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Mass Spectrometry Advances
Can Tandem and Time-of-Flight Combine Rather Than Compete?

By Frederick G. Strathmann, PhD

There is no denying the tremendous impact mass spectrometry (MS) has had in many areas of laboratory medicine thanks to its specificity in identifying targets from small molecules to intact proteins.

The many MS techniques available vary greatly in ways that require different skill sets and offer different advantages and disadvantages. Although quadrupole technology has dominated clinical MS recently, successful applications of time-of-flight (TOF) and quadrupole TOF-MS have challenged that dominance. Despite numerous journal articles, textbooks, and videos, both novice and advanced users can find it difficult to choose among technologies. This article focuses on ways to use TOF-MS in clinical testing that enhance the probability of success and describes its benefits and drawbacks.

Chromatographic Separation

MS by itself often cannot provide the specificity to identify a target compound. MS identifies a compound according the mass-to-charge (m/z) ratio, so it cannot differentiate between compounds with the same m/z ratio, such as isobars. For example, phentermine and methamphetamine are structural isomers—they have the same chemical formula but their atoms are arranged differently, and thus have the same mass. Other examples in toxicology that MS cannot differentiate include codeine and hydrocodone, morphine-n-oxide and oxymorphone, methylphenidate and normeperidine, and pentobarbital and amobarbital. Lots of non-drug compounds in biological matrices can also have similar m/z ratios.

For this reason, the vast majority of clinical laboratories incorporate chromatographic separation prior to analysis by mass spectrometry. In simple terms, chromatography aims to separate a sample into discrete fractions through the use of a stationary phase and a mobile phase. A compound that spends more time in the stationary phase takes longer to traverse through the chromatographic system, for a longer elution time. Conversely, compounds that prefer the mobile phase have shorter elution times. Each compound has a characteristic retention time in the chromatographic system, which provides one key parameter for compound identification.

Many laboratories also use a system that features a gas phase. Although many still maintain a gas chromatography single quadrupole MS system, most clinical MS is done using tandem or triple quadrupole mass spectrometry (MS/MS). In a tandem mass spectrometer, the first quadrupole filters gas-phase "precursor" ions based on m/z ratio, with the ability to resolve two compounds differing by 1 amu (for example, 286.1 from 287.1). After being filtered by the first quadrupole, the ions enter into a collision cell where they undergo characteristic fragmentation after colliding with an inert gas such as helium or nitrogen. The fragments or "product" ions are then filtered by the second quadrupole based on m/z ratio prior to being registered by the detector.

Tandem Mass Spectrometry

A tandem mass spectrometer can be set so the first and second quadrupole mass filters stabilize the flight of a specific m/z precursor and resultant m/z fragment from start to finish. The user can change these filter settings to monitor numerous combinations or "transitions." Clinical laboratories com-

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Tandem MS and TOF-MS

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monly monitor a primary transition and a secondary transition to identify a given compound. Users can also compare the abundance ratios between the two selected transitions to known values to provide another test of compound identification. Despite the specificity of MS/MS, the mass filtering involves an inherent limitation—it cannot measure the compounds it filters out. When only a small number of compounds are being monitored in a given assay, modern MS/MS instruments can cycle through the set points fast enough to obtain adequate data. But if the chromatogram is highly complex, such as in a comprehensive drug screen with a short chromatographic period, the time required to cycle between set points can result in low efficiency, poor sensitivity, and poor specificity.

Time-of-Flight MS

For these complex analyses, TOF-MS offers an alternative. At first glance, TOF-MS may seem foreign, but the principles are similar to those of MS/MS. In TOF-MS, gas-phase ions are separated based on m/z and the ions that reach the detector are counted; however, instead of flight stabilization for a single m/z at any given time, a TOF-MS sends a packet of a range of compounds into a drift or flight tube, where it is pushed by a voltage toward the detector. Small ions travel faster than large ions given an equal push.

