

Guidelines

Laboratory analyses for poisoned patients: joint position paper

National Poisons Information Service and Association of Clinical Biochemists

Abstract

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To enable consistency of investigation and the establishment of best practice standards, consensus guidelines have been formulated jointly by the UK National Poisons Information Service (NPIS) and the Association of Clinical Biochemists (ACB).

The types of laboratory investigation required for poisoned patients were categorized as either (a) essential common laboratory investigations or (b) specific toxicological assays, and also as either (i) common or (ii) specialist or infrequent.

Tests in categories (a) and (bi) are expected to be available 24 h per day, with a maximum turnaround time of 2 h. For the specialist assays, i.e. category (bii), availability and turnaround times have been specified individually. The basis for selection of these times has been clinical utility.

The adoption of these guidelines, along with the use of the NPIS online poisons information resource TOXBASE (www.spib.axl.co.uk), will enable the poisoned patient to receive appropriate, 'best practice' investigations according to their clinical needs and will avoid the use of unnecessary investigations.

Ann Clin Biochem 2002; **39**: 328–339

Introduction

Acute poisoning is a common reason for presentation to hospital. The great majority of such patients do not require any specific treatment and recover completely without serious complications. A small minority have life-threatening poisoning. The in-hospital mortality of acute poisoning in the UK is between 1 and 5 deaths per 1000 presentations.

Laboratory assays for toxins and/or their metabolites are a very important part of the management of patients with potentially serious poisoning. However, there is anecdotal evidence that laboratory toxicological investigations are overused by medical staff. There is also evidence that the availability of these investigations varies between hospitals, particularly when required outside normal working hours. This may present problems in management, particularly as many poisoned patients present during the night or at weekends.

The purpose of this document is to set out the laboratory assays that should be available for the management of poisoned patients and to define, where possible, the circumstances under which each should be used. The document concentrates on the measurement of specific drugs and toxins in blood and urine.

These measurement assays are divided into two groups: those that should be readily available in all acute hospitals and those for which alternative arrangements should apply. Guidance is also included on the appropriate availability of other supportive investigations for patients with suspected poisoning. Distinction is made between assays required urgently, for which 24-h availability is necessary, and those that can be performed routinely, i.e. during the next normal working day.

The document is not intended to be a comprehensive review of therapeutic drug monitoring or the forensic use of blood samples. It is intended to give guidance to acute hospitals on the current view regarding appropriate standards for the availability and use of laboratory assays for poisoned patients.

General principles

The indications for laboratory assays can be summarized as follows:

- To confirm the diagnosis of poisoning when this is in doubt
- To inform patient management, e.g. the need for:
 - further investigations
 - antidotes
 - haemodialysis or other extracorporeal methods

- To plan the re-institution of chronic therapy
- In the diagnosis of brain death and in assessing the suitability of potential organ donors
- For medico-legal or forensic reasons

The use of laboratory investigations out-of-hours should be restricted to those instances when an urgent result is needed to inform immediate patient management.

Reporting units

There is considerable variation between laboratories in the units used to report concentrations of drugs and other poisons. This creates confusion amongst medical and other staff and may lead to serious errors in interpretation. There is an urgent need to standardize units of measurements between laboratories. In the first instance, it is proposed that hospital laboratories and the National Poisons Information Service (NPIS) should standardize on the litre (L) as the unit of volume. The mass unit is preferred, particularly for drugs (other than lithium, methotrexate and thyroxine). It is recommended that, with the exception of these three agents, laboratories that report in molar units should also provide the result in mass units.

Sample collection

For most investigations relevant to poisoned patients, serum or plasma is suitable for analysis and these terms can be used interchangeably. Clinicians should check with their local laboratory for specific requirements. Exceptions are ethanol (plasma with fluoride/oxalate anticoagulant), carboxyhaemoglobin and methaemoglobin (heparinized whole blood), red cell cholinesterase (whole blood), and lead and mercury (whole blood anticoagulated with EDTA).

Target (therapeutic) and toxic concentrations

This document contains details of concentrations of toxins in blood and urine that may be associated with toxicity. It should be recognized that target and toxic ranges for these substances are approximate. Clinicians should take this into account when making management decisions.

More detailed information about the interpretation of laboratory assay results and on the clinical features and management of poisoning can be found via the NPIS on-line information resource TOXBASE, which is available free of charge to health professionals (www.spib.acl.co.uk). Advice is also available via the telephone information service (0870 600 6266), but it is important that enquirers access the information on TOXBASE before making a telephone enquiry.

Supportive investigations

The following laboratory investigations should be available on a 24-h basis to all hospitals where

patients with acute poisoning are admitted. Samples should be taken using appropriate containers and, when necessary, anticoagulants. Information on the interpretation of some of these investigations in the poisoned patient is provided in Appendices 1 and 2.

