emergency care journal

ecj

www.ecj.it

# Antidotes in Depth

## Clinical Toxicology, Substances of Abuse and Chemical Emergencies

## 2016

*Pavia, 21-23 September 2016*

## BLU DI METILENE

S.M. Signoretti*, M.S. Milella, M.C. Grassi

*Tossicologia d'Urgenza e Centro Antiveleni, Policlinico di Roma Umberto I - Sapienza Università di Roma*

*Corresponding Author: Susanna Signoretti, email: susanna.sig@tiscali.it*

Il blu di metilene è un colorante tiazinico della classe degli eterociclici aromatici che, a temperatura ambiente, si presenta come un solido cristallino e, dissolto in acqua, assume una intensa colorazione blu scuro [1]. È disponibile in fiale da 10 ml all'1% (100 mg/10 ml). Trova impiego in diversi campi: colorante in ambito medico ed alimentare, antisettico delle vie urinarie e disinfettante, tracciante per la mappatura del linfonodo sentinella, nelle procedure endoscopiche e per i test di tenuta delle suture chirurgiche, e attualmente è in corso di studio nel trattamento dell'ansia. È utilizzato, inoltre, nel trattamento dell'encefalopatia indotta da ifosfamide, anche se il meccanismo d'azione non è noto. Come antidoto è classificato in A1 dall'IPCS (International Programme on Chemical Safety), disponibile entro 30 minuti e di efficacia ben documentata per il trattamento della metaemoglobinemia. La metaemoglobina (MetHb) è una forma di emoglobina (Hb) nella quale il Ferro dell'eme è ossidato in forma ferrica (Fe+++) invece della normale forma ferrosa (Fe++). La forma ferrica dell'eme non può legare e trasportare ossigeno determinando ipossia tissutale. Le cause sono molteplici: congenite o acquisite da aumentata formazione di MetHb da parte di vari agenti esogeni. Il quadro clinico varia in funzione della percentuale di MetHb presente e si manifesta con segni di ipossia prevalentemente a carico dell'apparato cardiovascolare e del SNC [2]. Il trattamento antidotico è necessario sia quando il valore della MetHb è >30%, sia in caso di sintomi di ipossia cardiaca o cerebrale. Se preesistono anemia, malattia coronarica, recenti interventi chirurgici, sepsi e tutte le condizioni di aumentata richiesta metabolica, il trattamento antidotico va effettuato indipendentemente dai valori di MetHb. L'attività antidotica del blu di metilene è conseguente all'effetto catalizzatore delle reazioni ossidoriduttive con trasformazione della MetHb a Hb. Per la funzione antidotica è necessaria un'adeguata quantità di G6PD che genera NADPH. Il blu di metilene a basse concentrazioni, attraverso la MetHb-reduttasi e l'NAPDH, è ridotto a blu di leucometilene che, a sua volta, riduce la MetHb a Hb; ad alte concentrazioni esplica attività ossidante sull'Hb, convertendola in MetHb, analogo effetto si ha in caso di deficit di G6PD. La posologia è 1-2 mg/Kg sia nell'adulto sia nel bambino, somministrato endovena, lentamente, puro o diluito, in 5-30 minuti. La diluizione consente di ridurre il dolore locale da infusione. La riduzione dei valori di MetHb si osserva entro 30-60 minuti. Se i sintomi persistono e la MetHb permane a valori >30% può essere somministrata una seconda dose. In assenza di risposta bisogna considerare deficit di G6PD o MetHb reduttasi. Dosi eccessive, ≥ 7mg/Kg, possono causare metaemoglobinemia. Si possono verificare effetti collaterali aspecifici quali: sudorazione, nausea, dolori addominali, cefalea, vertigini, tachicardia. Per l'uso in gravidanza è stato assegnato dall'FDA alla categoria C del rischio. L'allattamento deve essere sospeso per 8 giorni dopo il trattamento con blu di metilene, soprattutto nel prematuro. Controindicazioni assolute all'uso del blu di metilene sono: favismo e ipersensibilità nota al prodotto; mentre il deficit di metaemoglobina reduttasi, la grave insufficienza renale, la metaemoglobinemia da nitriti nell'intossicazione da cianuri costituiscono controindicazioni relative [3]. La scorta minima suggerita per i Centri Antiveleni è 10 fiale da 100 mg.

**Bibliografia**

1. Goldfrank's, Toxicologic Emergencies, 2010.
2. Olson KR, Intossicazioni acute, 2° ediz. 2009.
3. Micromedex Solutions Truven Health Analytics.

## THE USE OF SODIUM THIOSULFATE IN THE INGESTION OF SODIUM HYPOCHLORITE

G. Ricci*, M. Zannoni, V. Costa, G. Turcato

*Emergency Department, Azienda Ospedaliera Universitaria Integrata Verona, Regional Poison Centre Verona*

*Corresponding Author: Giorgio Ricci, email: toxclin@hotmail.com*

**Materials and methods:** To study the effectiveness of sodium thiosulfate in the ingestion of caustic were evaluated 100 patients admitted at Emergency Department by ingestion of sodium hypochlorite solution from January 2009 to August 2016. In 68 subjects the contact occurred by accident, while in the remaining 32 the exposure to the substance was found to be associated with suicidal intent. All patients were subjected to supportive therapy and endoscopic examination performed at admission and after 12 and 36 hours after ingestion. In subjects in which the ingestion of the substance was accidental, the amount of sodium hypochlorite was found to be 10-30 ml and at a rate not exceeding 5%. In cases of intentional exposure, the patients ingested 50-100 ml of hypochlorite, in 27 at a concentration of 5% and of 15% in 5 cases. 75 patients underwent only supportive care, decision given the small amount of the substance allegedly ingested. Of these, at endoscopy performed, 13 had gastric and esophageal

lesions from mild to severe, 9 significant edema of the mucosa and esophageal stenosis, 3 patients were perforated. In 25 subjects sodium thiosulfate in oral suspension was administered, presumably at the same dosage of sodium hypochlorite ingestion: in 17 cases, intervention was timely and was achieved within 30 minutes of ingestion, in 8 cases between 30 and 90 minutes ingestion. Endoscopy examination subsequently carried out in 17 cases in which the administration of sodium thiosulfate was within 30 minutes, the local symptoms was very low: the patients complained only moderate pain on swallowing and chestburn. Above all, at the follow up controls, performed until six months after the event, there were no significant sequelae. As for the 8 patients who received the antidote from 30 to 90 minutes, in 5 the amount of sodium hypochlorite was found to be ingested 50-80 ml of 5%: in these cases discrete erythema of the oropharyngeal mucosa and oesophageal or mild edema of the upper portion of the esophagus was detected and required medical supportive therapy, in 3 cases the amount of sodium hypochlorite ingested was greater than 100 ml of 15% and this required the placing of a stent in emergency temporary and a follow-up endoscopic surgery of esophageal dilatation. **Discussion:** *Sodium hypochlorite* Is the salt of sodium 's hypochlorous acid. Its chemical formula is NaCl. A solution to about 5% sodium hypochlorite in water is known as bleach or chlorine, yellow, with a characteristic pungent smell. Pure is a salt pentahydrate (NaClO • 5 H2O) that melts at about 18°C and is particularly unstable. Frictional or heating at temperatures above 35°C may decompose in a violent way. Precisely for this reason it is never marketed and used pure, but used in water solution at concentrations generally not exceeding 25%. As the salt of a strong base with a weak acid, imparts an alkaline reaction to water. Because of oxidant action, sodium hypochlorite solutions are used primarily as bleaching agents and disinfectants. Sodium hypochlorite is a bactericidal, sporicidal one, a fungicide and a virocide. In solution it is commonly used for routine cleaning washable surfaces. In commerce, it is possible to find solutions with concentrations ranging from 3 to 7%, but for industrial purposes solutions to 15% are also obtainable. The toxicity of the substance is linked to its corrosive properties on skin and mucous membranes: the colliquative necrosis caused by hypochlorite cause saponification of fats and proteins with rapidly penetrating burns, thrombosis of tissue and consequent deficient circulation that contribute to the damage of mucosa and esophageal muscle layer and a high risk of perforation of the esophagus and stomach. The severity of burns is associated with the contact time, pH and the amount ingested. The symptoms may occur immediately or even delayed by several hours. Life-threatening injuries can occur even for exposure less than one minute. Injuries caused by caustic substance evolve in three stages: 1. Inflammatory state: occurs in the first 4-7 days, and is characterized by edema, erythema, vascular thrombosis and necrosis with a peak around 48h. 2. Granulation State: from 4 to 7 days. It begins with the proliferation of fibroblasts and collagen synthesis. In this phase, there is the maximum risk of perforation. 3. State of scarring: from 3 weeks to several years. Formation of fibrous tissue at various times with results in stenosis. Burns induce drooling mouth, pain, dysphonia, and dysphagia: an examination of the oral cavity can show erythema, edema, ulceration and necrosis. The pain can be intense, but also absent, because deep burns can destroy the nerve endings in the mucosa and produce anesthesia. The non-oral involvement does not exclude esophageal or gastric injury. Esophageal symptoms include drooling, odynophagia, retrosternal pain and tenderness in the neck, with "sniffing position", hematemesis. Epigastric pain, vomiting and heartburn may occur in case of burns of stomach. The more serious local complications are certainly perforation and digestive hemorrhage. These may occur immediately after the assumption or later. The perforation can develop spontaneously due to necrosis of the wall even 12 hours after taking the drug, particularly if alkaline, though it is more frequently caused by iatrogenic endoscopies performed in the wrong time. The esophageal perforation is indicated by an increasing severity of pain, often with respiratory distress. The bleeding is more common in patients taking acid substances, and occurs between the 7th and 15th day in the fall of scabs. In addition to local complications, we must remember the systemic damage: respiratory failure is common and can be caused by edema of the glottis, the direct action of caustic on the respiratory system caused by the inhalation, the formation of tracheo-esophageal fistula or by the development of aspiration pneumonia. The bacterial and fungal infection are frequent by translocation to the digestive tract to the mediastinum or peritoneum without perforation. In severe cases, more often in the presence of acute complications, the disease can 'move towards a multi-organ systemic involvement (MOF), where for a multifactorial renal failure (reabsorption of toxins, effect of bacterial toxins, relative hypovolemia), it can bind a liver failure and respiratory distress syndrome (ARDS) and a DIC, which often result in death. Deep burns, especially if large or circumferential, may be followed by fibrosis with stricture formation and obstruction of the esophagus. Endoscopy, performed preferably within 12-24 hours after ingestion in all symptomatic patients, documents the anatomical site and often the severity of the injury. *Sodium thiosulfate* The redox reactions are occurring simultaneously, in which the oxidation of a compound and the reduction of another. In these reactions involved substances or elements, respectively, oxidizing and reducing agents that is able to absorb or give up electrons to the substance you want to reduce or oxidize, respectively. Each oxidation reaction, therefore, runs parallel to a reduction reaction, and a reduction reaction to oxidation. The hypochlorite ion ($OCl^{-)}$ is an oxidizing agent in acid solution and we have:

$2e^{-}+OCl^{-}+2H^{+}\rightarrow Cl^{-}+H_2O$

Thiosulfate ion ($S_2O_3^{2-)}$ is a reducing agent, yielding electrons form ion tetrationato ($S_4O_6^{2-)}$ in acid solution.

$2S_2O_3^{2-}\rightarrow S_4O_6^{2-}+2e^{-}$

In the body, sodium thiosulfate reacts with sodium hypochlorite as follows:

$4NaClO+Na_2S_2O_3+2NaOH\rightarrow\rightarrow 4NaCl+2Na_2SO_4+H_2O$

Practically, the administration of sodium thiosulfate at a dose equal to the amount of hypochlorite allegedly ingested (since the two substances equimolar), the chemical reaction leads to the formation of sodium sulfate and sodium chloride (common salt), both substances completely harmless for the patient. The treatment of caustic esophageal lesions and / or stomach is still a problem not easily solved due to the difficulty of classifying patients into risk groups. From the epidemiological point of view it is clear that the accidental ingestions are generally less serious than those voluntary and usually caused by alkaline substances, which, being odorless, colorless, tasteless and are often stored in inappropriate containers occasional, lend themselves more easily to ' error. Also from our experience, like those expressed in the literature, it appears that the disease is expressed in three stages. An initial acute phase of the first hours after ingestion, in which our attention should be aimed at preventing the spread or evolve in injury complications, perforations and / or bleeding, which may impair the patient's life. The second, characterized by the repair of lesions caused by caustic and finally the third which is expressed even after years in scar stenosis. We agree with the literature that endoscopy is the gold standard to define the therapeutic approach and that this examination should be performed early to minimize the risk of iatrogenic complications. In our experience all patients underwent the examination within the first hour. We must say, however, that in all patients seen by us urgently, to better define the evolution of the disease was performed, with care, endoscopic control after a few days without any complications related to the exam. We believe it is important to monitor the progress of the lesions and the onset of complications such as fungal superinfection, to act quickly on them. Endoscopy, associated with clinical and laboratory data, can highlight those patients requiring quoad vitam, of a surgical emergency. As noted in the literature, even in our cases, the alkaline nature of substances have caused damage mainly located esophagus. This does not appear dependent on the non-alkali neutralization due to gastric acidity, but rather the physical state of being predominantly viscous substance that tends to stay in the esophagus. **Conclusions:** While the ingestion of sodium hypochlorite are not satisfied in the statistics of urgency, it is true that the use of sodium thiosulfate is simple and free from risk of side effects. In practice, the only contraindication to its use is linked to the possibility of esophageal perforation. If used a short time after the ingestion of sodium hypochlorite (no later than 30 minutes), sodium thiosulfate seems to be able to block the mechanisms that induce tissue colliquative necrosis. This, in combination with appropriate supportive therapy, can significantly improve patient outcome. The limitations of the procedure are related to its low palatability and unpleasant smell due to the presence of sulfur; this obstacle can be circumvented by administration, particularly in children, of the substance together with fruit juice. Not recommended, instead, its administration via nasogastric tube: as the action of sodium thiosulfate is in contact with the hypochlorite, the insertion of a probe would focus the action of the substance only in the stomach, "bypassing" the esophageal mucosa that, as we have seen, is the most affected by alkali injury.

