Comprehensive Toxicology Screening in Clinical and Post mortem Toxicology

Dr. Eric J.F. Franssen,
Hospital Pharmacist and Clinical Pharmacologist and Toxicologist, OLVG Hospital, Amsterdam, the Netherlands

Scope of the lecture:
This presentation will deal with state-of-the art analytical techniques that can detect drugs of abuse, novel designer drugs as well as potential overdoses of conventional drugs in patients. These techniques do shorten turn around times and make toxicology screening in clinical situation feasible. Further, we will address what skills are needed to obtain relevant results with these techniques and how to interpret the data to provide physicians at the Emergency Department and Intensive Care Units clinical relevant information that will help to select the best treatment of intoxicated patients.
In addition screening methods for post mortem toxicology will be addressed. How to design an extensive toxicological screening in post mortem blood and urine?

Learning objectives:
1. Drugs screening in clinical toxicology: what laboratory and screening techniques should be available in a clinical setting. How to apply LC-MS toxicology screening in a clinical setting. This point will be illustrated with spectacular real life complex cases.
2. What clinical impact may comprehensive toxicology screening have in improving patient management?
3. How to apply toxicology screening in post mortem toxicology? This point will be illustrated with real life cases.

Extended abstract:
What laboratory techniques and toxicology screening should be available in our hospitals and toxicology laboratories? For instance, the emergency department (ED) of OLVG hospital in Amsterdam is the busiest ED in the Netherlands. The ED of OLVG hospital in the Centre of Amsterdam receives approximately 50,000 patients annually. For a proper diagnosis and treatment in the ED, it is important to know whether the patient's condition is caused by drugs of abuse (DOA) or other substances. The clinical presentation of the patient may be the result of unintended (over)use of medicines. These cases can lead to serious adverse effects [1, 2].
In most hospitals in the Netherlands the hospital pharmacy is available for toxicological testing in blood and urine. At the ED of OLVG hospital a rapid triage is facilitated by a point-of-care test for drugs of abuse. Apart from the POCT, traditional laboratory methods are available at the central laboratory for confirmation analysis and/or quantification in blood/serum. Laboratory methods are important for the treatment of patients with potentially serious intoxications. On the other hand, it is also described that a laboratory result has little effect on patient outcome. There is anecdotal evidence that lab tests are misused and overused by clinicians [3].
An overview of laboratory methods for blood and urine is presented that should be available for the care of poisoned patients in the ED in the Amsterdam hospital setting (Table 1). It is also discussed in which conditions these methods could be optimally used. Furthermore, a distinction can be made between assays which should be available in all hospitals 24/7 and assays where other measures may be taken.
It is concluded that several (point-of-care-) laboratory tests should be available 24/7 in hospitals, because they may change patient management. Other tests may be postponed until

working hours the next day and possibly sent out to an external laboratory. Toxicological screening of recreational drugs seems most meaningful in a clinical setting in patients, who are unconsciousness and in patients with psychiatric and neurological symptoms. The tests are less helpful in patient who admitted their drug abuse at ED presentation. With this information ED physicians may use these tests more effectively.

On the other hand, a comprehensive toxicology screening in post mortem toxicology should cover most relevant substances since an absolutely complete screening is not possible and an almost complete screening is almost unaffordable. Therefore screening should be a smart combination of laboratory techniques that are technically feasible, can be routinely performed and are cost effective.
Thus far, the technical development from High Performance Liquid Chromatography (HPLC) to Ultra performance-LC made it possible to separate many more substances in a gradient within 10-15 minutes. Also the reproducibility of mass spectra obtained from a liquid chromatographic run has improved. It is possible to make spectral libraries that can be exchanged between laboratories. Until recently this was only possible with mass spectra obtained from gas chromatography.
Spectra can be obtained at different ionization voltages on a single quadrupole MS. This enables that detailed spectra can be obtained for a library search and subsequent toxin identification. Another possibility is the use of an Ion Trap MS and performing MS to the second or a higher order. Ion trap MS makes fragmentation less dependent on the composition of the LC-eluent, resulting in libraries that are interchangeable.
For both techniques validated software is available for a quick and automatic library search of all the peaks in the chromatogram, reducing the time necessary for the LC/MS-operators to evaluate results.
These MS techniques are relatively cheap as compared to e.g. the TOF-MS technique. In addition, the LC-MS equipment can also be used for other (routine) purposes, e.g. therapeutic drug monitoring in a clinical laboratory during the time t the LC-MS machine is not needed for toxicology screening. This makes LC-MS more cost effective.
In conclusion, for comprehensive toxicology screening the new generation LC-MS toxicology screening methods enable high quality rapid, extensive and cost effective (post mortem) toxicology analyses. The LC-MS procedure has proven its value already in various post mortem cases showing sometimes unexpected results. However, toxicologists should still be aware of false negative findings. In this regard, validation of negative findings should get more attention.
This kind of fast and comprehensive procedures can also play an important role in a clinical setting. This approach can be of added value in determining the cause of death as well as the cause of the clinical status of a patient in hospital.
Clinically trained toxicologists and/or clinical pharmacologists may help in interpreting the results and in deciding in what cases quantification of potentially toxic substances might be relevant after qualitative detection, either in a clinical setting or a post mortem setting.

