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# Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

*In This Issue:*



## The Unusual History of British anti-Lewisite (BAL)

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Many clinicians and laboratorians are vaguely familiar with the compound British anti-Lewisite (BAL, dimercaprol), but few know of its interesting history or its current role in modern medicine. At the start of World War II, the British had such great fear the Germans would use the chemical warfare vesicant lewisite they secretly developed an antidote. Unbeknownst to these researchers at the time, their BAL antidote would revolutionize the treatment of heavy metal poisonings, most notably with BAL being the first successful treatment of Wilson's disease. Even 75 years after its discovery and the development of safer, more efficacious chelating agents, BAL remains a crucial treatment for certain heavy metal poisonings and is often stocked by hospitals for such emergencies.

**The covert development of BAL**

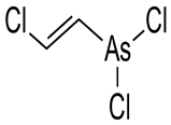
When World War II commenced in 1939, the British government was terrified that the Germans would again resort to chemical warfare as they had in World War I. At the time, Germany had a vast military-industrial complex that included the world's largest chemical manufacturing capacity for mass producing chemical weapons. One of England's greatest fears concerned the production of the organoarsenical lewisite ($C_2H_2AsCl_3$, Figure 1) that was more toxic than mustard gas (1). The British government responded by funding a team of biochemists at Oxford University to secretly synthesize an antidote. Correctly presuming lewisite's toxicity was due to arsenic and aware that earlier studies suggested protein thiols reacted with trivalent arsenical compounds, they first assessed if simple thiols could confer protection (2). They found that large excesses of monothiols like glutathione had little effect on lewisite's ability to preferentially inhibit the enzyme pyruvate dehydrogenase. Unsure what these disappointing results meant, they wisely investigated how protein thiol groups reacted with arsenic. At the time, the only readily available source of thiol-rich proteins was keratin found in human hair, which they

collected from local barbershops. Their experiments showed that most arsenic bonded to reduced keratin through two vicinal thiol groups. Over 40 dithiol containing chemicals were then assessed and on July 21, 1940 they discovered OX217 which could efficiently protect and reverse the effects of lewisite's enzyme inhibition. In 1941, OX217 was sent to the US for further development upon which the Americans renamed it British anti-Lewisite. Further characterization illustrated its remarkable *in vivo* efficacy in various animal models and human volunteers. Improved synthesis led to the development and fielding of BAL solutions and ointments. By the end of World War II approximately 56 million tubes of ointment had been issued to American troops, although thankfully neither lewisite nor any other chemical weapon was ever employed (3). Biochemical studies in the late 1940s revealed BAL's full mechanism of action. Lewisite was found to rapidly bind to the dithiol lipoic acid, a cofactor in several essential metabolic enzymes like the pyruvate dehydrogenase complex and alpha-ketoglutarate dehydrogenase (Figure 1). Lewisite had a greater affinity for BAL than lipoic acid and together they form a very stable five-member arsenical ring that is readily excreted. This effectively protected the critical enzyme cofactor and prevented lewisite's fatal inhibition of intracellular oxidative energy production.

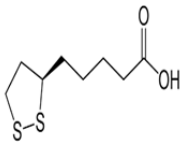
**Table 1. Structure and properties of BAL and its analogs**

| | British anti-Lewisite (BAL) | Succimer | DMPS |
|---|---|---|---|
| **Structure** | | | |
| **Chemical formula, Molecular mass** | $C_3H_8S_2O$ 124.2 g/mol | $C_4H_6O_4S_2$ 182.2 g/mol | $C_3H_8O_3S_3$ 188.3 g/mol |
| **Common Names** | 2,3-dimercaptopropanol, Dimercaprol | 2,3-dimercaptosuccinic acid, DMSA, CHEMET | 2,3-dimercaptopropanesulfonic acid, Unithiol |
| **LD50 (mice IP)** | 1.48 mmol/kg | 13.73 mmol/kg | 6.53 mmol/kg |
| **ED50 (mice IP)** | 0.169 mmol/kg | 0.037 mmol/kg | 0.055 mmol/kg |

