

The Story of Dimercaprol and its Use for Treating Wilson's Disease

By Dr Godfrey Gillett

Introduction

In this years newsletter Verity Longley describes her battle with Wilson's disease and how treatment helped. One of the drugs she used was dimercaprol or British Anti-Lewisite. Dr John Walshe wrote an article about this drug in a previous newsletter which is well worth looking up

(www.wilsonsdisease.org.uk/documents/WDSG_Newsletter_vol4issue1.pdf).

I shall go over some of that ground and mention some further points. The reason for this is partly for my benefit, so as to have a further item on the WDSG-UK website to refer doctors and patients to in future.

Discovery

Dimercaprol was a drug discovered in Oxford during the Second World War as an antidote to the war gas Lewisite (www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=190). This arsenical vesicant, the "dew of death", was first synthesised in 1904 and developed in the United States towards the end of the First World War by a chemical warfare research unit led by a Captain Lewis.

There are unconfirmed rumours that Lewisite was used by Japan against Chinese troops in the 1930s. It was feared that it could be used in future conflicts, and in 1939 the Ministry of Supply in the UK commissioned a research group at Oxford to find antidotes to chemical warfare agents, including Lewisite. This successful UK research which resulted in a drug to counteract the effects of Lewisite is recognised by an alternative name for dimercaprol, British Anti-Lewisite (BAL).

The story of the discovery of dimercaprol is described in a fascinating article by one of the principal researchers of the Oxford group, Dr Lloyd Stocken, who died in his late 90's in 2008 ("A contribution to chemical defence in World War II", Margery G. Ord and Lloyd A. Stocken, *Trends in Biochemical Sciences*, 2000;25,5:253-256, doi:10.1016/S0968-0004(00)01578-4).

The development and clinical applications of the drug are discussed in another readable article ("British Anti-Lewisite (dimercaprol): An amazing history", Joel A. Vilensky and Kent Redman, *Annals of Emergency Medicine*, 2003;41,3:378-383, doi:10.1067/mem.2003.72).

Therapeutic uses of dimercaprol

Arsenic poisoning. Fortunately, dimercaprol was not needed as an antidote to Lewisite during WW2 and was rapidly exploited in medicine, initially as an ointment in industrial arsenical accidents and, given intramuscularly, to counter some of the side-effects of arsenical drugs used in the treatment of syphilis.

Heavy metal toxicity. It was soon found to increase the urinary excretion of some heavy metals, e.g. mercury and gold, and was used successfully to treat mercury bichloride ingestion and the toxic effects of gold salts used in rheumatoid arthritis. Its use for treating Wilson's disease was suggested by Professor J. N. Cumings in his seminal 1948 article ("The copper and iron content of brain and liver in the normal and in hepatolenticular degeneration", *Brain* 1948;71:410-415, doi:10.1093/brain/71.4.410) on the basis of a serendipitous observation by B. M. Mandelbrote *et al.* (*Brain* 1948;71:212-228, doi:10.1093/brain/71.2.212).

Wilson's disease. The increase in copper excretion in Wilson's patients was subsequently demonstrated by Cumings and others (H. Porter, D. Denny-Brown). As Dr Walshe mentions in his WDSG article, dimercaprol was effective treatment for some but not all Wilson's patients and the beneficial effect tended to wear off. It was one such patient under the care of Professor Denny-Brown in Boston, Massachusetts whom Dr Charles Davidson was asked to see (while Dr Walshe was a Fulbright Fellow in his unit) who proved the clinical inspiration to

Dr Walshe to consider penicillamine for the treatment of Wilson's.