- Full blood count
- Sodium, potassium, urea, creatinine
- Glucose
- Calcium, albumin, magnesium
- International normalized ratio (INR)
- Liver function tests
- Anion gap (chloride and bicarbonate)
- Plasma osmolality (freezing point depression method) and osmolar gap
- Arterial blood gases
- Creatine kinase

Specific assays

Specific assays have been divided into two groups. The first group should be available on a 24-h basis in all hospitals that admit patients with acute poisoning. The second group are assays that are important in patient management but which are infrequently needed. For these, arrangements need to be in place so that the assays can be obtained from specialist laboratories if they are not available on site.

Group 1: assays that should be available on a 24-h basis in all acute hospitals

- Carboxyhaemoglobin
- Digoxin
- Ethanol
- Iron
- Lithium
- Methaemoglobin
- Paracetamol
- Paraquat (qualitative urine test)
- Salicylate
- Theophylline

Results should normally be available within a maximum of 2 h (or sooner if possible) unless otherwise stated. Their use is summarized in Appendix 3.

Carboxyhaemoglobin

- Carboxyhaemoglobin should be measured urgently in all patients with suspected carbon monoxide poisoning (including those with suspected smoke inhalation).
- A carboxyhaemoglobin percentage of $\geq 20\%$ indicates significant exposure. However, concentrations less than this do not exclude significant poisoning, and the relationship between carboxyhaemoglobin and severity of poisoning and/or clinical outcome is poor.

- Management should be determined by the clinical condition of the patient rather than the carboxyhaemoglobin concentration.
- High flow oxygen therapy should be administered pending the results of carboxyhaemoglobin measurement.

Digoxin

- Plasma or serum digoxin concentrations correlate poorly with the severity of poisoning, especially soon after acute overdose.
- The usual target range for digoxin is 1–2 µg/L (1.3–2.6 nmol/L). Severe toxicity is usually (but not invariably) associated with concentrations > 4 µg/L (5.1 nmol/L). Hypokalaemia enhances digoxin toxicity. In acute life-threatening poisoning, hyperkalaemia is usually present.
- Urgent measurement of plasma/serum digoxin concentration is essential if digoxin-specific antibodies are to be used. The digoxin concentration is useful in determining an appropriate dose of digoxin-specific antibodies, as well as confirming the diagnosis.
- In patients with life-threatening arrhythmias due to digoxin toxicity, treatment with digoxin-specific antibodies should not be delayed pending the results of plasma digoxin concentrations.
- Samples should always be taken before antibody administration as plasma digoxin concentrations cannot be interpreted once these have been given.
- Samples taken to investigate possible chronic digoxin intoxication should be taken at least 6 h after dosing and do not usually need to be analysed urgently, unless life-threatening features are present and use of digoxin antibodies is being contemplated.
- Repeat samples, analysed routinely, may help determine when to re-institute chronic therapy after acute overdose. However, these are not of value for several days following the administration of digoxin antibodies, as the elimination half-life of the complex under normal conditions is 16–20 h.
- Assays routinely used in the UK are not ideal for accurate quantification of digitoxin or plant glycosides, although they may provide qualitative supportive evidence of exposure.

Ethanol

- Plasma ethanol concentrations are usually not required in patients who have ingested ethanol, unless there is doubt about the diagnosis.
- Ethanol concentrations should be measured urgently:
 - in patients with undiagnosed coma or widened osmolar gap
 - in children with unexplained acidosis

– in patients with suspected severe ethanol intoxication, when haemodialysis is being considered.

- Concentrations > 1800 mg/L (1.8 g/L, 180 mg/dL, 39 mmol/L) are associated with disorientation. In the absence of other toxins, ethanol concentrations in excess of 3500 mg/L (76 mmol/L) are usually required to produce coma. Fatal poisoning is usually associated with concentrations > 4500 mg/L (98 mmol/L). Ethanol toxicity is enhanced in the presence of other sedative agents (and *vice versa*).
- Plasma ethanol concentrations performed urgently are essential for monitoring the use of ethanol as an antidote for poisoning with ethylene glycol or methanol, particularly if dialysis is also being used. Concentrations should be maintained in the range 800–1000 mg/L (17–22 mmol/L). This will require at least 2-hourly plasma ethanol estimation until plasma ethanol concentrations and ethanol infusion rates are stable.
- For conscious patients, breath alcohol measurement may be used for monitoring ethanol therapy, if facilities are available locally, aiming for target concentrations of 340–430 µg/L (34–43 µg/100 mL) breath. (This is equivalent to 800–1000 mg/L blood, if a blood–breath partition coefficient value of 2300 is used.)

Iron

- Plasma or serum iron concentrations help to determine prognosis and the need for antidotal treatment with desferrioxamine in patients with suspected iron poisoning.
- They should be measured urgently in:
 - asymptomatic patients who have ingested > 20 mg/kg elemental iron within 6 h
 - patients with symptoms (including transient symptoms) suspected to be due to iron intoxication.

