



How to use toxicology screening tests

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Introduction

The evaluation of poisoned patients presenting to the hospital predominantly relies on clinical assessment based on the history of ingestion/exposure and clinical symptoms/signs.¹ The role of toxicological screening is controversial. In the emergency department (ED), a toxicology screen (TS) can be used to detect a substance that causes the clinical features in an individual. Therefore, as a diagnostic test, the term 'screen' can be misleading. A toxicology screen generally involves qualitative detection of specific drugs or metabolites in biological specimens. Detection indicates that a substance is present; however, it does not indicate whether a patient's symptoms/signs are caused by the presence of this substance, and it is important to exclude other causes. Therefore, a toxicological screen performs poorly as a diagnostic test.²

In addition to a general TS, there are specific drug/chemical assays that can be used to guide clinical management of poisoned patients (see box 1).³ These are used to measure the concentration (or 'level') of a drug/chemical, and are the most useful type of screening used to manage a poisoned patient. The poisonings for which these are useful are those in which the serum concentration of the drug/chemical correlates to the clinical effects and toxicity, and will either determine treatment (eg, N-acetylcysteine treatment in paracetamol poisoning) or help guide it (eg, urinary alkalisation in salicylate poisoning) (box 1). These tests are ordered selectively when particular drug exposures are suspected, either on the basis of the history, or through characteristic clinical features.

The decision to use a toxicological screening test depends on clinical features, the suspected substances involved and the influence it may have on patient management. This paper presents the evidence for the role of toxicological screening in paediatric practice.

Physiological background: what is a toxicology screen, and how is it conducted?

A TS involves multiple tests performed on one or more biological specimens to determine whether drugs/chemicals are present. The extent of the screen and the number of drugs/chemicals included depends on the laboratory. Generally, the screen tests for common pharmaceuticals and/or several commonly abused recreational drugs (and/or their metabolites) including opioids, cocaine, cannabis, amphetamines and benzodiazepines. Hospital laboratories vary in their capabilities, some more able to perform assays for numerous drugs on biological specimens, including pharmaceuticals, recreational drugs and chemicals, such as toxic alcohols (eg, ethylene glycol, methanol) and novel recreational drugs.

Suitable biological specimens in paediatrics

Testing for drugs in different biological specimens offers many advantages, the most important of which is objectivity. In children, a variety of samples can be used, including venous blood, umbilical cord blood, urine, hair and meconium. Both venous and cord blood specimens will yield quantitative results giving a concentration of a drug—this is most useful for substances with a low volume of distribution for which the blood concentration correlates with overall body burden. Urine specimens supply qualitative data (presence or absence) and are suited for detecting drugs with a large volume of distribution and for confirmation of exposure. Although quantitative analysis can be undertaken on urine specimens, these cannot be used to guide treatment and generally, therefore, qualitative analysis, for example, an immunoassay, is used. These tests have good negative predictive value; however, positive results need to be interpreted with caution. Positive screening has a high sensitivity, but can lack

Box 1 Quantitative drug assays that determine or guide treatment

Drug concentrations that determine treatment
Paracetamol
Drug/chemical concentrations that guide treatment
Anticonvulsants (carbamazepine, phenytoin, valproate)
Aspirin
Carbon monoxide
Digoxin
Ethanol
Ethylene glycol
Iron
Methaemoglobin
Lead
Lithium
Methanol
Theophylline

specificity due to the inherent technical difficulties that are common with immunoassays, for example, interference by other pharmaceuticals, cross-reactivity with drug metabolites and with structurally similar substances (over-the-counter cold preparations cause positive results for amphetamines). It is therefore important that initial screening results are confirmed by further specific testing using a technique such as gas chromatography with mass spectrometry. This confirmatory analysis is labour intensive, requires specific skills, is expensive and time consuming. Therefore and because, generally, the management of patients with recreational drug toxicity can be guided by clinical features, confirmatory analyses are not routinely undertaken in either adults or children with acute recreational drug toxicity.

