Glucose-6-phosphate + NAD+ → 6-phosphogluconolactone + NADH + H+ (absorbs at 340 nm)

Efficient, reliable, in-house caffeine monitoring

Monitoring caffeine levels in-house on existing systems helps save valuable time and resources and may offer a potential source of new laboratory revenue. The Syva Emit Caffeine Assay delivers the following benefits compared to traditional testing methods:

- **No need for expensive HPLC equipment**—Reduces investment and maintenance costs
- **Less potential for human errors**—Less sample handling compared to HPLC helps increase the number of accurate results and reduces the need for retesting
  - No specialized instrumentation or sample preparation is necessary
- **Higher efficiency**—Reduces hands-on time and allows staff to focus on other tasks
- **Lower costs, higher profit**
  - Reduces internal handling and shipping of samples
  - Generates additional revenue by allowing your lab to accept send-ins from other labs and hospitals
- **Enhanced productivity**
  - Shares instruments and consumables with other Emit reagents
  - Significantly reduces turnaround time compared to send-outs
- **Flexible applications**
  - Adds caffeine monitoring to your current in-house testing menu
  - Enables caffeine testing on existing systems in the central lab
- **Excellent correlation**—Provides consistency of results between routine testing (e.g., Dimension Integrated Chemistry Systems) and specialty testing (e.g., Viva-E Systems)
- **Available on a broad variety of systems***—The Emit Caffeine Assay can run with other tests on a variety of routine and specialty chemistry analyzers

Viva-ProE® system

Atellica® CH system

Dimension® systems

Dimension Vista® systems

*Contact your local sales representativefor the availability of instrument-specific applications in your country.

Easier caffeine monitoring for better patient care

The Syva Emit Caffeine Assay allows easy, cost-effective, and timely monitoring of serum caffeine levels in neonatal patients. The assay provides clinicians with critical information they need to provide better care for vulnerable premature infants.

Now you can easily add this innovative assay based on reliable, proven Emit immunoassay technology to your testing menu, using instruments you already have in your lab.

Better Patient Care

Convenient, easy-to-use immunoassay

Faster turnaround time compared to send-outs

Reduced likelihood of human errors compared to HPLC

No additional equipment required

Available for many chemistry systems

Reduced costs, possible revenue generation for lab

Increased efficiency

To learn more about the Syva Emit Caffeine Assay and the entire Syva Emit testing portfolio, contact your area Siemens Healthineers representative or visit siemens-healthineers.com

Ordering Information

Catalog No.	SMN	Description
6P419UL	10445371	Syva Emit Caffeine Assay (includes calibrators) Emit Caffeine Calibrators 0, 1, 3, 7, 15, 30 µg/mL
6P499UL	10445372	Syva Emit Caffeine Control

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At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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