Piratox sheet #3: "Lewisite"

! Key points not to forget

→ The 1st emergency measures are:
- extraction of victims from the hazard area: mucocutaneous and respiratory protection of rescuers is essential;
- emergency decontamination (undressing first and foremost) of victims, possibly followed by in-depth decontamination depending on the context[1] (shower only after elimination of any traces of liquid by adsorption).

→ Lewisite is a sufficiently volatile and toxic liquid to constitute a **risk of intoxication** (vapours / liquid) and **of contamination** (liquid).

→ Clinical signs appear rapidly (contrary to yperite, for which they appear within a few hours).

→ In general, the shorter the symptom onset time, the more serious the intoxication and the more severe the symptoms.

→ Lewisite is not so lethal, but highly incapacitating.

→ The toxicity of lewisite is not only that of its component arsenic.

→ Victims should be treated as burns victims and, once decontaminated, handling them presents no hazards.

→ As for any skin affliction, check the victim's anti-tetanus vaccination status.

→ Due to the exceptional emergency situation, certain sections of the Summary of Product Characteristics (SPCs) for BAL® are relativized on the sheet (e.g.: pregnancy, breast feeding), or should be relativized (e.g.: contraindications). Continuation of antidote treatment requires reference to the complete SPCs for BAL®.

→ For additional information concerning the risk, assistance with patient treatment and follow-up, we recommend contacting the military health service, poison control centres, or referring healthcare establishments.

2. Pharmaco-toxicological class of the toxic compound

Lewisite is a chemical agent of the vesicant family (NATO denomination = L; CAS number: 541-25-3). The mechanism of action of Lewisite is poorly understood. It is a halogenated derivative of arsenic (2-chlorovinyl-dichloroarsine) combining vesicant properties with the general toxicity of arsenic. The general term refers to lewisite 1 (2-chlorovinyl-dichloroarsine); when not specified, it refers to this compound. Lewisite exists in the form of 2 isomers with different physicochemical properties. In ammunition and during storage, alongside additional impurities, lewisite 1 may also exist in mixture with lewisites 2 and 3, corresponding to derivatives with two or three 2-chlorovinyl groups respectively, replacing the chlorine atoms. In this sheet only lewisite 1 is considered..

[1] Decontamination procedures (*cf.*french circular no. 700/SGDN/PSE/PPS of November 7th 2008 and introduction sheet).

3. Physicochemical properties that may influence treatment

Lewisite is liquid at ordinary temperatures. It is odourless when highly pure, though impurities may give it a geranium oil smell. It is poorly soluble in water, though it hydrolyses rapidly when in contact with this latter, giving rise notably to water-insoluble oxide. Depending on the references, this oxide is said to possess identical or lower vesicant activity than lewisite. It is, however, admitted that ambient air humidity rapidly inactivates the toxic compound and reduces the hazard. A shower is sufficient to remove any insoluble oxide.

	Lewisite 1	**Comment(s)**
Probable physical state	Toxic compound liquid at ordinary temperatures, releasing vapours (significantly more volatile than yperite).	BP* = 190°C (varies with isomer, purity and mixture L1, 2.3) MP** = -13°C (varies with isomer, purity and mixture L1, 2.3)
Vapour density	Heavy gas	d=7.1
Water-solubility	Low	Around 0.5 g/L May give a vesicant oxide in contact with water, water-insoluble
Contamination potential	High	

*BP: boiling point = temperature of transition from liquid to vapour state.
**MP: melting point = temperature of transition from solid to liquid state.

4. Main intoxication characteristics

Similar to the other vesicant agent covered in these sheets (yperite), lewisite causes potentially serious intoxications, though not generally life-threatening in the short term. Treatment is mainly hospital-based, preferably in a specialist unit.

The toxicity of organic arsenic derivatives cannot be summarised as that of arsenic, either in qualitative or in quantitative terms. The exact mechanism by which lewisite exerts its biological effects is very poorly understood. The scientific literature abounds in contradictory observations and conclusions. In particular, the toxicity data are highly variable.