## IL BICARBONATO DI SODIO COME ANTIDOTO

F. Gambassi[1,*], A. Ieri[1], F. Gori[2], A. Del Vecchio[2]

*[1]SOD di Tossicologia Medica e Centro Antiveleni, AOU Careggi, Firenze; [2]Dipartimento NEUROFARBA, Sezione di Farmacologia e Tossicologia, Università degli Studi di Firenze*

*Corresponding Author: Francesco Gambassi, email: gambassif@aou-careggi.toscana.it*

Il bicarbonato di sodio (NaHCO3) è diffusamente impiegato come farmaco nell'uomo, spesso in situazioni di emergenza-urgenza. L'effetto farmacologico per via endovenosa inizia dopo 15 minuti dalla somministrazione, la durata di azione è 1-2 ore e il suo volume di distribuzione è il doppio di quello dei fluidi del compartimento extracellulare ed aumenta in caso di acidosi. L'NaHCO3 riveste un ruolo cruciale come antidoto non specifico nel trattamento di varie intossicazioni acute, diverse fra loro dal punto di vista del meccanismo farmaco-tossicologico, esercitando il suo effetto farmacologico mediante molteplici meccanismi di azione. Allo stato attuale, tuttavia, le evidenze scientifiche per il suo impiego come antidoto sono fondate non su studi clinici randomizzati e controllati, ma su evidenze emergenti dalla sperimentazione animale, su case reports e series nell'uomo, e su consensus di esperti in materia. L'NaHCO3 è comunemente impiegato, nelle intossicazioni da xenobiotici cardiotossici (antidepressivi triciclici, antiaritmici di classe IA e IC, cocaina) che agiscono come bloccanti i canali del sodio a livello delle cellule del miocardio. In numerose case series relative ad intossicazioni acute da xenobiotici bloccanti i canali del sodio, sia in età adulta che pediatrica, l'NaHCO3 si è dimostrato in grado di correggere il ritardo di conduzione atrio-ventricolare (QRS >100 msec, BBD), la tachicardia a complessi larghi e l'ipotensione indotta, mediante due distinti meccanismi di azione: 1) aumento del gradiente trans-membrana del sodio (azione sodio-dipendente) e 2) aumento della frazione non-ionizzata e più liberamente diffusibile, rispetto a quella ionizzata, responsabile per larga parte (90%) dell'effetto di blocco dei canali del sodio, dello xenobiotico (azione pH-dipendente). L'NaHCO3 svolge un efficace effetto antidotale nelle intossicazioni da salicilati, fenobarbital, metotrexato, erbicidi clorofenossici, clorpropamide, per alterazione della distribuzione ed aumento dell'eliminazione degli xenobiotici; alcoli tossici, come il metanolo ed il glicole etilenico, per correzione dell'acidosi metabolica indotta dai prodotti del loro metabolismo e facilitazione della loro eliminazione renale; metformina, per correzione dell'acidosi metabolica; gas clorurati per un'azione neutralizzante; mezzi di contrasto, per un'azione protettiva a livello renale del danno da radicali liberi e dimercaprolo per la riduzione della tossicità renale indotta dai metalli non legati al

chelante. Altri impieghi del NaHCO3 come farmaco, largamente diffusi ma controversi in quanto la sua efficacia non è universalmente condivisa, sono la rabdomiolisi, l'acidosi metabolica lattica, la resuscitazione cardiaca e la cheto-acidosi diabetica. L'NaHCO3 è disponibile in soluzioni all'8,4 % (1 M; 1 mEq/mL), 4,2% (0,5 mEq/mEq/mL), formulazione pediatrica e 1,4% (0,12 M; 0,66 mEq/mL). La somministrazione di NaHCO3, non è indenne da rischi associati, quali l'alcalosi, l'ipernatremia, l'ipopotassiemia, l'ipocalcemia ed il sovraccarico di liquidi, per cui la somministrazione in pazienti affetti da cardiopatia congestizia, insufficienza renale severa, edemi da ritenzione di sodio, richiede particolare attenzione. Nell' intossicazione acuta da salicilati l'iniziale alcalosi respiratoria è spesso accompagnata da alcalosi metabolica, per cui in questa fase la somministrazione di bicarbonato non indicata. Il bicarbonato di sodio è comunque un antidoto efficace di priorità 1, ampiamente disponibile e di basso costo e non dovrebbe mancare in nessun presidio di primo soccorso.

## ON THE NEUROTOXICITY OF TWO ITALIAN VIPER VENOMS

M. Pirazzini[1,*], G. Zanetti[1], C. Montecucco[1,2], C. Locatelli[3], D. Lonati[3], O. Rossetto[1]

*[1]Department of Biomedical Sciences, University of Padova, Italy; [2]National Research Council Institute of Neuroscience, University of Padova, Italy; [3]Pavia Poison Center and National Toxicology Information Centre, Toxicology Unit, IRCCS Maugeri Foundation and University of Pavia, Italy*

*Corresponding Author: Marco Pirazzini, email: marcopiraz@gmail.com*

Venomous snakes in Europe are essentially restricted to the vipers of the genus *Vipera*, which is characterized by many subfamilies (*V. berus, V. ammodytes, V. ursinii and V. aspis*). From the clinical point of view, viper snakebites are generally characterized by local symptoms (pain, edema, swelling and in some case local necrosis) accompanied by systemic effects such as gastrointestinal manifestations, chest pain, hypotension, and coagulopathy. Neurological implications are rarely reported in Italy and France. Within the limitations linked to the retrospective determination of the biting species, neurologic complications are associated to *V. aspis,* but not to *V. berus* bites. We report here a molecular and toxicological investigation of *V. aspis* and *V. berus* venoms aimed at defining their neurotoxic profile. We determined the electrophoretical pattern of the two venoms, finding that both display bands around 14 kDa, typical of snake phospholipases A2 (PLA2). Accordingly, we investigated PLA2 activity in vitro, finding both venoms capable to hydrolyze phospholipids. However, only *V. aspis* venom generates "neuron bulges", the hallmark of PLA2-neurotoxins activity in primary cultures of neurons. For the *in vivo* analysis we injected the venoms in the mouse hind limb, and then evaluated the NMJ functionality by mean of electrophysiological measurements on soleus muscle. Consistently with the experiments on neuron cultures, we found that the venom from *V. aspis* causes paralysis, as assessed by the lack of evoked junction potentials and muscle twitch. At variance, the venom of *V. berus* induced a huge hemorrhagic effect, but did not hinder neither evoked potentials nor the capability of muscle to twitch. The immunohistochemical analysis of the same muscles with pre- and post-synaptic markers, showed that *V. berus* venom does not cause evident morphological alterations, while *V. aspis* venom produces major damages both to muscle fibers and to motor axon terminals. We also tested the neutralizing activity of an antiserum, routinely used as antidote. Using immunoblotting, we found that the antiserum similarly recognizes the majority of components found in both venoms, but, surprisingly, it poorly protects from V. aspis venom *in vivo*. Collectively, our results show that the venom of *V. aspis* displays both myotoxic and neurotoxic activity, reconcilable with its PLA2 activity. At variance, *V. berus* venom, even though equipped with an active PLA2 cause neither evident myotoxic nor neurotoxic activity.

## LABORATORY ANALYSIS: CORRECT CLINICAL INDICATIONS IN ACUTE INTOXICATIONS

V. Danel*

*SAMU, Centre Hospitalier Universitaire Grenoble Alpes et Université Grenoble Alpes, France*

*Corresponding Author: Vincent Danel, email: vdanel@chu-grenoble.fr*

Before describing the different steps which may lead to laboratory analysis in acute poisonings, some short comments must be done previously. Clinical examination must precede any toxicological analysis: whenever a toxidrome is obvious and whenever it matches medical history and clinical examination, no toxicological analysis is needed in most cases. Routine biological analysis is very often more important than toxicological analysis. In most cases, initial supportive treatment aims at correcting vital and biological abnormalities; in some rare cases, specific treatment depends on toxicological analysis. Some simple biomarkers may be of great help to confirm poisonings and/or to assess poisoning severity, such as COHb with carbon monoxide, lactate with cyanides, etc. Systematic detection of most medicines and drugs in blood or urine by using immunoassays is useless in most cases. Blood dosage is rarely needed; it must have a real impact on the way treatment is carried out. However, caution must be taken whenever paracetamol poisoning is suspected: a blood dosage must be done when in doubt. Most analysis should be done in blood in which there is a better correlation between concentration and immediate or potential severity. Urine analysis may help sometimes as it gives information on the 24-48 previous hours' drugs consumption or when blood elimination occurs rapidly. Toxicological analysis by using chromatographic techniques in blood or urine is useful in those

cases when neurological symptoms remain unexplained, when a state of coma has no known origin, when a circulatory failure has no explanation, and each time medical history is completely unknown. In those situations, the clinician and the biologist must take the time to talk together to better assess the case they are looking after. The limits of every technique must be discussed. The different steps we propose are the followings. 1. Is a toxidrome clearly identified? Routine biological analysis and ECG are all that is needed in the vast majority of cases. Blood dosage is needed for the following substances only: carbamazepin, chloroquine, digoxin, glycol ethylene, iron, lithium, methanol, paracetamol, phenobarbitone, salicylates, theophylline, thiopentone, valproic acid. 2. As mentioned above, a thorough toxicological analysis must be done whenever vital symptoms remain unexplained, by using up to date chromatographic techniques often coupled with mass spectrometry. The same applies when no toxidrome can be identified. 3. Paracetamol blood dosage must be done whenever medical history is unclear and each time a drugs association is suspected. 4. Blood and urine samples must be kept sometimes on a routine basis. They may helpful later in some cases and for different purposes.

**References**

1. Bartoli M, Berny C, Capolaghi B, Danel V, Delahaye A, Desch G *et al.* Recommandations pour la prescription, la réalisation et l'interprétation des examens de biologie dans le cadre des intoxications graves. Ann. Fr. Med. Urgence 2012; 2: 414-428.
2. Bartoli M, Eysseric H, Danel V. Analyse toxicologique et intoxication aiguë. Spectra Biologie 2014; 207: 59-66.

## LABORATORY TOXICOLOGICAL ANALYSIS: ANALYTICAL ASPECTS

P. Papa*, L. Rocchi, L. Rolandi, M. Di Tuccio, A. Valli

*Fondazione IRCCS Policlinico San Matteo, Laboratorio di Tossicologia Analitica Pavia, Italia*

*Corresponding Author: Pietro Papa, email: p.papa@smatteo.pv.it*

The mission of the clinical toxicology laboratory is the detection, identification and measurement of xenobiotics in biological specimens to help in the diagnosis, prognosis, treatment and prevention of poisoning. The diagnosis of poisoning is often based only on clinical assessment and case history, but the analytical data is the only mean to evidence the intoxication and its severity. Because of cost constraints, existing technology and staffing problems, it is impractical for any clinical laboratory to provide a full range of toxicological analyses.[1] Often analytical difficulties cause controversial judgment about the role of toxicology laboratory; the recommendations for toxicological analyses to support intoxicated patient are highly dependent on the availability of toxicology tests.[2] In analytical toxicological practice, two different approaches are used: the direct determination of a potentially involved compound (targeted analysis) or screening procedures for a distinct drug class or a wide variety of different compounds (multi-targeted and untargeted analysis). Immunoassays are available for targeted analyses of drugs and screening of drugs of abuse; enzymatic tests are available for ethanol and GHB. Immunoassays, being rapid and highly automated, are often used in intoxications cases, but they have limitations in sensibility and specificity, and anyway, they cover a limited number of xenobiotics. The Toxicology Laboratory of Fondazione IRCCS Policlinico San Matteo of Pavia provides toxicological tests for 205 different analytes potentially responsible for poisonings (drugs, classic drugs of abuse, new psychoactive substances of abuse, pesticides, industrial compounds), but in emergency situations, only 20 tests (9 %) are executable with immunochemical techniques. In 2015, the laboratory received 2344 requests for toxicological analyses in suspected acute intoxications and immunoassays were applied in 1336 cases: 1229 cases of suspected intoxications by classic drugs of abuse (53 %) , and 107 (4%) by other compounds (drugs). The other analytical technique that is widely used in specialized toxicological laboratories is hyphenated chromatography consisting of either high-performance liquid chromatography or gas chromatography coupled to detectors such as a diode-array or mass spectrometer. These techniques can be used for targeted, multi-targeted and untargeted analyses, being useful in qualitative and quantitative analysis of a wide range of compounds. Our toxicology laboratory use chromatographic methods for the determination of 182 analytes ( 89 % of the total), and in 2015, about 789 (34 % of the total) request for toxicological analyses were performed with this techniques; among these requests, about 300 were for serum/plasma determination of antidepressants (tricyclic ADP, SSRI) and benzodiazepines that can be correctly quantified only with chromatographic methods not with immunoassays. Other xenobiotics, as neuroleptics methanol, ethylene glycol, metformin, colchicine, and new psychoactive drugs of abuse have been detected in chromatography, the only technique suitable for these analytes.[3,4] Compared with immunochemical techniques, chromatography requires a specifically trained technical staff, the turn around time is longer and the costs are higher. These quantitative methods have similar properties to the classic therapeutic drug monitoring (TDM) methods using hyphenated chromatographic methods: these methods may be usefully applied to intoxication cases. In general, in order to mitigate the toxicological analytical problems and maximize the value of analytical data is important: 1) the communication between clinician and laboratory. 2) a close agreement between the laboratory and poisons centers which provide i) informations about the epidemiology of poisoning ii) a guide for the choice of appropriate tests to the clinical situation, iii) inform clinicians about the existence of a specialized analytical service. 3) the organization of a regional/national analytical toxicological service for complex and less frequently needed analyses.

**References**

1. Flanagan RJ, Developing analytical toxicology services: principles and guidance.2005, ipc@who.int.

2. Wu A H B, McKay C, Broussard L A, Hoffman R S , Kwong T C, Moyer T P, Otten E M, Welch S L, Wax P. 2003, National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Recommendations for the Use of Laboratory Tests to Support Poisoned Patients Who Present to the Emergency Department. Clin Chem 49(3):357-379.
3. Papa P, Rolandi L, Rocchi L, Valli A. Diagnosi analitica d'urgenza per overdose da farmaci, sostanze d'abuso e altri composti in laboratori dedicati. 2012, XVI Congresso Nazionale Società Italiana Tossicologia(SITOX). http://congresso.sitox.org/archivio/2012//congresso_abs_view.php?id=137
4. Lonati, D., Buscaglia, E., Papa, P., Valli, A., et al., 2014, MAM-2201 (analytically confirmed) intoxication after "synthacaine" consumption, Annals of Emergency Medicine. 64, 6, p. 629-632.