Although blood and urine are typically used for toxicological screening, the presence of drugs in these fluids is generally short-lived. The time limit for detection varies, but is generally less than 24 h for parent drug, although metabolites may be detectable over longer periods. Therefore, detection becomes limited by time from exposure, and the use of alternative specimens may be more appropriate if confirmation of drug use is required at a later stage.⁴ This is especially true for newborns whose mothers have abused drugs during their pregnancy. In such instances, neonatal hair can be used to assess chronic drug exposure. Its advantages include ease of collection, specimen stability and a protracted window of drug detection.⁵ At the time of hair follicle formation, drugs can be incorporated into the hair shaft and remain in the shaft indefinitely, and can therefore be subjected to analysis.⁶ Hair grows at a rate of approximately 1 cm/month, therefore, analysis of sequential segments can provide an estimate of drug exposure over time.⁶ Neonatal hair begins to form at approximately 20 weeks of gestation, and like adult hair, will incorporate drugs present in the foetal circulation.^{7 8}

A limitation of adult hair analysis is the possibility of hair surface contamination from the environment which is not an issue in testing a newborn's hair if sampling takes place immediately postpartum and prior to discharge from hospital.

Toxicological testing may also be performed on meconium. Meconium begins to form at approximately 12 weeks of gestation on the initiation of foetal swallowing.⁹ The mechanism by which drugs are deposited into meconium is not clear. When a foetus is exposed to drugs through maternal consumption, it excretes them into bile/foetal urine into the amniotic fluid. Drugs are secreted into meconium by deposition from bile or swallowing of amniotic fluid.¹⁰ As meconium is not excreted in utero, it can be used as an estimate of in utero drug exposure as it is considered to be static once deposited in the foetal intestine.¹¹ Therefore, it can provide a longer retrospective view of foetal exposure than that afforded by blood, urine and even the newborn's hair.¹⁰

What procedures should be instigated once biological samples have been taken from a suspected case of deliberate paediatric poisoning?

The documentation of the presence of an illicit drug in a newborn, infant or adolescent can be challenged by the mother or family. Furthermore, reporting of positive findings to local authorities may result in issues relating to child custody, therefore, special care in performing and reporting tests is required. This may require a chain-of-custody documentation which provides proof that the specimen has been maintained appropriately and not been inappropriately interfered with. Details relating to those who handled the specimen, right from the specimen collector to the person responsible for the specimen disposal, should be recorded. The time and reason for each change in custody (ie, transfer from person to person) should be recorded. Aliquoting of the sample needs to be fully accounted for, and laboratory areas where processing, analysis and storage are involved, should be secure with restricted access only to those appropriately authorised individuals.

Clinical indications

Is a toxicology screen indicated in every newborn has signs or symptoms compatible with substance abuse?

The impact of prenatal drug abuse on neonatal health and development has been well documented and remains a major health concern.^{12–14} Rates of prenatal drug use determined by maternal reports and biological specimen analysis range from 3.4–31% for cocaine, 1–12% for cannabis, 1.6–21% for opiates and 0.1–4% for ethanol in general populations and those with a history of current/previous drug use.¹⁵ In the short term, newborns exposed to substance abuse during

Box 2 Example guideline for identifying at-risk newborns of prenatal drug exposure²²

Indications for newborn toxicology screening for prenatal drug exposure

Maternal factors

Infants whose mothers have any of the following:

- A. History of drug abuse in present or previous pregnancies
- B. Limited/no prenatal care
- C. History of hepatitis B, AIDS, syphilis, gonorrhoea, prostitution
- D. Unexplained placental abruption
- E. Unexplained premature labour

Newborn factors

Infants who have any of the following:

