

Enhanced photoemission spectroscopy for verification of high-risk i.v. medications

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Technology has provided an opportunity to improve safety in dispensing oral drug formulations with robotic assistance and bar-code systems. The checking of compounded i.v. drug products, however, has been more challenging. The i.v. compounding area in the pharmacy is high volume and high risk. Hospital pharmacies may compound hundreds of thousands of i.v. drug products annually, and, in most institutions, checking these products relies on human observation alone. Typically, a technician prepares a product and a pharmacist visually checks the work. This process has been in place in most institutions since the advent of centralized i.v. admixture services over 30 years ago. Even if the human error rate in this setting is extremely low, the high-risk nature of many of the products being prepared dictates that the pharmacy must strive for an error rate of zero.

Purpose. The sensitivity and specificity of enhanced photoemission spectroscopy (EPS) for performing an automated final check of compounded i.v. admixtures at a pediatric hospital pharmacy were studied.

Methods. A tabletop EPS device was used to test samples of seven high-risk drug-diluent combinations compounded in the pharmacy; the drugs were vancomycin, lorazepam, morphine, insulin, hydromorphone, gentamicin, and epinephrine. Ten sets of samples were prepared for each drug. Typically, a sample set consisted of dilutions ranging from 10-fold above to 10-fold below the targeted concentration. Testing was performed twice weekly between November 2005 and March 2006.

Results. The EPS device detected errors departing from the targeted concentration by 20% or more with a sensitivity of at least 95%. Specificity in distinguishing among

test medications at targeted concentrations was 100%. The percentage of passing samples with intermediate concentrations varied among the drugs.

Conclusion. A tabletop EPS device demonstrated acceptable sensitivity and specificity for validating the identity and concentrations of selected high-risk i.v. medications compounded for pediatric patients. The device may help prevent clinically important medication errors caused by inaccurate compounding.

Index terms: Aminoglycosides; Antibiotics; Anxiolytics, sedatives and hypnotics; Concentration; Control, quality; Diluents; Epinephrine; Errors, medication; Gentamicin; Hydromorphone; Injections; Insulin; Insulins; Lorazepam; Morphine; Opiates; Pediatrics; Spectrometry; Stability; Storage; Sympathomimetic agents; Vancomycin
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The Institute for Safe Medication Practices has identified the follow-

ing drugs as high risk: adrenergic agonists, epidural medications, ino-

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tropes, narcotics, heparin, insulin, and sedative agents.¹ Most of these products are prepared in laminar-airflow hoods or sterile i.v. rooms, after which the traditional human verification occurs. Confirmation bias may occur when a pharmacist selectively supports what he or she expects to see rather than what is actually present.² This may lead to failure to detect errors in i.v. medication preparation, even among very experienced pharmacists.² Many drug vials look similar, with similar colors and printing. These factors, coupled with typical pharmacy distractions, can promote an environment ripe for medication errors.³ Therefore, a need exists to improve the current system of visual checking.

Rare incidents involving incorrectly prepared sterile products that resulted in patient harm contributed to the development of the ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products, which was published in 1993 and updated in 2000.⁴ It was recognized that the small number of reported errors did not reflect the true frequency of the problem, and in 1997 Flynn et al.⁵ identified a 9% mean error rate for i.v. admixture compounding, excluding ready-made products. More important, the overall rate of potentially clinically significant errors was 2%. A dose in excess of 10% of the labeled concentration was compounded in 3.1% of cases. The incorrect drug was used for 0.6% of doses.

Enhanced photoemission spectroscopy (EPS), an expanded version of conventional fluorometry, represents a potential means of verifying the accuracy of i.v. drug compounding. EPS is a proprietary process for analyzing a composite returned-energy spectrum. Using EPS, the targeted material is interrogated with light energy with a specific range of wavelengths. The returned-energy spectrum is mathematically converted to an alternative domain and then analyzed in composite for-

mat by multiple methods, including fluorometry. This allows both drug and concentration validation while facilitating separation of drugs for unique identification. A pilot study we conducted showed that EPS was successful at detecting doses more than twofold above or below the targeted concentration. We developed a workflow process to prepare staff for integrating the technology into practice (Figure 1). However, further study was warranted to better understand the limits of the device.

The objective of this study was to evaluate the sensitivity and specificity of tabletop EPS for performing an automated final check of compounded i.v. admixtures at a pediatric hospital pharmacy.

Methods

Instrument. The study was conducted by the department of pharmacy services at C. S. Mott Children's Hospital. A tabletop instrument (ValiMed, CDEX, Inc.) was used to validate high-risk i.v. medications that are commonly compounded in the pharmacy and used as bulk products for additional compounding into patient-specific doses. The instrument generates ultraviolet light energy through its fiberoptics; the energy is directed at the medication sample to excite sample molecules. The energy returned by the medication, including that associated with fluorescence, is measured by a spectrometer.