For both groups, the sample should be taken after at least 4 h have elapsed since iron ingestion. It is important that the sample is not haemolysed.

- Severe toxicity is unlikely if symptoms have not developed within 6 h of ingestion. Under these circumstances, measurement of iron concentration is unlikely to be helpful. However, measurement of iron concentration is indicated in patients who develop early symptoms which have settled prior to presentation.
- Plasma iron concentrations following ingestion are interpreted as follows:

< 3 mg/L (55 µmol/L)	mild poisoning
3–5 mg/L (55–90 µmol/L)	moderate poisoning
> 5 mg/L (90 µmol/L)	severe poisoning
- Antidotal therapy with desferrioxamine is indicated without waiting for the plasma iron

concentration in patients with severe clinical features (e.g. unconscious, fitting or shocked).

- Antidotal treatment may also be indicated for patients with iron concentrations >3 mg/L (55 μ mol/L) if there is additional evidence of toxicity [e.g. prolonged (>4 h) gastrointestinal symptoms, leucocytosis or hyperglycaemia]. Further advice on individual cases can be obtained from the NPIS.
- All colorimetric iron assays are unreliable in the presence of desferrioxamine.
- Measurement of iron-binding capacity has no role in the management of iron poisoning.

Lithium

- Blood should be sampled immediately and the plasma lithium concentration measured urgently in patients who have:
 - suspected acute-on-chronic or chronic toxicity
 - acute lithium intoxication associated with relevant symptoms.
- In acute lithium overdose where there are no relevant symptoms, the serum concentration should be measured approximately 6 h after ingestion and the result obtained urgently.
- If severe poisoning is confirmed, or if a sustained release preparation may have been taken, the plasma lithium concentration should be repeated 6- to 12-hourly until the concentration is falling.
- Lithium–heparin tubes should not be used for the sample.
- The principal value of urgent lithium measurement is to determine the need for haemodialysis in severe poisoning. Low thresholds should be considered for haemodialysis in the presence of neurological or cardiac features, particularly if concentrations are increasing. Advice on the interpretation of lithium concentrations and on the appropriate use of haemodialysis can be obtained from TOXBASE and the NPIS.
- There is a risk of rebound increases in lithium concentration after haemodialysis, and lithium concentrations should be measured 6 h after haemodialysis is discontinued.
- Repeated measurements of lithium concentration, performed routinely, are helpful in timing the appropriate re-institution of chronic therapy following an episode of toxicity. The usual target range is approximately 0.4–1.0 mmol/L 12 h post-dose.

Methaemoglobin

- A range of poisons may cause methaemoglobin-aemia. Examples are:

- *Drugs*: nitrites, local anaesthetics (e.g. benzocaine), dapsone, sulphonamides, chloroquine and primaquine
- *Other chemicals*: aniline dyes, nitrobenzenes, naphthalene and chlorates.
- Measurement of methaemoglobin concentration is required to confirm diagnosis and assess severity. It is essential for it to be measured urgently when administration of methylene blue is contemplated.
- Methaemoglobin concentrations of less than 20% are not usually associated with symptoms and require no treatment. Concentrations $>20\%$ may require treatment with methylene blue. Further advice on individual cases can be obtained from the NPIS.

Paracetamol

- Measurement of plasma paracetamol concentration is essential for determining the need for antidotal treatment and should be performed urgently in all patients with known or suspected paracetamol overdose.
- The assays should have a lower limit of quantitation for paracetamol of 10 mg/L (0.07 mmol/L) or less. This is particularly important when assessing patients who have taken drug overdoses more than 12 h prior to blood sampling.
- Plasma paracetamol concentrations should also be measured urgently in all patients when there is a clinical suspicion that paracetamol poisoning may be present. Examples would be:
 - drug overdose patients, when the history appears unreliable
 - patients with undiagnosed coma where there is a clinical suspicion of drug overdose.
- Measurement of paracetamol concentrations in alert patients who deny taking paracetamol, when there is no clinical suspicion, rarely provides evidence of significant paracetamol toxicity and is therefore not routinely recommended.
- The sample must be taken 4 h after ingestion, or immediately, should the patient present after an interval of more than 4 h. The INR should also be measured and this should be repeated in patients at risk of, or developing, hepatotoxicity.
- Plasma paracetamol concentration measurement is occasionally helpful in some children with unexplained hepatotoxicity, although a negative result does not exclude paracetamol as a cause.
- For the great majority of patients, only a single measurement of paracetamol concentration is indicated. A second measurement, after an interval of 2–3 h, may be helpful for occasional patients who have taken staggered overdoses or when the timing of ingestion is particularly uncertain. Interpretation of the results is difficult and should be

discussed with the NPIS when there is uncertainty. In these cases it is often appropriate to give acetylcysteine pending the results of the second paracetamol measurement.

- Acetylcysteine may interfere with the measurement of plasma paracetamol concentration using enzymatic kits, when the method has been modified for use on certain types of clinical analyser. There is no interference if the kits are used manually in accordance with the manufacturer's instructions. Because of this, laboratories should be informed when samples are taken from patients already receiving acetylcysteine.

Paraquat (urinary qualitative assay)

- There is no specific treatment of proven value for paraquat poisoning. Investigations are directed at confirming exposure and determining prognosis.
- A qualitative urine test (dithionite spot test) should be performed urgently in all patients presenting with suspected paraquat poisoning to confirm exposure. This is a simple procedure that can be performed by any laboratory. Instructions for performing this test can be found on TOXBASE.
- In patients with a positive spot test, a blood sample should be taken for routine analysis in a specialist laboratory, as this provides valuable prognostic information [see 'Paraquat (quantitative plasma assay)' below].

Salicylate

- *There is no need to measure salicylate concentrations in conscious overdose patients who deny taking salicylate-containing preparations and who have no features suggesting salicylate toxicity.*
- Plasma salicylate concentration should be measured urgently for patients who are thought to have ingested >120 mg/kg of aspirin (acetyl salicylate) as well as those who have taken methylsalicylate (oil of wintergreen) or salicylamide.
- The sample should be taken at least 2 h (symptomatic patients) or 4 h (asymptomatic patients) following ingestion, since it may take several hours for peak plasma concentrations to occur.
- A repeat sample should be taken after a further 2 h in patients with suspected *severe* toxicity following recent ingestion because of the possibility of continuing absorption. Under these circumstances, measurements should be repeated until concentrations are falling.
- Salicylate concentration should also be measured in patients with unidentified poisoning or those with undiagnosed clinical features consistent with salicylate poisoning, e.g. coma, metabolic acidosis, respiratory alkalosis, tinnitus, etc.
- The severity of poisoning cannot be assessed from plasma salicylate concentrations alone, and

clinical and biochemical features should be taken into account. However, salicylate intoxication is usually associated with plasma concentrations > 350 mg/L (2.5 mmol/L).

- Patients with moderate salicylate poisoning may require urine alkalization, while those with severe poisoning may need treatment with haemodialysis. Advice on the interpretation of plasma salicylate concentrations and the need for urinary alkalization and haemodialysis can be obtained via TOXBASE and from the NPIS.
- Plasma salicylate concentrations should be repeated after dialysis.

Theophylline

- Patients with suspected theophylline poisoning should have the severity graded according to simple clinical indicators, including the plasma potassium and arterial blood gases.
- Plasma theophylline concentration should be performed immediately for patients with any clinical features suggesting theophylline toxicity, including hypokalaemia or acidosis. Theophylline concentrations should not be measured earlier than 4 h after exposure in patients who are asymptomatic.
- In patients with severe poisoning or theophylline concentration > 60 mg/L (333 µmol/L), the theophylline concentration should be repeated every 2–4 h, until peak concentrations have passed. This is particularly important if a slow release preparation has been taken.
- Advice on the interpretation of plasma theophylline concentrations and the need for multiple dose activated charcoal can be obtained from TOXBASE and the NPIS.

Group 2: specialist or infrequent assays

It is not necessary for the following assays to be available directly from all acute hospital laboratories. However, arrangements should be in place so that these assays can be accessed urgently when necessary. This may involve an arrangement with a supra-regional specialist toxicology laboratory or a subregional centre. It is the responsibility of each individual hospital to ensure that appropriate arrangements are in place and that staff can follow these arrangements when the need arises, including outside normal working hours. Laboratory staff should have contact details readily available for specialist laboratories providing these assays, together with information on how samples should be collected and transported.

Clinical staff should discuss the use of the following assays with a local clinical biochemist; advice is also available from the NPIS when required.

- Acetylcholinesterase
- Arsenic
- Carbamazepine
- Ethylene glycol
- Lead
- Mercury
- Methanol
- Methotrexate
- Paraquat (quantitative plasma assay)
- Phenobarbital
- Phenytoin
- Thyroxine
- Toxicology screen*

*(The scope of the toxicology screen may vary according to local needs.)