Assessments on humans are extremely rare, thus limiting the relevance of a precise description of symptoms and their onset chronology. The comparison of the human toxicity of yperite and lewisite gives controversial results, though it is currently accepted that the percutaneous dose of lewisite causing death within 24 hours is at least two times lower than for yperite. On initial approach, the symptoms can be considered to be relatively similar to those caused by yperite, though their onset is much earlier and they are generally more severe. These are characterised by immediate eye, skin and respiratory tract pain. These signs reduce the insidious nature of lewisite, leading to earlier implementation of protective, decontamination and treatment measures than during exposure to yperite.

The volatility of lewisite, the immediate sensation of irritation, possibly the smell, will probably be sufficient to alert the emergency services. Asymptomatic victims reporting to have smelt or felt the exposure must be undressed, or even more thoroughly decontaminated. Until undressed, victims able to sit down must not do so to avoid aggravating perineal lesions.
Victims deemed to be the most highly exposed must be kept under observation for a half-day. The other asymptomatic victims should be advised to consult in the event of appearance of eye irritation, breathing distress or erythema.

- Eyes

The immediate burning sensation is followed by conjunctival inflammation within an hour of contact.

- Respiratory apparatus

The first toxic effect of lewisite in vapour form is nasal irritation. Respiratory effects are similar to those caused by yperite, though their onset is more rapid.

- Skin

Greyish areas of dead epithelium appear within a few minutes around points of contact of lewisite with the epidermis, suggestive of caustic agent burns. Irritation onset is very rapid, followed by rash and blistering within a few hours, then necrosis. As previously stated, the skin lesions are more severe than those caused by yperite, particularly the vascular effects, but they would appear to heal more rapidly. Phlyctenules may contain hydrolysis derivatives with vesicant properties if left in contact with skin. The usual medical treatment procedures, however, should be sufficient to eliminate any risks for healthcare personnel. Overall, at all steps in progression, pain appears to be much more intense that after yperite intoxication, though it would seem to lessen after 48-72h.

- General

The clinical presentation, more severe than with yperite, may include gastrointestinal disorders with diarrhoea and vomiting, liver and kidney disorders and hypothermia. In its major forms, lewisite can cause a state of shock resulting from capillary leakage caused by burns. This may be accompanied by haemolysis.
Contrary to yperite, lewisite does not possess radiomimetic properties. The risk of immunosuppression is therefore lower. The long-term consequences of a single symptomatic exposure have not been studied. In the current state of knowledge, however, as arsenic derivatives have only been associated with cancer in the case of chronic exposure, this risk is negligible for acute exposure.

5. Non-specific treatment

Victim decontamination is the most urgent action to perform following extraction from the hazard area. After undressing, emergency decontamination aims to eliminate the toxic compound as much as possible and preventing spread of the contamination: if possible, use a powdering glove containing fuller's earth, or any other suitable devices, and shower as rapidly as possible (water + mild soap) to allow decontamination by entrainment.

6. Specific treatments

BAL (British Anti Lewisite; dimercaprol) - B.A.L®, IM injectable solution.

1. Pharmacological mechanism of action

Dimercaprol binds the arsenic in Lewisite, forming a stable and non-toxic water-soluble complex (cyclical product).

2. Indication(s)

Though BAL® was developed in 1945 to treat Lewisite intoxication, this indication is no longer specified in the Summary of Product Characteristics that only mentions acute intoxication with arsenic, mercury and gold salts, along with severe lead poisoning, in combination with EDTA calcium disodium.

3. Criteria for administration of systemic treatment

As BAL® causes side effects, several criteria should be checked before deciding to initiate systemic treatment.
a. Cough with dyspnoea and foamy sputum, possibly blood-laced, along with other signs of acute pulmonary oedema, or
b. A skin burn of an area at least equal to the palm of the hand, not decontaminated within 15 min of exposure, or
c. Skin contamination covering at least 5% of body surface, displaying signs of rapid onset skin affliction (greyish or bleached skin), or presenting an erythema appearing within 30 min.

4. Dosage regimens

In adults

Initiation of treatment

Perform a deep IM injection (as the product is very painful) as soon as possible (2 to 3 mg/kg, without exceeding 200 mg per injection), if possible using a glass syringe. Failing any specific studies, we cannot confirm the possibility of using a plastic syringe. In emergency, however, and if a glass syringe is not available, a plastic syringe may be used if the antidote is injected immediately after filling the syringe.

