Toxic responses of the heart: an overview

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A considerable and increasing number of xenobiotics, including drugs (e.g. antihistamines, tricyclic antidepressants, cardioactive drugs, anesthetics), natural products (hormones, cytokines, animal and plant toxins) and synthetic substances (e.g. drugs of abuse, chemical solvents, heavy metals, halogenated amines) can interact with cardiovascular system. This interaction may results from a direct action of the xenobiotic that can cause either structural alterations, generally with medium to long term time latency, characterized by anatomical and cellular lesions of the myocardial tissue either functional manifestations, usually with short term time latency, characterized by arrhythmic alterations and cardiac conduction disorders. Cardiotoxic manifestations should also result from an indirect interaction of the substance with other systems and may involve central nervous system (e.g cathecolamines regulation), peripheric receptor system (e.g. β1-adrenoceptor or muscarinic receptor interaction), endocrine system, electrolytes balance. Functional manifestations are mainly related to the vascular system and heart conduction and, in severe poisoning, can lead to lethal arrhythmias without evidence of macroscopic structural damage; myocardial structural alterations, such as myocardium cellular necrosis and inflammatory reactions, are frequently related to the direct effects of cardiotoxic xenobiotics. Functional changes involve mechanisms responsible for arrhythmias, such as voltage-gated ion channels, ion exchangers and ATP-ases interaction. Structural alterations mainly involve either the integrity and the functionality of structures and cellular organelles strictly related to myocardiocyte vitality and responsible for ATP and intracellular calcium homeostasis (e.g. myocytes cell membranes, mitochondria, sarcoplasmic reticulum). The mechanisms of cardiotoxicity are numerous and complex; several drugs (e.g. volatile anesthetics, tricyclic antidepressants, antihistamines, anthracyclines), substance of abuse (e.g. cocaine) and cardio-toxic substances (e.g. solvents / halogenated hydrocarbons)[1] are able to interact with the cardiovascular system through different mechanisms simultaneously. Acute tricyclic antidepressants overdose for example may cause severe arrhythmias through a complex mechanism that involve both sodium-channel blockade and muscarinic antagonism at cardiomiocyte cell. Conduction disorders due to volatile anesthetics and halogenated hydrocarbons acute poisoning may be related to several and simultaneous mechanism characterized by sodium, potassium and calcium voltage-gated ion channels blockade, β1-adrenoceptor agonism, muscarinic M2-receptors antagonism, cathecolamine re-uptake inhibition and electrical uncoupling due to gap junctions impairment[1]. Anthracyclines overdose (e.g. doxorubicin) can determine acute cardiotoxic effects characterized by conduction disorders (e.g. QRS widening, QT interval prolongation, ST-T changes, bundle branch block, premature ventricular contraction) related to calcium intracellular homeostasis alteration due to sarcoplasmic reticulum (SR) calcium release channel blockade and SR calcium ATP-ase impairment. Anthracyclines at high cumulative doses of 450-550 mg/m^2 can determine chronic cardiotoxic manifestations with late time onset (3-4 months up to years). Chronic anthracyclines cardiotoxicity typically characterized by dilated cardiomyopathy is related to several mechanisms: from iron metabolism alterations to free radicals and oxygen reactive species production[2,3]. Cardio-toxic effects may also results from synergistic interaction of several substances in both acute exposure (e.g. intake of cocaine and ethanol simultaneously) and in chronic therapy (e.g. chronic therapy with anthracyclines and taxanes)[4]. There are also physiological conditions (age, weight, sex etc.) and pathological aspects (e.g. long QT syndrome, ryanodine gene mutations, prior ischemia, metabolic acidosis hypokaliemia, hypotension) that can increase the susceptibility of a patient to toxic effects on the cardiovascular system. Recent studies published in the medical literature evidenced either an age-dependent change in myocardial cardiac glycoside receptor (Na,K-ATP-ase pump) concentration either an high renal cleareance of some cardioactive drugs such as nonselective beta-blockers in children; these aspects may be related with the different susceptibility to cardiotoxic effects of pediatric patients than adults[5,6]. The mechanisms of cardiotoxicity are often multiple and complex and can result in functional/arrhythmogenic alterations (acute/subacute) and/or cardiac lesional damage (subacute/chronic) with degrees of severity and time latency closely related not only to the substance (e.g. dose, route of exposure) but also to possible co-exposure to synergic or retardant substances (e.g anticholinergic drugs that reduce peristalsis, ingestion of cardiotoxic alkaloids with slow gastrointestinal absorption) and the patient background. These aspects are important for diagnosis (e.g. type and duration of monitoring) and management of patients with acute or chronic cardiotoxic effects or with potential risk of cardiotoxicity. Therapy may be both symptomatic and supportive (e.g. amines and fluids administration for hypotensive effects in beta-blockers and calcium channel blockers overdose) and, when possible and available, specific with antidotes (e.g. administration of sodium bicarbonate in the wide QRS complex arrhythmias in tricyclic antidepressant overdose).

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HFP and allergy: a significant difference

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The allergic reactions are an important part of access to Emergency Departments. Often they are phenomena of mild to medium intensity, but frequently severe reactions up to anaphylactic shock are observed.
In our ED, in addition to supportive care, we determine tryptase serum levels which is an interesting marker in subjects at risk of anaphylaxis. In this survey, we analyze the role of tryptase in order to differentiate real allergic syndrome from other syndromes causing similar effects with a different mechanism, avoiding diagnostic errors that might cause therapeutic difficulties, as in the case of Scombroid syndrome (Histamine Fish Poisoning, HFP), a complex of symptoms caused by biogenic amines, mainly the histamine, contained in fishfoods.
Tryptase is a serinprotease, stored in mast cells granula. Its molecular weight is 134 kDa and it is composed of 4 subunits, presenting in two isophorms: a-tryptase, ß-tryptase: a-tryptase is released during the cell degranulation and it is responsible of the basal seric level. ß-tryptase is released during anaphylactic reactions. In this case, there is a fast increase of the ß-tryptase.

Table 1
Main clinical features in the two groups of patients.

	HFP	Allergic syndrome
n° of cases	10	50
Male/Female	3/7	15/35
Median age (range)	49 y (21-58)	46 y (20-56)
Vomiting or diarrhoea	70%	3%
Abdominal pain	40%	15%
Rash	100%	100%
Itching	70%	100%
Hypotension	70%	3%
Mouth, tongue and lips oedema	20%	10%

If a blood sample is needed, it must be taken one or two hours from the beginning of the symptoms, the protein half-life being 90-120 minutes.
The histamine is a substance naturally present in mammals, it is contained in mast cells and basophilic granulocytes, and its biological effects are visible only when it is released at high doses in the course of allergic reactions or other. The effect is exerted by binding to cell membrane receptors in the respiratory apparatus, cardiovascular, gastrointestinal, and immune system.
Since the syndrome is due to the toxicity regard to histamine, there are variations in individual susceptibility, and clinical signs are more severe in those who take substances that inhibit histamine detoxicant enzymes.
In this work, we observed 50 patients with allergic reaction and 10 with HFP trying to correlate serum levels of tryptase with the severity of the clinical presentation, and medical history, noting that in case of certainly determined allergic reaction (insect stings, drugs, etc.), tryptase levels increased to varying degrees, while in cases of HFP (symptoms onset within minutes to hours after fish ingestion, developing a severe histamine-mediated reaction, without a history of previous allergic reactions), tryptase levels was unchanged.
Recognizing the HFP can be extremely difficult, especially in ED, but, although the basic treatment is basically the same as the allergic reactions, however in HFP may be useful other drugs and even gastric lavage to resolve symptoms. In addition, according to Italian legislation, HFP must be notified to authority.
We also tried to define a scheme of recommended treatment according to different physiopathological mechanisms of the two syndromes, suggesting a long term follow up in case case of HFP, considering that this illness is not a simple poisoning from histamine.
Notwithstanding it is linked to high levels of this substance in fishes of certain species contaminated by bacteria, the pathogenesis of HFP is still not clearly delineated.
Some of the responsible bacteria are present in the ordinary microbial flora of the fish; many of them derives from contamination that may happen at whatever level in the food processing chain.
The "key" for limiting the bacterial contamination (and of course the derived histamine), is a rapid refrigeration of the product immediately after the capture and the maintenance of the cold.

Therapeutics errors and adverse drug reactions in Poison Centre activity: results of a two years pharmacovigilance project

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Introduction

Poison Control Centres (in Italian, Centro Antiveleni or CAV), that carry out pharmacovigilance and toxicovigilance activities, provide specialistic consultations about adverse drug reactions (ADR), probable or suspected, and about therapeutic errors (TE) of prescription, dispensation and administration. Concerning the ADR, calls normally come from doctors and private citizens who are asking for the possible connections between treatment with traditional medicine, herbal or homeopathic products and pathological problems. In the other cases it is the Poison Centre specialist, faced with a particular clinical picture and through the study of the pharmacological history of the patient, who suspects an ADR. The intention of the FarViCav project, promoted by the Lombardy Region, is to focalize attention on the problems of ADR and TE that emerge from the activities of the three Poison Control Centres in Lombardy (Milan, Pavia and Bergamo).

Objectives

The objectives of this study are: 1) to report precociously the ADR cases to the Lombardy Region and AIFA (Italian Drug Agency) as requested for serious reactions; 2) value the prevalence of TE not otherwise detectable and provide the means of modification and to control eventual formulations involved; 3) to detect emerging problems providing an early warning system for the ADR particularly serious, frequent, not previously detected and/or involving recently marketed drugs; 4) acknowledge as ADR pathological events otherwise attributed to other causes; 5) to allow the comparison between ADR reported by CAV and those reported to the AIFA pharmacovigilance system. Reassuming, this project allows the existing farmacovigilance system to be potentiated, to detect problems not otherwise detectable and offers an efficient means for the prevention or the revision of drugs that are involved in repeated warnings.

Methods

According to the dispositions of the Lombardy Region, the work began on 1st April 2009 and will continue until the end of 2013. In the first months the data involved in this project were identified. These included: date and hour of the consultation; date and hour of the event (TE or ADR); detailed description of the event; substance involved (active ingredient, formulation, amount); eventual factors that contributed to the event; contemporary assumption of other substances (alternative medicines, alcohol, drugs of abuse, food); clinical picture; therapies and outcome. Included in this study were cases of TE and ADR that occurred in the Lombardy region and that were recorded by the three CAV of this region. Two forms for the data registration were prepared (one for the ADR and the other for therapeutic errors) and a data base that is shared by the three CAV. The data collection started on the 1st of September 2009 according to the defined criteria.

Results

In the first two years of the project, the Pavia CAV inputed in the FarViCAV system 461 cases that met the criteria of inclusion identified by the project (48% M; 52% F). The mean age was 27.8 years.

Four hundred and thirteen (90%) of the 461 cases were therapeutic errors. The mean age was 26.1 years (48% M; 52% F). The age was unknown in 19 cases. The agents most frequently associated with errors of administration or assumption were: medicine acting on CNS (16%), antibiotics (15%), acetaminophen (13%), antihistamines (9%), asthma medicine (9%) and cardiovascular medicine (6%).

Children under the age of 5 were involved in 174 cases (42%). The agents most frequently associated with errors of administration were acetaminophen in 24.7% of the cases, antibiotics in 19.5% and antihistamines in 13.7%. For these three pharmaceutical groups the therapeutic error was caused by parental distraction (22.7%), misunderstanding of the prescribed dose of antibiotics and antihistamines (11.8%), administration of a different medicine (8.9%), antibiotic preparation error (5.9%), prescription (2.9%) or dispensation error (2.9%). In 13.8% of cases, parents did not check correctly the dose to be given. In 31 cases (30.6%) the cause of the therapeutic error was unknown.

In general most cases of TE were recorded between 19:00 and 23:00 (when it can be hypothesized that the parents are tired and occupied with other choses), while there was no significant variation among the days of the week. In 54.2% cases the patient was at home when the CAV was called: 88.4% of these cases the patient was treated at home avoiding admission to the emergency services and eventual hospitalization.

The degree of seriousness of the TE cases was evaluated using the Poisoning Severity Score (PSS). This grading system has been used for more than ten years by European CAV to identify and confront the seriousness of the intoxications. PSS score is assigned by the specialist of the CAV twice, at the end of the first call and at the time of the conclusion of the consultation. Concerning the 413 cases of TE, in 74% of patients, a PSS of 0 degrees (absence of signs and symptoms) was confirmed at the end of the final evaluation of the clinical case. This indicates that CAV consultation about TE has high positive predictive value which translates into the saving of admission to the emergency services. In 20.6% of cases, a PSS of 1 degree (slight signs and symptoms) was assigned at the end of the first call and confirmed in 99% of cases at the end of the final evaluation of the clinical case. In only one case a PSS of 3 degrees (serious signs and symptoms) was assigned and then confirmed.

In the period of this study, calls on serious or unexpected ADR were 48 (10%). The mean age was 43 years (46% M; 54% F). Children under the age of 5 were involved in 12.5% of cases. The agents most frequently associated with ADR in the case series considered were: medicine acting on CNS (25%), medicine for gastrointestinal diseases (13%), antibiotics (8%), painkillers (8%) and cardiovascular medicines (8%). In 60% of cases, a PSS

of 1 degree was confirmed at the end of the final evaluation of the clinical case. A PSS of 2 degrees (moderate signs and symptoms) was assigned in 23% of cases and a PSS of 3 degrees in 10.4% of cases (confirmed in four out of five cases at the end of the evaluation).

Conclusions

Although based on preliminary data related to a single centre, the study permitted to increase of the reports to the regional and national pharmacovigilance systems and to quantify and characterize the event of TE, detecting the most frequent causes and highlighting the agents most frequently involved by age. The study also revealed the fundamental role of CAV in avoiding admission of a large number of patients to the emergency services, thus significantly saving resources for the National Health System. In fact, accidental error often involves taking low doses of medicine with the resulting signs and symptoms slight that can be treated at home. In the other cases, the early and proper treatment suggested by the CAV specialist can prevent the emergence or limit the severity of the intoxication, thus avoiding hospital admission or prolongation of hospitalization.

Weight loss agents and dietary supplements: use and abuse

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Pharmacological research is making a great effort to find safe, well tolerated and efficacious anti-obesity agents as obesity has become an epidemic of global proportions. There are a number of pharmacological approaches that have been used to control body weight in overweight and obese individuals but, actually, the pharmaceutical options available are limited. Currently, in Italy no one anorectic agent is approved for the treatment of obesity, even for short-term use. The terms "anorectic agent" or "appetite suppressant" are used to denote drugs that act on the neurochemical transmitters of the Central Nervous System (CNS) to reduce food intake[1]. In addiction to this class of substances, many other dietary supplements are used to lose weight. They include a huge number of dietary supplements containing herbs or other botanicals and extracts or concentrates thereof.

Appetite can be considered to be under the control of a number of peripherally generated factors that can be classed into either episodic (short-term inputs generated by meal intake) or tonic (inputs generated by the body's constant metabolic need for energy) signals. They differ in the nature of the input and the duration of their effects, but fluctuations in both produce strong feelings of either hunger or satiety. Both provide input into the CNS appetite regulating systems which are critical to long-term weight regulation. The monoamine serotonin (5-HT) and other classic neurotransmitters within the CNS such as noradrenaline (NA), dopamine (DA) and histamine (H) have been shown to be critical in controlling eating behaviour[2]. Amphetamine and desoxyephedrine were the first generation of sympathomimetic amines studied for their effects on food intake and appetite regulation but their side effects and potential of abuse limited their use. The second generation, developed before 1970, included sympathomimetic βphenethylamines such as phentermine and phendimetrazine, that were designed to reduce the side effects of the first generation drugs, while retaining their effects as appetite suppressants. The third generation of sympathomimetic drugs includes only sibutramine, a serotonin-noradrenaline reuptake inhibitor[1]. The side effects of many of these compounds, associated with their broad pharmacological activity and potential of abuse, have led to their withdrawal as obesity treatment in many countries. In 1959 phentermine, a noradrenergic agent, was approved by the US Food and Drug Administration (FDA) for use as a short-term adjunct to behavioural treatment of obesity. In 1973, the FDA also approved fenfluramine and its d-isomere dexfenfluramine, two setotoninergic agents, as appetite suppressants. These agents were afterwards combined on the presumption that the resulting reduction in the daily dosing of either drug alone would mitigate side effects while maintaining clinical efficacy[3]. However in 1997 Connolly described the first 24 cases of valvular heart disease induced by appetite suppressants assumption[4]. By the end of the same year, more than 100 reports of appetite suppressant-related valve disease had been reported to the FDA and fenfluramine was withdrawn from the US market.

Similarly, sibutramine, a noradrenaline and serotonin reuptake inhibitor, was approved by the US FDA in 1997 for long-term (> 12 months) management of obesity. At the time of its approval by the European Medicines Agency (EMA), it was already known in some studies that sibutramine increased blood pressure[5]. Thus, the SCOUT (Sibutramine Cardio-vascular OUTcomes) trial was initiated to study the long-term effects of sibutramine treatment on cardiovascular outcomes in subjects with high cardiovascular risk. The final results of SCOUT showed that sibutramine significantly increased the risk of serious non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, resuscitation after cardiac arrest or cardiovascular death) compared with the placebo[6]. Thereby, in January 2010, the EMA suspended marketing authorization for sibutramine or medicines containing sibutramine across the EU, and in October 2010 the FDA requested the withdrawal of sibutramine[7].

Serious adverse effects are also described for treatments with dietary supplements marketed for reducing body weight. Ephedra is a shrub that grows in many parts of the world. Different species vary in the amount of ephedrine alkaloids, the structure of which demonstrates significant similarity with amphetamines and other catecholamines. Thereby they possess β and βadrenergic agonist activity and, in addiction, they enhance the release of endogenous catecholamines[8]. Ephedra sales prospered in the '80 because the product was perceived by consumers as a "natural" and "safe" alternative to prescription weight loss products without the associated risk of harm. Actually adverse effects associated with ephedra use include headache, insomnia, anxiety, psychoses, hypertension, seizure and cardiovascular effects such as myocardial infarction, arrhythmias, stroke and death. FDA first warned the public of the risks of ephedra in 1994, following numerous reports of adverse effects associated with its use. In 1997 FDA was already in receipt of more than 800 reports of adverse effects related to ephedra and in 2004, after 117 deaths and 16.000 reports of adverse effects, all ephedra sales were banned. The use of several common herbs and dietary supplements has been also associated with hepatotoxicity, varying from asymptomatic elevations in hepatic enzyme levels to fulminant hepatic failure. Supplements with potential liver toxicity are, for example, Garcinia

Cambogia, Camellia Sinensis (the scientific name for green tea), Kava and Hoodia Gordoni. A typical pattern of liver injury was not found (biopsies noticed cholestatic, hepatocellular and autoimmune patterns)[9].
In addition to the adverse effects and the potential of abuse (i.e. amphetamine), risks associated with the use of appetite suppressant and dietary supplements come also from their wide availability on the Internet and by illegal trading. Thus patients may have access to medicines without any medical evaluation or prescription, banned drugs or dietary supplements contaminated (with toxic botanicals, heavy metals, pathogenic microorganisms, pesticides) or adulterated (with banned drugs or undeclared pharmaceutical ingredients). In a retrospective study conducted by reviewing all cases of poisoning suspected to involve use of illicit slimming products that were referred to the authors' laboratory, 66 poisoning cases were encountered and 81 products were analysed[10]. Analysis of the products demonstrated the presence of 12 ingredients that were classified in undeclared weight-loss drugs, drug analogues, banned drugs, drugs used for an inappropriate indication and thyroid hormones. Authors found up to six illicit agents within the same products. Sibutramine was the most commonly encountered illicit agent in the study.
The diagnosis of adverse effects associated with use of appetite suppressants and slimming products can be sometimes difficult due to the long latency of the onset of symptoms and the patient's reluctance to report the assumption of these products. Thus the use of slimming drugs and dietary supplements has to be included in the anamnesis of the patients, especially the young, in the case of cardiovascular problems or liver injury.

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Portal vein air embolism after hydrogen peroxide ingestion: an unexpected complication or an underdiagnosed finding?

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Background

It is known that hydrogen's peroxide (H_2O_2) can cause portal embolism due to the passage of oxygen bubbles into the portal vasculature. This is probably due to a sudden expansion of gas inside the gastrointestinal tube and a possible entry into submucosal tissue through ulcerative lesions. Hyperbaric oxygen therapy can be considered the definitive treatment of this lesion

Case report

A 35-years old woman with negative past medical history referred to the ED of Alessandria (Italy) 90 minutes after the accidental ingestion of a 30% solution of H_2O_2. She complained of abdominal pain, nausea and vomiting; vital signs were normal as her mental status. She was submitted to laboratory tests which did not show any particular change. She had a gastroesophageal endoscopy which showed some ulcerative mucosal lesions. Due to the persistence of abdominal pain, it was decided to perform an abdominal CT scan that showed air in the portal system (Figure 1a). Our Hyperbaric Chamber in Novara was alerted and the patient received an emergency treatment at about 11 hours after ingestion. She received HBO therapy at 2.8 ATA for 2.30 minutes. She had an immediate resolution of symptoms and was discharged home two days after a control CT that revealed a complete resolution (Figure 1b) with no occurrence of any other complication.

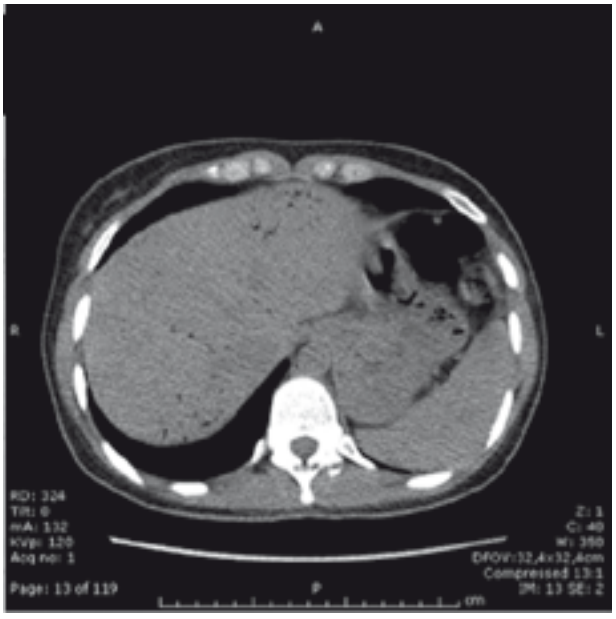

Fig. 1a

Discussion

The contact between H_2O_2 and the mucosa provokes its immediate dissociation in O_2 and water. Even a simple sip is able to produce even 3.4 L of oxygen gas[1] that can pass through the mucosa (especially if ulcerated) and produce a gas embolism than can result in portal hypertension, bowel edema and abdominal pain. HBO may act by reducing the volume of gas emboli and increasing solubility of oxygen into the tissues and blood.. Further reports and studies can make it clear if portal embolism is an unexpected complication or a more common consequence that is usually underestimated in its potential risks.

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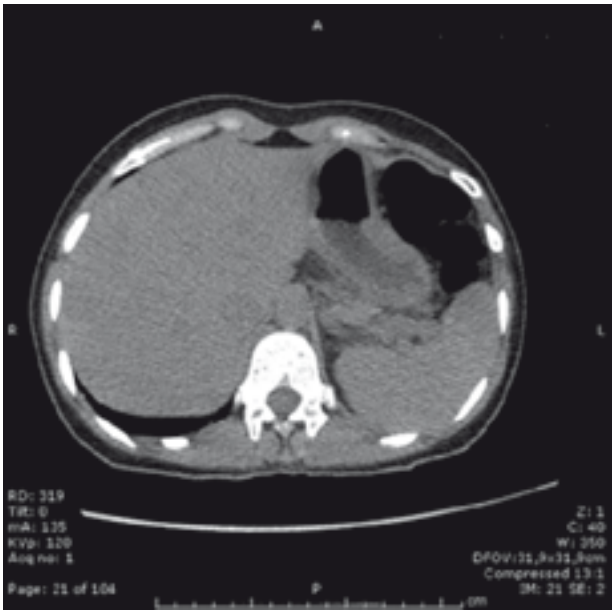

Fig. 1b

A case of acute myopericarditis due to high-dose cyclophosphamide intravenous infusion

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We report the case of a 55 years old woman with a diagnosis of Multiple-Myeloma (MM) IgA lambda. Her anamnesis reported hypertension and Monoclonal Gammopathy of unknown significance (MGUS) IgA lambda known since 2003. In December 2009, before the diagnosis of MM, an electrocardiogram showed sinus rhytm and normal morphology. The echocardiogram then showed a not dilated nor hypertrophic left ventricle with preserved global systolic function (EF 60%). Pulmonary arterial systolic pressures (PAPs) were normal. Two cycles of lenalidomide-dexamethasone were then performed without response until January 2010. Thus, from March to May 2010, she was switched to a therapeutic regimen consisting of four cycles of dexamethasone-liposomal doxorubicine-bortezomib (1.3 mg/m2), followed by mobilization with high-dose cyclophosphamide (CTX) in June 2010. The day after the administration of CTX (3g/m2, for a cumulative dose of 4.17 g) the patient complained retrosternal pain associated to a swelling lip feeling. The patient was dyspnoeic, normotensive but tachycardic. Physical examination showed third hearth sound without signs of stasis. The electrocardiogram was negative for ischemic signs, but movement of myocardial necrosis enzymes (TnI = 1,87 mcg/L), neurohormonal activation (NTpro-BNP = 25667 ng/L) occurred. An echocardiography showed akinesia of the anterior wall and anterior septum, marked hypokinesis of anterolateral and posterolateral wall, together with severely compromised left ventricular systolic function (EF 20%). Unbuffered pericardial effusion and increased PAPs were also present. Therefore, the patient was transferred to Cardiac Intensive Care Unit. In this setting, cardiac angiography showed the absence of atherosclerotic plaques. Beta-blockers, diuretics, and digital therapy was set, leading to a gradual clinical response. Follow-up echocardiography exam performed two months later showed an improvement of EF to values of 45%. One year after the acute event, the systolic function returned to normal values (EF 60%), PAPs returned to the normal range and pericardial effusion disappeared. She currently remains in good clinical conditions and the disease is stable.
In agreement with the literature, and in the light of clinical data, we starred the case as an acute myopericarditis due to CTX.
High-dose CTX intravenous infusion (120-240 mg/kg over 1 to 4 days) is associated with congestive heart failure and death from hemorrhagic myocarditis. Cardiac toxicity from CTX is acute, not related to the cumulative dose and it can be reversible. Cyclophosphamide-associated myocarditis is identified by asymptomatic and reversible decreasing systolic function. Although it is an uncommon toxicity, when it occurs it is characterized by high mortality due to a fulminant hemorrhagic myocarditis. Even if the exact injury mechanisms remains unclear, this seems to be due to endothelial damage which may cause a myocyte damage. These data highlight the need for close monitoring of patients during therapy with high doses of cyclophosphamide in order to minimize possible toxic effects.

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Rimozione endoscopica in *body packing*: descrizione di un caso clinico

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Un uomo di 53 anni si presenta autonomamente al Pronto Soccorso per dolore addominale, riferendo di avere ingerito, cinque giorni prima, 2 ovuli contenenti cocaina e 2 ovuli contenenti hashish, confezionati in modo artigianale e di dubbia tenuta. Poche ore prima di presentarsi in Pronto Soccorso, il paziente aveva assunto un prodotto lassativo, senza risultato.
Alla prima valutazione, il paziente risulta asintomatico e i parametri vitali sono stabili (PA 140/80 mmHg, FC 88 bpm ritmico, $SatO_2$ 98% con FiO_2 21%). L'esame obiettivo risulta nella norma: addome trattabile, lievemente dolente, peristalsi valida, alvo aperto a feci e gas.
Gli esami bioumorali mettono in evidenza un'alterazione dei marker di abuso alcolico (confermato dallo stesso paziente) e le urine risultano debolmente positive per benzoilecgonina e fortemente positive per cannabinoidi. L'ECG non mostra alterazioni patologiche. Opportunamente interrogato, il paziente riferisce uso sporadico di cocaina e THC per sniffing (con assunzione di entrambe le sostanze circa 15 giorni prima dell'evento).
Il paziente viene quindi sottoposto a radiografia diretta dell'addome, risultata negativa, e successivamente a TC senza mezzo di contrasto, che invece permette di rilevare la presenza di due corpi estranei di forma ovalare a livello gastrico e altri due a livello delle anse digiuno-ileali.
Data la lunga permanenza degli ovuli in ambiente acido gastrico, e nell'impossibilità di attribuire la cocainuria a precedente assunzione piuttosto che a un iniziale cedimento degli ovuli, viene deciso di procedere alla rimozione per via endoscopica, avendo il paziente rifiutato di sottoporsi a gastrotomia laparotomica.
L'EGDS eseguita mediante endoscopio standard (FUJINON Modello EG 250 ER) con accessorio cestello di 3 cm di diametro (ROTH NET-POLYP US-Endoscopy) permette l'asportazione a livello antrale di 2 ovuli, uno dei quali appare stabilmente incuneato e ostruente il piloro, risultati contenere cocaina. Il contenitore (doppio involucro di pellicola da cucina all'interno e lattice di condom all'esterno) appariva lesionato.
Il paziente viene quindi trasferito in reparto e inizia trattamento di decontaminazione gastrointestinale (Whole Bowel Irrigation) mediante la somministrazione di PEG (polietilenglicole, lassativo polimerico ad azione osmotica) che permette l'eliminazione di altri due ovuli localizzati nel lume intestinale. Durante la degenza le condizioni cliniche si sono mantenute sempre stabili. Dopo l'esecuzione di TC addome di controllo, risultata negativa per la presenza di corpi estranei a livello del tratto gastroenterocolico, il paziente viene dimesso e affidato alle forze dell'ordine.
La letteratura corrente è unanime nell'indicare la necessità di un approccio interventistico in casi di alto rischio di rottura di corpi estranei contenenti stupefacenti. Il trattamento chirurgico è da preferire nei casi di pazienti sintomatici o a rischio di tossicità acuta; la rimozione di corpi estranei contenenti sostanze stupefacenti mediante tecniche endoscopiche (soprattutto per ovuli confezionati in modo artigianale con condom, palloncini, ecc.) è da sconsigliare per l'alto rischio di rottura accidentale dell'involucro con successiva tossicità acuta.
Nel caso in esame, data l'opposizione del paziente all'intervento chirurgico, il numero limitato di corpi estranei presenti a livello gastrico, l'assenza di segni e sintomi di intossicazione acuta e, soprattutto, la possibilità di uno stop a livello pilorico, abbiamo ritenuto di poter procedere al trattamento del paziente per via endoscopica.
In base alla nostra conoscenza, questo sarebbe il quarto caso di rimozione di corpo estraneo contenente cocaina dalle alte vie digestive, mediante tecnica endoscopica, in paziente che ha rifiutato trattamento chirurgico.

Iperosmolarità in corso di intossicazione acuta da alcol

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Introduzione

L'intossicazione acuta da alcool è la più frequente causa di arrivo in Pronto Soccorso per un evento tossicologico ed è una situazione potenzialmente a rischio per il paziente.
La sintomatologia neurologica è variabile (dalla semplice ebbrezza al coma) e solo parzialmente correlata con il tasso alcolemico. Per il fenomeno della tolleranza questa correlazione non è valida negli etilisti cronici nei quali è frequente riscontrare livelli elevati di alcolemia senza segni grossolani neurologici di intossicazione. L'alcol diminuisce la secrezione di vasopressina (ormone antidiuretico), e la conseguente riduzione del riassorbimento di acqua a livello del filtrato glomerulare contribuisce all'aumento della diuresi che si osserva in seguito all'ingestione di alcol[1]. La concentrazione serica di alcune molecole alcoliche come l'etanolo porta a un aumento dell'osmolarità plasmatica (2,12 mOsm/l di osmolarità plasmatica per ogni 10 mg/dl di alcolemia)[2].
Riportiamo una casistica di pazienti giunti al Pronto Soccorso dell'Ospedale Fatebenefratelli di Milano per intossicazione acuta da alcol, per valutarne dati di laboratorio (relativi ad alcolemia e osmolarità) e la loro correlazione con la presentazione clinica.

Materiale e metodi

Dal sistema informatico, nel periodo di 6 mesi compreso dall'agosto 2010 al gennaio 2011, sono stati estratti e analizzati retrospettivamente i verbali di accettazione di pazienti con diagnosi conclusiva in cui veniva riportata l'assunzione di alcol.
Sono stati registrati in un data base i seguenti parametri:

- dati anagrafici;
- valutazione dello stato di coscienza tramite il metodo AVPU (Alert, Voice, Pain, Unresponsive);
- dati di laboratorio: concentrazioni seriche di alcol (mg/dl), Na (mmol/l), urea (mg/dl) e glucosio (mg/dl);

Tabella 1

Valori di alcolemia e di osmolarità distribuiti per classi AVPU.

	A	V	P + U
Alcolemia (mg/dl)			
media ± DS	209,1 ± 91,0*	219,2 ± 120,6#	293,8 ± 135,8*#
> 300 mg/dl			
n. pz	15	12	9
%	12,7	27,9	42,9
Osmolarità calcolata (mOsm/l)			
media ± DS	294,8 ± 8,5	296,6 ± 8,2	295,0 ± 8,5
> 295 mOsm/l			
n. pz	63	29	10
%	52,9	67,4	47,6
Osmolarità corretta (mOsm/l)			
media ± DS	340,3 ± 22,6 §	344,0 ± 25,9^	358,9 ± 32,0§^
> 295 mOsm/l			
n. pz	116	42	21
%	98,3	97,3	100,0

t-test di Student: *p < 0,0001; #p < 0,03; §p < 0,001; ^p < 0,05.

- calcolo della osmolarità plasmatica mediante la formula (F): 2[Na] + [glucosio]/18 + [urea]/2,8[3] e quella corretta per l'alcolemia: F + [alcol]/4,6[4];
- diagnosi di dimissione dal Pronto Soccorso ed esito.

Secondo quanto riportato in letteratura si sono considerati un'alcolemia > 300 mg/dl significativa per una intossicazione severa e un valore di osmolarità normale fino a 295 mOsm/l.
L'analisi statistica è stata eseguita mediante il t-test di Student per i confronti fra medie e con il test del chi-quadro per confronti fra proporzioni. È stato considerato significativo un valore di p < 0,05.

Risultati

Sono stati registrati 182 pazienti; l'età media era di 36 ± 16 anni; 121 erano maschi (66%). La classificazione AVPU era come segue: A 118 (64%), V 43 (24%), P 14 (8%) e U 7 (4%).
Per ottenere una maggiore significatività del campione i pazienti con le due classi AVPU più severe (Pain e Unresponsive) sono stati raggruppati in un'unica classe (21 pazienti).
I dati di laboratorio sono stati riportati come medie ± DS nella Tabella 1. L'alcolemia era aumentata significativamente con l'aumentare della severità neurologica; l'osmolarità calcolata non è risultata differente nelle diverse classi, mentre quella corretta per l'alcolemia era significativamente più alta nei pazienti con alterazioni dello stato di coscienza.
Sono state inoltre calcolate le percentuali di pazienti con alcolemia > 300 mg/dl e di osmolarità > 295 mOsm/l. Le differenze percentuali nelle diverse classi AVPU erano significative per l'alcolemia (chi^2 = 12,55; p < 0,002) e non per l'osmolarità calcolata. Nell'intera casistica è risultato molto elevato il numero di pazienti con osmolarità (corretta per alcolemia) > 295 mOsm/l (98%).
Analizzando i soggetti con alterazione dello stato di coscienza (V + P + U) (64 pazienti) e con alcolemia < 300 mg/dl (43/64 pazienti; 67%), l'osmolarità calcolata è risultata > 295 mOsm/l nel 65% dei casi.

Discussione

I valori di alcolemia solo in parte correlano con le alterazioni dello stato di coscienza. È noto che il grado di tolleranza a livelli elevati di alcolemia è un fattore soggettivo e dipende da molti altri fattori che in vario modo contribuiscono all'espressione dei sintomi[5]. La dose tossica di alcol dipende da individuo a individuo, per età, sesso, popolazione, alimentazione, malattie, assuefazione. I sintomi e i segni dell'intossicazione acuta sono molto variabili a seconda dell'individuo e dipendono anche dalla personale tolleranza all'alcol, la quale è aumentata nei bevitori abituali ed è ridotta nelle donne.
In corso di intossicazione acuta da alcol si osserva un aumento dell'osmolarità[6]. L'osmolarità plasmatica può essere misurata in laboratorio con l'osmometro oppure calcolata con varie formule[7]. È stato osservato che in corso di intossicazione da alcoli (tra cui l'etanolo) vi è una differenza fra l'osmolarità misurata e quella calcolata: tale differenza è nota come "gap osmolare". È necessario pertanto quando si calcola l'osmolarità, correggerla per i livelli di alcolemia[4-8].
Nella nostra casistica l'osmolarità calcolata, che è già di per sé elevata in più del 50% dei pazienti, quando viene corretta mostra un'alterazione nella quasi totalità dei casi. Inoltre è stata riscontrata una osmolarità elevata in pazienti con alcolemia < 300 mg/dl ma con alterazioni dello stato di coscienza. L'iperosmolarità potrebbe quindi essere un cofattore determinante lo stato di coscienza del paziente.
Tale aspetto deve essere tenuto in considerazione, soprattutto per interpretare in modo più completo le alterazioni dello stato di coscienza che probabilmente non sono solo legate a livelli di alcolemia ma a più complesse modifiche dell'omeostasi.
L'iperosmolarità inoltre è un'alterazione che è stata associata anche all'insorgenza di aritmie in pazienti con intossicazione acuta da alcol[9].
È pertanto necessario porre maggiore attenzione all'osmolarità nel paziente che giunge in Pronto Soccorso con un'intossicazione acuta da alcol, poiché questo è un fattore che non sempre viene tenuto in conto nell'assistenza di questi pazienti.

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New recreational drugs of abuse intoxication: Italian Network for early identification and monitoring

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Background and objective

In recent years, common drugs of abuse have been joined by new recreational drugs of abuse. The widespread growth of the web with its vast distribution of information has increased the acknowledgment, the accessibility and self-made synthesis of various substances[1]. At present, the number and the severity of patients admitted to the Emergency Departments (EDs) for new drugs abuse is unknown in Italy and in most cases the standard toxicological screening may be inadequate and could results negative. These factors may contribute to underestimate this new phenomenon and may have direct implication in the early diagnosis and specific clinical management. Moreover, the clinical and laboratory identification of cases of new drug of abuse intoxication is crucial to permit any regulatory action aimed to prevention and control[2]. At the end of 2008 the Department for Antidrug Policies – Presidency of the Council of Ministers (DPA) activated in Italy the National Early Warning System for Drugs, within which the Pavia Poison Centre (PPC) has been identified as Coordinating Centre for the clinical-toxicological aspects[3]. A study was conducted through the EDs network referring to PPC in order to evaluate the prevalence and clinical features of new recreational drug of abuse intoxications.

Methods

Study period: January 2010 - October 2011. All consecutive cases referred to the PPC of suspected/confirmed substances of abuse intoxication were evaluated. Cases presenting an history for new substances abuse or atypical clinical pictures after common drug abuse were included in the study. All cases has been assessed for age, sex, history, PSS severity score of the clinical manifestations[4], clinical evolution, overall management and sequelae. Laboratory of Analytical Toxicology of Pavia, identified as N.E.W.S. collaborative center for the monitoring of new drugs of abuse, performed standard and advanced toxicological investigations. Products and substances, when available, were also analyzed. Cocaine, opiates, cannabis, amphetamine and methamphetamine were identified as common drugs; all others substances were considered new substances. Single ethanol intoxication and body-packers were excluded.

Results

Among 665 cases of suspected/confirmed substances of abuse intoxication, 192/665 (29%) patients were included in the study. In 52/192 (27%) new substances use were declared; 7% of patient was unable to report the substance abused. The most common clinical manifestations were agitation (42%), tachycardia (37%), coma (22%), mydriasis (19%), gastrointestinal discomfort (18%) and hallucinations (14%); 2 fatal cases were registered.
Advanced lab investigations were performed in 94% of cases (181/192); in 127/181 (70%) the biological samples were delivered by courier by PPC. The new substances identified were: MDMA (25 cases), synthetic cannabinoids (17), ketamine (16), levamisole-tetramisole (13), GBL/GHB (6), caffeine (6), atropine-scopolamine (6), butylone (2), MDPV (1), amine/dimetyltriptamine (1), MDA (1), 4-MEC (1).

Conclusion

The network of EDs referring to PPC and the support of the advanced toxicological analysis are the basis for identification of sentinel/atypical cases of new recreational drugs of abuse intoxication. The toxicological evaluation and the laboratory identification new drug of abuse permit regulatory actions aimed to the prevention and control. These cases permitted to the DPA and Ministry of Health the activation of procedures to include these substances in the Italian list of drugs of abuse and illicit psychotropic substances.

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Drugs and Internet

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Introduction

Over the past 3 years, international organizations (INCB, UNODC, EMCDDA, etc.) have been paying particular attention to the dynamics of the illicit drug market that are changing from traditional forms to new ones, such as e-commerce, that is drug-marketing via Internet. This concern is also reflected at national level where the attention to online purchases comes from the increasingly frequent cases of acute poisoning related to substances purchased over the Internet.
The phenomenon has been growing over the past 3 years, especially after the appearance on the market, since the end of 2008, of vegetable mixtures containing synthetic cannabinoids purchased over the Internet and much more powerful than normal THC, and particularly dangerous for consumers' health: in fact, since 2010, only in Italy 25 cases of acute poisoning related to their intake have been recorded. Similar cases have been reported also for other substances purchased online, including mephedrone that in the United Kingdom has already been linked to the deaths of more than 20 people, and other synthetic cathinones. Such a scenario calls for a deep reflection on the potential that web technology provides and on the need to stem a phenomenon that is dangerous for the health of users, particularly for younger people. It is in fact, the young population the most affected by netsurfing and then exposed to a greater extent to online shopping.