- A. Unexplained neurological complications, for example, intracranial haemorrhage/infarction, seizures
- B. Evidence of possible drug withdrawal, for example, hypertonia, irritability, seizures, tremulous, muscle rigidity, decreased or increased drooling
- C. Unexplained intrauterine growth retardation

pregnancy may develop central nervous system irritability, decreased growth parameters and severe withdrawal symptoms.^{13 16–18} In the long term, effects include sudden infant death syndrome, abnormal neurocognitive/behavioural development and child abuse/neglect.^{19–21} Infants at high risk of substance exposure (box 2), therefore, need to be reliably identified (and followed up) when suggestive clinical features are present, such as unexplained neurological symptoms and/or symptoms of possible drug withdrawal. Previously, research groups have developed guidelines that identify maternal and newborn factors associated with substance abuse (box 2). Tested prospectively, these have demonstrated 89% sensitivity in confirming the association of specific maternal characteristics with maternal cocaine use.^{22 23} Toxicological screening performed in this way removes the bias in physician-ordered tests, therefore protecting their clinical decision. It reduces costs by avoiding universal screening and allows improved identification of newborns exposed to prenatal substance abuse.

Does a negative urine toxicology screen from at-risk newborns exclude maternal substance abuse during pregnancy?

Drug testing is one of the only methods of definitively identifying in utero drug exposure, as reliance on maternal history of drug use may prove unreliable.²⁴ Toxicological screening on neonatal blood and urine has a limited window of detection and reflects only foetal drug exposure during the previous hours or days before collection, and not chronic exposure. At times, sufficient neonatal plasma can be difficult to collect, and other matrices, for example, urine, is preferred.²⁵ Although less invasive, the drawback of

urine collection is that drugs clear rapidly from urine, and so the time required for successful collection is critical.²⁶ False negatives are therefore possible, and so a negative urine screen cannot definitely rule out maternal prenatal substance abuse.⁵ Furthermore, there are no recommended thresholds for testing clinical samples in laboratories. Adopted thresholds used in workplace drug testing may be too high versus the lowest detectable limits, contributing further to false negatives.

Toxicology screening for chronic drug use during pregnancy can be carried out on high-risk newborns by using meconium, or hair.¹⁴ For detecting first-time drug use by the mother just prior to delivery, meconium may give a false negative if the drug tested for has not had time to deposit in the meconium. In these cases, screening requires both urine and meconium analysis to cover potential time periods from drug exposure. Compared with meconium, hair can provide a chronological breakdown of drug exposure with the ability to differentiate between single/occasional and repeated drug exposure. However, the analysis of a newborn's hair is technically demanding and, therefore, only available in a few specialised laboratories.

Will the use of intrapartum opioids influence a newborn's urine toxicology screen?

Analgesics, such as opioids, are often used during labour and the immediate post-delivery phase for medical management of maternal pain, neonatal pain after delivery and maternal chronic medical conditions. Opioids can be divided into distinct groups; naturally occurring (morphine, codeine), semi-synthetic (heroin, oxycodone, pethidine) and synthetic opioids (fentanyl, methadone, tramadol). Synthetic opioids show little or no cross-reactivity in routine opiate immunoassays. Semi-synthetic opioids derived from morphine will show variable cross-reactivity, the extent of which depends on the manufacturer of the immunoassay. Clinicians need to be aware of the poor detection of these opioids, and that a positive test may not relate to the medical use of opioids during or around the time of labour. Additional tests would be required to exclude opioids used in pain management during labour.

Is toxicology screening of value in young children admitted to the emergency department with an apparent life-threatening event?