## MAJOR POISONINGS. CARBON MONOXIDE AND CYANIDE

F.J. Baud*

*Department of Anesthesiology and Intensive Care Medicine, SAMU de Paris, Necker Universitary Hospital; Paris Poison Control Centre, Fernand Widal Universitary hospital; University Paris Diderot*

*Corresponding Author: Frederic J Baud, email: baud.frederic@wanadoo.fr*

Astronomic observations resulted in the hypothesis that carbon monoxide (CO) and hydrocyanic acid (CN) belong to the class of prebiotic substances. Prebiotic substances include substances that existed in the Universe before life has started to exist. CO and CN have molecular weight within the same range of about 28 and 27 g/mol, respectively. However, CO is extremely stable at ambient pressure and temperature. The stability of CO results in the lack of metabolism in mammals. CO is absorbed through and acts within numerous organs whilebeing eliminated as unchanged CO. In humans breathing ambient air containing 21% of oxygen, the elimination half-life of CO in expired air is about 4 hours.In contrast, CN is highly unstable and results in spontaneous polymerization without stabilizers. This intrinsic reactivity of CN is considered as one of the prerequisite for having generated life on the Earth. Actually, CN is spontaneously metabolized to inactive forms, merely thiocyanate ($SCN^-$) at a rate of 0.017 mg CN/Kg/min by four pathways including two enzymatic pathways: i) the thiosulfate-cyanide transulfurase (rhodanese), ii) the β mercaptopyruvate-cyanide transulfurase, and two non-enzymatic pathways involving the spontaneous covalent binding with endogenous molecules including i) cysteine to 2-Imino-thiazoline-4-carboxylic acid which is an inactive metabolite, and ii) hydroxocobalamin to form cyanocobalamin, the active form of vitamin B12. Both chemicals are volatile at room temperature. Both gases exhibit physiological activities at low concentrations and belong to the class of gaseous neurotransmitters. Both gases exhibit a high affinity to the reduced form ofthe ferric ion in various enzymes, including cytochromes, transporters, including hemoglobin, and hemoproteins, including myoglobin. These features suggest that signs and symptoms induced by carbon monoxide and cyanide might be similar. A rough overview would result in such a conclusion. However, mono-intoxications with CO or CN clearly evidence this assumption does not hold true. This discrepancy is far more evident if the toxicodynetics of the signs and symptoms is taken into account. CO needs hours to cause organ failures meanwhile CN needs only minutes. CO merely causes transitory loss of consciousness and cardiac ischemia. CN causes the rapid onset of deep coma and immediately causes alteration in vital functions, including cardiovascular shock and even cardiac arrest, deep lactic acidosis inducing hyperpnea followed by the rapid onset of long-lasting apnea. Lactic acidosis caused by CO is mild [1,2] in the order of magnitude of less than 8 mmol/l while lactate levels are greater than 8 mmol/l in 80% of cyanide poisonings. As a matter of results, there are strong discrepancies regarding specific treatments. While oxygen, normobaric and/or hyperbaric, still stands the antidotal treatment of CO poisoning. Oxygen is of limited efficiency, if any, in cyanide poisonings which requires additional antidotal treatments, including hydroxocobalamin, sodium thiosulfate, and amyl nitrite to detoxify CN in the body. Owing to the progressive decline in CO poisonings,[3] the most frequent cause results from smoke inhalation produced in, residential fires. Awareness and preparedness of emergency physicians are required to treat appropriately fire victims suffering from CO or CN or CO and CN poisonings.

**References**

1. Cervellin, G., et al., Initial blood lactate correlates with carboxyhemoglobin and clinical severity in carbon monoxide poisoned patients. Clin Biochem, 2014. 47(18): p. 298-301.
2. Dogan, N.O., et al., Can initial lactate levels predict the severity of unintentional carbon monoxide poisoning? Hum Exp Toxicol, 2015. 34(3): p. 324-9.
3. Hampson, N.B., US Mortality from Carbon Monoxide Poisoning 1999-2014: Accidental and Intentional Deaths. Ann Am Thorac Soc, 2016.

## ORGANOPHOSPHATES INTOXICATIONS

R. Zoppellari*, I. Farinelli

*UO Anestesia e Rianimazione Ospedaliera, Azienda Ospedaliero Universitaria di Ferrara*

*Corresponding Author: Roberto Zoppellari, email: roberto.zoppellari@unife.it*

In the developing world organophosphorus (OP) poisoning is a potential candidate of mortality in comparison with infectious diseases due to its unregulated, easy availability as an agricultural pesticide. Some powerful organophosphates are chemical warfare agents.[1] OP inhibit acetylcholinesterase (AChE), which results in accumulation of acetylcholine (ACh) at autonomic and some central synapses and at autonomic postganglionic and neuromuscular junctions. As a consequence, ACh binds to, and stimulates, muscarinic and nicotinic receptors, thereby producing characteristic features.[2] Routes of exposure are: inhalation, ingestion and through contamination of skin, conjunctivas or mucosas. Parenteral poisoning is exceptional.[1] Cilinical

manifestations of OP poisoning are the acute cholinergic syndrome, the delayed polyneuropathy and the intermediate syndrome.[2] The variations in the acute toxicity of OP are the result of their different chemical structures and rates of spontaneous reactivation and aging.[1] The "aging" may occur by partial dealkylation of the serine group at the active site of AChE; recovery of AChE activity requires synthesis of new enzyme in the liver.[2] The acute cholinergic syndrome is characterized by signs and symptoms classified into muscarinic (vomiting, dyarrea, abdominal cramping, bronchospasm, bronchorrea, miosis, salivation, bradycardia), nicotinic (muscle fasciculations, cramping, weakness, respiratory muscle paralysis, mydriasis, tachycardia, hypertension) and central nervous system effects (excitability, lethargy, agitation, seizures, coma, death).[1] The common cause of death is respiratory failure.[1] Relapse after apparent resolution of these symptoms is termed intermediate syndrome. This involves the onset of muscle paralysis affecting particularly upper-limb muscles, neck flexors, and cranial nerves some 24-96 hours after OP exposure and is often associated with the development of respiratory failure. OP-induced delayed neuropathy results from phosphorylation and aging of at least 70% of neuropathy target esterase. Cramping muscle pain in the lower limbs, distal numbness, and paresthesiae are followed by progressive weakness, depression of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs.[2] The diagnosis of OP poisoning is based on the patient's history, clinical presentation and laboratory tests. The activity of two enzymes may be measured to confirm a diagnosis of OP poisoning. These are red-cell AChE and plasma butyrylcholinesterase. Both are surrogates for AChE activity in the CNS and peripheral nervous system, but the erythrocytes AChE is more specific as a marker of OP exposure.[3] All cases of OP poisoning should be dealt with as an emergency and all patients with more than minor symptoms should be admitted to a critical care unit as quickly as possible. The therapeutic combination of oxime, atropine, and diazepam is well established experimentally in the treatment of OP poisoning. Atropine competes with ACh for a common binding site on the peripheral muscarinic receptor, antagonizing its action in producing increased tracheobronchial and salivary secretions, bronchoconstriction and bradycardia. The pyridinium oximes reactivates AChE inhibited by OP, thus allowing ACh to be hydrolized in the usual way and resumption of normal cholinergic neurotransmission. Diazepam may also be of benefit by reducing anxiety, restlessness and muscle fasciculation, suppressing seizures and reducing morbidity and mortality when used in conjunction with oxime and atropine.[2]

**References**


1. Zoppellari R. Antidotal therapy and intensive management of organophosphate poisoning. In: (proceedings) Recent Issues in Clinical Toxicology Antidotes in Depth, Pavia 10-12.7.2000, p. 55-63.
2. Vale A, Lotti M. Organophosphorus and carbamate insecticide poisoning. Handb Clin Neurol. 2015;131:149-68.
3. King AM, Aaron CK. Organophosphate and carbamate poisoning. Emerg Med Clin North Am. 2015 Feb;33(1):133-51.


## LA PRESCRIZIONE NELL'ANZIANO COME ELEMENTO CRITICO PER TOSSICITÀ


E. Limido*, S. Casati, C. Bassino, C. Prete, D. Tettamanzi, M. Frigerio, M. Casartelli, D. Sala

*U.O. Medicina Generale – Ospedale Sant'Antonio Abate di Cantù – ASST Lariana Como*

*Corresponding Author: Eugenio Limido, email: eugenio.limido@asst-lariana.it*


Il reparto di medicina interna ha subito negli ultimi trent'anni una rivoluzione epocale. Negli anni '80 giovani medici curavano con pochi farmaci pazienti affetti da una singola patologia acuta con l'obiettivo della guarigione. L'evoluzione scientifica, farmacologica e tecnologica ha esaltato le specialità per diagnosticare e curare meglio patologie sempre più nuove e specifiche. I pazienti sono sopravvissuti ed invecchiati (così come i medici che li curavano) e gli anziani sono la fascia di popolazione in maggiore crescita. Oggi medici meno giovani curano pazienti anziani, fragili, spesso isolati socialmente, ed esposti a rischi di politerapia che raramente guariscono e frequentemente tornano ad essere ricoverati. In questi pazienti spesso la cura oltre che alla malattia è diretta ai sintomi e al conforto. Il termine politerapia (polypharmacy) si riferisce all'assunzione contemporanea di più di 5 o 10 farmaci e tale fenomeno coinvolge il 20-35% dei pazienti fra i 75 e gli 85 anni. Le possibili conseguenze di una politerapia sono, naturalmente, reazioni avverse ai farmaci, interazioni farmacologiche, prescrizioni inappropriate, cascate prescrittive ma anche ricoveri ospedalieri, mortalità, decadimento cognitivo e incremento dei costi. Il farmaco potenzialmente inappropriato o PIM è un farmaco in cui il rischio di un evento avverso prevale sul beneficio clinico atteso, in particolare quando esiste evidenza a favore di una terapia alternativa più sicura per la stessa patologia. Esistono criteri espliciti (Beers', STOPP) ed impliciti (MAI, POM) per individuare e riconoscere i PIMs. Ciascuno di essi ha vantaggi e limiti e richiede tempo per essere applicato. L'appartenenza o meno di un farmaco a un PIM non vuol dire né che il farmaco non sia necessario né che possa essere utilizzato in tutta sicurezza. Tutti i test descritti sono indicatori di processo e non di risultato ed è quindi difficile dimostrare vantaggi di outcome clinico. Nulla infine sostituisce l'analisi circostanziata della complessa situazione clinica del singolo paziente e il giudizio clinico. Ottimizzare la terapia farmacologica nel paziente anziano è una vera sfida per il clinico. Obiettivo prioritario dovrebbe essere identificare i casi in cui il farmaco perde il proprio ruolo di cura per essere esso stesso danno o malattia, tendere sempre ad un approccio multisistemico del paziente, tenendo conto dei cambiamenti legati all'età, della comorbilità, delle disabilità, della politerapia ed integrando i fattori psicologici , socio-economici e le preferenze personali. Perchè la politica della de-prescrizione sia efficace. essa deve entrare nella pratica

clinica quotidiana, accettata dai pazienti, dai medici e dai famigliari come parte integrante della "best practice". Le decisioni terapeutiche debbono essere basate anche su età biologica ed anagrafica, aspettanza di vita, obiettivi terapeutici e anche su di un equità distributiva delle risorse. La collaborazione fra le diverse figure professionali è indispensabile, particolarmente quando avviene un passaggio di cura. L'aiuto di strumenti informatici e di raccomandazioni deve essere stemperato in un approccio olistico, multiprofessionale e soprattutto di buon senso che tenga conto anche dei valori e bisogni del paziente. Solo questo approccio potrà spostare la nostra attenzione dal farmaco, dal medico, dalla clinica, dalla farmaco-economia verso il paziente.

## POPULATIONS FACING CHEMICAL WEAPONS IN THE MIDDLE-EAST. THE MÉDECINS SANS FRONTIÈRES EXPERIENCE

F.J. Baud*

*Referent toxicologist at MS, Department of Anesthesiology and Intensive Care Medicine, SAMU de Paris, Necker Universitary Hospital; Paris Poison Control Centre, Fernand Widal Universitary hospital; University Paris Diderot*

*Corresponding Author: Frederic J Baud, email: baud.frederic@wanadoo.fr*

The use of chemical weapons during the Iran-Iraq war in the mid-eighties was evidenced. The third Gulf war started in 2003, as a preventive war based on the alleged assumption by the USA government of likelihood use of mass destruction weapons by the Iraqian army. No evidence if any supported the use of chemical weapons during the war by itself. More recently, in July 2012, at the beginning of the civil war, "Syria manufactured and stockpiled chemical weapons", President Bachar El Assad said. At this time, a number of MSF structures were involved in various area in Syria to support civilians owing to the collapse of the National Health System. Owing to the recent past, the threat related to chemical weapons was considered highly credible. MSF considered mandatory to address this threat. On March 2013 a task force attempted at building a contingency plan Entitled "Chemical weapon threat in the Syrian context." The contingency plan aimed at addressing the following issues 1) To increase awareness and preparedness of the staff of medical structures toward chemical weapons. Indeed, the effects of chemical weapons, even if life-threatening, are limited in time as well as the area contaminated by, 2) To inform on how to protect the staff and in case of exposure how to decontaminate and treat casualties, 3) To provide knowledge to the staff allowing facing chemical casualties, emphasizing on decontamination, triage and use of selected antidotes. All the participants agreed that MSF staff will never attempt at going into a known contaminated area except for being part of the bombing area. Among the NRBC risk, the Task Force had to focus on chemical weapons. Even, in the limited area of chemical weapons, there are a great variety of agents. In March 2013, we agreed that the risk assessment should be limited to three classes of chemicals, including chocking (asphyxiant) gases, organophosphorus, and sulfur mustard. Among the different scenarii, we included a MSF structure being in an area targeted by chemical weapons. Therefore, the head of mission should have relevant information to perform at the scene of the attack the risk assessment to determine whether the best protection of the staff should be either confinement in the hospital or escape of protected care givers. We selected equipment that should be easily used by untrained individuals. Owing to this major limitation we selected escape hood for protection of the head, neck and respiratory airways, either personal protective suits or lighter equipment including aprons and clothes with long sleeves with gloves and boots. Gas masks were limited to care givers involved in the decontamination process. Dry as well as wet decontamination were both considered. Dry decontamination can be performed without any delay using flour while wet decontamination needs a number of facilities including large quantity of water, files to treat men and women separately, time for shower each casualty. Noteworthy, dry and wet decontamination have to be considered as complementary. A major issue was to advise as early as possible after exposure undressing, complete undressing in men, partial in women while putting contaminated clothes in plastic sealed bags. Previous experience showed this single measure able to prevent transfer of contamination to care givers. Stockpiling antidotes included atropine and pralidoxime. Reactive Skin Decontamination Lotion was not recommended for general population. A particular attention was paid to supportive treatments including, airway suction, oxygen supply, bronchodilators, and steroids either nebulized or IV. Till now, MSF had to face numerous exposure to liquid chlorine, a few attempts with organophosphates but the most deadly, killing thousands of people the 23rd of August 2013, and the last but not the least sulfur mustard attacks. Factors of vulnerability in the civilian population included low-weight children, women, and elderly.