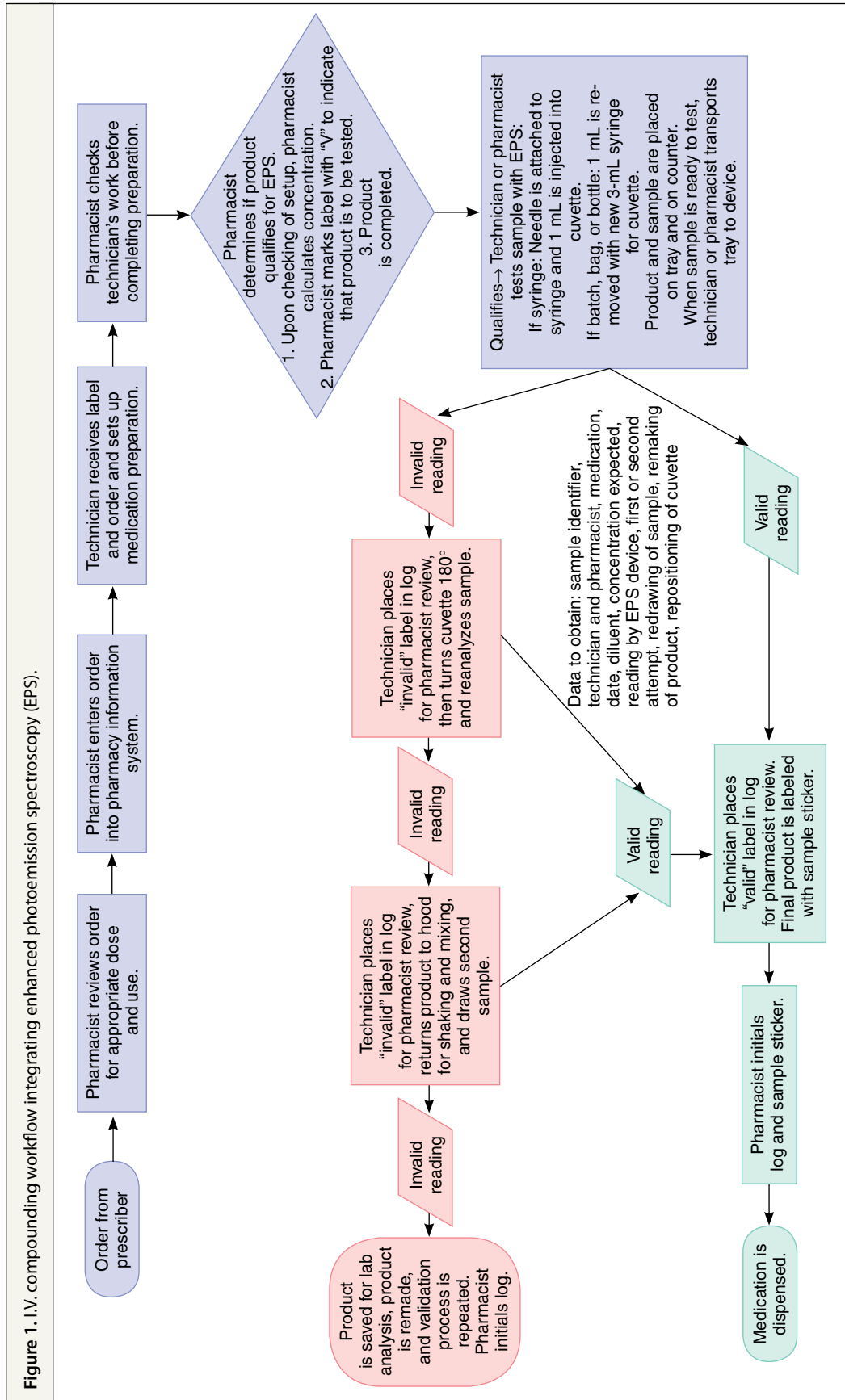
To determine a drug's unique fingerprint,⁶⁻⁹ a combination of the composite signature and the channel values is used. The composite signature is defined as the pattern of wavelength-dependent intensity resulting from emission of energy by an excited molecule, combined with scattered and specularly reflected components. The degree of photoemission and the wavelengths at which it occurs are used to mathematically validate the substance being tested. The channel value is defined as a point on the returned-

energy curve that represents the intensity strength of emitted energy at a particular wavelength. The shape of the curve is considered to be unique for each drug.

Once the fingerprint was created and ready for use, it was stored in the device's signature library. Two primary evaluations were completed by the device to validate a given sample. First, the instrument compared the scanned sample's unknown signature with that of the known signature within the library. Comparison with a known signature identified whether the sample was the intended medication defined by the properties and acceptable variance for a known signature. Second, signal strength was used to validate its concentration. The amplitude of signal intensity was compared with set variables in the device to identify the concentration within predefined ranges. This resulted in the sample being either validated as matching the known standard or not validated.

The EPS device was calibrated daily with a control, which was a specially designed cuvette that provided a consistent spectral return. The manufacturer periodically used data from the control to determine if any component degradation had occurred and whether adjustments were necessary.

Sample preparation. We chose seven drug-diluent combinations for the study. Selection of these drugs was based on the literature on medication errors,¹ as well as on institution-specific reports. They were epinephrine hydrochloride 0.02 mg/mL in 5% dextrose injection (D5W), gentamicin sulfate 10 mg/mL in D5W, hydromorphone 0.1 mg/mL in bacteriostatic 0.9% sodium chloride injection, insulin 0.1 unit/mL in 0.9% sodium chloride injection, lorazepam 1 mg/mL in 0.9% sodium chloride injection, morphine sulfate 1 mg/mL in 0.9% sodium chloride injection, and vancomycin 10 mg/mL in D5W. Ten sets



of samples were prepared for each drug. A sample set consisted of various dilutions ranging from 10-fold above to 10-fold below the targeted concentration. With vancomycin 10 mg/mL as an example, the following dilutions were prepared as a sample set: 1, 5, 8, 9, 10, 11, 12, 25, 50, and 100 mg/mL. The only exception to the sample-set dilutions occurred if a drug could not be further concentrated (e.g., gentamicin, which is commercially available only as a 40-mg/mL solution, or four times more concentrated than the standard concentration of 10 mg/mL). Testing was performed twice weekly between November 2005 and March 2006. All sample sets were mixed by the same person to eliminate any interoperator variation. Each sample was labeled with drug name, concentration, and sample-set number to track the sample through the testing.

Process validation. To provide a process validation of the compounding technique and ensure the validity of the dilutions prepared, for each drug we selected two sample sets at random to send to the hospital laboratory for analysis. A 5-mL volume from each set at the targeted concentration was labeled appropriately and delivered to the laboratory. The results for the two samples of each drug were averaged. A 5% compounding error was considered acceptable; this also takes into consideration bag overfill that is removed for bulk-compounded items (e.g., vancomycin, gentamicin).

Machine scanning and data collection. After thoroughly mixing the contents of each sample syringe, we transferred a 1- to 2-mL portion to an unused disposable cuvette. The cuvette was then wiped with clean, lint-free gauze on all sides to remove any fingerprints or oils. Tests for all dilutions of a given drug were performed with the same test button on the instrument, as though the sample were actually at the targeted concentration. Data from the sample scans

were recorded electronically in the instrument, including date and time of the scan, observed result of the scan (validated or not validated), and channel value of the scan in a text file format. The channel values were transferred to an Excel spreadsheet (Microsoft Inc.) for analysis.

Cross-testing. To study the instrument's ability to distinguish among the test drugs, a sample of each drug at the targeted concentration was scanned as though it were each of the other drugs being studied. For example, a 1- to 2-mL volume of vancomycin 10 mg/mL was scanned by using the signatures of each of the six other drugs. These results were recorded by the device and transferred to an Excel spreadsheet.

Data analysis. The sample size necessary was determined by the assumed sensitivity and specificity of the instrument, as well as by the desired width of the confidence intervals around the sensitivity and specificity. We assumed that the device was 95% sensitive at the targeted concentration and 95% specific for all dilutions other than the targeted concentration. By using a sample size of 10, we were able to conclude with 95% confidence that our assumption was correct, as long as the percentage of samples that passed testing fell within $95\% \pm 13.5\%$. To measure specificity, we assumed that concentrations within 20% of the targeted concentration (80–120% of goal concentration) were acceptable.

Results

For all seven medications, the instrument correctly did not provide validation when the concentration was 5- or 10-fold higher than the targeted concentration or more than 50% lower. For samples at targeted concentrations, the machine correctly validated the samples in 100% of cases (100% sensitivity). All the drugs at 90% and 110% of targeted concentrations were validated 80–100% of the time. For gentamicin sulfate,

hydromorphone, and vancomycin, all the samples were correctly validated. Five of the seven medications at 80% of targeted concentrations were validated 80–100% of the time. Six of the seven medications at 120% of targeted levels were validated in 60–100% of cases. Eighty percent of morphine and insulin sample sets at 50% of targeted concentrations were validated; this result is outside the 20% range of acceptable error. Sensitivity and specificity for lorazepam were acceptable when compared with other concentrations of lorazepam. However, cross-testing found that 20% of lorazepam samples at the standard concentration of 1 mg/mL were validated as gentamicin. This problem was communicated to the manufacturer so that it could adjust the signature, and the problem was corrected.

Discussion

Our results indicate that EPS is capable of validating the correct drug and concentration when incorporated into the i.v. admixture process for the preparation of high-risk agents. The technology consistently validated the correct solution, while dependably detecting as invalid the wrong drug or concentrations that departed substantially from the targeted standard. A 20% range of acceptable error was chosen, since it would detect potentially catastrophic errors and enhance patient safety while minimizing false nonvalidations that could have occurred because of variations in compounding practice or EPS technique. In most cases, such an error would not have a serious clinical impact. The goal was to protect the patient from receiving the wrong drug or doses severalfold different from those intended. Further increasing specificity could produce false nonvalidations and potentially encourage staff to bypass the machine.

In our pediatric hospital we currently test 40–50 samples of patient-specific high-risk products each

day. Staff support and training were provided throughout the trial, and the program has been well received. Training involved brief instruction on drawing medication samples, using screen functions, and inserting cuvettes into the device. Designated staff leaders addressed technical support issues.

Overall workflow was not detrimentally affected by the new verification process. On average, 30–60 seconds is needed to perform all the steps necessary to validate one sample. This might be prohibitive if the technology was applied to all i.v. products, so we elected to use the device only for high-risk medications. Work processes were modified during the trial to accommodate the increasing numbers of samples that were tested. The addition of a label printer allowed pharmacy technicians to run samples and have evidence of validation for final review by a pharmacist prior to dispensing. This precluded the need for the pharmacist to come to the machine to verify each test result.

During the 18 months since the technology was implemented, five potentially serious medication errors have been detected and avoided. Two of the incidents involved bulk vancomycin solutions that were compounded with only half of the required amount of vancomycin. The device did not validate the samples, and the pharmacist retraced the compounding steps. In another incident, an incorrect amount of morphine was used to compound the final product, resulting in a concentration that was three times higher than intended. Another potential overdose was detected in the fourth incident, in which 10 mL of lorazepam 2 mg/mL was added to 20 mL of 0.9% sodium chloride injection instead of 0.5 mL of lorazepam 2 mg/mL. The fifth error involved a mixup of dopamine and dobutamine.

Several nonvalidations were initially observed with lorazepam. After

investigation, it was noted that these products were being prepared correctly but that, because of lorazepam's high viscosity, the drug was not evenly dispersed in the final product, resulting in what appeared to be an incorrect concentration. Thoroughly mixing the admixtures helped to avoid false nonvalidations. Awareness of this variation has improved the consistency of compounding practice.

Because the amount of returned energy is related to the concentration of the substance being tested, EPS is capable of validating that both the desired drug and concentration are present. Refractometry, another technique that has been used to validate liquid drug products, measures the degree to which the compound refracts light passing through it. Experience at our institution indicated that refractometry does not have sufficient sensitivity and specificity to distinguish among the many drugs and concentrations that we sought to test in the i.v. admixture setting. Refractometry also has some deficiencies in testing controlled substances sent to the operating room, since some critical drugs do not refract light in a manner that can distinguish them from water.

There appear to be several limitations to testing with EPS. Medications that do not fluoresce and those with weak signals within the ultraviolet spectrum, such as potassium chloride, cannot be verified with this technology. The instrument works only for drugs for which reliable signatures can be established. Heparin sodium is one example of a heterogeneous drug that has been difficult to create a signature for. Signatures differentiating various concentrations of heparin—particularly low ones—have not yet been established. While testing has demonstrated acceptable performance in distinguishing among drugs and concentrations, the technology may not be able to adequately distinguish errors due to the

incorrect diluent (e.g., gentamicin 10 mg/mL in 0.9% sodium chloride injection instead of in D5W). Signatures have been established only for a limited number of high-risk medications at this point; work is ongoing to develop more signatures and to refine some of those that are currently in test mode. The EPS device is not an analyzer; it only provides information about whether a sample matches a programmed standard concentration.

We are interested in using EPS to verify chemotherapy drugs, as they are certainly high risk. One of the barriers to this is that most chemotherapy doses are individualized on the basis of body weight or body surface area; EPS works best when there is a standard concentration of a product to compare against a known signature. Also, there is currently no way to maintain a closed system to protect pharmacy personnel from drug exposure.⁴ Despite these limitations, many of the high-risk products prepared today in hospital pharmacies appear to be suitable candidates for EPS.

More work is underway to test the device further and additional drug, concentration, and diluent signatures are being developed. Problems identified in this study for some of the signatures were communicated to the manufacturer for adjustments. Those signatures are currently being tested. The manufacturer is planning to release a second-generation device that has a larger library of signatures and that will reduce the integration times needed to run samples; a study similar to this one will be needed to verify sensitivity and specificity.

Conclusion

A tabletop EPS device demonstrated acceptable sensitivity and specificity for validating the identity and concentrations of selected high-risk i.v. medications compounded for pediatric patients. The device may help prevent clinically important

medication errors caused by inaccurate compounding.

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