Penicillamine (and later trientine, tetrathiomolybdate, and zinc salts) became the principal drugs used in Wilson's from 1956 onwards. But in the late 1970s, Professors Herb Scheinberg and Irmin Sternlieb, the pioneers of Wilson's disease investigation and treatment in the USA, discovered that dimercaprol in combination with penicillamine could help

patients with neurological Wilson's especially where there was marked dystonia or rigidity. Dystonia is the term used to describe involuntary, sustained contractions of muscle where agonist and antagonist groups contract together and there is overflow of contraction into adjacent muscles. They discuss the treatment of this type of 'desperately ill' patient in their comprehensive textbook, (dedicated to Dr Walshe) "Wilson's Disease", (Major Problems in Internal Medicine, vol. 23, WB Saunders 1984, pp 145-8, ISBN-13 9780721679532).

The regime which they found to work was a combination of adequate nutrition (by nasogastric tube), high-dose penicillamine (2 g/d) and dimercaprol. Dimercaprol is poorly soluble in water so has to be dissolved in oil, which is peanut (arachis) oil in the preparations available in the USA and UK. Oily injections cannot be given intravenously and have to be given into muscle. This is very painful (as Verity found) and the injections are given daily for at least a month. The dimercaprol dose they recommend is 300 mg daily, five days a week for one to two months. Then a break for a week or two, and repeated, if there has been clinical improvement. Patients understandably get fed up with the course and doctors have to be flexible (e.g. allowing earlier breaks). Dr John Walshe and Dr N. A. R. Munro used this combination to treat a severely affected patient at the Middlesex Hospital who made a remarkable recovery (*Archives of Neurology*, 1995;52:10-11). It has been used occasionally since, usually when recommended by Dr Walshe to the patient's neurologist.

Formulations of dimercaprol

The dimercaprol used in the USA is made by Akorn Inc. (www.akorn.com) and is supplied as a 3 ml vial containing 300 mg. This is convenient for Wilson's treatment since it is one or two injections of the contents of one vial daily. Unfortunately, the preparation available in the UK from Sovereign Medical (www.amdipharm.com) is half this strength, 50 mg/ml, 2 ml vial. This means that patients in this country have to have twice the number of injections (since you can't reasonably give 6 ml as a single intramuscular injection). I've drawn this to the attention of the Drug Information pharmacists in Sheffield and we hope that it may be possible to import some of the more concentrated Akorn product for use in the UK.

Wouldn't it be much easier if the drug could be given intravenously, into a vein? Cambridge Professors R.A. McCance and his colleague E. M. Widdowson evidently thought so, and published their studies of the use of "BAL-Intrav" in the journal *Nature* in 1946 (doi:10.1038/157837a0). BAL-Intrav is dithioglycerol glucoside in a 25% solution and human volunteers were able to tolerate doses of up to 1 g. It causes a significant urinary excretion of copper, as least in sheep (the next paper in that issue of *Nature*, by Dr L. W. McDonald, doi:10.1038/157837b0). These very early reports were not exploited in the treatment of Wilson's patients and dithioglycerol glucoside isn't currently available. Perhaps it should be.

Another way of making drugs which are only soluble in oil suitable for intravenous injection is to make an emulsion. This technology is well-developed and several lipid-soluble drugs are supplied in this way. These include diazepam, the sedative, muscle-relaxant and hypnotic ('Diazemuls') and the short-acting anaesthetic agent, propofol. Preparing the emulsion is like making mayonnaise, only instead of using egg yolk, manufacturers get the water, drug and oil to mix using purified egg phosphatide (among other ingredients).

What we don't know, of course, is whether by making the dimercaprol more water-soluble or water-miscible, it may lose some or all of its beneficial effects in getting copper out of the brain (a very fatty structure) or of protecting the brain from the arsenical-like actions of copper. But we can only try and see.

A successful outcome for Verity

Congratulations to Verity for putting up with two courses: the excellent outcome must be due to her determination to get well in addition to the drugs. I suspect that an important aspect of successful treatment of poorly patients is to ensure that they get adequate nutrition and maintain their weight. Verity's dietitians in Southampton, Sarah Deacon and Nadine Hodgson, rose to that challenge and laboured to produce a copper-free feed that could be given first through the nasogastric tube and then through the percutaneous enteral gastrostomy or PEG. I hope that they will describe this in an article in a dietetic journal and maybe write a summary for us.

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