**Figure 1. Chemical structures of lewisite and lipoic acid**




**Lewsite**




**Lipoic acid**

## BAL properties and problems

Since BAL is highly lipid soluble and rapidly hydrolyzes in an aqueous solution, developers created a deep muscle injectable (IM) formulation. At the time a cheap, common solvent for lipid soluble compounds was peanut oil and BAL was quite stable in it. This remains the only form commercially available in the US. It is sold by Akorn, Inc (Decatur, IL) in packaged 3 mL ampules (100 mg/mL) that contain a transparent or slightly yellow, viscous liquid with a sulfur odor (Figure 2). Pharmacokinetic studies from the late 1940s revealed BAL is rapidly absorbed after IM injection with serum levels peaking 30-60 minutes post-administration. BAL levels then drop quickly with glucuronic acid conjugates accounting for about half of the dose at 6 hours and over 80% at 24 hours. Little parent compound is excreted in urine, however, some BAL is found in feces (4). BAL readily crosses cell membranes and has been found to concentrate in the liver, kidney and small intestine (5). Since acidic urine permits dissociation of the BAL-heavy metal chelate, it is recommended that the urine of patients be alkalinized with hypertonic $NaHCO_3$ to a pH of 7.5-8.0 to prevent liberation and reabsorption of heavy metals.

**Figure 2. Injectable BAL**

BAL has a small therapeutic index and numerous dose dependent adverse effects. At a dose of 5 mg/kg, there is a ~65% likelihood of an event occurring; the most common being tachycardia accompanied by up to a 50 mm Hg rise in both systolic and diastolic blood pressure (4). Other symptoms in decreasing order of frequency are nausea; emesis; headache; burning sensation of lips, mouth, and throat; lacrimation; rhinorrhea; salivation; diaphoresis; muscle pain and anxiety (4, 6). During therapy, approximately one in three children will develop a persistent fever and repeated deep IM injection can result in painful abscesses. BAL use is contraindicated in patients with hepatic insufficiency and those with peanut allergies. Treatment should be discontinued or very closely monitored if acute renal insufficiency develops. Iron should not be concomitantly administered as the BAL-iron complex is very toxic. Doses above 5 mg/kg should be avoided because of the high risk of convulsions and stupor (6). The exact mechanism of BAL toxicity is unknown but likely involves the removal of important metal cofactors causing widespread enzyme inhibition.

**BAL uses in medicine**

Towards the end of World War II clinical applications of the new antidote began to be studied that focused on IM BAL. It was immediately recognized that it could be used to treat accidental and iatrogenic heavy metal poisonings. The first observations centered on industrial arsenical accidents but BAL also proved effective in the treatment of complications from arsenical compounds used to treat syphilis. Patients receiving the arsenical antibiotic neoarsphenamine often developed severe dermatitis; IM BAL decreased its duration from 62 to 21 days by increasing arsenic urinary excretion (7). A Johns Hopkins study found BAL therapy dramatically increased the survival and recovery rates in patients who had ingested mercuric chloride that were presumably suicide gestures. Positive results were also observed in patients treated with BAL that exhibited gold toxicity attributed to their rheumatoid arthritis therapy (4). BAL therapy was also helpful in a range of other heavy metal poisonings, most notably lead. Unexpectedly, in 1951 BAL was shown to be the first curative therapy for Wilson's disease.

Wilson's disease is an autosomal recessive genetic disorder that causes copper accumulation in the liver, brain, kidneys and eye. Intracellular copper levels are increased due to reduced biliary export and impaired formation of plasma ceruloplasmin. In the early 1990s, it was discovered that Wilson's disease is caused by mutations in the ATP7B gene which encodes a P-type ATPase. These patients are often diagnosed during adolescence, with liver disease being the most common presentation and neurological manifestations developing later in life. When severely incapacitated patients received chronic BAL treatment, there were dramatic positive results that paralleled marked increases in urinary copper excretion (3). Although BAL had many adverse effects, it provided great relief to a community for which only palliative care was previously

available. In 1956, D-penicillamine was discovered to be a far less toxic therapy for Wilson disease, and it along with trientine are the current standard of care. However, BAL should be administered in rare cases where these drugs are ineffective.

In the US, injectable BAL is currently indicated to treat metallic poisonings involving arsenic, gold, and inorganic mercury and should be administered as soon as possible post-exposure. BAL therapy is also recommended in severe lead poisonings (> 70 mcg/dL), but must be used concomitantly with $CaNa_2EDTA$. It is essential to first administer a 4 mg/kg BAL injection followed by 4 hours later with $CaNa_2EDTA$ concomitantly with the second BAL dose. This treatment prevents the $CaNa_2EDTA$ from redistributing lead to the brain and is continued for 2-7 days depending on the clinical response. BAL should not be used in iron, cadmium, tellurium, organomercurials or selenium poisonings because the resulting BAL-metal complexes are more toxic than the original metal alone, especially to the kidneys.

