BRITISH ANTI-LEWISITE

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The outstanding achievement in the field of chemical warfare research in World War II was the discovery by Peters, Stocken and Thompson of the antidotal action of 2,3-dimercaptopropanol (British anti-lewisite, BAL) to lewisite and other arsenical compounds. The view that the toxic action of trivalent arsenical compounds is related to their reaction with essential thiol groups in the organism was advanced by Voegtlin, Dyer and Leonard in 1923. These workers also found that under suitable conditions certain monothiols can diminish or prevent the toxic action of arsenical compounds. The outbreak of World War II provided a stimulus for the search for antidotes to arsenical compounds, and in particular to chemical warfare agents such as lewisite (β-chlorovinyl-dichloroarsine). In 1940, Peters, Stocken and Thompson, in the course of a study of the interaction of lewisite and the thiol groups of kerateine, found that most of the arsenic in the derived protein was combined with two thiol groups and they were led to the conclusion that "simple dithiol compounds might form relatively stable ring compounds with lewisite and other trivalent arsenical compounds and so compete successfully with 'dithiol' proteins in the tissues". This, in turn, led to the important finding that the dithiol, 2,3-dimercaptopropanol is highly effective in preventing the local and systemic actions of lewisite.

Following the receipt of early accounts of the Oxford workers, it was decided to undertake a comparison of the toxicity of BAL and its antidotal activity in lewisite poisoning with those of a series of related compounds. For this purpose the following thiols were synthesized:

1,2-dimercaptoethane,
1,3-dimercaptopropane,
1,2-dimercapto-n-butane,
2,2'-dimercaptodiethyl ether,
and 3,3'-dimercaptodipropyl ether.
1,2-dimercaptopropane,
1,2,3-trimercaptopropane,
1,3-dimercapto-2-propanol,
2,2'-dimercaptodiisopropyl ether

The compounds, together with 1- and 2-mercaptopropane, 2-mercaptoethanol, and 2,3-dimercaptopropanol, were tested for their toxicity and their activity as antidotes to lewisite when applied to the skin of the rat. None of the compounds tested was found to be superior to BAL as an antidote to lewisite. Although none of the monothiols tested showed antidotal activity under the above conditions, all the dithiols and the trithiol studied gave evidence of some antidotal activity. Only in the case of 1,3-dimercapto-2-propanol did this activity approach that of BAL, however, and this compound proved to be much more toxic than BAL.

After being dosed with lethal amounts of lewisite on the skin, rats usually die within twenty-four hours. The lives of the animals are almost always saved, however, if BAL is applied to the dosed area of skin not later than two hours after dosing with lewisite. Even when treatment with BAL is delayed for longer than two hours after dosing with lewisite, the animals sometimes survive. Protection against the systemic effects of lewisite in rats also occurs when BAL is applied to a skin site other than that contaminated with lewisite or when BAL is applied to a skin site two hours, or sometimes even longer, before lewisite is applied to another area of skin. This prophylactic action can be explained by the fact that BAL is absorbed very slowly from the skin of the rat.

The Oxford workers found that there is an increased urinary excretion of arsenic after the administration of BAL to rats dosed with lewisite. This observation has been confirmed and extended. When BAL is applied to a skin site contaminated with lewisite, the urinary excretion of arsenic is increased. This is also true when the BAL is applied to a separate site or given by intramuscular injection. If the BAL is not administered until some hours after the lewisite, there is much less effect on the faecal excretion of arsenic. Although BAL exerts an antidotal action in sodium arsenite poisoning, its influence on the arsenic excretion under these conditions is slight.

It was decided to use radioactive sulphur as a tracer isotope in a study of the fate and absorption of BAL in the organism. Radioactive BAL, i.e., 2,3-dimercaptopropanol with radioactive sulphur (S^{35}) incorporated in the molecule, was synthesized by allowing 2,3-dibromopropanol to react in methanol with sodium hydrosulphide which had been prepared from hydrogen sulphide containing H_2S^{35}.

By the use of radioactive BAL, it was shown that BAL penetrates skin rather slowly. The average rate of percutaneous absorption of BAL in the rat over a period of six hours was found to be 0.38 mg./cm.^{2} of skin/hour. The rate of absorption of BAL from human skin over a period of three hours was found to be of the same order. When radioactive BAL is injected intramuscularly into rats, it soon passes from the site of dosing, for little S^{35} is present in the dosed muscle six hours after injection.

When radioactive BAL is administered to rats percutaneously or intramuscularly, S^{35} is distributed throughout the organism. The concentration of S^{35} is slightly higher in the intestine and its contents and in the kidney, but otherwise it does not appear to accumulate in any of the main organs. A striking feature of these experiments is the rapidity with which S^{35} is excreted in the urine. For example, after an intramuscular injection of 20 mg. of radioactive BAL in propylene glycol, the amount of S^{35} present in the urine at six hours after injection corresponded to about one-half, and at 24 hours to over

three quarters of the radioactive BAL administered. When radioactive BAL is administered to the rat by application to the skin, a similar rate of excretion is observed.

Most of the S^{35} excreted in the urine of rats, following the administration of radioactive BAL, is present in the form of neutral sulphur. It was found, by means of an isotope dilution experiment, that following the administration of 20 mg. of radioactive BAL in propylene glycol, less than 1% of the administered BAL was present in the urine in the unchanged form six hours after dosing.

Apart from its use as an antidote to lewisite, it has been shown by several investigators that BAL is of value in the treatment of some of the toxic actions brought about by therapeutic arsenical agents. It has also been used successfully in cases of mercury poisoning. The results of experiments with animals indicate that BAL is of value in preventing the development of pulmonary lesions after the inhalation of lewisite, cadmium or zinc fumes and is therapeutically active against the systemic toxic actions of antimony, gold, bismuth, chromium and nickel.

In the case of poisoning by certain of the heavy metals, other dithiols appear to be more efficacious than BAL. Furthermore, when BAL is administered to man by intramuscular injection in oil at a higher concentration than 3 mg. per kg., various toxic reactions are experienced. In an effort to find a relatively non-toxic substitute for BAL, Danielli and co-workers prepared the glucoside of BAL (BAL-INTRAV). This compound affords a high measure of protection against lewisite poisoning and its toxicity has been found to be extremely low when given by intravenous injection. However, BAL-INTRAV has proved to be difficult to prepare in the pure state and is rather unstable. There is evidence that BAL is excreted as the glucuronide when administered to rats. This suggests that when BAL is administered in cases of heavy metal poisoning, the metal may be excreted in the form of the metal BAL glucuronide. It is possible, therefore, that BAL glucuronide would prove to be much superior to BAL.