## AMORE TOSSICO: ANALISI RETROSPETTIVA DI TRE ANNI DI AGITI TOSSICOLOGICI AUTOLESIVI ATTRIBUIBILI A PROBLEMI SENTIMENTALI

P. Botti[2,*], F. Gambassi[1], A. Pistelli[1], C. Canzani[1], A. Mocarini[1], E. Masini[1,2], G. Mannaioni[1,2]

*[1]SOD di Tossicologia Medica e Centro Antiveleni, AOU Careggi, Firenze; [2]Dipartimento di NEUROFARBA, Sezione di Farmacologia e Tossicologia, Università degli Studi di Firenze*

*Corresponding Author: Primo Botti, email: primo.botti@unifi.it*

**Premessa:** Il suicidio è la decima causa di morte negli Stati Uniti d'America, e fra questi le intossicazioni autolesive rappresentano la terza causa (2.1/100.000 abitanti)[1]. Le intossicazioni deliberate autolesive (IDA) a scopo suicidiario rappresentano, nel

2013, il 10,5% di tutti gli interventi dei Centri Antiveleni Americani, gravate dal 31,7% di mortalità[2]. Nella nostra esperienza i problemi sentimentali sono una delle cause più importanti di IDA. **Obiettivi:** Lo scopo di questo lavoro è stato quello di investigare gli aspetti epidemiologici, demografici e clinici di questo peculiare argomento tossicologico. **Metodi:** È stata esaminata una serie consecutiva di n. 252 pazienti ammessi nella SOD di Tossicologia Medica dell'Azienda Ospedaliero-Universitaria di Careggi dal 1 Gennaio 2012 al 31 Dicembre 2014 con diagnosi di IDA (8,9% di tutte le intossicazioni acute). Abbiamo analizzato tutta la documentazione clinico anamnestica e di laboratorio, compresa la valutazione psichiatrica laddove presente. I pazienti privi di valutazione psichiatrica, considerata essenziale per focalizzare le cause e le tematiche psicologiche sottostanti al tentato suicidio, sono stati esclusi dallo studio. **Risultati:** Solo 157 (62,3%) su 252 pazienti sono stati sottoposti ad accurata e talora ripetuta valutazione psichiatrica. Le IDA correlabili a problemi sentimentali erano 39 (24,8%). L'età media era del 42.9% (range: 16-78 anni) con un rapporto maschio/femmina di 1 a 2,6. L'assunzione di farmaci era la noxa ampiamente prevalente (87%) seguita dall'ingestione di caustici (8%) e dall'inalazione deliberata di monossido di carbonio (5%). La coorte di pazienti con assunzione di farmaci è stata divisa nelle seguenti categorie: singolo psicofarmaco (59,3%), ingestione di diversi farmaci psicoattivi (31,5%), farmaci non psicoattivi (12,5%), ingestione di farmaci psicoattivi insieme ad altri (9,1%). La durata media dell'ospedalizzazione è stata di 3,9 giorni (range:1-22 giorni). Tutti i pazienti sono sopravvissuti senza sequele. Le cause psicologiche dell'IDA che i pazienti hanno confermato allo psichiatra erano: pura delusione amorosa (28,2%), delusione amorosa come fattore contribuente o precipitante (25,6%), separazione o divorzio ((20,5%), violenze subite dal partner o abuso (12,8%), abbandono da parte del/della partner (7,6%) e morte del/della partner (5,1%). **Conclusioni:** Le IDA attribuibili a problematiche sentimentali, talora sottaciute, rappresentano una delle cause più frequenti di intossicazione acuta e sono attuate principalmente con assunzione di quantità incogrue di farmaci. In questi casi, il tossicologo, e soprattutto lo psichiatra, hanno il compito di indagare compiutamente il substrato biologico e psicopatologico del paziente, poiché ideazione suicidiaria, IDA e suicidio portato a termine possono essere parte di un *continuum* prognosticamente insidioso. L'amore è un fenomeno biologico e il fallimento di un rapporto amoroso può avere effetti disastrosi.

**Bibliografia**

1. http://www.cdc.gov/violenceprevention/pdf/suicide-datasheet-a.pdf.
2. Mowry GB et al: Clin toxicol, 2014; 52:1032-283.

## A VOLUNTARY INTAKE OF RODENTICIDE: A CASE REPORT

L. Barutta[1,2], G. Bergese[1], F. Corsini[1], D. D'Arrigo[1], S. Franco[1], E. Pizzolato[1,2,*], M. Versiero[1], G. Lauria[1]

*[1]Emergency Medicine Department, Santa Croce and Carle Hospital, Cuneo, Italy; [2]School of Emergency Medicine, University of Turin, Italy*

*Corresponding Author: Elisa Pizzolato, email: eli.pizzolato@gmail.com*

A 52-year-old male came to our Emergency Department complaining about faintness, dizziness and multiple downfalls. He was diagnosed with bipolar disorder, on antidepressant therapy. He denied assuming of any other drug or substance of abuse. Medical examination showed hypotension, tachycardia and fever; many bruises were detectable on his body. Neurologic examination was normal, except for tendency to fall backward. Laboratory tests showed a serious anaemia with normal sized RBC and very prolonged PT-INR and aPTT. An abdomen CT scan was performed because of a large gluteal hematoma, but no inner bleeding was found; The CT brain showed a minimal subdural hematoma, no need of neurosurgery treatment. The patient was given a blood transfusion with RBC, fresh-frozen-plasma (FFP) and vitamin $K_1$. He was admitted in hospital and daily blood tests were performed: hemoglobin levels stabilized, but PT-INR and aPTT stayed prolonged. Several days after admission, the patient claimed voluntary ingestion of "rat poison"; then rodenticide *brodifacoum* was found in his blood sample. Oral phytonadione 10 mg TID was administrated with progressive PT-INR and aPTT normalization; the patient was eventually discharged with witnessed daily phytonadione 10 mg and weekly analysis of PT-INR and aPTT. *Brodifacoum* is the most potent of the second generation anticoagulants (so-called "superwarfarin" agents, long-acting anticoagulants rodenticides-LAARs) because of its 100-fold increase in potency over warfarin. Toxicity usually occurs by ingestion. *Brodifacoum*, as well as warfarin, inhibits vitamin $K_1$ 2,3-epoxide reductase, preventing carboxylation of vitamin $K_1$-dependent coagulation factors II, VII, IX and X into active clotting factors. It causes prolonged inhibition of vitamin K-dependent coagulation factors due to its long half-life time (56-69 days) when compared to warfarin (15-58 hours), because of its enterohepatic cycling and high lipophilic properties, with liver accumulation. Clinical features are mucosal and skin bleeding, muscle and intracranial hemorrhages. Because warfarin also inhibits VIT. $K_1$ activity-dependent of anticoagulant proteins C and S, a transient hypercoagulable state may occur with "paradoxical" thrombosis. Current guidelines recommend early treatment with FFP and vitamin $K_1$; recombinant activated factor VII and prothrombin complex concentrate (PCC) are good alternatives in order to decrease infusion volume and to avoid trasfusion allergic reaction. Effective vitamin $K_1$ start dose is not clearly stated: from 0.1-3mg\kg (3-4 daily doses) to 500-800 mg\die. It can be given orally, subcutaneously or intravenously. Serious bleeding require intravenous administration; for long-term treatment (from several months to one year) the oral route is the first choice. In addition to vitamin $K_1$ therapy, phenobarbital may increase hepatic elimination of *brodifacoum*; lipid emulsion infusion

enhances redistribution of the drug away from storage organs (liver, mainly), and cholestyramine (bile acid binding resin) is also used in order to increase fecal excretion.

**References**

1. King N, Tran MH. Long-Acting Anticoagulant Rodenticide (Superwarfarin) Poisoning: A Review of Its Historical Development, Epidemiology, and Clinical Management. Transfus Med Rev 2015;29:250-8.
2. Feinstein DL, Akpa BS, Ayee MA, *et al.* The emerging threat of superwarfarins: history, detection, mechanisms, and countermeasures. Ann N Y Acad Sci 2016;1374:111-22.

## SMOKING, BATHING AND ...VOMITING. OVERLOOKED CANNABIS TOXICITY?

M. Berri[1], E. Squillari[1], B. Di Marco[1], N. Brondino[1], A. Goggi[2], F. Pavone[2], E. Farinella[2], P. Politi[1], M. Rocchetti[1,*]

*[1]Department of Brain and Behavioral Sciences, University of Pavia, Italy; [2]Department of Mental Health, ASST of Pavia, Italy*

*Corresponding Author: Matteo Rocchetti, email: rocchetti.matteo@gmail.com*

**Case report:** Male, 22 years old. History: Fabry disease treated with agalsidase-alfa, self-interrupted since six months. In this period, after several access in the A&E for vomiting and compulsive hot bathing and several negative investigations the patient was referred to outpatient psychiatric service for support. In this period he received a diagnosis of major depression with psychotic symptoms and was treated with sertraline 50 mg plus paliperidone 3 mg. Recurrent use of cannabis was known since the first contact. In January 2016, he was admitted to the psychiatric ward due to hypochondriac anxiety, social withdrawal and cachexia resulting from vomiting of unknown origin, associated with hot bathing/showering (max 20/day) to relieve the symptoms. The patient also had a pilonidal abscess with hyperpyrexia. At a first examination the clinical picture was characterized by anxiety, depressed mood and slow thinking. Recent cannabis use was confirmed by urinalysis. During the hospital stay paliperidone has been increased, sertraline suspended, and mirtazapine and levosulpride has been introduced, the abscess has been treated and a nutrient supplementation has been set. Furthermore, a complete abstinence from cannabis was possible. In twenty days, the patient reached a complete remission of nausea and vomiting, with no further need of soothing behavior as warm showering. He also reached a small weight gain and overall improvement of his mental state. Three months later, he was admitted again, due to recurrence of the same symptomatology after a cannabis relapse, while the prescribed drug therapy was regularly taken. During the ten days of hospitalization the paliperidone has been interrupted; an electrolyte imbalance, due to the recurring vomiting, has been successfully treated. Finally, a new period of abstinence has been obtained with complete remission of symptoms. Cannabinoid hyperemesis syndrome (CHS) was first recognized in 2004 [1], diagnostic criteria have been recently proposed after an observational study with retrodiagnosis of CHS [2]. Despite a growing number of published case reports, and quite evocative symptoms, this syndrome is likely underdiagnosed. We performed a systematic search on Web of Knowledge™ for any clinical data on CHS. Only case reports and case series have been retrieved. Overall 117 clinical cases descriptions were found and analyzed (male 71%, mean age 29,68). 70,9% received a diagnosis of CHS after more than one year from symptoms onset, (misdiagnosis lasted in mean 3,7 years). Compulsive hot bathing had a serious impact in almost half of these patients. Several patient received a psychiatric diagnosis for the abnormal behavior (7) or along the extenuating course of the condition (13). Despite the large number of treatment used, the only definitive therapy appeared to be cannabis use cessation. The pathophysiology and epidemiology of the syndrome are still unknown and surprisingly under-investigated. Late diagnosis may conduct to a very low quality of life (with irrepressible vomiting and bathing behavior) along with many hospitalizations, many unrequired exams, wrong therapies and surgical procedures.

**References**

1. Allen JH *et al.* Gut. 2004;53(11):1566-1570.
2. Simonetto DA *et al.* Mayo Clin Proc. 2012;87(2):114-119.

## THYROTOXICOSIS AND ANORECTIC PILLS: A CASE REPORT

M.S. Milella*, S.M. Signoretti, O. Staltari, M.C. Grassi

*Emergency Toxicology and Poison Control Centre Unit, Policlinico Umberto I - "Sapienza" University of Rome, Rome, Italy*

*Corresponding Author: Michele Milella, email: michele.milella@gmail.com*

Iatrogenic thyrotoxicosis is a potentially fatal medical emergency. Excess of thyroid hormones potentiate the adrenergic activity at cardiovascular, gastrointestinal, and neurological level. Sinusal tachycardia, anxiety, agitation, headache, nausea and emesis are typically observed, with arrhythmia, hyperthermia, psychosis and seizures in more severe cases.[1] There are reports in literature of life-threatening intoxications associated with anorectic pills containing variable, and often undisclosed, amounts of levothyroxine.[2] Clinical case. In February 2016 a 38-year-old woman presented to the Emergency Department of Policlinico Umberto I in Rome referred by a neurologist. According to family members, she suffered spatial-temporal disorientation and headache in the previous days, with an episode of fever 10 days before admission. On examination, psychomotor agitation, global aphasia, marked tachycardia (170 beats per minute) with normal blood pressure and body temperature were present. Head MRI and cerebrospinal fluid showed no abnormalities. Blood test showed hyperthyroidism: TSH 0,01 µUI/ml, FT4 7,77 ng/dl, FT3 32,55 pg/ml (normal range: TSH 0,27-4,2

µUI/ml; FTA 0,23-1,97 ng/dl; FT3 2,2-4-4 pg/ml). Medical hystory revealed she had been taking pharmacist-processed pills for the treatment of obesity for months, each containing levothyroxine 25 µg, paroxetine 7.5 mg, spironolactone 30 mg and caffeine 180 mg among other active principles. The patient was sedated and ECG monitored, and support therapy with metoprolol and fluids was initiated, leading only to partial control of heart rate (160 bpm). Pavia Poison Control Center suggested the administration of propranolol 40 mg (os), idrocortisone 250 mg (ev) and midazolam 5 mg (os). On day 2, the patient was transferred to the Intensive Care Unit, intubated and monitored. Treatment with propylthiouracil was then initiated on day 3, 400 mg/day: 150 mg at 00:00, 100 mg 6:00AM, 150 mg 4:00PM. An EEG showed a generalized non-convulsive epileptic status, and phenytoin was also started. On day 10, blood assessment showed thyroid hormone levels back to normal, and treatment with propylthiouracil was discontinued on day 13. The development of a pneumonitic process required sedation and prolonged the hospital stay. She was then discharged a month later, with complete recovery. Discussion. The case report allows the following observations: i) the long half-life of levothyroxine (approx. 7 days) and the time required to be fully metabolized into the active molecule T3 explains the latency in onset of symptoms of intoxication; ii) propylthiouracil and corticosteroids may be effective in decreasing conversion of T4 to T3 and are therefore indicated in severe cases, baring in mind the potential risks;[3] iii) the clinician should always suspect thyrotoxicosis (in some cases "factitia") when evaluating malaise in patients on dietary pills; iv) it's important to discourage the use of these pharmacist-processed anorectic preparations, because of the inherent risk of dosage errors, presence of undisclosed active principles, and the possibility of pharmacological interactions with other prescribed or administered drugs.

