REVIEW ARTICLE

Toxidrome-based Approach to Common Poisonings

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Abstract

Poisoning remains a major cause of hospital admission into the emergency department and intensive care unit. Proper diagnosis is the cornerstone for optimal management of poisoned patients. Since the definitive analytical confirmation of the nature of the toxicant involved in the poisoning cannot be rapidly obtained in the majority of healthcare facilities, diagnosis relies on the medical history and the rigorous clinical examination of the patients well as results of the routine biological tests and the electrocardiogram. Identification of the toxidromes addresses not only the correct diagnosis but also rules out other differential diagnoses. Despite no definitive predictive value, this clinical approach facilitates making decision on empirical treatments and emergent antidotes. Pharmacodynamic tests using specific antidotes including naloxone for opioids and flumazenil for benzodiazepines and its analogues are also helpful to assess the final diagnosis in comatose patients. The objective of this article is to review the toxidrome-based approach to common poisonings before toxicological analysis enables the confirmation of the initially suspected toxic etiology.

Keywords: Anticholinergic Syndrome; Poisoning; Serotonin Syndrome; Substance Withdrawal Syndrome; Toxidrome

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INTRODUCTION

Drug poisoning, either accidental or intentional, accounts for one of the most common causes of admission to the emergency department and intensive care unit (ICU). The most common causes of poisoning reported by the U.S. poison control centers are the followings (1): analgesics (11.8%), cosmetics (7.8%), household products (7.4%), sedatives (5.8%), antidepressants (3.6%), cardiotropic drugs (3.3%) and pesticides (3.2%). In France, 19 of 20 most common medications involved in the reported exposures by the Poison Control Centre of Paris are psychotropics (2).

Intoxication can be serious owing to: 1) the severity of the presenting symptoms (coma, seizures, respiratory distress, alveolar hypoventilation, circulatory failure or arrhythmias or cardiac conduction abnormalities); 2) the need for close monitoring, due to exposure to a large amount of a toxic substance; 3) an underlying condition with great vulnerability (severe comorbidities, advanced age or otherwise, newborn). Severely poisoned patients should be routinely admitted to the ICU. In 2006, an official recommendation of experts for the management of severe drug poisoning in ICU was published by the French Society of Intensive Care (3). In this article, the diagnostic process that should be undertaken for a patient suspected for poisoning and clinical presentation of common acute poisonings are discussed.

1. General principles of diagnostic procedures in poisonings

Upon admission, three distinct clinical situations should be individualized for each patient (4):

1) The patient has been exposed intentionally or accidentally to a toxic agent, but his/her clinical examinations are normal. In the emergency department, it is not necessary to be certain of poisoning; only the suspicion of poisoning is enough for reasoning. The severity of poisoning is based on the nature of the toxic agent, the dose and the time elapsed since exposure. Calling a poison control center (especially for toxic chemicals) is recommended to find out the extent of toxicity, intensity of potential problems and consulting for hospital/ICU admission.

2) On clinical examination, signs and symptoms of exposure to a specific toxic agent are present. The process begins with the close assessment and treatment of critical condition. Here, saying "treat the patient before treating poison" totally makes sense. The physician must be aware of the situations with immediate life-threatening risks for abrupt diagnosis and prompt treatment. Hence, it would be necessary to clarify the circumstances of the exposure and characterize the clinical condition of the patient.

3) The patient has signs and symptoms for which a toxic etiology is suspected without clear initial clue. If taking history from the patient or his/her entourage is impossible, only a careful clinical examination and analysis of laboratory tests can provide information for diagnosis.

Whatever the previous situation is, the diagnosis in medical toxicology is essentially based on history and clinical approach. Clinical examination should be systematic and

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rigorous, and is essential to be performed dynamically. It includes performing an electrocardiogram in serious cases that are under observation or suspected for poisoning. When a blood sample is obtained, the routine laboratory tests (serum electrolytes, serum creatinine, glucose, calcium, blood cell counts, liver function tests and arterial blood gases) are in priority compared to the toxicological analysis. To assess the patient's prognosis, the following factors should be taken into account: the amount to which the patient has been exposed (for example, the assumed ingested dose of the drug), formulation (rapid or slow releasing), patient's background, time interval between exposure and treatment, delayed onset of symptoms and the occurrence of complications.

1-1. Specification of the circumstances of poisoning

Taking a though history from the patient or his/her entourage is an essential step in the diagnostic process. It helps to identify the circumstances of the findings in the poisoned patients. Thus, the presence of an outdated fireplace in the house or detection of the patient in a garage with working engine of a car is suggestive of poisoning by carbon monoxide (CO) or car exhaust gases (5). Conversely, finding a patient in the street, deviates any attention from CO poisoning, in the first place. Determining depression history or previous suicide attempts can support the poisoning etiology. Likewise, known comorbidities identify a vulnerable patient. Patient's occupation may help to easily access to certain medications (muscle relaxants, insulin, potassium, short-acting barbiturates for physicians and paramedics) or chemical agents (cyanide or mercury for a chemist, solvents for an industry worker). Identifying the recent prescriptions for the patient is an essential prerequisite as patients are mostly poisoned with pharmaceutical products available to them and usually with their own medications that exist in their house.

1-2. Establishment of thorough clinical examinations

General examination: After clarifying the circumstances of clinical findings, a detailed clinical examination should be performed. The presence of injection site leads the physician to opioids, insulin or cocaine overdose. A particular toxic odor from patient's breath can easily direct the physician to certain toxic substances including ethanol, ether, isopropyl alcohol (acetone), trichlorethylene or organophosphorus pesticides (smell of gasoline), arsenic (garlic odor), cyanide (bitter almonds), hydrogen sulfide (rotten egg odor), fire smoke (burnt smell). The bright pink color of the skin can be found in the cyanide poisoning and rarely in CO poisoning (6). The presence of jaundice may be related to cholestasis, a delayed manifestation of absorption of hepatotoxic products (for example, acetaminophen or Amanita phalloides). Skin flushing can be manifested during alcohol-antabuse syndrome (that arises from ingestion of alcohol and disulfiram), or a massive histamine release in scombroid syndrome (that develops after having a dish of specific poisonous fishes). A bluish discoloration of the skin with a chocolate-brown blood during blood collection is suggestive of methemoglobinemia that can be occurred after inhalation or ingestion of dapsone, poppers, chlorates, aniline or metoclopramide in neonates. It should be noted that metheomoglobinemia can usually be tolerated as opposed to a true cyanosis due to a massive hypoxemia. Red colored urine can be seen after taking rifampicin while dark brown color urine evokes suspicion of a toxic cause of rhabdomyolysis such as *elapidae* snakebite envenomation (7), intravascular hemolysis or massive methemoglobinemia. Alopecia can be seen in the consequence of exposure to ionizing radiation, chemotherapy, colchicine, arsenic or thallium. Moreover, the association of gastroenteritis, peripheral neuropathy and alopecia is pathognomonic for exposure to the two latter toxic agents a week earlier. A choleriform syndrome (epigastric pain, watery diarrhea, vomiting, fever and dehydration) should raise the suspicion for colchicine poisoning (8).

Respiratory Status: The immediate existence of bradypnea or even apnea in a poisoned patient is due to the interaction of toxic agent with the respiratory centers which can be caused by an opioid, a barbiturate, cyanide, CO or hydrogen sulfide (9,10). Generally, ingestion of a benzodiazepine does not result in decreased respiratory function. Tachypnea occurs in the presence of hypoxemia (cyanosis or low SpO_2) secondary to a bronchial obstruction or aspiration pneumonia (respiratory distress) and in the absence of low SpO_2, due to a toxic psychostimulant (amphetamine, cocaine) or an associated metabolic acidosis (Kussmaul breathing).

Circulatory Status: The measurement of blood pressure and heart rate as well as performing an electrocardiogram (ECG) is necessary. The combination of hypotension and tachycardia usually predicts circulatory failure and ventricular or supraventricular disorder associated with irregular rhythm. Hypotension and bradycardia suggests conduction disorders after taking a beta-blocker (sinus bradycardia may be the only presentation), a calcium channel blocker, a sodium channel blocker or digitalis (bradycardia is usually isolated) (11). Profound hypoxemia (respiratory depression) or tissue hypoxia (cyanide poisoning) can also induce bradycardia and hypotension. The combination of tachycardia and hypertension is an outcome of alpha-sympathetic stimulation (cocaine, amphetamines, phenylephrine and monoamine oxidase inhibitors) (12). The combination of hypertension and bradycardia implies a massive vasoconstriction (sympathomimetics, central alpha-2 agonists), but it might stem from a central neurological complication following a hypertensive crisis (cerebral hemorrhage following cocaine abuse).

Body temperature: Some toxic agents can disrupt central body temperature. Hypothermia usually occurs following prolonged coma. In case of extreme vasodilatation, superimposed heat loss via the skin may follow. Hyperthermia may result from excess heat production related to muscle stiffness (malignant neuroleptic syndrome), convulsions, extreme agitation (antihistamines) or excessive vasoconstriction (cocaine) (13). Other possible mechanisms of hyperthermia are: oxidative dephosphorylation (aspirin and phenols), inhibition of sweating (anticholinergics) or direct exposure to heat (fire). Fever may also occur in the setting of aspiration pneumonia. Aspiration pneumonia can be confirmed by chest radiograph.

Neurologic examination: Poisoning induced coma is suspected in the absence of focal neurologic signs. Evaluation of five following parameters in neurologic examination is helpful for proper diagnosis: spontaneous motor activity (calmness or agitation), vascular tone (hypo- or hypertonia), deep tendon reflexes (hypo- or hyperreflexia), cutaneous plantar reflexes (CPR, indifference or presence of a Babinski sign) and size of pupils (mydriasis or miosis). Calmness of the patient (or maybe a sedated patient) is suggestive of taking sedatives or hypnotics; conversely, an agitated patient (tremor, convulsions) reminds taking psychostimulants or hypoglycemia. Myorelaxation syndrome (hypotonia, hyporeflexia and indifferent CPR) implies taking hypnotics, tranquilizers or ethanol, which is unlike a pyramidal syndrome (hypertonia, hyperreflexia and increased CPR) caused by antidepressants, phenothiazines, piperazines or hypoglycemia, and extrapyramidal syndromecaused by neuroleptics including substituted benzamides or butyrophenone (14).

Obviously, variations may exist; hence, coma associated with massive ingestion of meprobamate (Mepronizine® or Equanil®, recently retrieved from the French market) is generally hypotonic but may be hypertonic in 10% of cases (15). Miosis predicates the abuse of morphinomimetic or anticholinesterase agents (organophosphate or carbamate insecticides); in contrast, bilateral mydriasis and unreactive pupils to light prognosticates taking a tricyclic antidepressant, serotonin reuptake inhibitor (SRI), phenothiazine antihistamine, sympathomimetic agent or cocaine (16). Ophthalmoplegia or strabismus can occur after poisoning with carbamazepine or tricyclic antidepressant. Visual disturbance propels the mind towards quinine, ethambutol or cyclosporine poisoning, but especially for late presentation of methanol poisoning (originally irreversible blindness). Multiple toxicants can cause seizures (Table 1), including antiepileptics themselves (17). Finally, a state of apparent death with isoelectric line in a electroencephalogram may have come from a massive acute poisoning with barbiturates, benzodiazepines, carbamates or chloralose, particularly in the presence of associated hypothermia.

1-3. Identification of the toxidrome

The set of clinical manifestations, biological tests and / or ECG suggestive of a poisoning defines a toxidrome or toxic syndrome (3). These manifestations are direct effects of the toxicodynamic action of xenobiotics. Toxidrome represents characteristic and typical aspects of poisoning; however, it may not be specific for one toxic etiology. Accordingly, poly-or non-specific complications of toxicity can affect the clinical picture of the typical form (Figure 1). Furthermore, certain drug classes or a single product may induce one or more toxidromes. Nevertheless, toxidrome-based approach is helpful to move towards a final diagnosis and also exclude other differential diagnoses, especially in a non-examinable patient, due to an unstable state of consciousness, extreme agitation or confusion and respiratory or systemic circulatory failure. Following the ingestion of psychotropic drugs, it is of high value to calculate Glasgow Coma Scale (GCS) in order to evaluate the depth of a presumed toxic coma and to follow its progression.

Table 1. Toxic agents that are common causes of seizure

Pharmaceuticals
Tri-or tetracyclic antidepressants
Serotonin reuptake inhibitors
Lithium
Antihistamines
Cough piperazines
Chloralose
Toxic hypoglycemia
Isoniazid
Minaprine
Chloroquine
Xanthine bases: theophylline
Salicylates (in children)
Atropine (in children)
Psychotropic drug-related withdrawal syndrome (benzodiazepines, ethanol, barbiturates)
Non-pharmaceuticals
Cocaine
Amphetamines
Carbon monoxide
Organophosphates
Carbamates
Organochlorine
Metaldehyde
Camphor and terpene derivatives (e.g. menthol)
Ethylene glycol
Fluorides and oxalates
Water intoxication in potomania

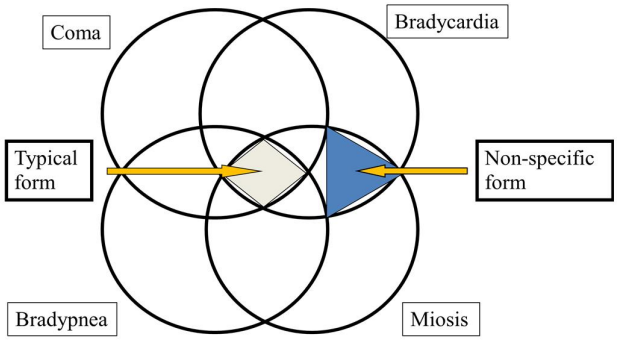

Figure 1. The opioid toxidrome. In practice, mild forms of toxidromes are more frequent than severe typical forms.

Assessment of GCS also facilitates making decision on intubation; however, it is not prudent to only rely on this score. On the other hand, assessment of GCS is not suitable for evaluation of toxic encephalopathy, because it may underestimate the severity of poisoning (presence of extreme agitation or trouble in swallowing, in early stages).

Following the ingestion of cardiotoxic agents, the main risks are shock, arrhythmias or cardiac conduction disorders (11). In this regard, both clinical signs and ECG are important for correct diagnosis that should be with a special attention to heart rate, systolic-diastolic pressure difference, QRS widening and QT prolongation. Having knowledge about the mechanisms involved in the circulatory failure (hypovolemia, vasodilatation or impaired contractility) is vital for the subsequent appropriate treatment of the patient (18). This principle justifies conducting early invasive or non-invasive hemodynamic explorations. This is why any symptomatic patient following the ingestion of cardiotoxic drugs should be admitted to the ICU (3).

2. Main toxidromes

2-1. Myorelaxation syndrome

It consisted of deep coma, hypotonia, or simple hyporeflexic drowsiness, which may be associated with hypotension or respiratory depression (19). The most likely causes are overdoses of benzodiazepines, imidazopyridine (zolpidem, zopiclone), barbiturates, meprobamate, sedative phenothiazine, phenytoin, sodium valproate or ethanol. The administration of flumazenil can be used as a pharmacodynamic test in a patient with myorelaxation syndrome without seizure, co-ingestion of a pro-convulsant psychotropic drug (particularly antidepressants), antimuscarinic signs, ECG abnormalities or complications of coma (decreased SpO_2due to aspiration). The test should be done under clinical monitoring and titration according to the following suggested protocol: initial dose of 0.3 mg in 1 min, followed by additional doses of 0.1 mg per min until a cumulative dose of 1-2 mg (3). The absence of clinical response in over 2 mg flumazenil questions the diagnosis of a pure poisoning with benzodiazepines or related substances. The rational use of flumazenil with respect to the toxidrome prevents from complications related to this antidote and can help in some cases to avoid tracheal intubation (3).

2-2. Opioid syndrome

It is made up of the following pathognomonic triad a) deep coma along with hypotonia and hyporeflexia or with a simple sedation; b) bradypnea (defined as respiratory rate <12 breaths/min) or apnea; c) a tight bilateral pinhole miosis (20,21). There might be sinus bradycardia and hypotension. If the loss of consciousness is not deep, bradypnea may still occur and respiratory rate can even be accelerated as the subject is stimulated by voice. This toxidrome follows by an opioid overdose; however, the set of manifestations is not specific for any kind of opioids.

Moreover, the emergency urine screening test identifies natural opioids (morphine, 6 -mono- acetylmorphine [the main metabolite of heroin], codeine, pholcodine, and codotheline) but it misses synthetic opioids (i.e. buprenorphine, methadone, propoxyphene, tramadol) and thus performing specific laboratory tests may be required.

Buprenorphine (Subutex®, Suboxone®) that is a partial agonist at the opioid receptors can even induce poisoning in its recommended effective dosage. Its clinical picture similarly includes coma and central respiratory depression while the severity is not remarkably different with overdose of other pure opioid agonists (9). The occurrence of such poisoning has been linked to the misuse of buprenorphine (intravenous injection of crushed tablets) or concurrent use with particular psychoactive benzodiazepines (9,22). The main threat of progression of opioid overdose is respiratory arrest, that can be counteracted by administration of naloxone, with titration (slow intravenous injection of 0.1 per 0.1 mg, repeated every 2-3 min). The therapeutic target should be assessed according to an increase in respiratory rate to over 15 breaths/min, without seeking full recovery of the poisoned subject. Reversal of neurological signs and respiratory depression is also a pharmacodynamic test that confirms the diagnosis (21). In case of buprenorphine overdose, the response to naloxone is debated in the literature. In our experience, no reversal was observed with routinely used doses (0.4 to 0.8 mg), because of the strong affinity of the buprenorphine to mu-receptors (9). The lack of complete awakening after naloxone administration should call for evaluation of a co-poisoning by another psychotropic drug or brings up anoxic brain damage in late presentation.

2-3. Anticholinergic syndrome

It initially manifests with: a) encephalopathy, associated confusion, hallucinations, delirium, dysarthria, tremor, agitation, seizures (frequent), or coma (not profound) and b) the antimuscarinic signs including sinus tachycardia, bilateral mydriasis, dry mucous membranes, acute urinary retention and / or reduction of bowel sounds. Urinary retention may cause an exacerbation of agitation in an encephalopathic patient. Coma is usually not profound without focal signs and is associated with pyramidal signs and restlessness. A deep coma with quick progression (< 6h) is suggestive of poor prognosis (23). It generally resolves in a few hours, so its extension beyond 48 hours requires seeking out a complication (anoxia) or co-ingestion of other psychotropic drugs.

Seizures (incidence: 6-11% with antidepressants, one of the main causes of toxic convulsions) are early-onset, widespread and uncommon beyond 24 hours (24). They are multiple (50%) and sometimes brief (30-60 seconds). Incoordination may exist with myoclonus to stimuli. Their occurrence is correlated with QRS widening and can lead to hemodynamic deterioration (Table 2) (25). Certain antidepressants (dosulepin, amoxapine, maprotiline) are specific convulsants.

The identification of anticholinergic toxidrome is suggestive of the ingestion of polycyclic antidepressants, some neuroleptics, certain antihistamines H1, antiparkinsonian drugs, or *Datura stramonium*. Administration of flumazenil increases the risk of seizure and is thus contra-indicated. The combination of hemodynamic instability and ECG changes directs to tricyclic antidepressant poisoning.

Table 2. Evaluation of the risk of neurological (seizures) and cardiovascular complications (ventricular arrhythmias) during a tricyclic antidepressant poisoning from the width of the QRS complex measured on the electrocardiogram (adapted from Boehnert et al. (25))

Ventricular QRS duration (msec)	Risk of seizure	Risk of arrhythmia
100	negligible	Negligible
100-160	moderate	Negligible
>160	High	High

2-4. Cholinergic syndrome

It is mainly related to poisoning with anticholinesterase pesticides including organophosphates or carbamates (26). These compounds represent a large family of chemical compounds that has been developed from the 40s, as a chemical weapon and pesticide. They are globally used in agriculture, veterinary medicine and are toxic agents that are frequently abused in poisonings, either accidentally or intentionally (for suicidal purposes). It is a public health problem and global issue. According to the World Health Organization, about three million cases of severe poisoning with over 220,000 mortalities occur annually, particularly in developing countries (26). In contrast, in western countries, these poisonings have become rare as organophosphates have been gradually replaced by less toxic compounds such as pyrethroids. Fortunately, terroristic or warfare use of organophosphates is rare. Recently, sarin has deliberately been released in Syria causing more than 1,500 deaths at several places in the country (27). In addition, in Mutsumoto, Japan in 1994 and in the Tokyo subway in 1995, this toxic gas caused 18 deaths (28).

The cholinergic syndrome is consisted of the following elements (26,29): a) muscarinic syndrome that causes bradycardia and hypotension, a tight miosis inducing visual disturbances and eye pain, rhinorrhea, sialorrhea, bronchorrhea and bronchospasm mimicking acute pulmonary edema, and an increase in the abdominal peristalsis with pain, bloating, involuntary defecation and urination; b) nicotinic syndrome that is associated with weakness, fasciculation, cramps, involuntary movements and paralysis that can affect respiratory muscles. In the paravertebral ganglia, nicotinic action opposes the muscarinic effects that results in tachycardia, hypertension and elevated circulating catecholamines, responsible for hyperglycemia, hypokalemia, hypophosphatemia and lactic acidosis; c) central cholinergic syndrome that manifests with confusion, ataxia, coma or even seizure. The effect on the respiratory centers exacerbates acute respiratory failure and also affects the vasomotor centers and cardioregulatory hemodynamics.

The typical organophosphate poisoning develops in three stages, early, middle and late (26). In early stage, three syndromes may develop in various degrees, depending on the toxic substance and route of exposure. After ingestion, gastrointestinal symptoms appear first. Upon dermal or mucosal exposure, the ocular and central neurologic manifestations (headache) appear earlier. Hence, during the Tokyo subway sarin gas attack, miosis was observed in 99% of symptomatic victims (30).

The cholinergic syndrome in carbamate poisoning may last less than 24 hours and never results in nicotinic signs. Moreover, the cholinergic syndrome caused by an insecticide of any kind can be associated with related disorders of its petroleum solvent including digestive disorders, loss of consciousness and also aspiration pneumonia that leads to additional hypoxia (29).

The diagnosis of cholinergic syndrome in its typical form is relatively easy due to the semiologic richness of the clinical picture. In atypical cases, the diagnosis is more difficult, especially when the symptoms are predominantly of gastrointestinal origin. Consequently, the diagnosis can be based on the measurement of the plasma butyryl cholinesterase (or pseudo-cholinesterase) activity. Unlike sensitivity and availability in emergency departments, this test is not specific, as it may decrease during pregnancy, anemia or liver failure. In case of high clinical suspicion, the physician must use a specialized laboratory test for measuring the activity of acetylcholinesterase that expresses on the surface of red blood cells (red blood cell cholinesterase).

The identification of marked muscarinic signs necessitates immediate intravenous administration of high dose atropine (2-4 mg stat, followed by repeated injection of 2 mg/10 min). It is a competitive antagonist of acetylcholine and thus it is a toxicodynamic antidote to muscarinic effects that acts in minutes on cholinergic receptors. The therapeutic goal is to obtain dryness of secretions and relief of bronchospasm. It is not necessary to achieve mydriasis, which should rather be regarded as a sign of overdose.

2-5. Adrenergic syndrome

It includes the set of (31): a) autonomic signs with psychomotor agitation, bilateral mydriasis, sweating, tremors and/or convulsions; b) cardiovascular signs with tachycardia, hypertension (for toxic alpha-stimulants) or hypotension (for toxic beta-2-agonists), palpitations and/or chest pain; c) ECG changes with sinus tachycardia or ventricular arrhythmias; d) metabolic signs with hyperglycemia, lactic acidosis, hypokalemia, leukocytosis and/or hypophosphatemia. This toxidrome can be observed as a result of poisoning with cocaine, amphetamines, lysergic acid diethylamide (LSD), ephedrine or caffeine (toxic alpha-stimulants) and theophylline or salbutamol (toxic beta-2-agonists). A cocaine overdose can be complicated with myocardial infarction (through coronary vasospasm) and ischemic stroke (through vasoconstriction of cerebral vessels) or intra-cerebral hemorrhage (through accelerated hypertension). In a patient presenting with an

Table 3. Diagnostic criteria of serotonin syndrome (adapted from Sternbach (34))

History	
	Recent introduction or increased doses of a "pro-serotonergic" agent in the absence of modification of the dose regimen of the current neuroleptic medication
Clinical Signs: Presence of at least 3 of the following signs	
	• Higher function: confusion (50%), agitation (35%), coma (30%), anxiety (15%), minor mania (15%), seizures (12%), headache, insomnia, hallucinations, dizziness • Autonomous system: fever (45%), increased sweating (45%), sinus tachycardia (35%), hypertension (35%), mydriasis (25%), tachypnea (20%), hypotension (15%), chills; nausea, flushing, diarrhea, hypersalivation • Neuromuscular system: myoclonus (60%); hyperreflexia (50%) muscle rigidity (50%), hyperactivity (50%), tremor (45%), incoordination (40%), clonus (20%), bilateral Babinski's sign (15%), nystagmus, trismus; bruxism, opistothenous; paresthesia
Differential Diagnosis	
	The differential diagnosis must exclude infection, metabolic disorders, neurological disorders or other toxidromes

emergency hypertensive crisis and identification of adrenergic toxidrome, suspected for cocaine overdose, it is prudent not to use pure α or βblockers because of high risk for development of coronary spasm (32), but preferably an alpha-beta-blocker such as labetalol (Trandate®) can be administered.

2-6.Serotonin syndrome

The clinical picture includes (33): a) neurological disorders including agitation, confusion, hallucinations, myoclonus, tremor, pyramidal syndrome, seizure, coma; b) autonomic disorders such as mydriasis, sweating, tachycardia, tachypnea, hyperthermia, chills, hypotension, diarrhea or even respiratory arrest; c) biological abnormalities such as hyperglycemia, leukocytosis, hypokalemia, hypocalcemia, disseminated intravascular coagulation, lactic acidosis and rhabdomyolysis. The clinical diagnostic criteria were defined by Sternbach (Table 3) (34). Diagnosis requires firstly to rule out metabolic or infectious etiology or withdrawal complications and secondly to differentiate the clinical findings from other toxidromes (Table 4). Myoclonus is usually at the forefront and should be pursued as a priority, as it is shown in the Hunter diagram (Figure 2), that provides more specificity in the diagnostic process (35).

Serotonin syndrome occurs more frequently than it is reported, as it is underestimated due to inadvertency to signs observed. It can be life-threatening. It is either a side effect of pro-serotonergic drugs taken in pharmacological dose facilitated by drug interaction or the result of an overdose. It reflects the increased brain serotonergic activity induced by substances such as the SRIs, monoamine oxidase inhibitors, lithium, tricyclic antidepressants, ecstasy and L-tryptophan (33). During this complication, the 5-HT1A and 5-HT2 receptors are involved (36,37). The identification of this toxidrome requires discontinuation of the suspected drug (in a drug interaction) or a symptomatic approach to prevent the malignant hyperthermia, multisystem complications and death. In severe forms, external cooling, respiratory support and muscle relaxation should be considered. No specific treatment has been shown to be effective for the serotonin syndrome in randomized trials. Nevertheless, the use of cyproheptadine (Periactine®) or dantrolene (Dantrium®) has been suggested (33,38,39).

2-7. Malignant neuroleptic syndrome

It is an undesired effect of taking neuroleptics and less often a consequence of an overdose. This syndrome should be considered in a set of hyperthermia (body temperature> 38°C), confusion, impaired consciousness, generalized hypertonia with osteotendon hyperreflexia, axial rigidity of muscles, sweating, hemodynamic instability as well as rhabdomyolysis (40). Fever may exceed 43°C and be life-

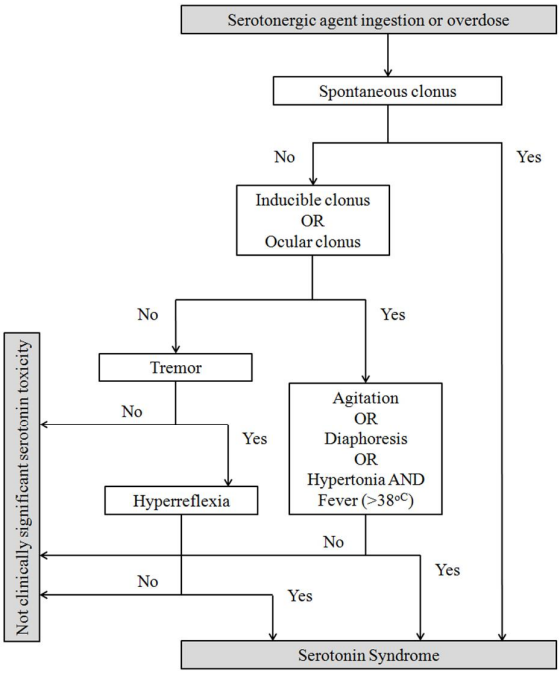

Figure 2. Hunter diagram for diagnosis of serotonin syndrome (adapted from Isbister et al. (35)).

Table 4. Differential diagnoses for serotonergic origin of a clinical presentation

	Serotonin syndrome	Anticholinergic syndrome	Malignant neuroleptic syndrome	Malignant hyperthermia
Toxic agent	Proserotonergic	Anticholinergic	Dopamine agonists	Inhaled anesthetic
Delay in clinical manifestations	< 12h	< 12h	1 to 3 days	30 min - 24h
Risk of life-threatening organ failure	+++	+	+++	++++
Pupils	Mydriasis	Mydriasis	None	None
Mucosal	Sialorrhea	Dryness	Sialorrhea	None
Skin	Diaphoresis	Dry erythema	Diaphoresis	Diaphoresis
Digestive sounds	↑	None or ↓	↓	↓
Muscle tone	↑, lower limbs	↑, none	↑↑	Rigor mortis
Deep tendon reflexes	Hyperreflexia, clonus	None	Bradyreflexia	Hyporeflexia
Consciousness	Coma, agitation	Delirium, agitation	Stupor, mutism, coma	Agitation

threatening. The onset of signs ranges from a few hours to 7 days for short acting neuroleptics and 2 to 4 weeks for long acting forms. This set of manifestations should be distinguished from malignant hyperthermia associated with serotonin syndrome (as a result of ecstasy for example) or a halogenated anesthetic (Table 4). The identification of this toxidrome requires an urgent symptomatic treatment with copious rehydration and cooling. The dantrolene (Dantrium®) and bromocriptine (Parlodel®) have been proposed as specific treatments (38).

2-8. Withdrawal syndrome of psychotropic drugs

Withdrawal syndrome should be considered for an opioid addict who had a reduced access to opioid substances and also in any patient with long-term psychotropic medication use who stopped consuming abruptly. Other psychotropic drugs that potentially can cause withdrawal syndrome are benzodiazepines, meprobamate and ethanol. Clinical manifestations initiates within 6 to 24 hours after last use/abuse and up to 5 days (in case of benzodiazepines) (41). The molecular mechanism of action is depending on the used/abused substance, usually consisting of the deregulation of the inhibitory GABAergic system and excitatory glutamate system or adrenergic and serotonergic hyperstimulation. The use of pharmacodynamic antidotes (flumazenil or naloxone) may accelerate acute withdrawal and therefore justifies careful administration and close monitoring.

Table 5. Toxic agents with and without membrane stabilizing effects

Pharmacological Classes	Products
Toxic agents with membrane stabilizing effects	
Class I Anti-arrhythmic drugs (Vaughan Williams classification)	Quinidine, lidocaine, phenytoin, mexiletine, cibenzoline, tocainide, procainamide, disopyramide, flecainide, propafenone, ...
β-blockers	Propranolol, acebutolol, nadoxolol, pindolol, penbutolol, labetalol, metoprolol, oxprenolol
Polycyclic antidepressants	Amitritptyline, imipramine, clomipramine, dosulepin, maprotiline
Antiepileptics	Carbamazepine
Neuroleptics	Phenothiazines
Analgesics	Dextropropoxyphene
Antimalarials	Chloroquine, quinine
Illicit drugs	Cocaine
Toxic agents without membrane stabilizing effects	
Calcium channel blockers (predominantly of cardiac action)	Nifedipine, nicardipine, verapamil, diltiazem, nimodipine, amlodipine, nitrendipine, bepridil, perhexiline
Other cardiotropics	Meprobamate, colchicine, beta-blockers without membrane-stabilizing effects, certain antihistamines H1, organophosphates, aconite, *Taxusbaccata*, Scombroid syndrome

The set of manifestations includes reversal of circadian rhythm, insomnia, headache, visual or auditory hallucinations, agitation and aggression, and even seizures or coma. Development of autonomic signs such as diarrhea, mydriasis, hyperthermia, sweating, cutis anserina, tachycardia and cramps are also possible. Treatment includes administration of supportive and replacement therapy or sedation or reintroduction of the drug interrupted (42,43).

2-9. Membrane-stabilizing effects

Membrane-stabilizing effect that is also known as "quinidine-like effect" is the inhibition of the sodium channel responsible for current sodium entering the cell during the phase 0 of the action potential (44). This property contributes to the pharmacological action of certain compounds such as anesthetics or anti-arrhythmic drugs, whereas for some other compounds, it may only appear at toxic doses (Table 5).

Poisonings with membrane stabilizing activity manifest with cardiovascular, neurological, respiratory and metabolic disorders and may even result in death (44,45). Cardiac disorders demonstrate early in the ECG with a flattening of the T wave, prolongation of the QT interval (except for the class IC anti-arrhythmic drugs according to Vaughan Williams classification including flecainide and propafenone) and widening of the QRS complex (best seen on the lead II) and signs of intra-ventricular conduction block (Table 6 and Figure 3). The highest risk is the development of ventricular arrhythmia which increases in parallel to the QRS prolongation (Table 2) (25): For QRS $\leq$ 100 msec, the risk is absent, for QRS between 100 -160 msec, the risk is low (10%) and for QRS $\geq$ 160 msec, the ventricular arrhythmias are common (50%). Some authors have proposed other indices in ECG to predict the risk including right axis deviation of the last 40 milliseconds (T40-ms), QRS $\geq$ 120, the amplitude of the R wave ($\geq$ 3 mm) or R/S ratio in aVR lead. A recent article offered a simple way to calculate the T40-ms (46).

Brugada patterns have also been described on the ECG, particularly with tricyclic antidepressants (incidence 15%), cocaine or class I anti-arrhythmic drugs; however, patients showing such ECG abnormalities may not experience considerably worse outcomes (47,48). With respect to ECG abnormalities, the predominant mechanism of the toxic shock is cardiogenic, but may sometimes be associated with a component of vasoplegia. A spontaneous convulsive coma can result not only from brain-specific toxic effects but also from cerebral hypoperfusion secondary to hemodynamic instability. Respiratory depression is usually associated with moderate coma. Severe poisoning with lipophilic beta-blockers may induce central apnea. Dextropropoxyphene may cause central respiratory depression with bradypnea by stimulation of mu-opioid receptors (49). Hypoxia and acidosis worsen the membrane-stabilizing effects on the heart. In severe forms, late-onset acute respiratory distress syndrome appears in the absence of aspiration and may be complicated by intra-alveolar hemorrhage (as with chloroquine). In case of hypoxia and respiratory acidosis associated with metabolic lactic acidosis secondary to collapse or repeated transient hypokalemia, seizures may occur. Hypokalemia is particularly marked in severe chloroquine poisoning (50). Hypoglycemia has been reported during disopyramide poisoning (51).

The identification of a membrane stabilizing effect on ECG necessitates the administration of a hypertonic sodium salt (molar sodium bicarbonate or lactate), with the aim of correcting the QRS in ECG to reduce the risk of ventricular arrhythmia (18,52).

2-10. Metabolic acidosis and elevated anion gap

In the presence of a positive history and a compatible clinical picture, the hypothesis of poisoning should be

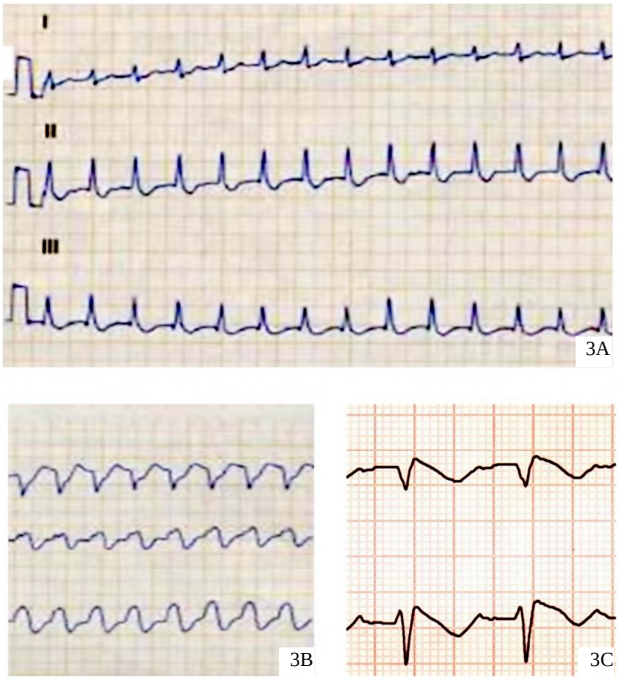

Figure 3. Electrocardiographic findings in poisoning with tricyclic antidepressants: Sinus tachycardia related to the anticholinergic effect (3A), membrane-stabilizing effect with QRS widening (3B) and "Brugada syndrome" with J-point elevation and ST segment depression or upwardly concave hammock (3C).

Table 6. Major electrocardiographic signs in membrane stabilizing effects

The earliest sign is a diffuse T-wave flattening
A QT prolongation with QT/QTc* > 1 is very specific and relatively early
An enlargement of QRS duration (measured in the bypass D2)
Other signs: - Appearance of Brugada syndrome - Enlargement of the PR interval - Extension of the P wave

* QTc: QT corrected

Table 7. Guide on metabolic acidosis with elevated anion gap

Metabolic acidosis with high anion gap ($[(Na^+ + K^+) - (Cl^- - HCO3^-)] > 17$ mEq/L)		
Mechanism	The increase in lactate explains high anion gap	The increase in lactate does not explain high anion gap
Non-toxic	Cardiovascular collapse Severe sepsis Repeated generalized seizures Hepatocellular insufficiency Severe tissue intestinal ischemia	Renal insufficiency (constant acid retention) Ketoacidosis (diabetes, fasting, chronic alcoholism)
Toxic	Metformin and other biguanides Cardiotoxic agents (shock) Paracetamol (liver failure) Cyanide Theophylline and other adrenergics Propylene glycol Carbon monoxide (moderate elevation) Side effects of antiretroviral therapy	Salicylates Ethylene glycol (metabolized to glycolate) Methanol (metabolized to formate) Paraldehyde (metabolized to acetate)

considered in any metabolic acidosis and elevated anion gap ($([Na^+] + [K^+]) - ([HCO3^-] + [Cl^-]$, Normal: 12-16 mEq/L) (Table 7). The combination of hyperventilation, neurosensory disorders (including tinnitus or hearing loss), dehydration, hyperthermia and sweating necessitates the search for poisoning with aspirin and its derivatives. A patient who drunk a toxic alcohol is not usually symptomatic in the first 12 hours post-ingestion. Nevertheless, in later stages, hyperventilation and signs of organ toxicity including visual disturbances for methanol and renal failure for ethylene glycol may appear (53,54). Measurement of osmolar gap (difference between osmolarity measured with delta cryoscopic method and calculated osmolarity: 1.86 $[Na^+]$ + [uremia] + [glucose])/0.93 mmol/L, Normal: 10-15 mosmol/Kg) demonstrates the presence of low molecular weight and high concentration osmols. An osmolar gap $\geq$ 25 mosmol/Kg in a patient with metabolic acidosis and elevated anion gap$\geq$1mEq/L is suggestive of an alcohol or glycol poisoning though they are not specific (Table 8). The osmolar gap is usually zero at the late phase of poisoning, even if metabolic acidosis is very severe (55). Correspondingly, the absence of anion gap should not precociously rule out a poisoning. The diagnosis can be made with the measurement of the involved alcohol or glycol in the plasma and/or urine using gas chromatography or high performance liquid assays as well as an enzymatic method. Because of its potential damages, upon suspicion of poisoning with a toxic alcohol, prior to development of metabolic acidosis with high anion gap not induced by the elevation of lactate, a loading dose of fomepizole (15 mg/Kg intravenously or orally) should be administered. Fomepizole is a competitive inhibitor of alcohol dehydrogenase that prevents any alcohol metabolism and stops the production of its toxic metabolites (56). The administration of the antidote should not be delayed for the laboratory confirmation of the diagnosis.

Massive acetaminophen poisoning can rarely result in hyperlactatemia prior to the development of liver failure, due to inhibition of the mitochondrial oxidative phosphorylation attributed to the interaction of paracetamol and N-acetyl-p-benzoquinonimine (its toxic metabolite) with mitochondrial complexes I and II (57,58). However, this effect can be fully reversed by early administration of N-acetylcysteine. In this setting, persistent or late metabolic acidosis in the absence of liver failure is not likely due to paracetamol and should prompt a search for other causes of metabolic acidosis.

Table 8. Differential diagnosis to an increase in the osmolar gap (> 25 mosmol/Kg) and/or anion gap (>17 mEq/L)

Diagnosis	High osmolarity	High anion gap
Ethanol	Increased	Normal
Ethylene glycol	Increased	Increased
Methanol	Increased	Increased
Isopropanol	Increased	Normal
Other toxic alcohols	Increased	Rarely increased
Lactic acid	Normal	Increased
Ketoacidosis	Slightly increased	Increased
Acute renal failure	Normal	Slightly increased

CONCLUSION

The etiologic evaluation in a presumed poisoned patient requires a targeted history and also a thorough physical examination, ECG and, if necessary, routine biological analysis, to find out a toxidrome. Emergency treatment decisions are relied on the initial clinical approach. For a comatose patient, screening with immunochemistry analysis of psychotropic and narcotic drugs has a limited place for the management of the emergency patient. The only toxicologic analysis that is useful to establish diagnostic certainty and prognosis evaluation is measurement of blood concentration of a toxic agent guided by the initial clinical approach based on toxidromes.

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