Acetylcholinesterase

- Measurement of plasma or red cell cholinesterase is useful to confirm exposure to substances that inhibit cholinesterase, e.g. organophosphate or carbamate compounds. This may occur as a result of exposure to pesticides (farm workers, treatment of pests) or nerve agents.
- Optimal clinical management requires rapid access to an assay result which should ideally be available within 3 h, including journey time.
- Clinical features that might suggest organophosphate or carbamate poisoning include:
 - *Early features*: anxiety, restlessness, confusion, insomnia, tiredness, dizziness, headache, nausea, vomiting, abdominal colic, diarrhoea, sweating, hypersalivation, chest tightness, small pupils, muscle weakness and fasciculation
 - *Severe poisoning*: widespread flaccid paralysis (including ocular and respiratory muscles), convulsions, coma, pulmonary oedema with copious bronchial secretions, bronchospasm and cardiac dysrhythmias. Hyperglycaemia and glycosuria may be present.
- Plasma cholinesterase activity is simpler to measure and is inhibited more rapidly in poisoning. However, reduced activity is less specific and may also occur in genetic pseudocholinesterase deficiency (suxamethonium apnoea), early pregnancy, liver disease, malignancy and hypoalbuminaemia.
- Measurement of the red cell cholinesterase activity is more specific and may be used to confirm severe organophosphate or carbamate poisoning when the diagnosis is in doubt. For optimum clinical management, a red cell cholinesterase activity result should be available within 6 h, allowing for journey times.
- Antidotal treatment, initially with atropine and subsequently (in selected cases) with pralidoxime mesylate (P2S), should not be delayed pending the

result of assays, when severe poisoning is suspected.

- Plasma and red cell cholinesterase activity is usually reduced to < 50% with clinical poisoning and to < 10% in severe cases.
- Plasma cholinesterase falls and recovers more rapidly after exposure than red blood cell (RBC) cholinesterase. It may take 90–120 days for RBC cholinesterase to recover to normal values.
- Advice on the interpretation of acetylcholinesterase assays and on the use of antidotes can be obtained from TOXBASE and the NPIS.

Carbamazepine

- The acute management of carbamazepine poisoning, including the need for multiple doses of oral activated charcoal, is determined by the clinical picture. There is no need for a carbamazepine assay in the great majority of patients who have taken an overdose.
- Urgent measurement of plasma carbamazepine concentrations is only required when multiple dose activated charcoal is being considered or when there is doubt about the diagnosis, for example in patients with:
 - coma
 - respiratory depression
 - arrhythmias.
- When indicated, optimal clinical management requires that an urgent result from this assay should be available within 2 h.
- Serious complications are unusual at plasma concentrations less than 25 mg/L (105 μ mol/L). Most patients with life-threatening toxicity have plasma carbamazepine concentrations in excess of 40 mg/L (170 μ mol/L).
- Non-urgent measurement is helpful in determining when to restart chronic carbamazepine therapy.

Ethylene glycol (1,2 ethanediol) and methanol

- Serious ethylene glycol or methanol intoxication is uncommon; however, when these do present, urgent measurement of plasma or serum ethylene glycol or methanol concentration is essential for optimum management. These assays are not readily available and their use should be discussed with a senior local biochemist and the NPIS. When an assay is indicated, optimal clinical management requires that a result should be available within a maximum of 4 h.
- It is reasonable to restrict use of these assays to:
 - patients who give a history of substantial ingestion and who display evidence of intoxication
 - patients with suspected severe toxicity as evidenced by metabolic acidosis, especially pH

<7.2 (hydrogen ion >60 nmol/L) in the presence of an increased anion gap, with or without an increased osmolar gap, when a reliable history is unavailable.

Antidotal treatment should be commenced pending the result of the assay.

- Toxic concentrations of ethylene glycol may not be associated with an increased osmolar gap because of the large molecular weight of the compound.
- As it takes several hours for toxic organic acids to be formed from ethylene glycol and methanol, the anion gap will be normal in the early stages of methanol and ethylene glycol poisoning, even when life-threatening amounts have been ingested.
- Antidotal treatment with ethanol or fomepizole is indicated for patients with evidence of severe poisoning. (Fomepizole is licensed in the UK for the treatment of ethylene glycol poisoning. It is not licensed for methanol poisoning but there is evidence of efficacy for this indication.) Advice on the criteria for antidotal treatment and haemodialysis can be obtained from the NPIS.
- Antidotal treatment should be continued until the plasma ethylene glycol or methanol concentration is less than 50 mg/L (0.8 mmol/L and 1.6 mmol/L, respectively) and the patient is asymptomatic with a normal pH.
- Haemodialysis should be continued until the plasma ethylene glycol or methanol concentration is less than 50 mg/L (0.8 mmol/L and 1.6 mmol/L, respectively).
- Plasma concentrations should be repeated a few hours after haemodialysis as rebound increases in concentrations have been reported.
- Daily measurement of ethylene glycol or methanol concentrations is helpful in determining the appropriate time to discontinue dialysis and/or antidotal treatment.
- Ethylene glycol is metabolized to oxalic acid which forms complexes with calcium, so close monitoring of the plasma calcium concentration is required.

Heavy metals

- Acute poisoning with heavy metals is rare. Measurement of plasma and/or urinary heavy metal concentrations is useful in confirming the diagnosis. Urgent assays are rarely indicated. Urgent measurement is, however, occasionally justified for patients with suspected severe poisoning with lead or mercuric salts. Urgent use of these assays must be discussed with a senior local biochemist and the NPIS. When urgent analysis is indicated, optimal clinical management requires that a result should be available within 24 h.
- Samples should be taken into a metal-free container. A whole blood specimen is essential for

lead and mercury analysis, as these metals are bound predominantly to red blood cells. Advice on appropriate specimen collection and use of anti-coagulants should be obtained from the laboratory performing the analysis.

- Advice on the management of heavy metal poisoning, including the use and interpretation of assays and the utility of chelation therapy, can be obtained from the NPIS.

Arsenic

- Arsenic poisoning may occur after ingestion of wood preservatives or in the production of glass, alloys, rodenticides, pesticides, marine paints and semiconductors.
- Clinical features of acute arsenic poisoning include abdominal pain, vomiting, a garlic odour on the breath, diarrhoea (sometimes with blood), myocardial depression, vasodilation, electrolyte disturbances, acute renal failure, cerebral oedema, coma, convulsions and ventricular fibrillation.
- Chronic ingestion may cause anorexia, weight loss, diarrhoea, peripheral neuropathy or skin rashes, including palmar keratosis.
- Blood arsenic concentrations should be measured in cases of suspected acute arsenic toxicity to confirm the diagnosis, particularly if chelation therapy is being contemplated. However, concentrations correlate poorly with the severity of poisoning.
- Following acute toxicity, blood arsenic concentrations decline rapidly into the normal range in spite of continuing evidence of clinical toxicity, and may be undetectable more than 4 h after ingestion of potentially fatal amounts.
- Toxicity is usually associated with blood concentrations >100 µg/L (1.3 µmol/L), while concentrations >200 µg/L (2.7 µmol/L) indicate significant acute exposure.
- Measurement of urinary arsenic concentrations is useful for late presentations of acute poisoning and for assessing chronic toxicity.

Lead

- Lead poisoning may occur following exposure to lead paint, leaded petrol, contaminated drinking water, and ethnic remedies or cosmetics. Occupational exposure may occur in plumbers, lead miners, shipbuilders, construction workers, pottery manufacturers and demolition workers.
- Clinical features of acute and chronic lead poisoning are described on TOXBASE.
- Non-urgent measurement of whole blood lead concentration is required in patients with suspected lead exposure or toxicity to confirm the diagnosis. This is particularly important if

chelation therapy is being contemplated. However, urgent measurement of plasma lead concentration is only necessary in children with suspected lead encephalopathy.

- Whole blood lead concentrations are normally $< 200 \mu\text{g/L}$ ($1 \mu\text{mol/L}$). Patients with concentrations higher than this should be discussed with the NPIS. Concentrations in excess of $600 \mu\text{g/L}$ [$3 \mu\text{mol/L}$] (children) or $800 \mu\text{g/L}$ [$4 \mu\text{mol/L}$] (adults) are usually associated with severe toxicity. (Note that molar units have been rounded up.)

Mercury

- Measurement of whole blood mercury concentration is helpful in patients with suggested mercury intoxication from acute exposure to mercuric salts or mercury vapour. The clinical features are described on TOXBASE.
- It should always be measured prior to administration of antidotes such as DMPS and use of antidotes should be discussed with the NPIS.
- Urgent measurement is only indicated in patients with suspected severe acute poisoning from mercuric salts.
- Whole blood mercury concentrations are usually less than $25 \mu\text{g/L}$ (125 nmol/L). Patients with concentrations higher than this should be discussed with the NPIS. Chelation therapy should be considered in symptomatic patients with blood mercury concentrations $> 100 \mu\text{g/L}$ (500 nmol/L) and in any patient with concentrations $> 200 \mu\text{g/L}$ (1000 nmol/L).
- Urinary mercury should be measured in patients with suspected chronic mercury intoxication.

Methotrexate

- Acute methotrexate overdose is rare but a measurement of plasma methotrexate concentration 4–6 h after ingestion is helpful if this assay is available.
- To be clinically useful, a turn-around time of $< 24 \text{ h}$ is necessary.
- Methotrexate drug concentrations help determine an appropriate initial dose and the timing of discontinuation of folinic acid. However, treatment should not be delayed pending a result.
- Treatment with folinic acid, with or without urine alkalinization, should continue until the plasma drug concentration is $< 0.1 \mu\text{mol/L}$ (10^{-7} mol/L).

Paraquat (quantitative plasma assay)

- In patients with a positive urine test (dithionite spot test) [see 'Paraquat (qualitative urine test)' above], a single plasma sample should be taken for routine analysis in a specialist laboratory.
- Relating the paraquat concentration to the time since ingestion provides valuable prognostic

information, when a plasma sample is available within 24 h of exposure. In patients presenting later than this there is less information available, but a concentration of $> 0.4 \text{ mg/L}$ is likely to indicate a fatal overdose. Further information on interpretation can be obtained from the NPIS.

- The result of this assay is not required urgently.

Phenobarbital (Phenobarbitone)

- Most patients who have taken overdoses of phenobarbital do not require measurement of plasma concentrations. This applies even if poisoning is severe, provided the diagnosis is not in doubt.
- It is sometimes appropriate to obtain phenobarbital concentrations urgently in patients with severe toxicity when there is doubt about the diagnosis. Examples would include:
 - Patients with unexplained unconsciousness, where phenobarbital poisoning is suspected.
 - Patients with clinical features consistent with phenobarbital toxicity being considered for multiple-dose activated charcoal, when the diagnosis is in doubt and in the absence of a clear history of phenobarbital exposure.
- Urgent measurement of plasma phenobarbital concentration is also occasionally required to monitor anti-epileptic treatment in neonates. Use of assays for therapeutic drug monitoring is outside the scope of this guidance.
- The usual target range for phenobarbital is $10\text{--}20 \text{ mg/L}$ ($43\text{--}86 \mu\text{mol/L}$). Serious toxicity is usually associated with concentrations in excess of 75 mg/L ($325 \mu\text{mol/L}$), while concentrations $> 150 \text{ mg/L}$ ($645 \mu\text{mol/L}$) suggest life-threatening toxicity.
- Optimal clinical management requires that the results of urgent phenobarbital assays should be available within 2–4 h.
- Routine measurements may be useful to monitor anti-epileptic therapy or to time the re-institution of chronic therapy after overdose.

Phenytoin

- Most patients with acute phenytoin overdose do not require measurement of plasma phenytoin concentration.
- An urgent phenytoin concentration is helpful (but not essential) if multiple-dose activated charcoal is being contemplated, particularly if the diagnosis is in doubt, e.g. in patients with coma, respiratory depression or arrhythmias. However, the clinical value of this elimination method for phenytoin intoxication is unproven.
- Rarely, urgent measurement of the phenytoin concentration may help to differentiate between convulsions due to phenytoin toxicity and those resulting from inadequate anticonvulsant concentrations.

- Optimal clinical management requires that, when indicated, the results of urgent phenytoin assays should be available within 2 h.
- Patients with suspected chronic phenytoin toxicity as a result of therapeutic dosing should have their plasma phenytoin concentration measured, but there is no need for this to be done urgently.
- The usual target range for phenytoin is 8–15 mg/L (32–60 $\mu\text{mol/L}$). Symptomatic toxicity is usually associated with concentrations in excess of 20 mg/L (80 $\mu\text{mol/L}$), while concentrations >40 mg/L (160 $\mu\text{mol/L}$) suggest serious toxicity.
- Routine measurements may be useful to monitor anti-epileptic therapy or to time the re-institution of chronic therapy after overdose.

Thyroxine

- Plasma free thyroxine should be measured in patients presenting with thyroxine overdose. There is no need for this to be done urgently.
- Patients with high free thyroxine concentrations 6–12 h after thyroxine ingestion should have out-patient review 3–6 days after ingestion to detect delayed-onset hypothyroidism.

Toxicology screen

- Various types of urine screening tests are available, either as immunoassays or as commercial or

in-house thin layer chromatography (TLC) systems.

- Immunoassays are targeted towards specific drugs or groups of drugs, e.g. methadone, benzodiazepines and opiates, whereas chromatographic systems such as TLC detect a much wider range of substances. However, a negative result does not rule out poisoning, even when both techniques are applied, as there is a host of compounds that they will not detect. A positive result does not prove that the substance identified is the cause of the patient's clinical features. Use of these screening tests without an understanding of their potential limitations is hazardous.
- Toxicology screens are useful under some specific circumstances, for example:
 - for determining previous ingestion of illicit drugs
 - in the diagnosis of unexplained coma
 - as an aid to the confirmation of brain death and for assessing suitability for organ donation
 - for forensic reasons.
- Close cooperation is required between local laboratory and clinical staff to choose a test that reflects local needs and to ensure that clinical staff obtain optimum use of these assays and understand their limitations.

Appendix 1

Some agents causing biochemical abnormalities in patients with drug overdose

Serum analyte	Reference range	Increased	Reduced
Sodium	135–145 mmol/L	Ecstasy (rarely)	Ecstasy (commonly) Diuretics (chronic)
Potassium	3.5–4.5 mmol/L	Digoxin	Theophylline Salbutamol Digoxin Diuretics (chronic) Insulin Sulphonylureas
Glucose	3.5–6.0 mmol/L (fasting)	Theophylline Salicylates	Insulin Sulphonylureas Ethanol Salicylates Sodium valproate
Calcium	2.20–2.65 mmol/L		Ethylene glycol Hydrofluoric acid
Anion gap (Na ⁺ +K ⁺) – (HCO ₃ ⁻ +Cl ⁻)	12–16 mmol/L	Ethanol Ethylene glycol Iron salts Isoniazid Methanol Metformin Paraldehyde Salicylates Toluene	
Osmolar gap = measured – calculated osmolarity Calculated osmolarity = 2Na+urea+glucose	< 10 mmol/L	Ethanol Ethylene glycol Acetone Isopropranol Hyperosmolar IV solutions (e.g. mannitol)	

Appendix 2

Substances causing arterial blood gas abnormalities in patients with poisoning

pH status	Metabolic	Respiratory
<i>Acidosis (pH < 7.35)</i>	<i>pCO₂ < 4.5 kPa (34 mmHg)</i> <i>Base deficit present</i> Carbon monoxide Cyanide Ecstasy Ethylene glycol γ hydroxybutyrate Iron Isoniazid Metformin Methanol Paracetamol Paraldehyde Salicylates* Sodium valproate Theophylline Tricyclic antidepressants	<i>pCO₂ > 6.0 kPa (45 mmHg)</i> <i>Base deficit absent</i> Sedative agents e.g. Barbiturates Benzodiazepines γ hydroxybutyrate Ethanol Opiates Tricyclic antidepressants
<i>Alkalosis (pH > 7.45)</i>	<i>pCO₂ normal, base excess present</i> Bicarbonate	<i>pCO₂ < 4.5 kPa (34 mmHg)</i> <i>Base excess absent</i> Salicylates* Theophylline Ecstasy

*A mixed picture, e.g. metabolic acidosis and respiratory alkalosis, is commonly observed in salicylate poisoning, and may occur with poisoning with other agents.

Appendix 3

Summary of use of common assays for drugs and other toxins

Assay	Indication	Timing of sample post-exposure	Repeat samples	Clinically significant concentrations*
Carboxyhaemoglobin	Suspected CO or smoke inhalation	Immediate	No	> 20% indicates significant exposure n.b. Poor relationship with clinical severity/outcome
Digoxin	Severe digoxin toxicity prior to use of digoxin antibodies	Immediate	No	> 2.0 ng/L (2.6 nmol/L)
Ethanol	Undiagnosed coma, with widened osmolar gap Prior to anaesthesia Severe intoxication; being considered for dialysis Use as an antidote	Immediate	2-hourly samples for monitoring use as an antidote Repeat following haemodialysis	800–1000 mg/L for use as an antidote > 1800 mg/L for significant toxicity (in the absence of other agents)
Iron	> 20 mg/kg elemental iron ingestion within 6 h Symptoms suggesting iron toxicity at any time after overdose	> 4 h after overdose	No	3 mg/L (55 μ mol/L)
Lithium	Suspected acute or chronic lithium poisoning	Immediate for suspected chronic or acute-on-chronic poisoning, or for patients with symptoms suggesting lithium intoxication After 6 h for asymptomatic acute overdose	6–12-hourly in severe poisoning or following use of sustained-release preparation, until concentrations are falling Following haemodialysis	Target range 0.4–1.0 mmol/L (12 h post-dose)
Methaemoglobin	Exposure to relevant toxins	Immediate	Worsening symptoms	> 20% n.b. Poor correlation with clinical severity
Paracetamol	Suspected paracetamol overdose Drug overdose where paracetamol poisoning has not been reliably excluded	> 4 h	Rarely required, unless timing of overdose uncertain	Refer to nomogram Toxic concentrations depend on patient's individual risk
Paraquat (urine spot test)	Suspected paraquat exposure	Immediate	Repeat if initial sample was taken within 4 h of exposure and was negative	Positive indicates the need for plasma analysis
Salicylate	Salicylate overdose (suspected > 120 mg/kg) Ingestion of methylsalicylate or salicylamide Unidentified poisoning with clinical features suggesting salicylate toxicity	\geq 2 h if symptomatic \geq 4 h if asymptomatic	After a further 2 h in patients with suspected severe toxicity Measurements should be repeated until concentrations are falling	Serious toxicity usually associated with concentrations > 350 mg/L (2.5 mmol/L)
Theophylline	Clinical features suggesting theophylline toxicity	Immediate if clinical features present \geq 4 h if asymptomatic	Repeat 2–4 hourly in patients with severe poisoning or concentration > 60 mg/L (333 μ mol/L), especially if a slow-release preparation was taken	Serious toxicity usually associated with concentrations > 60 mg/L

*These concentrations are given for general guidance only. Drug/toxin concentrations may not correlate closely with the severity of poisoning in individual patients and values may vary between laboratories.

Appendix 4

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