The ions travel through a reflectron that serves as an ion mirror. This reduces the variations in the spread of energy that identical ions bring into the mass spectrometer that could contribute to poor resolution. A given ion's flight time to the detector is what translates into its m/z ratio and provides the specificity of TOF-MS.

Most TOF-MS instruments used in clinical settings can resolve compounds within 5 to 10 parts per million, translating into the ability to resolve a compound of mass 234.1234 from one of mass 234.1175. The high-resolution capability of TOF-MS and the capacity to transmit all ions present without mass filtering gives TOF-MS capabilities that MS/MS instruments lack. Rather than focusing on sets of transitions, a TOF-MS measures all the ions and stores data as dictated by instrument set points.

Further, although libraries can be used to pull out specific compounds for targeted testing, TOF-MS data can be interrogated retrospectively to look for compounds not originally considered. Past data can be used to determine the frequency with which new compounds are found, find new analytes to replace or supplement existing ones, and provide a potential avenue for clinical research investigations or semi-targeted discovery workflows.

Drawbacks of TOF-MS

If TOF-MS is so specific, why haven't all laboratories switched to it? Because a system that does not use fragmentation and allows for a high percentage of ion transmission is a double-edged sword. Like some of the systems discussed previously, TOF-MS cannot differentiate compounds with the same m/z ratio.

TOF data can include additional parameters, such as isotope spacing and isotope ratios, that can be used to build a compound profile to enhance specificity (Figure 1). Isotope spacing and ratios are predictable based on a compound's elemental composition and the known prevalence of naturally occurring isotopes, such as carbon-13 or nitrogen-14. However, in compounds with the same elemental composition, the isotope spacing and isotope ratios are also identical, so even with this information, the TOF-MS cannot resolve two such compounds.

Even more troublesome, an isotope of one compound can interfere with the measurement of another compound, which is the case with morphine and noroxymorphone.

Internal Standards

Another potential difficulty is the use of internal standards. For each compound being targeted, it is good practice to include an internal standard that contains deuterium substituted for hydrogen or carbon-13 for carbon-12 to ensure that the mass spectrometer can resolve the compound from the internal standard. However, extreme care is needed because each internal standard can potentially interfere with other compounds. For example, morphine-d3 (3 hydrogens replaced with 3 deuteriums) interferes with the second isotope of noroxymorphone.

Other challenges in implementing TOF-MS include a potentially complex data review process, large data file sizes, small peer groups of other users, and a lack of tried-and-true industry standards for quality set points.

As more laboratories explore this technology, a better understanding of what is needed to produce quality results will continue to evolve. But given its limitations, TOF-MS remains a problematic choice. In comparison, modern MS/MS instruments have incredibly fast cycle times that allow for a high number of mass transitions to be monitored. In addition, software continues to evolve in ways that also increase the total number of transitions that can be monitored.

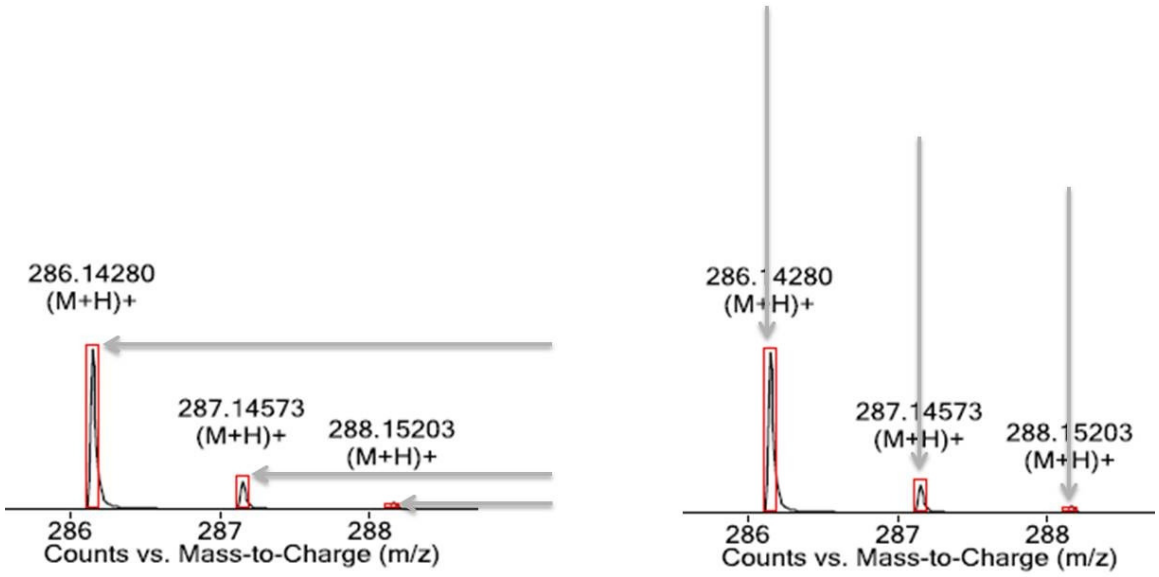

Figure 1. Isotope ratio and isotope spacing for a compound measured using TOF-MS

On the left, the arrows indicate the expected relative heights of the M+0, M+1, and M+2 isotopes for a representative compound. On the right, the arrows indicate the expected spacing between measured m/z ratios for the M+0, M+1, and M+2 isotopes for a representative compound.

Powerful Combination

Currently, there are no clear criteria for deciding between TOF-MS and MS/MS in regard to compound number and chromatographic time. The decision requires a clear understanding of the expectations for the proposed test. The specificity of MS/MS could allow for a shorter chromatographic time and higher throughput compared with TOF-MS. Many laboratories already have MS/MS instrumentation and expertise, so can easily calculate whether their MS/MS instrument can measure the compounds needed in the time desired.

However, TOF-MS is a potential replacement for the broad screening typically done by immunoassays, which have well-known performance issues and are often not readily available for all compounds of interest. Using TOF-MS as a qualitative screen could allow broad compound coverage, eliminate the specificity and sensitivity issues of many immunoassays, and eliminate the wait for vendor-supplied kits when new drugs emerge. Further, the combination of TOF-MS as a presumptive screening tool with the specificity of MS/MS for confirmation could present a powerful partnership of two technologies often considered mutually exclusive.

Quadrupole Time-of-Flight MS

Perhaps the best of both worlds can be found in the so-called hybrid instruments such as quadrupole time-of-flight mass spectrometers (QTOF-MS), which use an MS/MS arrangement but with a flight tube replacing the final quadrupole mass filter. In these instruments, the quadrupole can be used as an ion guide, the collision cell can be set to be inactive, and the flight tube can provide high mass accuracy measurements in a similar manner to conventional TOF-MS. As needed, the collision cell can be activated, the quadrupole can be used as a mass filter, and the product ions can be collected with high mass accuracy.

Rather than measuring sets of mass transitions at unit resolution, a QTOF-MS measures all product ions. The result is a characteristic fingerprint reminiscent of gas chromatography-MS using electron ionization, but with the added benefit of high mass accuracy. Not surprisingly, QTOF-MS instruments come with a higher price tag, have even less standardization of performance characteristics for routine clinical use, and feature higher data complexity compared with MS/MS.

Although QTOF-MS systems are high-powered with enormous capability, using them for routine clinical testing is probably out of reach for most laboratories and is arguably overkill for even the most complicated methods.

Conclusion

In summary, TOF-MS is still in its infancy in the clinical laboratory despite having been around longer than MS/MS. A better understanding of the strengths and limitations of TOF-MS is needed in order to achieve high standards. TOF-MS and MS/MS are both powerful tools, and the idea that a laboratory must choose between them is flawed. Instead, TOF-MS and MS/MS can be combined in a powerful partnership.