Children are exposed to toxic substances more frequently than any other age group.²⁷ Annual statistics taken from the American Association of Poison Control Centres for 2009–2010 show that 51.9% of total paediatric exposures (approximately 1.6 million) were in children <6 years old, and 38.9% in children ≤2 years old.²⁷ The majority are unintentional, small ingestions that do not result in significant clinical features. However, a small minority are potentially life threatening. From the same data, 6.8% of total deaths (1158 deaths) occurred in paediatric patients, with

1.8% occurring in those <6 years old, and 1.4% occurring in those ≤ 2 years old.²⁷

It is, therefore, important to consider a toxicological aetiology in infants with unexplained symptoms/changes in behaviour as an apparent life-threatening event (ALTE). The diagnosis of an ALTE is often not immediately evident; however, poisoning, intentional or unintentional, has been described as a cause in a number of cases.²⁸ In a systematic study of 274 children <2 years old presenting to the ED with an ALTE, a comprehensive urine TS was completed.²⁹ Results of 8.4% were found to be positive with clinical findings that were thought to represent a possible cause. Furthermore, 4.7% of screen results were positive for an over-the-counter cough and cold preparation; however, the finding was not compatible with the respective drug history and was not admitted to being given by the child's carer. While such poisoning in young children may inadvertently occur through breastfeeding, it may also be more overt during misguided attempts to treat the symptoms of a viral or other non-specific illness. Furthermore, the possibility of deliberate harm as part of a malicious exposure by carers should also be considered. Although there are no consensus guidelines supporting the routine use of TSs in ALTEs, the authors of this study suggest that it be part of their routine evaluation.

Can a toxicology screen alter hospital management in older children and adolescents suspected of poisoning?

Drug exposures in older children, and in particular adolescents, are similar to those in adults, and often involve intentional ingestion of medications and recreational drugs.³⁰ These are generally associated with higher rates of morbidity/mortality than the exposures in younger children. In 2009 in the USA, 6.2% of all paediatric drug exposures occurred between the ages of 13 and 19 years, with 4.2% of all mortality from drug exposure occurring in this group—an increase of 2.3 times compared with children <6 years.²⁷ Despite this, toxicology screening in this age group seldom influences management. In a retrospective study of 338 paediatric patients (77% >12 years old) in whom a TS had been performed in the ED as part of routine clinical assessment, 22 (7%) were found to have an unexpected positive result.³¹ Samples were analysed by gas chromatography with mass spectrometry, but the specific drugs/chemicals screened for were not described. Based on the unexpected results, three patients (1%) had an alteration in medical management (admission to hospital). In these cases, each child had an abnormal physical examination and vital signs that, retrospectively, were consistent with the drug ingested, including two with tricyclic antidepressant toxicity and one with Munchausen's syndrome, by proxy, involving phenobarbital/carbamazepine toxicity. The authors concluded that toxicology screening rarely alters medical management, and that emergency

physicians should re-evaluate the indications for such testing in the paediatric population.³¹

In a further retrospective study, 463 comprehensive TSs from paediatric patients (mean \pm SD age 11 \pm 6 years) incorporating >550 potential toxins were reviewed.³² Of 234 positive tests (51%) for one or more toxins, 7 (3%) occurred in cases in which there was no documented suspicion of an exposure. However, none resulted in a change in medical management. Furthermore, the estimated cost of the analysis (\$2315 per patient) appeared excessive in relation to the lack of impact on clinical management or outcome. In another study, treating physicians were prospectively asked to document whether TS affected a patient's management using a utility rating scale pre- and post-screening.³³ In total, 158 TSs from paediatric patients were requested due to a history of ingestion or altered mental status. A total of 90% of children >12 years old had TS compared with 60% <6 years ($p < 0.001$). In total, 78 (49%) screens were positive, and in 53 (34%) cases the treating physician stated that this result impacted on patient management. Of these, significant differences in pre- and post-test utility values were found for serum assays ($p = 0.008$), altered mental status ($p = 0.005$) and patients with a negative drug test ($p = 0.003$). Of 17 unexpected findings, only 4 (3% of total) influenced patient management. The study concluded that toxicology screening is influential on patient management when it involved quantitative serum assays, for example, paracetamol, aspirin, but not qualitative toxicology screening.³³

What are the main limitations of toxicology screening?