The online dissemination of psychoactive substances

A survey carried out by the National Early Warning System of the Department for Antidrug Policies has showed a great abundance of Internet web sites promoting the purchase of illicit drugs or legal substances with similar effects to those of illicit drugs. By using the Google search engine and searching for keywords like "buy+cocaine" "buy+ecstasy" or "buy+hashish", the web sites resulting from the researchare over 4,000,000.
The purchasing methods by which you can buy products at the sites (online drugstore) are very similar to each other and are characterized by the extreme ease with which the operation can be performed. In fact, as with any product purchased via web, the orders are executed by computers with an Internet connection, the payment by credit card, money transfers, money orders and other forms of online payment (eg. Paypal), the order made will be directed to a site of "orders collection" from which the order is forwarded to the manufacturer; the manufacturer, therefore, shall deliver the purchased equipment, using postal and courier services that can quickly reach the buyer.
For the promotion of products for sale, companies that manage the sites have adopted real marketing strategies.
For many substances, effects similar to those of illicit drugs are described. For example, Salvia divinorum, and Hawaiian Baby Woodrose are described as substances that induce hallucinogenic effects similar to LSD. Kratom is often described as a substitute for opiates, many herbal preparations are described as alternatives for cannabis and the so-called "party pills" are sold as alternatives to MDMA. The party pills, may also contain plant material or semi-synthetic or synthetic substances. Their main ingredient is often benzylpiperazine (BZP). Among the online drugstores, however, there are also variations so as to freely market party pills even in countries where benzylpiperazine is under control.

The projects of the Department for Antidrug Policies

Since 2010 the Department for Antidrug Policies has been performing a number of activities about web monitoring. Specifically, the Institute of Legal Medicine of Verona University has been entrusted with the "Smart Search Project", aimed at searching for pharmacologically active compounds in commercial products through the use of high-resolution mass-spectrometry. The project led to the analysis of 56 products which were found to contain synthetic cannabinoids analogues of sidenafil, stimulant and hallucinogenic compounds. A project for monitoring and preventing online drug trafficking through via Internet is "Drugs & Internet", entrusted to the Italian Red Cross, thanks to which about twenty websites selling drugs illegally were pointed out.
Finally, thanks to the "Rave Parties Prevention" Project, entrusted to the Italian Red Cross, it has been possible to detect and prevent illegal music events, at high risk of alcohol and drug-related death and disability, promoted through web sites. The online monitoring has allowed the reporting to law enforcement agencies and the prevention of the occurrence of more than 15 raves and the management of a dozen, thanks to the controls performed by the Police.

Main activities and results of the Italian National Early Warning System in 2010

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Introduction

In compliance with European guidelines, in 2008 the Department for Antidrug Policies has set up also in our country the National Early Warning and Rapid Response System for Drugs (NEWS). In fact, in compliance with the European Council Decision n° 2005/387/JHA of 10th May 2005, also Italy, as member state, must ensure the delivery to Europol and to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) of information on the manufacture, trafficking and use, including medical use, of new drugs and preparations containing these substances, taking into account the respective mandates of these two organs. In Italy, the National Early Warning System is a tool that ensures the information flow through the Reitox Focal Point of the Italian Department for Antidrug Policies of the Presidency of the Council of Ministers. The National Early Warning System is also part of the activities of the Permanent Observatory, established at the Department for Antidrug Policies, according to Presidential Decree 309/90, Art. 1 paragraphs 7 and 8 for the verification of the drug addiction phenomenon.
The system is aimed, on one hand, at early detecting potentially dangerous phenomena to public health, related to the appearance of new drugs and new ways of consumption on the Italian territory, on the other, at activating the early warning system signals involving agencies with responsibility for health protection and promotion and for the possible activation of appropriate measures in response to the emergencies reported.
Below is a summary of the main activities and results that the system has achieved over the last 2 two years (2009-2010), thanks mainly to the work and commitment of its collaborating centers (about 50 around all of Italy), and in particular to the internal coordination of the System, the National Institute of Health, to the Pavia Poison Control Center, the Department of Addiction ULSS 20 Verona, really appreciable for their availability and their activism.

Main activities and results

In 2010, the National Early Warning System received 106 signals, most of which (34.9%) from the European Monitoring Centre on Drugs and Drug Addiction, from the media (19.8%), from the analysis laboratories (19.8%) and from the Police (12.4%). The signals concentrated in June and July. Compared to 2009, the number of signals increased of 73.8%. 48 were signals sent form the System to the output network, the majority were informative notes (72.9%) and warnings (16.7%). Compared to 2009, there were 12 and 5 informative alerts more.
One pre-alert, 7 alerts of grade 2 and one alert of grade 3 were activated. The pre-alert activated in January evolved over the same month in grade 2 and remained active until January 2011. In 2009, 2 alerts more than in 2010 had been activated.
The network of experts has been consulted 4 times through the Attention notes in order to request background information, for knowledge or direct experience regarding the subject matter of communication. In 2009, the Collaborative Centers were contacted 10 times. The information sent by the system during 2010 were 35, mostly concentrated in July (22.9%). In 2009, the information had been 29. It should be noted that since September 2010, the system has ceased to transmit to the Collaborative Centers the signals from the EMCDDA through information and has adopted the tool "Communications EMCDDA" that groups such signals and forwards them monthly.
The system also uses other types of communications, not directly addressed to the Collaborative Centers. In 2010, most of these communications were confidential communications (67.7%), reporting forms to the EMCDDA (19.4%) and EMCDDA Communications (12.9%).
The accessions to the input/output network have increased by 42.8% compared to 2009, from 35 to 50 Collaborating Centres.
The signals generated informative reports after an average of 17 days (at least 4 hours, max 80 days). The signals generated the activation of an alert, however, after a median time of 4 days (at least 4 hours, max 10 days). The alerts, in fact, require fast response time to report events and/or situations that may pose a real risk and imminent danger to the health of consumers.
In order to keep constantly updated the network and other partners, the system has also used other tools. It has been developed the N.E.W.S. Activity Report, the bimonthly magazine addressed to the Collaborating Centres aimed at updating and informing about the recent activities of the System. Two training workshops were organized and one of them has been addressed to the laboratories of chemical and toxicological analysis of the System, the other to the structures of the emergency/urgency, not yet part of the system. We participated to 2 international work tables and to 14 international events to promote the organizational and operational structure of the system and the results of its activities.
In June 2010, the Department for Antidrug Policies, in collaboration with the Ministry of Health, succeeded in including the synthetic cannabinoids JWH-018 JWH-073 and the synthetic cathinone Mephedrone on banned substance list. In addition, on May 16, 2011 in the Official Gazette, the decree signed by the Minister of Health to update the consolidated law on the regulation of narcotic drugs and psychotropic substances of 1990 was published, with some molecules belonging to the category of synthetic drugs. The specific substances included in Schedule I of the DPR 309/90 are: the 3,4-Methylendioxypyrovalerone synthetic cathinone (MDPV), the synthetic cannabinoids JWH-250 and JWH-122, and all derivatives of 3-phenyl-acetylindole and of 3-(1-naftoil) indole, thus making virtually illegal all the JWH series synthetic cannabinoids.
During 2010, the Department of Medicine of the National Institute of Health researched, procured and supplied to the network laboratories the standards for the substances included in Schedule 1 to June 2010: JWH-018, JWH-073; mephedrone. Standards references of JWH-200, JWH-250, CP 47.497, 4-Fluoramphetamine, MDAI molecules were also distributed.
Finally, in July 2010, the Department of Antidrug Policies activated the Police to carry out checks on all the shops selling herbal blends or other products containing synthetic cannabinoids and the synthetic cathinone included in the list of the banned substances. This initiative led to the closure of smart shops in 17 cities, to the closure of a distributor (wholesaler) company in Milan, to the seizure of tons of products like herbal blends and to the arrest of 8 persons involved in trafficking and in smuggling of drugs.

proceedings

Insulina e glucosio

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La terapia insulinica ad alte dosi (HDI), unitamente alla somministrazione di glucosio in quantità necessaria al mantenimento dell'euglicemia, risulta essere efficace nel trattamento delle intossicazioni acute da farmaci beta-bloccanti e calcio-antagonisti, importanti dal punto di vista epidemiologico e associate a un'alta morbilità e mortalità per la loro tossicità cardiovascolare. Le molecole dotate di maggiore tossicità risultano essere propanololo e verapamil rispettivamente[1].
La bradicardia e l'ipotensione fino allo shock cardiogeno associati alla riduzione delle resistenze periferiche, sono gli aspetti clinici caratteristici e più rilevanti nel sovradosaggio da calcio-antagonisti e beta-bloccanti, imputabili soprattutto all'effetto inotropo negativo. Poiché il calcio entra nel miocardiocita e nella miocellula vascolare attraverso i canali voltaggio-dipendenti tipo L, in risposta a una serie di stimoli che comprendono anche l'attività dei recettori β-adrenergici, si comprende come il quadro clinico determinato dal sovradosaggio sia spesso sovrapponibile per le due classi di farmaci.
Tradizionalmente il trattamento dell'intossicazione acuta da beta-bloccanti e calcio-antagonisti prevede una terapia sintomatica e di supporto basata sulla somministrazione di liquidi e farmaci adrenergici allo scopo di contrastare l'ipotensione e lo shock, ma è universalmente riconosciuta anche una terapia antidotale specifica con glucagone e sali di calcio. Nei casi più gravi può essere necessario il ricorso al supporto elettrico o meccanico.
Negli ultimi anni molta attenzione è stata posta sul fatto che il blocco dei canali del calcio a livello della β cellula pancreatica riduce la secrezione di insulina e induce una deplezione delle riserve intracellulari di glucosio proprio nel momento in cui il cuore stressato diventa dipendente dal metabolismo dei carboidrati. A seguire, una serie di studi sperimentali hanno evidenziato come la somministrazione di insulina ad alte dosi, nel sovradosaggio di farmaci calcio-antagonisti, abbia una maggiore efficacia sul ripristino della performance cardiaca e sulla stabilità emodinamica, rispetto alla terapia tradizionale[2].
Questo effetto dell'insulina ad alte dosi sarebbe legato a: 1) effetto inotropo positivo tramite l'azione sul metabolismo del calcio e la via del fosfatidilinositolo-3-fosfato; 2) aumento del trasporto intracellulare di glucosio che, in condizioni di stress, diventa il substrato energetico principale dei miocardiociti rispetto all'ossidazione degli acidi grassi che prevale invece in condizioni fisiologiche; 3) attivazione della nitrossido-sintetasi endoteliale che determina una rapida vasodilatazione sistemica ma soprattutto coronarica e polmonare, con conseguente aumento della perfusione, senza comportare l'aumento della richiesta di ossigeno caratteristica delle catecolammine.
In assenza di trial clinici progettati per confrontare l'effetto della HDI rispetto ad altri trattamenti, la valutazione della sua efficacia nelle intossicazioni umane è riposta in una serie, ormai numerosa, di case reports significativamente concordanti. Fra i vari proposti, il protocollo che prevede la somministrazione di insulina inizialmente in bolo (1 UI/kg) e successivamente in infusione continua (0,5-1 UI/kg/h) risulta quello maggiormente condiviso. I valori plasmatici di glucosio e potassio dovranno essere valutati prima del trattamento e attentamente monitorati e corretti durante tutta la somministrazione di insulina[3].
In conclusione, la HDI risulta una terapia efficace nel contrastare l'instabilità emodinamica conseguente alle intossicazioni da beta-bloccanti e calcio-antagonisti e relativamente sicura, dato che gli effetti avversi più frequenti (ipoglicemia e gli squilibri elettrolitici) possono essere facilmente evidenziati e corretti.

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Calcium channel blockers overdose: our experience

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Introduction

Calcium channel blockers (CCB) are the leading cause of cardiovascular drug overdose and are responsible for 48% of deaths related to cardiovascular drug exposure. CCB overdoses may present with altered mental status, bradycardia and hypotension. Hyperglycemia and lactic acidosis occasionally occur. Ischemic colitis may rarely occur more than 24 hours post ingestion. We report two cases of calcium channel blockers overdose treated in our ED.

Case 1

A 39-year-old woman presented to the Emergency Department (ED) 5 hours after ingesting 20 verapamil-SR 240 mg. She was slightly lethargic with a pulse of 43/minute and blood pressure of 50 mmHg systolic. The Pavia Poison Center was consulted at this time. She received one dose of activated charcoal in the ED. Two liters of NS were administered without an improvement in the blood pressure.
Dopamine was started and she was given 2g of calcium chloride IV. Her vital signs remained unchanged. After consultation with the Pavia Poison Center and their medical toxicologist on-call, the patient received glucagon 1 mg followed by glucagon 3 mg. She responded to the second glucagon dose and an infusion of glucagon at 7 mg/hr was started. The patient was intubated and admitted to the ICU. The patient was extubated on hospital day 3 and did not develop any additional complications from this overdose.

Case 2

A 46-year-old woman brought to our hospital with complaints of recurrent vomiting following ingestion of 100 mg of amlodipine and few sustained release tablets of diclofenac, four hours earlier. The Pavia Poison Center was consulted at this time. In ED gastric lavage was performed and she was treated with intravenous fluids and dopamine infusion. On examination, in the ICU of our hospital, she was drowsy but responsive on light stimuli. Her heart rate was 80/min, regular, sinus rhythm and her blood pressure was 60 mmHg systolic. In addition to the standard resuscitative measures, the patient was treated with 30 ml of 10% calcium gluconate over 5 min followed by an infusion of 10 ml/h of calcium gluconate. 10 mg of glucagon was administered intravenously as a stat dose, and an infusion of glucagon at 3 mg/hr was continued. Infusions of normal saline and noradrenaline was used to support the blood pressure. With these measures, the patient started showing improvement in her hemodynamics. The patient was treated with diuretics and oxygen for pulmonary edema. Over the next 48 h she showed gradual improvement in her clinical condition.

Conclusions

The Poison Center can provide invaluable help and expertise in the management of these poisonings. The initial approach to treatment of these poisonings is to place the patient on a cardiac monitor, establish oxygenation, and administer intravenous fluid boluses to correct the hypotension. Calcium channel blockers overdose can be treated successfully with early GI decontamination, resuscitation with calcium and glucagon infusion, judicious use of inotropes and careful monitoring of possible complications.

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Digoxine-immune Fab

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Digoxin-immune Fab is a lyophilized powder of antigen binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep immunized to produce antibodies specific for the antigenic determinants of the digoxin molecule.
Each vial contains 38 mg of digoxin-specific Fab fragments which will bind approximately 0.5 mg of digoxin (or digitoxin), and is administered by intravenous injection after reconstitution with sterile water for injection.
Digoxin-immune Fab binds molecules of digoxin, making them unavailable for binding at their site of action, (sodium, potassium) ATPase pump. The Fab fragment-digoxin complex is accumulated in the blood, from which it is excreted by the kidney.
Digoxin Immune Fab is indicated for treatment of potentially life-threatening digoxin and digitoxin intoxication, because the risk of imminent cardiac arrest.
Manifestations of life-threatening toxicity include severe ventricular arrhytmias (ventricular tachycardia or ventricular fibrillation), or progressive bradyarrhythmias (severe sinus bradycardia or second or third degree heart block not responsive to atropine), or severe hyperkalemia (> 5 mEq/L).
The dose of digoxin immune Fab required to neutralize the known or estimated amount of digoxin or digitoxin in the body is calculated by specific formulas.
For acute ingestion of known amount of digoxin or digitoxin we can calculate the total number of vials required by dividing the total digitalis body load in mg by 0.5 mg/vial. In case of calculations based on known steady-state serum digoxin concentrations, the dosage in number of vials can be calculated using formulas depending from the body weight in kg.
In general, a large dose of digoxin immune Fab has a faster onset of effect but may enhance the possibility of a febrile reaction. The physician may consider administering an initial dose of 10 vials with close monitoring of clinical response, followed by an additional dose of 5-10 vials if clinically required.
During chronic therapy, 6 vials (228 mg) usually is adequate to reverse most cases of toxicity for adults; in infants and small children (≤ 20 kg) a single vial usually is enough.
Digoxin Immune Fab is administered by the intravenous route over 30 minutes. If cardiac arrest is imminent, it can be given as a bolus injection.
Following administration of digoxin immune Fab improvement in signs and symptoms of digitalis intoxication begins within one-half hour or less.
Allergic reactions to digoxin immune Fab have been reported rarely. Sometimes side effects are observed. Low cardiac output states and congestive heart failure could have been exacerbated by withdrawal of the inotropic effects of digitalis. Hypokalemia may occur from re-activation of (sodium, potassium) ATPase pump. Patients with atrial fibrillation may develop a rapid ventricular response from withdrawal of the effects of digitalis on the atrioventricular node.
Digoxin immune Fab will interfere with digitalis immunoassay measurements. The total serum digoxin concentration may rise precipitously following administration of digoxin immune Fab, but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body. Serum digoxin concentration measurement can be clinically misleading until the Fab fragment is eliminated from the body.
The kidney excretes the Fab fragment-digoxin complex. In humans with normal renal function, the half-life appears to be 15 to 20 hours. The risk of digoxin release with recurrence of toxicity is potentially increased when excretion of the complex is slowed by renal failure. Such patients should be monitored for a prolonged period for possible recurrence of digitalis toxicity.
Digoxin immune Fab have been used successfully in the management of severe poisoning with a range of digoxin structurally related compounds, including cardiotoxins from Nerium and Thevetia sp. (oleander) and Bufo sp. (toads).

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Antidotic treatment with glucagon

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Glucagon is a polypeptide hormone produced by alpha cells in the islets of Langerhans in the pancreas. It was discovered by Murlin and Kimball in 1923, less than 2 years after the discovery of insulin. The positive inotropic effects of glucagon were first described in 1960, and since then, much interest has been taken in the use in heart failure as well as in β-blockers (BB) intoxication.
The effects of intravenous glucagon begin within 1-3 minutes, are maximal at 5-7 minutes and last 10-15 minutes. Elimination half-life is short, 8 to 18 minutes. Many organs respond to the influence of glucagon. In the liver both gluconeogenesis and glycogenolysis are stimulated, resulting in an increase in blood sugar. Smooth muscle is relaxed in the gastrointestinal tract and bronchial tree.
Glucagon is used to treat severe hypoglycemia, particularly in diabetic patients when intravenous glucose is not available and it is also used by radiologists for its inhibitory effects on the gastrointestinal tract. Moreover, intravenous glucagon could be effective for treating biliary tract pain due to cholelithiasis[1], improving pulmonary function tests in patients with asthma[2], for clearing meat impaction by relaxing the lower esophageal sphincter[3] and in cardiogenic shock refractory to other inotropic agents[4].
Few adverse reactions have been reported: nausea and vomiting due to the delay in gastric emptying caused by glucagon[5], hyperglycaemia and hypokaliemia[6].
Glucagon increases the force of contraction of the heart, with little or no effect on the heart rate, bypassing β-receptors and activating directly to Gs protein to stimulate conversion of ATP to cAMP. Based on many case-reports, although there are no human controlled trials of glucagon for BB toxicity, it is considered useful in the treatment of the former poisoning according to the International Programme on Chemical Safety (IPCS) guidelines.
In case of BB intoxication, if failure of symptomatic treatment with atropine and volume expanders occur, glucagon is the first-line treatment; moreover, it is used as an additional therapy for calcium channel antagonists (CCA) overdose[7].
A bolus of 5-10 mg (150 µ/kg) over 1-2 minutes is an appropriate starting dose. If necessary repeat boluses may be administered every 5-10 minutes and a continue infusion of 2-10 mg/hour (50-100 µ/kg/h) should follow bolus administration. In addition to glucagon for BB poisoning, catecholamines are frequently required for blood pressure support and occasionally intravenous pacing may be necessary for severely poisoned patients. In few other instances, glucagon failed to increase the heart rate in patients intoxicated by BB and CCA[8-10]. The variability in response to glucagone therapy is likely due to differences in the type and dose of ß-blocker ingested, patient-specific factors, timing or content of therapy[11].
In conclusion, although there are no human controlled trials of glucagon for BB and CCA toxicity, it seems to be most effective in increasing heart rate and the available animal data, human clinical experience and minimal adverse effects, support the use of glucagon in the course of both BB and CCA poisoning.

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Bad grass never dies

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Introduction

Aconitum napellus is a herbaceous plant highly diffused in mountainous areas of Central Europe and Italy. The whole part of the plant, especially the roots, contain different highly toxic alkaloids, mainly aconitine. The ingestion of 3 grams of aconitum can lead to death in a few hours. This plant, known since Homer's time, to date is employed in homeopathic medicine, especially in the South East areas and in India. Often, ingestion is accidental since it resembles wild asparagus and turnips.

Case report

Wife and husband come to the Emergency Department suffering from severe abdominal pain with vomiting, dysphagia and paraesthesia localized to face and arms.
They say they had eaten, about 30 minutes before the symptoms appeared, a huge meal of *risotto* with mushrooms and mountainous herbs, picked in the nearby mountains by a relative who presented them as an "absolute rarity".
During the examination both presented with hypotension,

bradypnea and tachycardia; the husband's ECG showed monomorphic ventricular tachycardia, while the wife's one an atrial fibrillation. The patients were treated with intensive monitoring of the vital parameters, positioning NGS, respiratory and rehydrating supportive care. Both these arrhythmias are treated with continuous infusion of amiodarone. At the first presentation the clinical and anamnestic element led to mushrooms poisoning and to confirm this hypothesis urinary amanintin was undertaken, resulting negative. The chemical and toxicological exams were negative, except for slight hypokalaemia in the woman.
Meanwhile, the man suffered convulsive and incoming crises that required a high dosage sedation; his wife, after developing dysarthria and dysphagia, developed xerostomia, tremors, diplopia and altered vision to green and yellow.
With a more accurate anamnesis, it emerged that mountainous herbs were similar to wild asparagus. This information combined to clinical signs and symptoms, led to a test for aconitine, which resulted positive.

Conclusions

Aconitine's main effect consists of the blockage of voltage dependent sodium channels with a consequential increase of the membrane potential's refractory period (phase 4).The case report presented, shows that anamnesis is also a fundamental part of the work in the Emergency Department; in this case the keystone for making the diagnosis was the asparagus's resemblance to aconitum. At the very beginning the diagnostic hypotheses were addressed to mushrooms poisoning, but symptoms didn't match with times and presentation modality; persevering with this hypothesis would have led to an inadequate treatment.
Fundamental for the resolution of this case has been the close team work of doctors and toxicologists. Finally it highlights the importance of a good toxicology knowledge in order to diagnose and solve unusual cases.

Human health effects of algal toxins

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The term "algal toxins" is used to define a structurally heterogeneous group of molecules produced by several different species of marine microalgae. These molecules can be either lipophilic or hydrophilic, but in both cases are heat-stable and, for this reason, represent a risk for human health, associated to their entrance into the food chain. In fact, these molecules can be accumulated by shellfish or edible fish in considerable amount and, since they are not inactivated by cooking procedures, they can cause a wide variety of toxic effects after ingestion.
Algal toxins can be classified, according to their main biological effect, in different groups. Okadaic acid (OA) and Dinophysistoxins (DTX), are considered responsible of the so-called DSP (Diarrheic Shellfish Poisoning) intoxications. OA and DTX are produced by several species of dinoflagellates of the genus *Dynophysis* and exert their diarrheic effects at intestinal level mainly through the inhibition of the protein phosphatases 1 and 2A. Other toxins, such as azaspiracids, whose mechanism of action is still unclear, are also known to cause gastrointestinal problems and implement the number of molecules that may represent a risk in this respect.
Among algal toxins a big family of compounds is defined as neurotoxic, due to its action on the nervous system. In particular, algal neurotoxins can be responsible of several syndromes such as, Neurotoxic Shellfish Poisoning (NSP), but also Paralitic Shellfish Poisoning (PSP) and Amnesic Shellfish Poisoning (ASP). Some of these intoxications, like PSP and ASP are life-threatening. NSP, a not very severe poisoning, is caused by brevetoxins that impair ionic conductance of neurons blocking Voltage Dependent Sodium Channels (VDSC). VDSC are also the molecular target of other toxins such as Saxitoxins (STXs). STXs are produced by several marine dinoflagellates, including *Alexandrium* ssp., *Pyrodinium bahamense* and *Gymnodinium catenatum* and some of them are responsible for lethal PSP cases of intoxications. The toxins responsible for ASP are Domoic Acid and its analogues; these toxins are structurally related to kainate being tricarboxylic amino acids. Thanks to their peculiar structure these toxins, not only enter the blood-brain barrier, but also interacts with Kainic acid receptors inducing excitotoxic response in central nervous system.
In addition to toxins whose effects are mainly diarrheic and those that are mainly neurologic there are also toxins, that have to be classified separately. Among these, there are ciguatoxins (CTX) and palytoxins (PLTXs). CTX are responsible for ciguatera poisonings that occur mainly in tropical regions. Even if variation in symptoms can occur, ciguatera is typically associated to initial gastrointestinal symptoms, later followed by peculiar neurologic disturbances, such as long-lasting pruritus, circumoral numbness and weakness, associated also to cold allodynia. In comparison to ciguatera, intoxications due to PLTX are less documented; the ingestion of PLTX-contaminated seafood seems to be associated to relatively mild gastro intestinal symptoms later followed by muscular pain, and paralysis due to the interaction of the toxin with Na^+/K^+ ATPase.

Intossicazione acuta da fiori di ginestra

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Introduzione

La Ginestra (*Spartium junceum*) è un arbusto spontaneo della famiglia delle leguminose alto fino a tre metri, a fronde flessibili povere di foglie, dai fiori giallo acceso, che vive in pendii aridi e rocciosi; il frutto è un legume villoso contenente semi neri. La tossicità di questo arbusto è dovuta alla presenza di alcaloidi (lupanina, sparteina, citisina) contenuti in ogni parte della pianta. La loro azione si esplica in particolare a livello degli apparati gastrointestinale, respiratorio, cardiovascolare e del sistema nervoso, e si manifesta con nausea, vomito, diarrea, midriasi, salivazione, sudorazione e vertigine. Questa pianta rientra nella lista del Ministero della Salute per l'impiego non ammesso nel settore degli integratori alimentari.
Gli unici casi segnalati in letteratura di intossicazione acuta da ginestra riportano ingestione di fiori o steli utilizzati come ingredienti di ricette facilmente reperibili su siti web in assenza di controlli tecnico-scientifici e quindi potenzialmente pericolose.

Obiettivo

Si riportano due casi di intossicazione acuta da ginestra a seguito di ingestione di frittata cucinata con i fiori di tale leguminosa. Si tratta del secondo *case report* in Italia di intossicazione nell'adulto.

Caso clinico

C.N. e R.E., moglie e marito, giungevano presso il nostro Pronto Soccorso in seguito alla comparsa di vomito e diarrea dopo circa 45 minuti dall'ingestione di pasto a base di frittata con fiori di ginestra. Al momento della visita entrambi i pazienti si presentavano in buon compenso emodinamico e respiratorio con parametri vitali nella norma, l'addome era trattabile e l'obiettività neurologica negativa. Entrambi i pazienti non mostravano alterazioni ECGrafiche né dei valori emogasanalitici. Contattato il Centro Antiveleni di Pavia è stata eseguita gastrolusi e sono stati somministrati carbone vegetale attivato, catartici (solfato di magnesio) e antiemetici (metoclopramide). Sono stati eseguiti controlli ematochimici seriati senza evidenza di alterazioni degne di rilievo in particolare per quanto riguarda elettroliti, marker di citonecrosi, funzionalità epatica, renale e pancreatica. Durante l'osservazione entrambi i pazienti hanno presentato ripetute scariche diarroiche e sono stati pertanto sottoposti a terapia reidratante per via endovenosa con ripristino ottimale della volemia. Entrambi sono stati dimessi in buone condizioni cliniche dopo 24 ore di osservazione e rinviati al medico curante per un controllo ematochimico a distanza che non ha evidenziato modificazioni.

Conclusioni

A differenza di altri casi clinici (3 in totale) segnalati in letteratura, i nostri pazienti presentavano esclusivamente una sintomatologia di tipo gastroenterico risolta con decontaminazione, terapia sintomatica e reidratante, con risoluzione dei sintomi in 24 ore.
Rimane il dubbio se la gravità della sintomatologia sia stata influenzata dal diverso metodo di cottura e/o dal quantitativo di tossico ingerito. Ricordiamo infatti che nell'altro, unico, *case report* (intossicazione da risotto cucinato con i fiori di ginestra), i pazienti mostravano anche sintomi di tipo neurologico.
L'impazzare di ricette alternative e salutistiche a base di vegetali e fiori "nuovi e di moda" senza prove scientifiche e adeguata documentazione possono portare a intossicazioni molto gravi, potenzialmente letali.

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Viper bites and coagulation disorders

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There are four species of vipers distributed throughout Italy: *Vipera aspis*, *Vipera berus, Vipera ammodytes, Vipera ursinii*. Their venom contains a wide variety of toxins that are responsible for the clinical symptoms in bitten patients. The main enzymes are phospholipase A2, hyaluronidase, metalloproteinases and proteases.
Few data exist on coagulation disorders provoked by venom of Italian vipers; proteins with coagulation toxicity have been isolated through a limited number of studies *in vitro* and may have procoagulant or anti-coagulant effects; they can inhibit platelet aggregation, activate thrombin, induce fibrinolysis or fibrinogenolysis[1].
From a clinical point of view, alterations of physiologic coagulation cascade have been described in bitten patients, but adequate monitoring and indications for therapy are still under discussion.
After a viper bite generally 2 fang marks are recognizable with an approximate distance of 0,5-1 cm. Though, clinical presentation is variable from case to case, so a Gravity Severity Score (GSS) has been proposed, that identifies 4 classes of gravity[2].
Along with clinical observation, also general exams should be performed: coagulation parameters, renal function, transaminases, creatinphposphokinases, leukocytes, haemolytic parameters.
According to the findings *in vitro* and to the clinical experience reported in Literature, two main coagulation alterations may develop: Thrombosis and Disseminated Intravascular Coagulation (DIC).
Thrombosis can be diagnosed through association of clinical presentation, predisposing factors, and high D-dimer, which represents a sensible, but unspecific marker.
An algorithm has been proposed for diagnosis of DIC in non-viper related diseases, which considers mainly platelet count, PT prolongation, fibrin related markers[3].
A retrospective casistic of Pavia Poison Centre considering the years from 2008 to 2010, identified 241 cases of confirmed viper bites; among these, one patient admitted with GSS 2 developed spleen multiple infarctions due to micro-thrombi, two patients with GSS 3 also developed thrombosis: one cerebral, the other at the tibial vein of the bitten leg.

