Toxicology Testing and the Use of Rapid Test Kits

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Testing for drugs (prescription or illegal) in biological fluids is useful in the management of potential overdose patients, as well as other clinical situations. Historically, the laboratory used simple chemistry, or spot tests, progressing to thin layer chromatography, laboratory-based immunoassays and specific chemical assays, gas chromatography/liquid chromatography coupled with mass spectrometry, and rapid test kits or Point of Care Test (POCT) devices. Modern toxicology laboratories in North America today still use immunoassays and specific chemistry tests, but sophisticated mass spectrometry systems and minimal sample pre-treatment methods are the gold standard in the opinion of toxicologists.

Knowledge of the specific substances involved in an overdose case can certainly be valuable to the medical team in determining and delivering treatment as rapidly as possible, particularly if an antidote is available for the toxin in question. In the past (and even in some labs today) mass spectrometry was employed to perform broad screens for drugs in patients presenting with suspected overdose (comprehensive drug screens). The limitation with such testing, even with today's modern equipment and methods, is that the turnaround time to produce results is not rapid enough to influence clinical decisions and treatment. Medical teams in emergency rooms evaluate patients on the basis of their signs and symptoms, plus any other available history or evidence, looking for toxidromes that suggest the class or type of drug or toxin involved, in order to provide lifesaving treatment as soon as possible. For example, if the patient has the typical signs and symptoms of an opioid overdose (pale and clammy skin, constricted pupils, limp body, purple/blue fingernails or lips, gurgling/vomiting, unresponsive/coma, respiratory and cardiac compromised/failure), or if this is even suspected, multiple doses of naloxone (Narcan) will be given and if the patient recovers the diagnosis is made.

Intensive supportive therapy, including mechanical ventilation, is used to keep the patient alive, while the clinical diagnosis progresses or until the effects of the drug are reduced, or an antidote has eased the symptoms. For the most part comprehensive drug testing, including that based on mass spectrometry, is not useful to guide clinical intervention for emergency overdose patients. Given these limitations, emergency room physicians and medical toxicologists recommend to evaluate emergency overdose patients on the basis of their signs and symptoms and treat patients with supportive measures as a first approach, unless rapid laboratory testing can identify a potential toxin with a high degree of certainty and an antidote is available (Christian et al., Clin. Tox. 10-21, 977-980, 2017; Stellpflug et al., J of Emerg. Nurs. Vol 46 (6), 923-931, 2020) Journal of emergency nursing, Vol.46 (6), 923-931, 2020).

However, specific chemical testing for salicylates, acetaminophen, ethanol, blood gases and basic chemistry parameters can be very useful, particularly where the results can be provided quickly (in less than an hour), are quantitative, and a specific antidote is available. In Alberta, the Toxicology Working Group, advising Alberta Precision Laboratories (the provincial laboratory service network), drafted a guideline for clinicians after a detailed investigation and consultation, stating, "Qualitative Toxicology Testing in an Emergent setting or situation is not recommended because it has not been shown to impact management or disposition of patients". While comprehensive drug testing is not considered useful for the emergency managing overdose patients, there is potential value in collecting patient samples, particularly early in the presentation before drugs may be metabolized or therapeutic medications can confuse test results. Such samples can then be tested as routine samples, if needed, with less impact on laboratory resources. Indeed, these results can be useful in confirming the clinical diagnosis and specific drugs involved, allowing for identification of trends in drug abuse, guiding potential improvements to medical care, and even influencing government action to address drug abuse. My laboratory has implemented a monthly report on the number of drug tests performed, the origin of the samples, and the drugs detected. Such information can be useful in the development of strategies to address drug abuse, and refine and improve the detection and management of overdose cases.

POCT devices, that typically use immunoassay technology to detect drugs, are widely used for drug testing applications, and may appear to be useful in managing overdose patients, particularly because of their technical ease of use and rapid test results, but there are many limitations. POCT devices are only able to detect a small number of the huge spectrum of legal and illegal drugs available, and as well many substances are known to cause false positive results with immunoassay tests, thus false negative and false positive results with POCT devices can be problematic. POCT devices do not have the sensitivity and specificity required to detect important, often very low levels of some drugs in biological fluids, as compared to MS systems. When considering a POCT, or any immunoassay-based drug test, it is important to recognize that not all test systems perform equally and their performance needs to be evaluated. Different manufacturers' assays for the same drug can be based on antibodies with different sensitivity, specificity and cross reactivity with the primary drug, metabolites and other substances, leading to widely different results when using different devices. For example, a test that detects only fentanyl would not be as sensitive or specific at detecting fentanyl use as a test that detected both fentanyl and the nor-fentanyl metabolite. POCT devices, like all immunoassay drug tests, are often directed at the family of drugs (opioids, amphetamines, benzodiazepines, barbiturates, etc.) and a positive result does not identify which specific drug in the family is actually present, as can be achieved with MS testing.