Negative toxicology screens

TS can provide physicians with 'objective' reassurance; however, this is generally unhelpful clinically because of the limited capability of most screening tests and the time frame for which drugs (and/or their metabolites) remain detectable. A negative qualitative TS cannot entirely exclude exposure to a compound, but conclude that the compound, at the time of testing, was not present at the minimum threshold quantity. In such cases, a physician may be misled by a negative result interpreting it as meaning 'drug not present' when in fact it only means 'drug not detected'.³⁴ When interpreting a negative TS, a physician must be aware of the extent of the screen used both in terms of the drugs/chemicals screened for and the sensitivity/limit of detection.

Positive toxicology screens

Specific quantitative serum assays have a greater impact on patient management than a positive qualitative toxicology screening assay. However, defining the severity of intoxication and/or guiding specific treatment based purely on the concentration of a drug/chemical in a blood sample is not always possible. While qualitative assays are extremely sensitive, they

lack specificity and are at risk of false positives. As such, a positive result does not confirm that a drug is present in a clinically significant quantity. It may also be misinterpreted, as drug metabolites and many other substances can cause interference and cross-react with drug-of-abuse assays for many days following exposure.¹ Furthermore, while a positive result may help explain a clinical presentation, consideration and exclusion of other treatable causes are required. A TS is designed as an adjunct to facilitate a diagnosis and must be interpreted in the context of both, the clinical features present and other indicators, such as acid-base and other biochemical features.

Future research

Toxicology screening using urine and/or blood samples can be effective in facilitating a diagnosis in children. However, in neonates, it remains unclear as to which biological specimens are best to evaluate in utero exposure, or indeed whether monitoring pregnant women who are suspected of illicit drug use can be linked to observed neonatal or later developmental outcomes. To effectively assess the effects of illicit drugs on a foetus, further research is required into maternal monitoring to establish when monitoring should commence, the frequency of monitoring, whether quantitative drug concentrations are helpful and which sampling method is most suitable. Blood and urine have been the preferred biological samples for drug testing; however, non-invasive methods, such as hair, sweat and oral fluid are now possibilities that require further validation in this setting.

Clinical bottom line

Paediatric toxic exposures are common, and while a few do result in significant morbidity/mortality, they are often treatable. Physicians using a combined assessment of history and clinical examination are often able to predict substance abuse,³⁵ although histories from patients (or their carers) suspected of drug ingestion may be unreliable. Data on the use and clinical utility of comprehensive drug testing in children is sparse. Hospital laboratories vary in the comprehensiveness of the toxicology screening that they can perform. Clinicians ordering a TS should, therefore, ensure that their request is tailored to the clinical presentation and the type of poison suspected. Laboratories offering comprehensive toxicology screens can add to the clinical decision making for patients suspected of drug overdose. This provides reassurance and improves agreement among physicians on patient outcome and, therefore, potentially saving resources.^{33 36 37} However, routine qualitative toxicology screening, often for drugs of abuse, has been shown to rarely influence overall clinical management.³¹⁻³³ Specific quantitative screening for specific poisons, for example, paracetamol, aspirin, lithium (box 1) assists in patient management, and is

probably the most helpful of available toxicology tests.

A rational and pragmatic approach to toxicology screening should be applied in paediatric care where its utility differs across different age groups. On the basis of the literature reviewed in this paper, we believe that toxicology screening may be of benefit in the following situations:

1. In neonates, to confirm drug exposures for forensic purposes, such as assessing for in utero exposure to illicit drugs or detecting malicious drug exposure.
2. In children, to screen for illicit drugs, where the presenting history is questionable, or unexplained symptoms are present (eg, coma, altered behaviour), and ingestion is in the differential diagnosis and/or malicious drug exposure is suspected.
3. In children and adolescents, when a specific therapy might be initiated based on a high serum level, for example in paracetamol or aspirin ingestion.

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