**Improved chelating agents**

The early BAL clinical studies quickly revealed its main limitations: a narrow therapeutic index, poor patient tolerance, and the potential to redistribute arsenic to the brain. This led to the development of alternative treatments that have largely supplanted BAL's utility in developed countries. In the late 1950s, scientists in the Soviet Union and China developed the water soluble BAL-analogs **succimer (**2,3-dimercaptosuccinic acid, CHEMET) and DMPS (**2,3-dimercaptopropanesulfonic acid)**. These compounds can be taken orally so lack the drawback of IM and do not cause any metal redistribution to the CNS. Side-by-side animal studies with BAL showed that both were more effective at treating arsenic poisoning, exhibiting a more than 13.5 fold higher therapeutic index (Table 1) and higher LD50s (7). Both are generally well tolerated with 10-20% of patients experiencing mild gastrointestinal disturbances and a sulfurous odor to body secretions (4, 8). Succimer was approved by the FDA in 1991 and is the current first line treatment for arsenic and mercury poisonings as well as in patients with blood lead levels exceeding 45 mcg/dL. It is supplied as 100-200 mg capsules for oral administration as well as an IV form and iron can be safely co-administered (9). Adult chelation therapy usually involves 10 mg/kg three times a day for five days followed by 10 mg/kg twice daily for two weeks. Although DMPS has similar efficacy to succimer, it is considered an investigational agent by the FDA. In Germany it is sold as tablets and in an IV form (8). Like BAL, for greatest benefit, succimer and DMPS should be given promptly post-exposure. While these compounds are the current first line treatments BAL is indicated in patients with a compromised gastrointestinal tract.

Seventy-five years after its discovery, BAL is only one of two FDA-approved arsenical antidotes and remains on the World Health Organization List of Essential Medicines for the treatment of

heavy metal poisoning (10). Even though better chelating agents have largely supplanted BAL therapy in modern medicine, it is still commonly used in developing countries. In today's hostile world climate where chemical weapons are a potential threat; lewisite could make an effective terrorist weapon as it can be manufactured with simple pesticide-manufacturing technology (3). Due to this, BAL has an important role that should not be forgotten and should remain stocked in our emergency departments.

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The opinions or associations contained herein are the private views of the authors and do not reflect the views of the Army, the Army Reserve, the Army National Guard, or the DoD.

# Musings from the Chairman,

Spring has sprung and summer is almost upon us. Hope all is well where ever you are. Of course with the sunshine come thoughts of the annual AACC Meeting which this year will be in *Hot'lanta.* We are looking forward to having you all down for our annual family (of sorts) reunion. We will be holding our annual membership meeting and luncheon on Monday the 27th from noon until 2:00 at the Hyatt Regency. Please check your program for the specific room name. This year the meeting will feature our 3 abstract award winners as well as a presentation from last year's winner, Dr. Mark Marzinke.

Also this year, in an effort to provide younger members of AACC opportunities to build connections and relationships within the Divisions we have donated 5 annual division memberships to be raffled off during the SYCL mixer on Saturday 7/25 from 5:30 to 7:30 at the Georgia Aquarium, which is just across the park from the convention center. Feel free to drop in if you'd like.

Again this year Dr. Patrick Kyle has volunteered to lead the TDM/TOX poster walk on Wednesday (7/29) from 12:30 till 1:00. This will be the third year in a row that we have participated in the poster walks. The poster walks can be a great way to learn the latest techniques, see what your colleagues are up to, and to make new acquaintances. I urge you all to attend.

Finally, its election time again. This year we are seeking a new Treasurer and two new members of the nominating committee. The nominating committee is seeking candidates for these offices now and self nominations are acceptable

That's' all for now. Hope to see ya'll next month.

Jim

## Upcoming Conferences

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|---|---|---|---|
| AACC 2015<br>July 26-30<br>Atlanta, GA | ASCLS<br>July 28-Aug 1<br>Atlanta, GA | 2015 Northeast Lab Conference<br>Oct 20-22<br>Portland, ME | G2: Lab Institute<br>Oct 14-16<br>Washington D.C |
| ASCP<br>Oct 28-30<br>Long Beach, CA | | LAB QUALITY CONFAB<br>Nov 3-4<br>New Orleans, LA | |

# Editorial Board



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