Two haematochemical parameters were analyzed: leucocytosis and D-dimer.
High D-dimer was not always related to coagulation disorders; it was always high in patients that developed thrombosis, but not proportional to the severity of the clinical picture. As expected, leucocytosis seemed correlated to severity of clinical picture.
Antidotic treatment – antibody fragments derived from equine (F[ab']2, Zagreb) or ovine serum (Fab, ViperaTAb) – is generally indicated in patients with GSS 2 or 3, through iv administration, with very low risk of allergic reactions. Nevertheless indications to administration are not as clear when clinical picture slowly worsens during observation. Low molecular weight heparin is generally suggested in patients with bites at lower limbs, for the risk of deep vein thrombosis, and in patients with GSS 3 for higher risk of DIC; anyway the real efficacy of this therapy in viper bites is still under discussion.
Although a correlation among anemia, piastrinopenia, leucocytosis and GSS has been demonstrated, there are no studies that help to correlate these data with the risk of coagulation disorders. As evolution to thrombosis or DIC may be rapid and of difficult diagnosis, strict monitoring of coagulation and haemolytic parameters is recommended. Early application of the diagnostic algorithm proposed for DIC may be hypothyzed in viper bitten patients.

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Su di un caso di sindrome neurolettica maligna da antipsicotici (olanzapina)

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Case report

Un paziente di 51 anni noto da anni ai Servizi psichiatrici per schizofrenia, veniva trovato per strada in stato confusionale; accompagnato in Pronto Soccorso si riscontrava un quadro clinico caratterizzato da rigidità muscolare, iperpiressia (41°C), leucocitosi (15,150), rabdomiolisi (CPK 7378 U/l, mioglobinemia 1462 ng/ml, AST 134 U/l), insufficienza renale (creatinina 1,99 mg/dl), per cui veniva diagnosticata sospetta ipertermia maligna da neurolettici e ricoverato presso il reparto di Terapia intensiva. Dall'anamnesi emergeva che il paziente aveva in passato subito vari ricoveri in SPDC per esacerbazione del quadro psicopatologico, per cui aveva nel tempo assunto numerosi antipsicotici (aloperidolo, risperidone, olanzapina) senza mai riscontrarsi sintomi riconducibili a manifestazioni avverse a tali farmaci; recentemente, tuttavia, onde migliorare la *compliance* del paziente, era stata introdotta terapia con olanzapina im *long-acting* di cui erano state eseguite, fino al momento della comparsa della sintomatologia in oggetto, un totale di 3 somministrazioni (1 somministrazione ogni 15 giorni). Durante il ricovero si assisteva a un progressivo miglioramento del quadro clinico con normalizzazione dei parametri laboratoristici (leucociti 8,81, CPK 52 U/l, AST 10 U/l, creatinina 0,92 mg/dl), per cui il paziente veniva trasferito presso il Servizio Psichiatrico di Diagnosi e Cura.

Discussione

La sindrome maligna da neurolettici (SMN) è una grave reazione idiosincrasica (mortalità media attorno al 20%), che si verifica nello 0,02-2,5% dei pazienti trattati con antipsicotici, in particolare quelli di vecchia generazione c.d. "tipici". La sintomatologia compare in genere dopo i primi giorni (nella maggior parte entro 10 giorni) dall'inizio o dopo un aumento del dosaggio terapeutico; il quadro completo si sviluppa nell'arco di 48 ore ed è caratterizzato da rigidità, acinesia, mutacismo, ipertermia, alterazioni neurovegetative (tachicardia, ipo/ipertensione, iperidrosi), alterazioni della coscienza (*delirium*, *stupor*, fino a coma). Laboristicamente si rileva leucocitosi, aumento enzimi epatici, aumento CPK, mioglobinemia e mioglobinuria, ma nessuno di essi è patognomonico. Per fare diagnosi è necessario, infatti, avere un quadro completo dei sintomi descritti onde non confondere la SMN con altri quadri clinici, anch'essi precipitati dall'assunzione di antipsicotici, come la catatonia (ove manca la febbre e le alterazioni neurovegetative) e l'ipertermia da neurolettici (ove mancano la rigidità, l'acinesia e i disturbi neurovegetativi). Se non si interviene tempestivamente la morte può sopraggiungere per varie complicanze: shock, insufficienza renale, insufficienza respiratoria, disidratazione, infezioni interricorrenti. Il trattamento prevede la sospensione immediata degli antipsicotici, monitoraggio cardiovascolare e renale, idratazione, stabilizzazione equilibrio elettrolitico, benzodiazepine, dantrolene (miorilassante periferico), bromocriptina (agonista dopaminergico).
Il caso in esame merita particolare attenzione in quanto l'insorgenza della SNM è avvenuta in un paziente a basso profilo di rischio (risultando maggiore l'incidenza, infatti, in soggetti giovani, non schizofrenici, tossicomani, alcolisti) a seguito della modificazione della via di somministrazione (passaggio dalla via per os a un *long-acting* im), di un farmaco, quale l'olanzapina, che presenta un basso rischio di SMN, risultato peraltro ben tollerato dal paziente che l'assumeva già da tempo per os, e con comparsa della reazione avversa abbastanza tardivamente rispetto all'introduzione della nuova formulazione (dopo la terza somministrazione im, a circa un mese dall'inizio della terapia).

Toxicological problems induced by Ostreopsis algae in the Mediterranean Sea: experience of the Marseille Poison Centre

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Ostreopsis ovata and *O. siamensis* are tropical unicellular algae that have been found recently in the Mediterranean. Both of these dinoflagellates produce palytoxin-like toxins that are powerful vasoconstrictors in mammals. Since 2003, *Ostreopsis* blooms in Italy and Spain have been accompanied by reports of respiratory problems and skin/mucosa irritation in persons in contact with toxic microalgal cells (epiphytes, plankton, or sea spray) or associated toxins. In France, a surveillance network has been set up to monitor water conditions and to protect swimmers from contamination due to *Ostreopsis*. Between 2006 and 2009, a total of 9 blooms were observed on the French Mediterranean coast including 5 that led to manifestations in divers, swimmers, and shoreline inhabitants. A total of 47 patients presented symptoms of involving benign or mild skin, mucosal, and/or respiratory irritation that regressed spontaneously without treatment within 12 to 72 hours (4 to 12 hours with non-steroidal anti-inflammatory drugs). During the study period, 5 beaches were temporarily closed. In the Mediterranean *Ostreopsis* blooms induce skin and respiratory disorders when human beings are exposed to saltwater with a high concentration of algal cells. However palytoxin dosages carried out on the food chain (urchins, mussels) indicate that this risk of toxins accumulation in seafood must be taken into account and that the surveillance network should be upgraded accordingly.

Sinfonia dolceamara

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L'esperienza clinica con idrossicobalamina nell'avvelenamento acuto da ingestione di cianuro resta limitata. Il caso riguarda una donna di 35 anni, affetta da disturbi mentali giunta all'osservazione del nostro Pronto Soccorso e Unità di Tossicologia Clinica. I genitori della paziente riferiscono di aver trovato la loro figlia in salotto, circondata da albicocche, da cui aveva estratto e mangiato il contenuto dei noccioli. Ulteriori indagini hanno rivelato che la donna aveva ingerito 20-30 noccioli di albicocca, ipotizzando quindi un consumo di circa 10-15 grammi di "mandorle amare". Il tempo trascorso dall'assunzione era approssimativamente di circa 30' prima dell'arrivo in PS. In sala visita, la paziente appariva non cooperante ed asintomatica. La pressione arteriosa era di 120/70 mmHg, FC 120 battiti/min, frequenza respiratoria 26 atti/min, temperatura 37,5 °C e SpO_2 in aria ambiente 98%. L'emogasanalisi faceva rilevare una lieve acidosi metabolica (pH 7,33, pO_2 90 mmHg, pCO_2 35,5 mmHg, e HCO_3 -20 mmol/l). Il gap anionico al momento del ricovero era di 19 mEq/l. Non sono stati misurati i lattati e non sono state notate variazioni significative dell'ECG.
Quaranta minuti dopo il ricovero (circa 70' dopo l'assunzione dei noccioli), la paziente inizia a lamentare mal di testa, nausea e dispnea, con ipotensione, ipossia e tachipnea. PAO 75/50 mmHg, FC 145 battiti/min, frequenza respiratoria 30 atti/min e SpO_2 93% (con maschera di ossigeno supplementare: 3 l/min). L'emogasanalisi evidenzia una acidosi metabolica (pH 7,20, pO_2 75 mmHg, pCO_2 34,2 mm Hg e HCO_3 -16 mmol / l). Il gap anionico è ora 23 mEq /l. Vengono somministrati due flaconi da 1 ml di nitrito di amile 5% per inalazione, e infusione endovenosa di 50 ml di tiosolfato di sodio al 10% in 1000 ml di soluzione glucosata al 5% (tasso di infusione di 5 ml /min). Dopo tale terapia, il livello di metaemoglobina del paziente sale al 10%; si continua a idratare e a ventilare la paziente in maschera con reservoir . Si assiste quindi ad un miglioramento dei parametri, con una PAO di 80/60 mmHg. Dopo circa 30' (appena resasi disponibile), vengono somministrati 5 g di idrossicobalamina, con rapida normalizzazione della pressione arteriosa e dei parametri vitali della paziente.
Molti alimenti hanno componenti tossici. In piccole quantità questi alimenti non possono causare effetti negativi, ma se vengono ingeriti in grandi quantità (per ignoranza o a scopo autolesivo), possono essere letali.
Gli antidoti per l'avvelenamento da cianuro, ben conosciuti, sono l'idrossicobalamina (5-10 g per via endovenosa), inalanti come il nitrito di amile (15% in 1 ml fiala ripetuto dopo 30 min) e il sodio tiosolfato (10% in flaconcino da 10 ml). L'idrossicobalamina viene somministrata per chelare il cianuro con formazione di cianocobalamina e contrastarne gli effetti ipotensivi. Normalmente, l'idrossicobalamina è ben tollerata e viene anche comunemente usata per trattare la carenza di vitamina B12, anche se in dosi molto minori (1 mg invece di g 5-10). Il nitrito di amile sequestra cianuro agendo in concorrenza con la citocromo ossidasi per formare cianometaemoglobina. Il nitrito di amile risulta efficace portando i livelli di metaemoglobinemia al 10-20%, anche se questo effetto può rivelarsi tossico riducendo la capacità del sangue di trasportare ossigeno alle cellule. Il sodio tiosolfato è un donatore di zolfo che riduce la tossicità del cianuro attraverso la conversione sulfurtransferasi-mediata del tiosolfato in tiocianato escreto immodificato nelle urine.
L'intossicazione da cianuro a volte prende strade molto particolari ed è importante, per il medico dell'Emergenza, saper interpretare segni e sintomi particolari correlandoli ad un'accurata anamnesi, avendo a disposizione antidoti efficaci se prontamente utilizzati. Il cianuro c'è… perché lo si cerca!