Be wary of sales people, or others, who minimize the technical challenges of using POCT devices for drug testing, and claim that such devices are "fool proof". In laboratories in North America, Laboratory Accreditation agencies have determined that all POCT testing is under the jurisdiction of the laboratory, even testing that is performed by non-laboratory staff, such as medical staff, nursing staff or others. As such it is the laboratory that is responsible to ensure that POCT drug testing devices are implemented and used appropriately, including test evaluation/validation, staff training, standard operating procedures, and appropriate internal and external quality control. That is not to say that POCT devices do not have a place in other types of drug testing aside from guiding the management of overdose patients. A warning regarding the potential problems that can be associated with the improper use of POCT devices is illustrated by a recent report in the New York Times of more than 1,600 inmates unjustly penalized based on incorrect use of rapid drug tests (NYT, Jan. 5, 2022).

Having outlined the limitations of POCT devices and immunoassay testing in emergency overdose testing, these devices do have applications in other non-emergency toxicology testing, when used appropriately and ideally when MS is available to confirm positive results (ie. non-emergency settings, psychiatric patients, pain management, drug treatment, employment drug testing, etc). However, it is important that laboratory toxicologists work with clinicians to determine what their testing needs and goals are, and if POCT/immunoassay testing will be appropriate, and establish the criteria under which testing can be used. Thereafter, laboratory toxicologists need to be available to provide advice and consultation to clinical staff on the use and interpretation of tests. Obviously, the evaluation and validation of POCT/immunoassays is the responsibility of the laboratory, as it would be for any other test. A cardinal rule with POCT testing is to always confirm a positive result by another more specific testing method, which is typically a mass spectrometry device. Given that MS confirmation is not feasible in all circumstances, a comment indicating that testing was performed by immunoassay, and was not confirmed by MS should be clearly added to the results.

It is understood that mass spectrometry is not available in many labs, even in North America, never mind in developing countries. These systems are expensive to purchase, maintain and operate and require a high level of specific staff expertise. In developing countries that can find the funds to purchase MS systems, finding qualified operators can be a limiting factor. Another problem is the lack of vendor support for systems to respond to the not infrequent technical problems and the routine maintenance that MS systems require. The most sophisticated equipment is useless if it does not have qualified staff to operate it and maintain and repair it. I recognize the serious limitation that these places on toxicology testing in developing countries, and innovative solutions are required.

Poisoning from alcohols, such as methanol, isopropyl alcohol, and ethylene glycol, presents a serious problem in North America and in many developing countries (Nekoukar et al., Annals of Medicine and Surgery, 06-01, Vol 66, 2021). Testing for alcohols is relatively quickly and easily accomplished by gas chromatography, and ethanol can also be conveniently measured by specific chemical methods. Again, gas chromatography systems are not readily available in most small rural laboratories in North America as well as in developing countries. An alternative is to use pH, anion gap and osmolal gap to screen for the presence of a toxic alcohol. There is mixed opinion on the specificity and sensitivity of this approach particularly in cases with early presentation, and it is certainly not comparable to gas chromatography (Krahn and Khajuria, Clin. Lab. 57, 297-303, 2011). A minimal requirement for implementation of this approach would be laboratory validation of the cut-off values and not simply using literature values. Small differences in the test methods used to calculate the anion/osmolal gap can result in significant differences in results between laboratories, and invalidates the application of reference ranges from another laboratory. It is also important to note that osmolal gap can only be calculated from measurements made using freezing point depression as opposed to a vapor pressure osmometer (Rifai et al., Tietz textbook of clinical chemistry and molecular diagnostics (sixth edition) Chap 41: 837-838, 2018). One possible benefit of this method may be to at least reduce the number of samples that need to be tested by a specific chromatographic method, if applying a wider cut-off range.

In summary, toxicology testing can be valuable in the diagnosis and management of drug overdose and drug use. While clinical utility in emergency settings is limited, it is useful in other situations, particularly when MS testing is available. The use of POCT devices without MS confirmation may be the only alternative to many laboratories in developing countries, and this type of testing should be implemented with a thorough understanding of the limitations, device evaluation/validation by the laboratory, and ongoing communication and support for clinical groups using the test results.