References

1. Lager PS, Attema-de Jonge ME, Gorzeman MP, Franssen EJF. Toxicology screening tests for drugs of abuse help in diagnostics but have little influence on treatment.
<Toxicologische screeningtests voor drugs of abuse beïnvloeden de diagnose maar hebben beperkte invloed op de behandeling.> Pharm Weekblad 2013;7(1): 2-5. Date of Publication: 18 Jan 2013.
2. Attema-de Jonge ME, Peeters SYG, Franssen EJF. Performance of Three Point-of-care

Urinalysis Test Devices for Drugs of Abuse and Therapeutic Drugs Applied in the Emergency Department. J Emerg Med 2012; 42 (6): 682-691
3. Watson I. Laboratory analyses for poisoned patients: joint position paper. Ann Clin Biochem 2002; 39: 328-339.
4. Local Dutch guidelines. Nederlandse Vereniging van Ziekenhuisapothekers; Toxicologische behandelinformatie [Internet]. [Cited on 31 Mar 17] Available from: www.toxicologie.org
5. Truven Health Analytics Micromedex Solutions [Internet]. [Cited on 17 Apr 17] Available from: http://www.micromedexsolutions.com

Table 1. Laboratory tests in blood/urine that should be available for intoxicated patients [3, 4, 5]

Laboratory test for	Antidote or specific treatment?	Haemodialysis or other extracorporeal method?	Cardiac symptoms	Neurological symptoms/ unconsciousness	Organ failure?	Frequent intoxication?	Acute†	Not acute‡
Acetone	-	+	-	+	-	-	X	
Acetylcholinesterase inhibitor	+	-	+	+	-	-	X	
Antidiabetic agents	-	-	-/+	+	-	+/-		X
Antipsychotics	+/-	-	+	+	+/-	+	X	
Arsenic	+	-	-	+	+	-	X	
Baclofen	-	+	+	+	+	-	X	
Carbamazepine	+	-	+	+	+	+/-	X	
Digoxin	+	-	+	+	-	+/-	X	
Drugs Of Abuse (POCT)	-	-	+	+	+	+	X	
Ethanol	+	+	+	+	+	+	X	
Ethylene glycol	+	+/-	+	+/-	+	+/-	X	
GHB (POCT)	+/-	-	+	+	-	+	X	
Lead[ʿ]	-	+	-	+/-	-	-	X	X
Lithium	-	+	+	+	-	+	X	
Mercury[ʿ]	+	-	+	+	+	-	X	X
Methanol	+	+/-	+	+	+	+/-	X	
Methotrexate	+	+/-	-	-	+	-	X	
NSAIDs	-	+/-	-	+	+	-		X
Paracetamol	+	-	-	+	+	+	X	
Paraquat	-	+/-	+	-	+	-		X
Phenobarbital	-	+	+	+	+	-	X	X
Salicylate	+	+	-	+	+	+/-	X	
SSRI	-	-	+	+	-	+		X
Theophylline	+	+	+	+	+/-	-	X	
Toxicological screening	**?**	**?**	**+**	**+**	**?**	**?**	**X**	
Tricyclic antidepressants	+	-	+	+	-	+	X	X
Valproic acid	-	+	-	+	-	+/-	X	
Verapamil	+	-	+	+	-	-	X	

† Tests that should be available 24/7 and should be performed within 2 hours.

‡ Test assays that could be performed next day, include both common assays that are frequently used, and more specific chromatographic assays.

ʿIn most cases a chronic intoxication and not acute laboratory testing.