**References**

1. Olson K, Intossicazioni acute, 2° ediz. 2009.
2. Ioos V *et al.*, Therap and Clin Risk Manag, 2008.
3. Woeber KA, JAMA Internal Medicine, 2000.

## INTOSSICAZIONE ACUTA DA INGESTIONE DI NICOTINA LIQUIDA

C. Ialongo, M.S. Milella*, S.M. Signoretti, R. Perciballi, D. Fabretti, M.C. Grassi

*Tossicologia d'Urgenza e Centro Antiveleni, Policlinico Umberto I, "Sapienza" Università di Roma*

*Corresponding Author: Michele Milella, email: michele.milella@gmail.com*

Le sigarette elettroniche, o "e-cigarettes", sono dei dispositivi che, attraverso un processo di riscaldamento di una soluzione contenente nicotina, consentono l'inalazione del principio attivo in forma di vapore da parte del consumatore. Introdotte sul mercato nel 2006 e pubblicizzate anche come presidio per ridurre gli effetti nocivi del fumo di sigaretta "tradizionale", hanno acceso intenso dibattito in merito alla loro sicurezza. In particolare, gli "e-liquids" usati per ricaricare i dispositivi contengono nicotina ad alte concentrazioni (fino a 52 mg/ml), pertanto un uso improprio del prodotto, volontario o accidentale, può determinare un'intossicazione anche mortale [1]. **Caso Clinico:** Il Centro Antiveleni (CAV) del Policlinico Umberto I di Roma è stato contattato nel mese di luglio 2016 per il caso di un giovane maschio di anni 14 i cui genitori riferivano l'ingestione accidentale di liquido per la ricarica di sigaretta elettronica contenente nicotina avvenuto circa 10 minuti prima. La circostanza era stata causata dallo scambio, avvenuto da parte del nonno del ragazzo, del flaconcino da 50 mL di "Heaven Juice" con quella di un integratore alimentare multivitaminico. I genitori riferivano l'ingestione di circa 10 mL di prodotto (corrispondenti a circa 180 mg di nicotina), alla quale faceva seguito a pochi minuti vomito incoercibile, malessere e dolori addominali. Presso il presidio locale (provincia di Ragusa) il giovane veniva sottoposto ai controlli di base, pressione sanguigna, battito cardiaco, glicemia e saturazione, che risultavano nella norma. All'esame obiettivo non si oggettivavano segni di iperstimolazione colinergica nicotinica (scialorrea, rinorrea, miosi, nistagmo), con l'unico reperto di conati di vomito ed emissione di materiale gastrico. Predisposta la somministrazione di un gastro-protettore, l'emesi frequente rendeva impossibile l'uso di carbone attivo. Entro trenta minuti il paziente veniva trasferito presso l'ospedale di Ragusa, dove riceveva opportuna terapia di supporto per la reidratazione ed il controllo dell'emesi. A due ore dal ricovero i parametri vitali e biochimici rimanevano stabili con una progressiva normalizzazione del quadro gastrointestinale e dello stato di malessere lamentato, senza bisogno di ulteriori interventi terapeutici. **Conclusioni:** Si ritiene che la dose letale di nicotina nell'uomo sia di 60 mg, con segni di intossicazione lieve a partire da 0,3 mg/kg. In questo specifico caso, l'assenza di segni di rilievo a fronte dell'ingestione di quasi 180 mg di nicotina (corrispondenti a circa 3,3 mg/Kg per il soggetto in questione), devono ragionevolmente essere imputati alla bassa biodisponibilità orale (circa 20%), il peso corporeo e l'età (55 Kg, 14 anni), ma soprattutto l'immediata e protratta emesi che ne ha limitato l'assorbimento[2,3]. Da un punto di vista di sorveglianza di questi eventi accidentali, intendiamo rimarcare come la confezione del prodotto sia per forma, ambratura del recipiente, modalità di apertura del tappo e per la colorazione dell'etichetta difficilmente distinguibile da quella di un comune prodotto per integrazione alimentare. In virtù della potenziale tossicità del contenuto, specialmente per i bambini, sarebbe opportuna una regolamentazione delle caratteristiche dei flaconcini per renderli meglio distinguibili, prevenendo così intossicazioni come nel caso descritto.

**Bibliografia**

1. Cameron *et al.*, Tob. Control, 2014.
2. Goldfrank's Toxicologic Emergencies, 2010.
3. Olson KR, Intossicazioni acute, 2° ediz. 2009.

## ARRESTO CARDIACO IN SEGUITO A INTOSSICAZIONE DA *NERIUM OLEANDER*

A. Ieri[1], J. Attene[2], F. Bui[2], M. Cirronis[4], U. Giannotti[2], F. Gori[4], S. Grotti[2], A. Paolini[3], P. Botti[*]

*[1]SOD Tossicologia Medica e Centro Antiveleni, AOU Careggi, Firenze; [2]UO di Cardiologia/UTIC Ospedali Riuniti della Valdichiana Senese; [3]DEA Ospedali Riuniti della Valdichiana Senese; [4]Dipartimento NEUROFARBA, Sezione di Farmacologia e Tossicologia, Università degli Studi di Firenze*

*Corresponding Author: Primo Botti, email: primo.botti@unifi.it*

Introduzione Il Nerium Oleander è un arbusto appartenente alla famiglia delle Apocynaceae che cresce spontaneo in tutte le regioni del Mediterraneo. Tutte le parti della pianta sono tossiche se ingerite, per la presenza di glicosidi cardioattivi quali oleandrina, folinerina, digitoxigenina e adinerina. Il quadro clinico dell'intossicazione è costituito da sintomi gastroenterici (scialorrea, nausea, dolori addominali, vomito e diarrea) e neurologici (confusione mentale, tremori, disturbi della visione, midriasi). Gli effetti cardiaci sono dovuti all'inibizione della pompa Na+/K+ ATPasi che determina un incremento della concentrazione di calcio intracellulare con conseguente aumento della contrattilità miocardica, riduzione della frequenza cardiaca, rallentamento della conduzione atrio-ventricolare e comparsa di blocchi, aritmie ventricolari ed asistolia. L'iperpotassiemia, per accumulo di potassio extracellulare da blocco della pompa Na+-K+ ATPasi, predispone i pazienti ad aritmie ventricolari e costituisce quindi un indice prognostico negativo. Case report: una donna di 75 anni affetta da malattia di Alzheimer e diabete mellito giunge in DEA degli Ospedali Riuniti della Valdichiana Senese (Montepulciano) 5 ore dopo aver ingerito un numero imprecisato di foglie di Nerium Oleander e vomitato ripetutamente. All'esame obiettivo la paziente presenta agitazione psicomotoria, vomito profuso, ECG nella norma, mentre gli esami ematici evidenziano potassiemia 5,5 mEq/l, digossinemia 1,52 ng/ml e glicemia 3,9 g/l. Viene contattato il CAV di Firenze che indica, oltre alla terapia supportiva, la somministrazione di Fab anti-digossina. In attesa dell'antidoto, prontamente inviato dal CAV di Firenze, la paziente viene trattata con fluido-terapia, insulina ed atropina 0,5 mg in bolo per comparsa di bradicardia sinusale (FVM 28 bpm) con risposta temporanea. Nonostante la terapia in atto la paziente, il cui ECG evidenzia un blocco atrio-ventricolare (AV) completo, va incontro ad un arresto cardiaco, risolto con le opportune manovre rianimatorie previste dall' algortimo ALS; segue extrasistolia ventricolare e fasi di blocco AV 2:1. Dopo somministrazione in 30 min. dei Fab anti-digossina (200 mg ev diluiti in 50 ml di salina), si ottiene il ripristino di un ritmo sinusale normo-frequente. Discussione: il meccanismo dell' intossicazione da glicosidi contenuti nella pianta di oleandro è analogo a quello dell'intossicazione da digossina. Il trattamento prevede la decontaminazione con carbone vegetale attivato (CVA) alla dose di 1 g/Kg seguita dalla somministrazione di dosi ripetute di CVA, per interrompere il circolo enteroepatico, non somministrato per abbondante emesi e scarsa compliance della paziente. Il trattamento della tossicità cardiaca prevede la somministrazione di fluidi, atropina e utilizzo temporaneo di pacing cardiaco. Nel situazioni in cui la concentrazione ematica di potassio è maggiore di 5,5 mEq/l ed è necessario somministrare dosi ripetute di atropina per correggere la bradicardia, è indicata la somministrazione precoce di Fab anti-digossina. Le dosi consigliate di Fab sono più elevate di quelle usate nell'intossicazione da digossina per la minore affinità dell'anticorpo per l'oleandrina. Nel caso in esame la somministrazione di basse dosi di Fab anti-digossina è stata risolutiva. La digossinemia, rilevante ai fini diagnostici, non costituisce un indicatore prognostico dell'outcome dei pazienti intossicati da oleandro.

**Bibliografia**

Boswell BR *et al.*, Psycosomatics 54:4, 2013.
Rajapakse S., Clinical Toxicol 47:206-213, 2009.
Langford SD *et al.*, Toxicology 109:1-13, 1996.

## ATTIVAZIONE DEL MONITORAGGIO DEGLI EVENTI D'INTOSSICAZIONE PRESSO IL PRONTO SOCCORSO DELL'AZIENDA OSPEDALIERO-UNIVERSITARIA DI FERRARA

S. Lapadula[1,*], A. Ricci Frabattista[1], D. Sighinolfi[2], R. Zoppellari[2], P. Scanavacca[1]

*[1]Dipartimento Farmaceutico Interaziendale, Azienda Ospedaliero-Universitaria di Ferrara; [2]Dipartimento di Emergenza, Azienda Ospedaliero-Universitaria di Ferrara*

*Corresponding Author: Silvia Lapadula, email: s.lapadula@ospfe.it*

**Introduzione:** Da febbraio 2016 è stato attivato il monitoraggio degli accessi in Pronto Soccorso (PS) attribuibili a intossicazioni presso l'Azienda Ospedaliero - Universitaria di Ferrara (AOUFE). I medici, qualora si trovino di fronte a un evento d'intossicazione, nella compilazione del referto hanno la possibilità di selezionare l'opzione "ADR a farmaco/intossicazione". Tra gli obiettivi del monitoraggio vi è quello di implementare la banca dati delle intossicazioni del portale antidoti del Centro Regionale di Riferimento (CRR) Antidoti, con sede presso la Farmacia dell'AOUFE. Scopo del lavoro è quello di analizzare le intossicazioni rilevate nei primi 6 mesi di attivazione del monitoraggio. **Materiali e Metodi:** Per il periodo 5 febbraio - 5 agosto 2016, sono stati analizzati i referti di PS relativi ai casi d'intossicazione. Sono stati individuati i tossici responsabili, gli antidoti utilizzati, genere/età dei pazienti, l'esito dell'evento. Le intossicazioni in cui erano presenti sia tossico sia antidoto sono state inserite nel database del portale antidoti, essendo due campi vincolanti nella compilazione della scheda di descrizione dell'evento. Per l'inserimento, i tossici responsabili sono stati raggruppati secondo la classificazione E della "Classificazione delle malattie,

dei traumatismi, degli interventi chirurgici e delle procedure diagnostiche e terapeutiche" del Ministero del Lavoro, della Salute e delle Politiche sociali. L'elenco antidoti è predisposto e stabilito dal CRR, basato sulla Risoluzione CE del 03/12/1990 e aggiornato in relazione all'entrata in commercio di nuovi antidoti e alle evidenze del CAV. **Risultati:** Sono stati rilevati 39 casi di intossicazione. Il genere più colpito è stato quello maschile (20 casi) e la fascia d'età 20-49 anni (17/39 casi). I tossici responsabili sono stati: farmaci (71,8%), alimenti (10,2%), sostanze psicotrope (5,1%), sostanze chimiche (5,1%), non specificato (2,6%), integratori (2,6%), monossido di carbonio (2,6%). Dei farmaci, al primo posto si trovano gli ipnotici benzodiazepinici (33%), seguiti da antipsicotici (11,6%), antidepressivi (9,3%), antitrombotici (7%), antiepilettici (6,9%), ipnotici non benzodiazepinici (4,6%), FANS (4,6%), farmaci modificanti i lipidi (2,3%), oppioidi (2,3%), ipnotici non specificati (2,3%), diuretici (2,3%), altri farmaci per il Sistema Nervoso (2,3%), corticosteroidi (2,3%), betabloccanti (2,3%), antiparkinsoniani (2,3%), antigottosi (2,3%), stimolanti cardiaci (2,3%). Dei 39 casi, 25 hanno visto la somministrazione di antidoti, in 9 casi non sono stati utilizzati antidoti, in 5 casi sono stati somministrati antiacidi e cortisonici come sintomatici. Nel database del portale antidoti, pertanto, sono state inserite 25 intossicazioni, in cui erano individuabili tossico e antidoto. Gli antidoti utilizzati sono stati: flumazenil (42%), carbone vegetale attivato (19,5%), vitamina K (9,7%), magnesio solfato (6,4%), naloxone (6,4%), Peg 400 (6,4%), ossigeno iperbarico (3,2%), dimeticone (3,2%), N-acetilcisteina (3,2%). Gli esiti degli eventi d'intossicazione sono stati: dimissione (49%), ricovero (36%), trasferimento in altra struttura (15%). **Conclusioni:** Il monitoraggio delle segnalazioni in PS può contribuire a sensibilizzare i medici alla tematica delle intossicazioni. La registrazione degli eventi d'intossicazione nel database del portale antidoti, permessa dalla connessione con il sistema di refertazione aziendale, consente un inserimento puntuale del caso e un monitoraggio della correttezza nella compilazione dei referti stessi, con l'indicazione precisa dell'agente causale (quando noto), della diagnosi e dei trattamenti antidotici somministrati dal punto di vista quali/quantitativo.

## SEVERE IFOSFAMIDE RELATED ENCEPHALOPATHY IN A 6-YEAR-OLD PATIENT: SUCCESSFUL TREATMENT WITH METHYLENE BLUE

F. Bedussi[1,*], M. Provenzi[2], A. Giampreti[1], J. Eleftheriou[1], M. Gallo[1], C. Foglia[2], R. Butera[1], E. Giraldi[2], L. Cavalleri[2], L. Faraoni[1], G. Bacis[1]

*[1]Poison Control Center and Teratology lnformation Service, Papa Giovanni XXIII Hospital, Bergamo, Italy; [2]Division of Pediatric Hematology/Oncology, Papa Giovanni XXIII Hospital, Bergamo, Italy.*

*Corresponding Author: Francesca Bedussi, email: fbedussi@asst-pg23.it*

**Background:** Ifosfamide is used in the treatment of solid and hematologic tumors. It causes drug-related encephalopathy in 10-30% of patients receiving high-doses. The mechanism of encephalopathy is not understood. The use of methylene blue in Ifosfamide-related encephalopathy is controversial and mechanism of action unclear. The case reports available in literature involving mainly adult patients.[1] No pediatric patient treated with methylene blue for severe Ifosfamide-induced encephalopathy are reported. **Case Report:** A 6-year-old boy 22 kg body-weight with neurofibromatosis type 1 was diagnosed for stage IV nephroblastoma with subpleural pulmonary nodule and diffuse anaplasia at histological evalutation. From December 2015 to January 2016 he received neoadjuvant chemotherapy with Actinomycin-D (1,35 mg/m2 week 1,3,5), Vincristine (1,5 mg/m2 week 1-6), Doxorubicin (40 mg/m2 week 1,3) (regime E, protocol TW AIEOP 2003). In February 2015, he underwent left nephrectomy and pulmonary metastasectomy followed by adjuvant radiation therapy (19.8 Gy / 11 fraction) and adjuvant chemotherapy with Actinomycin-D (1,35 mg/m2 week 1,5), Doxorubicin (20 mg/m2 week 3) and Vincristine (1,5 mg/m2 week 1-6) (regime D, protocol TW AIEOP 2003). In March 2016 he continued chemotherapy with Doxorubicin (40 mg/m2 day 1) and Ifosfamide (3000 mg/m2/die day 1,2). At day 2, promptly after the ifosfamide infusion, the patient developed a NCI-CTCAE grade 4 encephalopathy with hallucinations, lethargy, disorientation, hypotonia and extrapyramidal symptoms (dystonia and bruxism).[2] Electroencephalography showed electrical abnormalities compatible with encephalopathy. Ifosfamide-induced encephalopathy was suspected and methylene blue 30 mg/m2 was i.v. administered in 45 minutes every 4 hours. He received six doses in 24 hours. A progressive improvement of clinical manifestations was observed with the patient fully alert and oriented 36 hours after starting methylene blue. In subsequent chemotherapy cycles Ifosfamide was replaced with Cyclophosphamide (750 mg/m2 day 1,2) without further toxic effects. **Discussion:** Different mechanism of action have been suggested for Ifosfamide-induced neurotoxicity. Chlorethylamine, the principal neurotoxic metabolite of Ifosfamide, can inhibit the electron-binding flavoproteins of the mitochondrial respiratory chain through the formation of thialysine ketamine. Another important pathway may be mediated by monoamine-oxidases in the extrahepatic tissues and in the plasma by which chloracetaldehyde can be formed from Ifosfamide.[1,3] Methylene blue may act as an alternative electron acceptor replacing the Ifosfamide inhibited flavoproteins and restoring mithocondrial respiratory chain; moreover it may also inhibit chloracetaldehyde formation through monoamine-oxidases. At present, in medical literature, methylene blue has been described for pediatric patients only in older children or in cases with mild symptoms. In our patient, methylene blue successfully reversed a severe toxic encephalopathy due to Ifosfamide chemotherapy in a 6-year-old patient. The use of methylene blue can represent a valid treatment of Ifosfamide-related encephalopathy even in the pediatric population and, as suggested by some authors,

it could be considered as prophylaxis in at risk patients (*e.g.* lysis syndrome, co-medication with neurotoxic drugs, central-nervous system tumors).[3]

**References**

1. Pelgrims J *et al.* Br J Cancer. 2000 Jan;82(2):291-4.
2. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 June 14, 2010.
3. Kupfer A *et al.* Eur J Clin Pharmacol. 1996;50(4):249-52.

## NEONATAL ABSTINENCE SYNDROME OR SEROTONIN TOXICITY AFTER IN UTERO USE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS A CASE-SERIES WITH NEONATAL DRUG CONCENTRATIONS

F. Bedussi*, G. Eleftheriou, R. Butera, A. Giampreti, L. Faraoni, M. Gallo, F. Lorenzi, A. Sangiovanni, M. Carrara, G. Contessa, G. Bacis

*Poison Control Center and Teratology Information Service, Papa Giovanni XXIII, Bergamo, Italy*

*Corresponding Author: Francesca Bedussi, email: fbedussi@asst-pg23.it*

**Background:** Selective-serotonin-reuptake-inhibitors (SSRI) in pregnancy may determine abnormal neonatal neurological manifestations. These may be related to a neonatal abstinence syndrome, due to prenatal maternal use of SSRI once the placental access to the substance is no longer available, or to a serotonin toxicity syndrome resulting from the overstimulation of the serotoninergic system in neonate. The differential diagnosis between neonatal SSRI withdrawal and toxicity is critical and debated, with symptoms of the two being similar.[1] **Objective:** To describe presentation, clinical course and drugs concentrations in neonates exposed in utero to SSRI, in order to evaluate criteria for diagnosis of neonatal abstinence syndrome and serotonin toxicity. **Methods:** Neonates from mother under SSRI therapy admitted from 2013 to 2016 to the neonatal intensive care unit of our hospital were evaluated. Mothers were evaluated for SSRI and co-medication. Alcohol, tobacco, herbal-medicines, drugs of abuse during pregnancy were investigated. Infant gender, birth weight, gestational age and symptoms were recorded. Infant blood serum was collected in the first 24 hours from delivery to enable measurement of antidepressant concentration. **Results:** Nineteen neonates (11M/8F; one-male-twin) were included. The 18 mothers took sertraline (8), paroxetine (3), citalopram (3), escitalopram (3), duloxetine (1). Nine (50%) took SSRI with benzodiazepines. Alcohol and drug of abuse were denied in all but one in therapy with methadone. Ten neonates (10/19; 52%) presented symptoms: nine at birth and one 24 hours after birth. The mean gestational age in this symptomatic group was 36+2 weeks with a mean body weight at birth of 2.5 kg. Manifestations were: hypertonia (6/10;60%), respiratory distress (4/10;40%), tremors (4/10;40%), hypoglycemia (2/10;20%), hypotonia (2/10;20%), neck extensor hypertonia (2/10;20%), irritability (1/10;10%), jitteriness and abnormal crying (1/10;10%), myoclonus and head retraction with opisthotonus (1/10;10%). All the 9 symptomatic patients at birth presented SSRI's blood concentration > limit-of-quantification (LOQ): 7 under therapeutic levels, 1 at lower extremity of therapeutic range and 1 presented SSRI concentrations within therapeutic range. Among these, clinical manifestations improved 12-24 hours after delivery. The patient with symptoms 24 hours after delivery do not present SSRI in blood and clinical resolution appeared 5 days after delivery. The remaining nine asymptomatic neonates presented a mean gestational age of 39 weeks with a mean body weight at birth of 3.1 kg. Two presented SSRI's blood concentration at birth <LOQ, six presented SSRI's blood concentration under therapeutic levels and one presented antidepressant concentration in therapeutic range. **Discussion:** In our case series the triad of: neonatal symptoms at birth after in utero exposure to SSRI, detectable drug concentrations and improvement of symptoms during the first days after the delivery leads to a diagnosis of serotonin toxicity rather than withdrawal syndrome. Drug levels were unrelated with the onset and severity of the symptoms, but in all symptomatic neonates the drug was present, although in low concentrations. Another important aspect of our cases is the incidence of serotonin toxicity in all premature infants; premature could be more susceptible to SSRI effects.

**Reference**

1. Haddad PM *et al.* J Psychopharmacol. 2005;19(5): 554-7.

## REVERSIBLE QT PROLUNGATION AND DIFFERENT ELECTROCARDIOGRAM ALTERATIONS IN A CASE OF PIMOZIDE POISONING

M. Conte[1], A. Dilaghi[1], A. Missanelli[2], B. Occupati[2], F. Gambassi[2], E. Taurino[3], N. Cini[4], G. Mannaioni[1,2], P. Botti*

*[1]Dipartimento NEUROFARBA, sezione di Farmacologia e Tossicologia, Università degli Studi di Firenze; [2]SODc di Tossicologia Medica e Centro Antiveleni, AOU Careggi, Firenze; [3]Centro Regionale Toscano di Farmacovigilanza, Firenze; [4]Laboratorio Generale, Sezione di Farmacotossicologia, AOU Careggi, Firenze*

*Corresponding Author: Primo Botti, email: primo.botti@unifi.it*

**Introduzione:** La pimozide è un antipsicotico tipico utilizzato per il trattamento dei disturbi psicotici e della sindrome di Gilles de la Tourette. Il dosaggio terapeutico non deve superare 0,2mg/kg/die (o 10mg/die): sono stati segnalati 1 casi di morte improvvisa associata a prolungamento dell'intervallo QT per dosaggi superiori a 1mg/kg o 20mg/die. Il farmaco, somministrato per os, è assorbito per il 50%, con picco plasmatico a 6-8 ore dall'assunzione, metabolizzato a livello epatico, con lunga emivita (circa 55 ore) ed escrezione renale. **Case Report:** Una donna di 59 anni in terapia con pimozide da oltre 30 anni, viene trovata al proprio domicilio in

stato soporoso in seguito all'ingestione di 4 mg (40cp) di pimozide, 2mg (40cp) di clonazepam e alcolici. Durante il trasporto in ospedale compaiono battiti ectopici ventricolari in coppie e triplette, seguiti da episodio di torsione di punta, trattata MgSO4 1 g ev. Alla visita in DEA, la paziente è soporosa ma risvegliabile (GCS 14), presenta miosi scarsamente reagente e nistagmo laterale. L'anamnesi fa stimare il momento dell'assunzione del farmaco fra le 15 e le 20 ore precedenti, pertanto si soprassiede alla gastrolusi e viene somministrato carbone vegetale 1gr/kg. In conseguenza del precedente evento aritmico e per il rilevamento di un QT di 610msec, (QTc 653msec) vengono somministrati 500mL di NaHCO3 all'1,4% (83mEq). Gli esami ematici evidenziano alcolemia <0,2g/L, kaliemia 3,6mEq/L, benzodiazepinemia 317mg/L, indici di funzionalità epatica e renale nella norma, Vengono prelevati campioni ematici seriati per la determinazione plasmatica della pimozide, effettuata in modalità differita. Dopo un'ora la paziente presenta episodio di tachicardia ventricolare di durata 1-2 min, per cui è stata ripetuta la somministrazione di MgSO4 2g ev. Per il persistere di episodi recidivanti di tachicardia ventricolare polimorfa a tipo torsione di punta e riscontro di QT lungo, la paziente è trasferita in UTIC, e trattata con infusione continua di MgSO4 1g/ora e potassio cloruro 8 mEq/ora per 12 ore, associata a terapia catartica e diuresi alcalina. Dalla seconda giornata la paziente è asintomatica, ritmo cardiaco sinusale, permane intervallo QT allungato. In 5° giornata la paziente viene trasferita in psichiatria, controllo ECG e normalizzazione dell'intervallo QT in sesta giornata. La concentrazione plasmatica di pimozide all'ingresso era 154,6ng/mL, 15 volte il range terapeutico (4-10ng/mL). **Conclusioni:** Il prolungamento del tratto QT e le aritmie correlate rappresentano una delle più temibili complicanze dell'overdose da pimozide e in considerazione della lunga emivita del farmaco, il monitoraggio ECG dev'essere prolungato fino alla normalizzazione dell'intervallo QT. La pimozide, a causa della sua scarsa maneggevolezza, viene utilizzato ormai in un set ristretto di patologie e, quando possibile, sostituita con farmaci con minore cardiotossicità. Il suo uso è sconsigliato in pazienti con familiarità per il QT lungo, in caso di recenti cardiopatie ischemiche, ipokaliemia o ipomagnesiemia.

**Bibliografia**

1. Sallee FR, Pollock BG, Stiller RL, Stull S, Everett G, Perel JM. Pharmacokinetics of pimozide in adults and children with Tourette's syndrome. J Clin Pharmacol. 1987, 27: 776-81.

## INTOSSICAZIONI RARE: *SE NON CI PENSI LA DIAGNOSI NON LA FAI*

C. Bonenti[1,*], M. Carollo[1], D. Franchi[2], G. Garzena[2], G. Ruffino[3], A. Marroni[4], M. Chiaranda[1]

*[1]Scuola di Specializzazione in Anestesia e Rianimazione Università degli Studi dell'Insubria, Varese; [2]Articolazione Aziendale Territoriale (AAT) Varese-Centro unico di risposta (CUR) 112-Azienda Regionale Emergenza Urgenza Lombardia; [3]Direttore Sanitario Comando Incursori (Comsubin) Marina Militare Italiana- La Spezia; [4]Presidente DAN Europe*

*Corresponding Author: Chiara Bonenti, email: chiara.bonenti@yahoo.it*

**Introduzione:** La Ciguatera è un'intossicazione alimentare causata dal consumo di pesce contaminato (generalmente tropicale o subtropicale). Le Ciguatossine sono una famiglia di tossine di origine non batterica, presenti in molti microrganismi e in particolare nel dinoflagellato Gambierdiscus toxicus.[1] Il meccanismo d'azione consiste nell'attivazione dei canali del sodio voltaggio dipendenti con aumento della permeabilità di membrana agli ioni sodio e depolarizzazione delle cellule nervose. I segni e i sintomi sono di natura gastrointestinale, cardiovascolare, neurologica e neuro-psichiatrica. Generalmente l'esordio è caratterizzata da una sindrome gastroenterica che si manifesta da 4 a 24 ore dall'assunzione e regredisce in genere in 4 giorni. Successivamente compaiono parestesie e/o disestesie alle estremità degli arti e in regione perilabiale, inversione sensibilità caldo-freddo, alterazione del gusto, marcata astenia, urgenza minzionale, disautonomie e allucinazioni. I sintomi neurologici possono persistere per settimane, mesi o anni, definendo la forma cronica. La diagnosi è fondamentalmente clinica associata all'anamnesi di ingestione di pesce. Il trattamento dell'acuzie si basa sulla somministrazione endovenosa di mannitolo e terapia sintomatica.[2] **Caso clinico:** La paziente è una donna di 34 anni, istruttrice di subacquea in Thailandia. La sintomatologia esordisce nel Dicembre 2014, quando durante un safari di tre giorni inizia ad accusare un intenso mal di testa e parestesie a mani e piedi, che spontaneamente regrediscono, per ricomparire dopo circa una settimana associati ad astenia. Sospettando una patologia da decompressione (PDD) viene sottoposta a trattamento iperbarico per 3 giorni e dimessa con diagnosi "Sintomi residui di PDD". A distanza di 2 mesi circa la sintomatologia peggiora, con comparsa di febbre, dissenteria, vomito e parestesie diffuse anche a braccia e gambe, mialgie, sensazione di freddo e vampate di calore, nonostante la terapia prescrittale da un neurologo con Pregabalin ed integratori vitaminici. Le vengono quindi prescritte analisi ematiche per valutare gli indici di flogosi, la crasi ematica e successivamente RM encefalomidollo spinale ed EMG, che risultano tutte nella norma. Nel marzo 2015 la paziente, visto il perdurare della sintomatologia, viene messa in contatto con il Divers Allert Network (DAN) , il cui personale medico esclude qualsiasi forma di disbaropatia. Basandosi su una rianalisi dell'anamnesi, e in particolare al consumo di pesci tropicali in loco, viene posto il sospetto di INTOSSICAZIONE DA CIGUATOSSINA. **Conclusione:** Negli ultimi dieci anni si è assistito ad un incremento dei casi di Ciguatera in Europa[2] e questo è da imputare all'aumento della temperatura globale dell'acqua marina che ha determinato la proliferazione di microalghe tossine-producenti nel Mar Mediterraneo, che entrano nella catena alimentare di pesci come la Lampuga (ampiamente pescata e consumata in Italia). Avendo

tale intossicazione e la PDD medesimo quadro sintomatologico, devono essere poste in diagnosi differenziale, soprattutto nella popolazione di subacquei spesso anche consumatori di pesci marini.

**Bibliografia**

1. Thomas Y. K. Chan. Ciguatera Fish Poisoning in East Asia and Southeast Asia. Mar. Drugs 2015, 13, 3466-3478.
2. Mattei C, Vetter I, Eisenblätter A, Krock B, Ebbecke M, Desel H, Zimmermann K. Ciguatera fish poisoning: a first epidemic in Germany highlights an increasing risk for European countries. Toxicon. 2014; 91:76-83.

## INTOSSICAZIONE ACUTA DA GLIFOSATO (ERBICIDA): CASO CLINICO

M.L. Maifreni*

*Pronto Soccorso e Medicina D'urgenza, ULSS 9 Veneto, Treviso*

*Corresponding Author: Maria Luisa Maifreni, email: mlmaifreni@gmail.com*

Il paziente è stato ricoverato il giorno 1 luglio dopo assunzione volontaria di circa 100 ml di glifosato (erbicida) seguita da vomito a domicilio. All'ingresso in PS il paziente si presentava vigile e collaborante lamentando solo faringodinia. Sottoposto ad accertamenti (EGDS e TAC addome per il sospetto di perforazione intestinale non confermata) dopo circa quattro ore il pz ha manifestato sopore, ipossia, acidosi metabolica pH 7.11, shock vasoplegico quindi ricovero in rianimazione. Vi è stata necessità di ventilazione meccanica ed ha sviluppato Multi Organ Failure (MOF): polmonite, insufficienza renale con anuria e dialisi, piastrinopenia, marcata leucopenia, iperpotassiemia, epatite e causticazione del tratto intestinale superiore e sanguinamento da quello inferiore (lesioni da erbicida? piastrinopenia? entrambe?) - senza segni di perforazione. Utilizzo di Cytosorb per l'importante vasoplegia e uso di amine ad alte dosi (noradrenalina e dopamina). Su indicazione dei Centro antiveleni di Pavia è stato trattato con NAC e posta indicazione a trattamento cortisonico. Estubazione dopo otto giorni e trasferimento in MGU: il paziente ha presentato un progressivo danno epatico di tipo colestatico (escluse cause ostruttive) con importante epatocitolisi, ittero e colestasi. Il sensorio inizialmente fluttuante forse anche legato all' andamento della bilirubina. Successivamente trasferito in Gastroenterologia il paziente è stato sottoposto ad agobiopsia epatica (esame istologico ancora in corso) per la definizione del quadro istologico. A distanza di circa 6 settimane dall'ingestione si sono osservate inoltre anemia normocitica senza segni di perdita o di emolisi (possibile inibizione midollare) e marcata ipercolesterolemia che ha richiesto correzione farmacologica con statine. Data la terapia steroidea ad alte dosi, è stato necessario correggere i valori glicemici con insulina. Alla dimissione il paziente è vigile, asintomatico, canalizzato e si alimenta senza problemi. L'ittero è in notevole riduzione (picco bil 20 mg/dL, ultima 5 mg/dL). Valori ematochimici massimi o minimi raggiuntii durante la degenza: creatinina 4,62 mg%; got/gpt 268/826 u/l; bil tot 21,3; bil dir 19,9 mg%; fosf alcal 826 u/l; pH 7,34 all'ingresso e 7.11 dopo quattro ore; ggt 1481 u/l; piastrine 16.000; amilasi 166 u/l; leucociti 1.390; lipasi 420 u/l; ammonio 145 micrmol/l; cpk 1080 u/l; colesterolo 939 mg%; troponina 0,11 ng/ml. Il quadro clinico complessivo è stato monitorato e gestito in accordo con i colleghi del Centro Anti Veleni di riferimento di Pavia.

## CYANOSIS IN A PREMATURE INFANT INDUCED BY TOPICAL ANESTHESIA

G. Eleftheriou[1,*], R. Butera[1], M. Gallo[1], L. Faraoni[1], F. Bedussi[1], G. Bacis[1], F. Varsalone[2], C. Vercellati[3]

*[1]Poison Control Center and Teratology lnformation Service, Papa Giovanni XXIII Hospital, Bergamo, Italy; [2]Unit of Neonatology, Hospital Bolognini, Seriate, Italy; [3]Divison of Hematology, Hospital Maggiore, Milan, Italy*

*Corresponding Author: Georgios Eleftheriou, email: jorgos_2002@yahoo.com*

**Background:** Methemoglobinemia is a rare cause of cyanosis in pediatric patients and it is characterized by increased quantities of hemoglobin in which the iron of heme is oxidized to the ferric ($Fe^{3+}$) form. The condition may arise as a result of a genetic defect in red blood cell metabolism or hemoglobin structure, or it may be acquired following exposure to various oxidant drugs or toxins. **Case report:** A premature male infant was born to a 32-year-old healthy woman after 32 weeks of gestation. The 1630-g baby was apparently healthy at birth, Apgar scores were 9 and 9 at one and five minutes. At seven days of life a peripherally central venous catheter for parenteral nutrition was needed: 1 gram of an eutectic mixture of lidocaine 2.5% and prilocaine 2.5% ointment (EMLA, Astra Zeneca) was placed to a large extent on the inner surface of the forearm 40 minutes before starting the procedure. Eight hours after dermal application the patient showed a dusky discoloration and appeared drowsy and hypoactive. His cyanosis persisted and his transcutaneous oxygen saturation was 94% with supplemental oxygen. There was no clinical or culture support for sepsis or cyanotic congenital heart disease and airway abnormalities. Chest radiograph revealed a normal heart shadow with clear lung fields. Echocardiography confirmed a normal cardiac anatomy with adequate function. Methemoglobinemia was suggested and an arterial blood gas revealed hemoglobin level 15.1 g/dl and methemoglobin level 24.6%. The infant was given an intravenous methylene blue infusion at a dose of 1 mg/kg (1.5 mg in 30 minutes) which promptly cleared his central cyanosis and restored normal oxygenation. Methemoglobin level dropped to 3% two hours after methylene blue administration. Lidocaine serum concentrations were below the limits of quantitation 8 hours after skin application. Cytochrome-b5-reductase enzyme activity level was 11.9 IU/g (normal value 15.36-23.06 IU/g). Inborn errors of metabolism for succinylacetone, acylcarnitine and aminoacidemia were

excluded. **Discussion:** Preterm neonates are exposed to a range of painful procedures and topical anesthetics as EMLA are used routinely for pain management. On the other hand, newborns are unusually susceptible to the development of methemoglobinemia after exposure to toxic agents, as there is an increased sensitivity of fetal erythrocytes to oxidizing agents causing formation of fetal methemoglobin; moreover, there is transient physiologic immaturity of NADH cytochrome-b5-reductase activity in neonates (that have only about 60% of normal adult levels of CYB5R3 and do not attain mature levels before 2 months of age); finally, there is an increased absorption, due to skin immaturity, particularly during the first week of life. Because premature neonates are low weight and consequently they are easily overdosed, routinely use of EMLA should be carefully evaluated.

## LACTATION IN BETA-THALASSEMIA MAJOR: IS DEFERASIROX COMPATIBLE? THE FIRST CASE WITH CLINICAL DATA AND BREASTMILK LEVELS

A. Giampreti[1], F. Mattioli[2], L. Faraoni[1], F. Bedussi[1,*], C. Spada[3], M. Gallo[1], G. Eleftheriou[1], G. Bacis[1]

*[1]Poison Control Center and Teratology Information Service, Papa Giovanni XXIII, Bergamo, Italy; [2]Department of Internal Medicine, Pharmacology and Toxicology Unit, University of Genoa, Genoa, Italy; [3]Neonatologia, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy*

*Corresponding Author: Francesca Bedussi, email: fbedussi@asst-pg23.it*

**Background:** Breastfeeding in newborns from patients with beta-thalassemia major and deferasirox (DFX) therapy represent a debated aspect concerning drugs in lactation. At present no cases involving lactation with this drug are available and, with the exception of few animal data, no literature exist on DFX in human milk.[1] We describe clinical course and iron status of a newborn exclusively breastfed by a mother with beta-thalassemia major on chronic therapy with DFX. Breastmilk concentration of DFX have also been evaluated. **Case report:** A 28-year-old caucasian woman (64 kg body-weight) with beta-thalassemia major treated with blood transfusions (once every three weeks), delivered a healthy baby (2350 g body-weight), at 35+1 weeks. Due to the potential transfusion's related iron overload, DFX oral therapy 2250 mg/die (35 mg/kg/die) was started in the mother one week after delivery. Breastfeeding was started the day of the delivery and iron status of the infant monitored. Blood tests in the infant at 1, 10, 30 days after starting DFX therapy revealed normal serum ferritin of 190, 218, 96 ng/mL (normal value 22-275 ng/mL) and normal sideremia of 101, 77, 71 mcg/dL (normal value 60-170 mcg/dL). In the first month, growth (41° percentile) and length curve resulted normal. In the breastmilk, collected from the mother 2 hours after the drug ingestion, one week after childbirth (the first day of DFX therapy), no measurable DFX was found. Breastmilk was analyzed by adapting a validated high performance liquid chromatography method already described for plasma.[2] **Discussion:** DFX is an iron chelating agent, used in chronic iron overload due to transfusion therapy in patients with beta-thalassemia or sickle-cell disease. Deferasirox is excreted approximately 3% of the received dose in the milk of lactating rats.[1] Despite no clinical and pharmacokinetic data available in human milk from women on chronic DFX therapy, its high apparent volume of distribution (14.4 L/kg) and high percent of protein binding in maternal circulation (99%) make this drug theoretically low concentrated in human milk. In our case the newborn was exclusively breastfed by the mother on chronic therapy with DFX, his growth curve resulted normal during the first month of lactation and his iron status do not present significant alterations. DFX concentration on the mother milk has been evaluated on a sample at 2 hours from therapy, within the range of time to expect serum peak concentration (1.5-4 hours): the drug was not present (below the limit of detection of 0.1 mg/L). Despite the limitation of a case report, in our experience deferasirox therapy in a beta-thalassemia affected mother resulted compatible in breastfeeding, do not modify the growth curve and the iron status of the newborn and seemed at least very low excreted in the mother breastmilk. **Acknowledgements:** The authors acknowledge mothers and the Leche League Italia (*www.lllitalia.org*) that collaborate for the collection of the "blank" sample of the breastmilk used to prepare calibration standards.

**References**

1. Bruin GJ *et al.* Drug Metab Dispos. 2008 Dec;36(12):2523-38.
2. Mattioli F *et al.* Eur J Haematol. 2015 Apr;94(4):310-7.

## NEUROTOXICITY CAUSED BY *MORCHELLA ESCULENTA* – A CLINICAL CASE

M. Versiero[1,*], S. Franco[1], L. Barutta[1], S. Servo[2], E. Pizzolato[1], T. Morgillo[1], G. Lauria[1]

*[1]Emergency Medicine Department, Santa Croce and Carle Hospital, Cuneo, Italy; [2]Division of Neurology, Santa Croce and Carle Hospital, Cuneo, Italy*

*Corresponding Author: Marco Versiero, email: mailpermarco@tiscali.it*

**Introduction:** Major forms of mushroom poisoning are well known and classified. In the latest years, however, toxic effects have been reported after consumption of edible mushrooms.[1] Here we describe a case of neurological toxicity occurred after ingestion of the edible mushroom *Morchella esculenta.* **Clinical case:** An otherwise healty 48 years old male comes to our Emergency Department (ED) in the morning, complaining about dizziness, faintness and a single episode of vomiting. Symptoms started when he woke up. He has no headache, dyspnoea, abdominal pain or diarrhoea. The evening before (14 hours before symptoms onset) he has eaten a meal with considerable amount of "Morels", an edible mushroom. He found and cooked Morels by himself and ate them with a friend, who actu-

ally has no symptoms. The patient identifies eaten mushrooms as *Morchella Esculenta*. The visit shows normal vital signs and body temperature. Abdominal findings are normal. Neurological examination is normal but, in the standing position, the patient describes dizziness and feels imbalance. Few minutes after standing, an episode of syncope occurs, followed by involuntary urine loss. We perform a CT scan of brain and an EEG, both normal. A neurological consult confirms dizziness without other alterations. Blood test (blood cells count, liver and kidney function, serum electrolytes) are normal. Normal saline (750 ml) and Levosulpiride (25 mg) are administered. After 2 hours the patient reports partial relief from dizziness. He is discharged at home with prescription of oral Levosulpiride (25 mg bid). At phone follow-up, 2 days later, he reports complete relief from symptoms within 24 hours. **Discussion:** A diagnosis of *Morchella Esculenta* self-limiting neurotoxic syndrome was made. Major intoxications are sometimes caused by confusion of *Morchella* with *Gyromitra Esculenta* (the so-called false morel). *Gyromitra* can cause agitation, epilepsy, liver dysfunction and haemolytic anemia[1]. In our case *Gyromitra* intoxication was ruled out by normality of blood tests, absence of symptoms in the other dinner, identification of ingested mushroom. In the last 10 years several cases of *Morchella* toxicity have been described[2]. Some authors have defined "*Morchella neurotoxicity*" as a late-onset syndrome (starting more than 12 hrs after ingestion), characterized by dizziness and tremors (50% of cases), ataxia (20%), visual disturbances (20-25%), sensitivity impairment (5%). Gastrointestinal symptoms are usually mild or absent. Mechanisms of toxicity are unknown. Hydrazine-like molecules may be involved (hydrazines cause *Gyromitra* toxicity). Cooking the morels does not prevent the syndrome. Usually, symptoms follow consumption of high amounts of mushrooms. The syndrome is self-limiting in 24-36 hours [2-3]. **Conclusions:** *Morchella Esculenta* can occasionally cause a neurotoxic syndrome. Clinical history, blood tests and a short period of observation are helpful in ruling out other serious intoxications. The clinical course is favourable and symptomatic drugs can be beneficial.