Each type of mass spectrometry has strengths and weaknesses that can potentially be offset by the

other. Rather than deciding which single type of MS to use, laboratories should focus on which type is most applicable to each situation. MS techniques have the potential to replace many routine chemistry tests, with, for example, TOF-MS overcoming many of the problems of immunoassays.

As MS technologies continue to develop, their use in combination could greatly advance laboratory medicine.

Learning Objectives

After reading this article, the reader will be able to list the techniques commonly used to ensure data integrity in time-of-flight mass spectrometry and describe the use of time-of-flight mass spectrometry in areas currently dominated by quadrupole mass spectrometry.

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Frederick G. Strathmann, PhD, is a medical director of toxicology and associate scientific director of mass spectrometry at ARUP Laboratories and assistant professor in the department of pathology at the University of Utah. Email: frederick.g.strathmann@aruplab.com.

ICP-MS' Versatility:

Technique Offers Advantages and Limitations in Elemental Analysis

By Peter Wegwerth, BS, and Melissa Maras, BA

Quantitative elemental analysis became an important part of toxicology and forensics with the introduction of atomic absorption spectroscopy (AAS) in the 1960s (1). In recent years, inductively coupled plasma optical emission spectroscopy (ICP-OES) and ICP mass spectrometry (MS) joined AAS as new techniques for elemental analysis. ICP-MS offers advantages over AAS and ICP-OES, particularly considering its different options for analysis and sample introduction.

Principle of ICP-MS

In ICP, the plasma is formed by applying a spark to argon gas flowing through the concentric channels of a quartz tube called a torch. It is then stabilized by a magnetic field generated by radiofrequency passing through a copper coil. When a sample is introduced, it is positively ionized by the plasma and travels through the mass spectrometer under vacuum pressure. The detector converts the ions to an electrical signal that the data handling system can read as a concentration (1). Figure 1 shows general instrument schematics for AAS, ICP-OES, and ICP-MS.

Advantages of ICP-MS

ICP-MS has several advantages over AAS and ICP-OES. First is its ability to perform rapid multi-element analysis. AAS relies on a light source that emits an element-specific wavelength; thus the light source must be changed for each element, which increases analysis time (1). Although ICP-OES is capable of multi-element analysis, there can be a long delay in making readings due to sample washout and the time required to reach equilibrium.

ICP-MS also offers lower detection limits, which can reach parts per trillion, compared with the parts per million of AAS and parts per billion of ICP-OES.

ICP-MS' quadrupole MS function separates elemental isotopes based on mass-to-charge ratio (m/z). This separation is accomplished by the simultaneous application of a direct current (DC) field and time-dependent alternating current (AC) of radiofrequency on opposing pairs of the four rods of the quadrupole. The DC/AC ratio is optimized to allow ions of a selected m/z to pass through while ions of any other m/z are ejected. (1). Quadrupole MS resolution can range from 0.3 to 3.0 amu but is most commonly set to 0.7 amu, which provides the best balance between selectivity and sensitivity. This technique is effective

for most low- and high-mass elements, but in the mid-mass range, polyatomic interferences can introduce overlapping m/z that the quadrupole cannot differentiate.

ICP-OES has an advantage over basic ICP-MS in the mid-mass range because it does not suffer from polyatomic interference. However, some techniques can be used with ICP-MS to chemically remove or physically separate the interferences. These include dynamic reaction or collision cell technology, triple quadrupoles, time-of-flight instruments, and magnetic sector field (SF). Figure 1 provides a general schematic of these techniques; Table 1 compares various techniques for elemental analysis.

Techniques to Remove Interferences

Instruments with cell technology can be used to overcome polyatomic interferences. This technology adds a second quadrupole (or octopole for collision cells) before the analyzing quadrupole and comes in three types: dynamic reaction cells (DRC), collision cells, and universal cells, which can operate as either a DRC or collision cell.