Maintenance dose

Five further injections shall be performed, at 4-hour intervals; same protocol the following day, *i.e.* 6 injections on the 2nd day; four injections per day on the 3rd day, then two injections per day for 7 to 10 days.

Predicted treatment duration

10-13 days.

Topical applications to the skin may be considered and could be beneficial if applied within minutes of contact. No dosage form is available for this type of use, however; in particular, there is no eye drop form for eye contact.

In children

The previous protocols shall be used.

In newborns and infants

No data available

5. Contraindications (should be relativized in exceptional emergency situations)

Hypersensitivity to dimercaprol and butacaine or to one of the other components of the injectable solution.

6. Main adverse effects (due to their frequency or severity)

Side effects, reversible within a few hours, may appear in numerous subjects (tachycardia, acute high blood pressure, anxiety, nausea, vomiting, burning sensations on the hands, face and mouth, ptyalism, rhinorrhoea, sweating, lacrymal hypersecretion, etc.).

7. Precautions for use

Injections must be strictly intramuscular, using a glass syringe whenever possible. The benefit to risk ratio of BAL administration should be considered under the following conditions:

- Known G6PD deficiency (risk of massive haemolysis due to the presence of butacaine).
- Allergy to groundnut or hypersensitivity to components.

8. Interactions and incompatibilities (physicochemical)

When applied to the skin, dimercaprol is incompatible with silver sulfadiazine; the two products must therefore not be combined when dimercaprol is applied topically.

9. Use of antidote in specific populations

Pregnancy: due to the life-threatening situation, the use of BAL is possible during pregnancy, whatever the term.

Breast feeding: not relevant in exceptional emergency situations.

In the event of continued antidote treatment, see the SPCs for BAL®.

Water-soluble chelating agents

Various water-soluble chelating agents have been synthesised. Two molecules are used in clinical practice: meso-2.3-dimercaptosuccinic acid (DMSA) 2.3-dimercapto-1-propanesulfonic acid (DMPS).

In absolute terms, these different molecules do not display any significant efficacy differences in terms of chelation compared to BAL®. Water-soluble analogues, on the other hand, show improved tolerance and allow the administration of a loading dose (if the intravenous route is available) and higher accumulated doses. Pharmacokinetic differences, however, in terms of the ability to reach different body compartments, should be taken into consideration, as are the toxicokinetic differences of arsenic compounds. As toxicokinetic data for lewisite are very limited, it is difficult to make a definitive pronouncement concerning the efficacy of water-soluble analogies in all lewisite intoxication situations.

Moreover, in France, DMSA (dimercaptosuccinic acid; succimer) is available only in capsule form, SUCCICAPTAL® 200 mg, capsule, indicated for the treatment of lead and mercury intoxications. In the strict context of acute lewisite intoxications, no data are available for the enteral form. The highly variable absorption of DMSA is a negative element. Furthermore, as intoxication is likely to cause diarrhoea and vomiting, this route of administration is not recommended, thus further emphasizing the benefits of an injectable form. The possible availability of an injectable form of water-soluble chelating agent will be considered. For the moment, therefore, BAL® remains of prime interest.

In the absence of specific knowledge concerning the posologies of DMSA capsules to use lewisite intoxications, those specified in the SPC shall be applied:

In adults

The posology is of 10 mg/kg (or 350 mg/m^2) administered every 8 hours for 5 days (i.e. 30 mg/kg/day), then 10 mg/kg or 350 mg/m^2 every 12 hours for 2 weeks (i.e. 20 mg/kg/day). The posology should not exceed 1.8 g/day in adults.

In children

The adult dosage regimen is used. The doses according to weight are thus as follows:

Weight (kg)	Dose* (mg)
8 - 15	100
16 - 23	200
24 - 34	300
35 - 44	400
> 45	500

* to be administered every 8 hours for 5 days, then every 12 hours for 2 weeks.

7. Symptomatic treatments

In respiratory, ophthalmic, skin and pain-related terms, the treatment is comparable to that of yperite intoxication.

Antidotes

Summary of product characteristics

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION DU MEDICAMENT

B.A.L., solution injectable I.M.

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Dimercaprol……..10,00 g

Butacaïne…….0,05 g

Pour 100 ml de solution injectable.

3. FORME PHARMACEUTIQUE

Solution injectable I.M.

4. DONNEES CLINIQUES

4.1. Indications thérapeutiques

Intoxication aiguë par l'arsenic, le mercure et les sels d'or.