**References**


1. Kimberlie A. Graeme Mycetism: A Review of the Recent LiteratureJ. Med. Toxicol. (2014) 10:173-189
2. Pfab R *et al.*; Cerebellar effects after consumption of edible morels; Clinical Toxicology (2008) 46, 259-260
3. Saviuc P *et al.*; Can morels (Morchella sp.) induce a toxic neurological syndrome? Clin Toxicol (2010) 48(4):365-372


## GRAVE CHETOACIDOSI METABOLICA CON *ANION GAP* AUMENTATO DA ASSUNZIONE DI ALCOL DENATURATO


F. Gambassi[1,*], A. Missanelli[1], A. Rotulo[2], A. Zotto[2], M. Conte[2], G. Mannaioni[1,2]

*[1]SOD di Tossicologia Medica e Centro Antiveleni, AOU Careggi, Firenze; [2]Dipartimento NEUROFARBA, sezione di farmacologia e Tossicologia, Università degli Studi di Firenze*

*Corresponding Author: Francesco Gambassi, email: gambassif@aou-careggi.toscana.it*


**Introduzione:** L'alcol etilico viene denaturato secondo il Regolamento (CE) n. 2205/2004, aggiungendovi Red 24 (colorante rosso) e metiletilchetone al 4-10%. **Case Report:** Una donna di 56 anni, con storia di etilismo cronico, giunge al DEA della AOU Careggi, dopo essere stata ritrovata in stato confusionale su una panchina. Riferisce di aver ingerito 24 ore prima circa 500mL di "alcool rosa", insieme a una quantità non precisata di vino. La paziente è vigile (GCS 15), presenta alitosi aromatica, PA 140/70, FC 87 BPM, tachipnea (>30 atti/min), $SatO_2$ 98% in aria. L'Emogasanalisi evidenzia pH plasmatico di 6,89, $PaO_2$ 140 mmHg, $PaCO_2$ 11 mmHg, ABE -29mmol/L, AG 26 mEQ/L, lattati 4.3 mmol/L. Gli elettroliti ed gli indici di funzionalità renale sono nella norma, mentre i markers di abuso cronico di etanolo (MCV 105 $\mu^3$, YGT 362 U/l, AST 157 U/l) sono alterati, etanolemia assente. La paziente viene prontamente sottoposta ad idratazione e correzione dello squilibrio metabolico con somministrazione di $NaHCO_3$ 200 mEq, in due boli successivi a distanza di 30 min. con aumento del pH ematico a 7,11 e correzione parziale degli altri parametri emogasanalitici. Sulla base dei dati anamnestici di ingestione di alcool denaturato, bioumorali ed emogasanalitici, grave acidosi metabolica con elevato *anion gap,* stante il rischio incombente di danni da intossicazione da alcool e/o chetoni tossici, si ritenne opportuno sottoporre la paziente ad una seduta emodialitica, a terapia antidotale con fomepizole e al prelievo seriato di campioni ematici per la determinare, in modalità differita, le concentrazioni ematiche degli alcoli, chetoni e loro metaboliti. Durante la seduta emodialitica, i parametri vitali della paziente si sono mantenuta stabili e la tachipnea si è notevolmente ridotta. Al termine della dialisi i parametri all'EGA erano i seguenti: pH 7,52; $PaO_2$ 95,4; $PaCO_2$ 22,1; $HCO_3$ -20,7; ABE -4.5; AG 14,8; lattati 0,8 mmol/L. La paziente è stata trasferita in Terapia Sub-Intensiva, dove è stata proseguita la terapia antidotale con fomepizole ev, con una dose d'attacco di 15 mg/kg, seguita dalla dose di mantenimento di 10 mg/kg/12 ore per le 48 ore successive, con progressiva risoluzione del quadro metabolico. La paziente è stata dimessa dopo 72 ore con terapia anti-astinenziale per il potus e presa in carico dall' ambulatorio tossicologico per programma di disintossicazione da alcool. La ricerca degli alcoli tossici e chetoni nei campioni ematici seriati, eseguiti con la tecnica dello spazio di testa in GC/MS, hanno evidenziato la presenza di metanolo, acetone e metiletilchetone, in tracce, con andamento decrescente tempo-correlato. Nell'unico prelievo effettuato sul dializzato è stata confermata la presenza sia del metanolo che dell'acetone, ma non del metiletilchetone. **Discussione:** I risultati ematochimici non indicano una chiara eziopatogenesi da alcoli e/o chetoni tossici, Il quadro clinico è indicativo per una cheto-acidosi alcolica, non rara negli etilisti cronici, caratterizzata da acidosi metabolica con aumento dell'*anion gap*, favorita dalla malnutrizione, disidratazione e deficit di tiamina[1].

**Bibliografia**

1. Nuralamin MN, Krishna B, Sharpstone D: Alcoholic ketoacidosis: a case report and review of the literature; Oxf Med Case Reports 2016 (3): 31-33.

## GLI ERRORI TERAPEUTICI: LA CASISTICA DEL CENTRO ANTIVELENI DI FIRENZE NEL PERIODO 2011-2015

M. Cirronis[1], A. Dilaghi[1], F. Gambassi[2,*], B. Occupati[2], G. Mannaioni[1,2], A. Ieri[2], A. Missanelli[2], A. Pistelli[2]

*[1]Dipartimento di NEUROFARBA, Università di Firenze; [2]SODc di Tossicologia Medica, AOU Careggi, Firenze*

*Corresponding Author: Francesco Gambassi, email: gambassif@aou-careggi.toscana.it*

**Introduzione:** L'errore terapeutico può essere definito come "qualsiasi errore nell'iter di prescrizione, dispensazione, preparazione, somministrazione o monitoraggio della terapia farmacologica, indipendentemente dal verificarsi o meno del danno"[1]. Gli errori terapeutici sono ampiamente descritti in ambiente ospedaliero, mentre poche informazioni sono disponibili per quelli che si verificano in ambito extraospedaliero. I dati epidemiologici provenienti dai Centri Antiveleni (CAV) consentono una valutazione della diffusione degli errori terapeutici nella popolazione generale. **Risultati:** Nel periodo compreso dal 1 gennaio 2011 al 31 dicembre 2015 sono stati registrati 1.143 errori terapeutici pari al 5,48% delle richieste totali giunte al CAV di Firenze, SODc di Tossicologia Medica, AOU Careggi. Le richieste sono pervenute da privati cittadini (n= 469; 41,03%), ospedali (n=372; 32,54%), guardie mediche (n=206; 18,02%) e da medici curanti (n=48; 4,19%). La maggior parte degli errori terapeutici (n=1076; 94,20%), si è verificata in ambiente domestico o sul luogo di lavoro, mentre il 5,8% in strutture sanitarie. Nel campione totale gli adulti sono il 50,5% (n=577); i bambini sotto i 5 anni di età il 33,7% (n=378), mentre nel 13,39% (n=153) hanno un'età compresa tra i 6 e i 18 anni. I farmaci maggiormente coinvolti risultano essere molecole attive sul SNC (22, 5%), antibiotici (10,77%), FANS (9,89%), farmaci cardioattivi (9,63%), farmaci utilizzati nella patologia respiratoria (9,19%), oppioidi (4,90%), ormoni e vitamine (2,63%), mentre il restante 26,94% comprende singole molecole appartenenti ad altre classi farmacologiche. I farmaci più rappresentati negli errori terapeutici sono quelli attivi sul SNC, analgesici oppioidi, farmaci endocrino-metabolici e molecole cardioattive nella fascia di età adulta, mentre nei bambini sotto i 5 anni sono più frequenti errori terapeutici con FANS, antibiotici e farmaci per patologie respiratorie. Oltre il 75% dei pazienti per cui è stata richiesta una consulenza (n=866) è risultato asintomatico. A prescindere dalla presentazione clinica (presenza o assenza di sintomi) è stata data indicazione ad effettuare una valutazione medica o a recarsi in ospedale solo nel 15% dei casi. Più frequentemente il paziente è rimasto al proprio domicilio e non è stata necessaria alcuna terapia (69,26%); un trattamento sintomatico è stato sufficiente nel 20,22% dei casi, manovre di decontaminazione sono state consigliate nell'8,4% dei casi ed in meno del 2% dei casi è stata necessaria la somministrazione di farmaci antidotali. **Conclusioni:** Per quanto il tasso di ospedalizzazione sia basso e la consulenza tossicologica telefonica riduca ulteriormente l'impropria afferenza dei pazienti alle strutture sanitarie, gli errori terapeutici potrebbero essere prevenuti e/o limitati mediante adeguate strategie basate sulla collaborazione tra CAV, centri di farmacovigilanza, medici prescriventi e industrie farmaceutiche.

**Bibliografia**

1. Koren G. Trends of medication errors in hospitalized children. J Clin Pharmacol 2002; 42: 707-10.

## AN ATTEMPTED SUICIDE WITH COPPER SULPHATE INJECTED INTRAVENOUSLY: A CASE REPORT

O. Spagnolello[1], O. Staltari[2], A. Garramone[1], L. Lombardi[3], D. Lonati[4], G. Bertazzoni[1], M.C. Grassi[2,*]

*[1]Department of Emergency Medicine, Policlinico Umberto I - "Sapienza" University of Rome, Rome, Italy; [2]Emergency Toxicology and Poison Control Centre Unit, Policlinico Umberto I - "Sapienza" University of Rome, Rome, Italy; [3]Department of Immunohematology and Transfusion Medicine, Policlinico Umberto I - "Sapienza" University of Rome, Rome, Italy; [4]Pavia Poison Control Centre and National Toxicology Information Centre, Toxicology Unit, IRCCS Maugeri Foundation, Pavia, Italy*

*Corresponding Author: Maria Caterina Grassi, email: caterina.grassi@uniroma1.it*

**Background:** Copper (Cu) is an essential trace metal in humans not poisonous in its metallic state but some of their salts such as Copper Sulphate (CuS) are poisonous.[1] It is used commercially in whitewashing, leather manufacture, fungicides and insecticides.[2] Chronic intoxication is often occupational related. Acute Copper Sulphate Poisoning (ACuSP) usually results from oral ingestion with suicidal purpose, and rarely from parenteral exposure: only few cases of parenteral ACuSP have been reported in literature.[2,3] **Clinical case:** A 37-year-old man was admitted at Emergency Department three hours after that he attempted suicide by self-injecting intravenously an unknown amount of a CuS solution. The patient had a history of heroin and cocaine use disorders. At the admission, he was conscious, GCS 15, T 36.5°C, RR 18 breaths/min, SpO2 96% on room air, BP 105/75 mmHg, HR 120 beats/min. He presented tremors and diffuse myalgia. Laboratory results were within the normal range. One day later, a blood sample was collected to assess Serum Cu levels, which reached 263 µ/dL (normal range 70-140 µ/dL). On day 3, he was alert and oriented, GCS 15, T 38°C, RR 18 breaths/min, SpO2 96%, BP 130/70 mmHg, HR 72 beats/min. Physical examination revealed pallor, jaundice, brown to red urines, signs

of extravasation by the antecubital area of both arms and he was complaining epigastric pain. Laboratory findings showed: normochromic normocytic anaemia with signs of intravascular haemolysis, rhabdomyolysis, methaemoglobin 5.2%. The patient received fluids therapy, electrolyte correction, and was transfused with 4 Units of Packed Red Blood Cells. N-acetilcysteine and D-penicillamine were started. Moreover, piperacillin/tazobactam and clindamycin were administered for peri-injection cellullitis, salicylic acid as antipyretic and omeprazole for gastric protection. As critical condition was persisting, Therapeutic Plasma Exchange (TPE) was performed on day 5 and on day 6 to support the drug therapy, on day 7 he was transferred to the intensive care unit and then to the surgery unit for wounds toilet. On day 12 he was moved to the psychiatric unit, on day 13 D-penicillamine was discontinued due to increasing liver function tests. On day 22 he was admitted to the medical department to continue the diagnostic and therapeutic process. On day 32 he was discharged asymptomatic and with normal laboratory values. **Discussion:** ACuSP is an uncommon event in the worldwide.[2,3] The management is symptomatic and supportive. Chelation therapy should be initiated when hematologic or hepatic complications as well as other manifestations of poisoning are present. D-penicillamine, British-Anti-Lewisite and Ethylene-Diamine-Tetra-Acetate have been used as antidotes. Haemodialysis is indicated only in case of persistent renal failure. Very few cases of using of TPE in the setting of ACuSP are available. In this case the antidotic and antioxidant therapy resulted effective to reverse haemolysis and rhabdomyolysis and to prevent hepatic and renal damage. The TPE should be considered as an addictive measure.

**References**

1. Ashish B, *et al.* Copper Toxicity: A Comprehensive Study. Res J Recent Sci 2013; 2:58.
2. Oldenquist G, Salem M. Parenteral copper sulfate poisoning causing acute renal failure. Nephrol Dial Transplant 1999; 14:441.
3. Behera C, *et al.* An unusual suicide with parenteral copper sulphate poisoning: a case report. Med Sci Law 2007; 47 (4):357.