DRCs are most applicable with complex matrices in which reactive interferences can form. The DRC is filled with a reactive gas like ammonia (NH_3). The gas transfers an electron to potentially interfering ions, which makes them neutral and causes

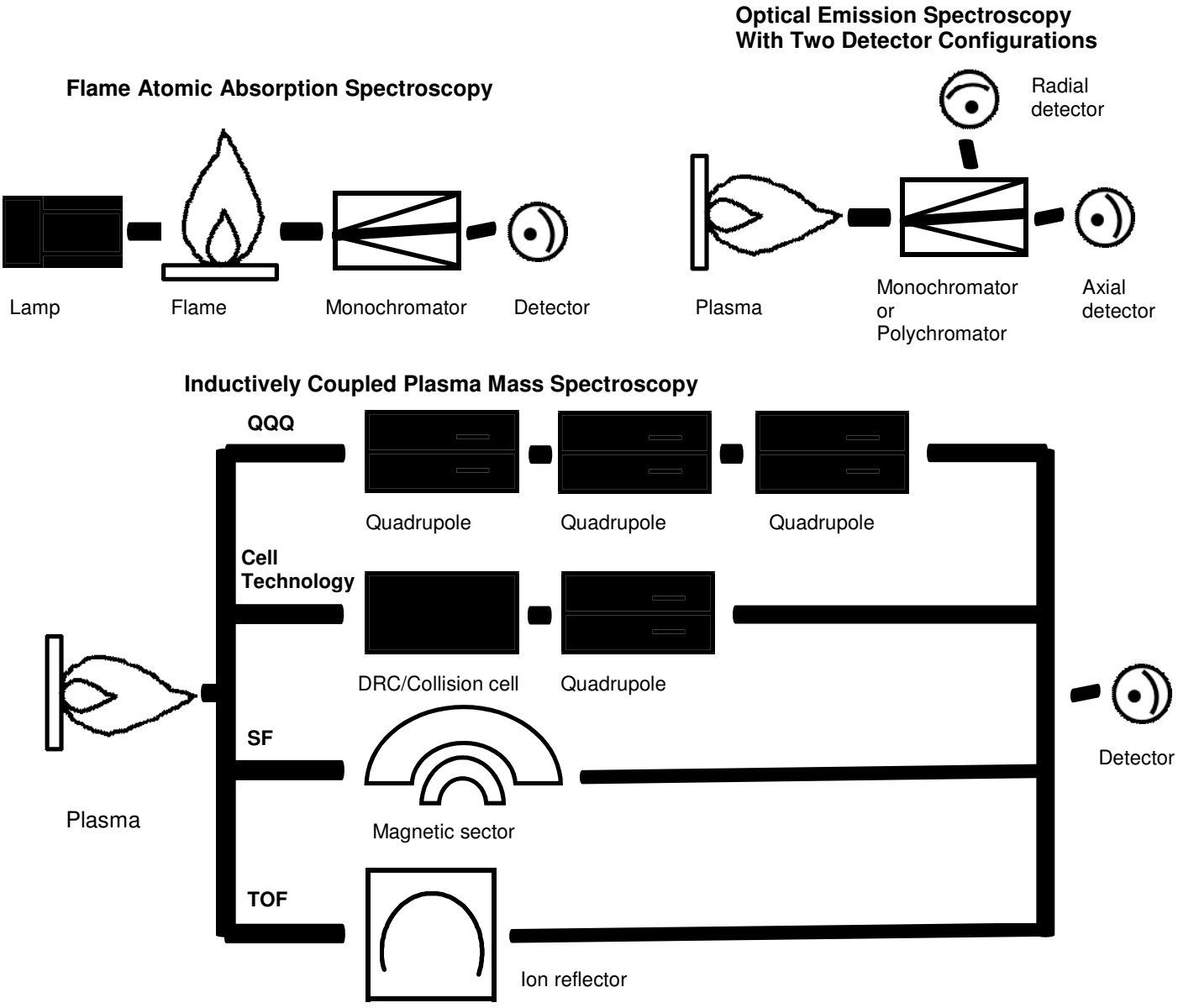

Figure 1. Schematics of Spectrometry Techniques
DRC = Dynamic reaction cell; QQQ = Triple quadrupole; SF = Magnetic sector field; TOF = Time-of-flight

Table 1. Performance and Cost of Elemental Analysis Instruments

Instrument	Typical Detection Limits			Multi-element Analysis	Interference Removal		Isotopic Elemental Analysis	Cost	
	PPM	PPB	PPT		Isobaric	Polyatomic		Purchase	Operating
AAS									
FAA								$10,000 to $50,000	<$10,000
ETA									
ICP-OES									
Radial								$50,000 to $100,000	<$10,000
Axial									
ICP-MS									
DRC								>$100,000	$10,000 to $50,000
Collision									
TOF									
SF									
QQQ									

Abbreviations: AAS = atomic absorption spectroscopy; DRC = dynamic reaction cell; ETA = electrothermal atomization; FAA = flame atomic absorption; ICP-OES = inductively coupled plasma optical emission spectroscopy; ICP-MS = inductively coupled plasma mass spectrometry; PPM = parts per million; PPB = parts per billion; PPT = parts per trillion; SF = magnetic sector field; TOF = time-of-flight; QQQ = triple quadrupole

Relative performance: Good Moderate Poor

them to be expelled from the system. For example, in the analysis of ^{56}Fe, $^{40}Ar^{16}O$ can be an interferent. The NH_3 transfers an electron to the ArO^+ to form neutral argon and oxygen atoms, which are ejected from the cell [$ArO^+ + NH_3 \rightarrow Ar + O + NH_3^+$] (3).

DRCs can also reduce interference by the elemental ion of interest reacting with the gas in the cell, which moves it to a new m/z, away from the interfering polyatomic ions. An example is the analysis of arsenic; arsenic can react with oxygen to form $^{75}As^{16}O^+$ at m/z 91$^+$ [$As^+ + O_2 \rightarrow AsO^+ + O$]. Both of these processes use a band pass filter to prevent side reactions between the reaction gas and sample matrix because such side reactions can lead to new interferences (1).

Collision cells can be used to reduce nonreactive interferences. These cells are filled with a nonreactive gas, typically helium, that collides with any ions present, reducing their kinetic energy. Because of their larger size, polyatomic ions have more collisions than elemental ions with the same m/z. More collisions cause them to lose more energy, so they cannot overcome the energy barrier to exit the cell and enter the quadrupole—therefore attenuating their ability to interfere (1).

For analyses that suffer from an abundance of interferences, triple quadrupoles can improve selectivity by introducing an additional quadrupole before the dynamic reaction or collision cell to reduce the number of ions transmitted into the cell (1).

Time-of-flight instruments are preferred for applications that have a simple sample matrix and require the acquisition of large amounts of data in a short time. In this technique, small packets of ions are injected into an ion reflector, where they are "reflected" back to the detector. The difference in the times it takes ions of different masses to reach the detector physically separates them, which allows rapid quantification of multiple elements (1).

Magnetic sector field is suitable for single-element applications in which an abundance of interferences are present and cell technology cannot achieve adequate attenuation. In this technique, a large electromagnet physically separates the ions. It can achieve a resolution down to 0.001 amu, but the increase in resolution can come at the cost of sensitivity (1). In addition, multi-element determination takes time because the instrument's exit and entrance slits must be physically moved to tune for different elements.

Sample Phase and Introduction

Sample phase is also an important consideration when deciding which system to use. Although AAS, ICP-OES, and ICP-MS can all analyze liquid samples, they cannot differentiate elemental species or oxidation states in these samples. For these applications, ICP-OES and ICP-MS can be coupled with reverse-phase high pressure liquid chromatography, ion exchange chromatography, or reverse-phase ion pair chromatography, although AAS cannot (1).

Gas chromatography can also be combined with ICP-OES and ICP-MS for the analysis of volatile and semi-volatile compounds in complex gases. An example of this is the speciation of mercury from off-gas chemistry, which is an important environmental concern (4).

Solids can be analyzed using laser ablation as part of the sample introduction. In this technique, the sample is exposed to a laser, turning it into an aerosol that is transported to the ICP-OES or ICP-MS via a carrier gas. Laser ablation can be used to analyze virtually any solid without dissolution while retaining high sensitivity (1).

Conclusion

When choosing an instrument for elemental analysis, it is important to consider current and future needs. Although AAS and ICP-OES are appropriate for many applications today, the ability to perform rapid multi-element analysis, expanded linear range, and compatibility with a variety of sample introduction options make ICP-MS more versatile.

Learning Objectives

After completing this article, the reader will be able to describe the advantages of inductively coupled plasma mass spectrometry compared with other elemental analysis systems as well as describe its configurations and sample introduction options.

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Peter Wegwerth, BS, and Melissa Maras, BA, are development technologists in the metals laboratory at the Mayo Clinic in Rochester, Minn. Emails: wegwerth.peter2@mayo.edu; maras.melissa@mayo.edu

ICP-MS in Practice

Technique Offers a Host of Clinical and Forensic Applications

By Nathan Hines, MLS(ASCP), Hiwote Woldeysus, BA, and Patrick L. Day, MLS(ASCP)

Elemental metals are ubiquitous in the environment. People are exposed through daily interactions with nature, occupations, implanted medical devices, and consumption of food, water, and medications. Exposure to these metals can have a variety of consequences.

Some metals, such as arsenic, lead, mercury, and cadmium, are toxins that can significantly impair biological processes. Others, such as cobalt, copper, zinc, and iron, are essential co-factors and components of cells needed to maintain normal homeostasis. Therefore, it is important to have effective ways to identify, quantify, and monitor these elements. The accompanying article by Wegwerth and Maras describes the technologies used to measure metals, focusing on the advantages and limitations of inductively coupled plasma mass spectrometry (ICP-MS). In this article, we will describe some forensic and clinical applications of ICP-MS.

Case Study

A 29-year-male entered an outpatient clinic complaining of diarrhea and weight loss. He had suffered regular diarrhea for more than a year and lost 10 kg in the past four months. His blood pressure was 147/102 mm Hg; pulse, 80 beats per minute; and temperature, 36.8 ºC. His basic hematology and renal tests were normal, but other tests indicated possible liver damage: His alanine aminotransferase (ALT), aspartate aminotransferase (AST), and ferritin were elevated. An in-depth history revealed no chronic alcohol use. Laboratory tests ruled out viral hepatitis. Eventually, a 24-hour urine test and liver biopsy for copper were performed to differentiate between Wilson disease and hemochromatosis (1).

Wilson disease is caused by a genetic defect in the copper efflux pump ATPase 7B that leads to copper accumulation in tissues at a level that can cause

organ damage (2). Symptoms include hepatic and neuropsychiatric dysfunction. Wilson disease can be diagnosed through a liver biopsy, with ICP-MS determining the copper concentration in a sample. A liver copper concentration greater than 250 µg/g dry weight and clinical symptoms such as Kayser-Fleischer rings, behavioral changes, and liver disease are indicative of Wilson disease.

Hereditary hemochromatosis is caused by gene-dependent abnormalities in proteins involved in iron absorption, storage, or modulation that result in tissue iron overload (3). Symptoms include liver cirrhosis and damage to the pancreas and heart. Although elevated serum iron, transferrin saturation, and ferritin all suggest hereditary hemochromatosis, these results are also present in other inflammatory liver disorders.

Genetic testing and liver biopsy can help confirm the diagnosis of hereditary hemochromatosis, with ICP-MS determining the iron concentration in the liver. A hepatic iron concentration greater than 10,000 µg/g dry weight is often associated with cirrhosis and is seen only in hereditary hemochromatosis or chronic transfusion-related iron overload conditions associated with treatment for thalassemia or sickle-cell disease (4).

Iron staining and periodic acid-Schiff staining with diastase digestion showed no hepatocytic iron or globules in the patient's biopsy sample.

His liver biopsy revealed a copper value of 1,360 µg/g dry weight. A value greater than 1,000 µg/g dry weight is considered virtually diagnostic of Wilson disease (1). The patient was treated with trientine, a drug that binds with excess copper so it can be eliminated via the kidneys. Since the treatment, the patient's diarrhea has resolved and he reports increased energy and appetite. He has regained about 5 kg (1).

This case study illustrates how the wide calibration range of ICP-MS allowed for accurate determination of copper, aiding in the diagnosis of this condition.

Forensic Testing and Occupational Monitoring

ICP-MS is also a valuable tool for forensic and occupational monitoring of whole blood, blood products, urine, hair, nails, and tissue in situations in which several toxic elements could be of concern.

In a forensic setting, analysis of hair and nail samples for toxic metals can aid in the determination of the cause and manner of death. For example, arsenic binds strongly with the sulfhydryl groups of cysteine found in the keratin of hair and nails (4). Hair or nail analysis can identify chronic exposure to arsenic, which can be particularly useful in decomposition cases when other samples are not available.

ICP-MS methods can also help in the determination of a sea drowning because strontium from sea water enters the body via the lungs, leading to strontium blood levels above a normal reference range (5).

The Occupational Safety and Health Administration recommends monitoring of workers who may be exposed to toxic metals from the smelting and refining processes in manufacturing steel, batteries, light bulbs, and more.

Therapeutic Drug Monitoring

ICP-MS can also be used to monitor patients taking therapeutic drugs that contain metals. For example, because of its cytotoxic properties, platinum is used in several chemotherapy regimens for various cancers (6). These treatments must be monitored to ensure that the appropriate therapeutic dosage is maintained. ICP-MS can rapidly determine trough and peak levels of these drugs in plasma, plasma ultrafiltrate, serum, blood, urine, and cerebrospinal fluid.

ICP-MS Interference

As with any clinical analysis, several interferences can lead to unreliable results. One type of interference of great concern in clinical specimens occurs when low levels of an element compete with a second element of interest in the ion path (7). This competition most typically occurs with patient samples that have a high concentration of iodine or gadolinium.

Because of their high masses, iodine and gadolinium dominate the ion beam and push the analyte of interest away from the beam. The resulting suppression of analyte signal decreases sensitivity. This kind of interference can be avoided through proper sample collection and close monitoring of the internal standard. For example, samples should not be drawn for at least 96 hours after a patient has had an MRI with contrast media. The suppression in internal standard signal indicates the presence of an interfering substance.

Conclusion

ICP-MS is a reliable way to test for multiple elements, with more clinical and forensic applications than we have space to cover in this article. Whether a clinician is looking for a clinical diagnosis, a medical examiner is attempting to determine the cause of death, or an employer is monitoring workers for exposure to toxic metals, ICP-MS is a useful and reliable way to identify, quantify, and monitor many elements.

Learning Objectives

After completing this article, the reader will be able to describe various applications in which inductively coupled plasma mass spectrometry can be used for forensic and clinical analysis of elemental metals.

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Nathan R. Hines, MLS(ASCP), is a technical specialist, Hiwote K. Woldeysus, BA, is a clinical laboratory technologist, and Patrick L. Day, MLS (ASCP), is a medical laboratory scientist, all in the metals laboratory at Mayo Clinic Rochester in Rochester, Minn. E-mails: hines.nathan@mayo.edu; woldeysus.hiwote@mayo.edu; day.patrick@mayo.edu.

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