Intoxication saturnine sévère en association avec l'E.D.T.A. calcicodisodique.

4.2. Posologie et mode d'administration

Voie parentérale: voie intramusculaire stricte.

La posologie est de 3 mg/kg par injection soit pour un adulte d'environ 70 kg:
les 2 premiers jours: 1 injection toutes les 4 heures, soit 6 injections;
le troisième jour: 1 injection toutes les 6 heures, soit 4 injections;
les 10 jours suivants: 2 injections par jour.
Dans les néphrites mercurielles aiguës (en l'absence d'anurie: cf chapitre précaution d'emploi): 5 mg/kg et par injection.

Débuter le traitement par ¼ d'ampoule (50 mg) pour rechercher la sensibilité individuelle du malade.
Comme pour toute solution injectable non aqueuse, administrer au moyen d'une seringue en verre.

4.3. Contre-indications

Ce médicament est contre-indiqué en cas de:
hypersensibilité au dimercaprol et à la butacaïne ou à l'un des autres constituants de la solution injectable.

4.4. Mises en garde spéciales et précautions d'emploi

Mise en garde

La toxicité de ce médicament (en relation avec son pouvoir réducteur) est augmentée en cas de lésion rénale ou d'insuffisance hépatique.

Il doit donc être administré avec précaution chez les malades présentant une insuffisance rénale ou hépatique.

Des précautions doivent être prises également chez les malades hypertendus (cf chapitre effets indésirables).

En cas de déficit en G6PD, ce médicament peut entraîner une hémolyse.

Précautions d'emploi:

L'injection doit se faire strictement par voie intramusculaire et avec une seringue en verre.

L'utilisation du dimercaprol dans les néphrites mercurielles aiguës ne se fera qu'en l'absence d'anurie.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif (anesthésique local) pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopages.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

Sans objet.

4.6. Grossesse et allaitement

Les études effectuées chez l'animal ont mis en évidence un effet tératogène.

Il n'existe pas actuellement de données pertinentes, ou en nombre suffisant, pour évaluer un éventuel effet malformatif ou fœtotoxique du dimercaprol lorsqu'il est administré pendant la grossesse.

En conséquence, compte tenu de ces données et au regard de l'indication, cette association peut être prescrit pendant la grossesse si besoin.

En raison de l'absence de données du passage de ce médicament dans le lait maternel, l'allaitement est à éviter pendant l'utilisation de celui-ci.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

Sans objet.

4.8. Effets indésirables

Douleurs au point d'injection, hypertension, tachycardie, nausées, vomissements, céphalées, sensations de brûlures du visage.

4.9. Surdosage

En cas de surdosage, il a été observé une hypertension, des convulsions et un coma.

5. PROPRIETES PHARMACOLOGIQUES

5.1. Propriétés pharmacodynamiques

ANTIDOTE

(V: divers)

Le dimercaprol se combine avec l'arsenic, le mercure ou l'or.

Il a une plus grande affinité que les protéines pour ces métaux et forme avec ces derniers un composé stable, rapidement excrété par le rein.

5.2. Propriétés pharmacocinétiques

Après administration par voie IM, la concentration maximale plasmatique est atteinte en 1 à 2 heures.

Le produit est rapidement et entièrement métabolisé et excrété par voie rénale en moins de 24 heures.

5.3. Données de sécurité préclinique

Non renseignée.

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Benzoate de benzyle, huile d'arachide.

6.2. Incompatibilités

En l'absence d'études de compatibilité, ce médicament ne doit pas être mélangé avec d'autres médicaments.

6.3. Durée de conservation

3 ans.

6.4. Précautions particulières de conservation

Pas de précautions particulières de conservation.

6.5. Nature et contenu de l'emballage extérieur

Ampoule bouteille autocassable en verre brun de type I de 2 ml.

6.6. Précautions particulières d'élimination et de manipulation

Pas d'exigences particulières.

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

SOCIÉTÉ D'ETUDES ET DE RECHERCHES BIOLOGIQUES
53, RUE VILLIERS DE L'ISLE ADAM
75020 PARIS

8. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE

300 906-5: 2 ml en ampoule (verre brun), boîte de 12

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

Date de l'AMM : 29/09/1997

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste II