Trivalent Arsenic Compounds

| [P. 31] Tabellae Carbarsoni (B.P.C.). Contain 4 gr. (0.25 g.) unless otherwise stated. |
| [P. 31] Carbarsone Vaginal Suppositories (Lilly). Each containing carbarsone 2 gr. in a glyco-gelatin base. For Trichomonas vaginalis infection. |

**Tryparsamidum (B.P.). Syn. GLYPHENARSINUM, TRYPARSONUM.**

Sodium N-phenylglycineamide-p-arsonate. 

\[ \text{Na(OH)}_2 \cdot \text{AsO}_2 \text{C}_6 \text{H}_4 \text{NH} \cdot \text{CH}_2 \cdot \text{CONH}_2 \cdot \text{H}_2 \text{O} = 305 \text{. I.} \]

**Dose.**—15 to 30 grains (1 to 2 g.) by subcutaneous, intramuscular or intravenous injection. Up to 45 grains may be given for a dose.

White, odourless, crystalline powder. The dried substance contains 25.1 to 25.5% of As.

**Soluble** 3 in 10 of water, forming a neutral solution; almost insoluble in alcohol 95%, chloroform, ether, and benzene. Should be stored in small, well-closed containers, protected from light, in a cool place.

**Antidotes.** As for Neosarphenamine, p. 211.

**Toxic Effects.** The arsenical and direct toxicity of tryparsamide is low, even minor disturbances are rare, though dizziness and tinnitus may sometimes occur, and occasionally there may be vomiting and slowing of the pulse rate immediately after an injection. Rarely, toxic hepatitis may occur. On the other hand even the smaller therapeutic doses may produce impairment of vision which in most cases is of a minor and temporary character but may sometimes become serious and even result in blindness. The occurrence and outcome of these visual disturbances are unpredictable and unavoidable, though they most frequently occur after the first injection and seldom after the fourth injection. Blurring of vision is a contraindication to further treatment, and the drug should be employed with caution in neurosyphilis with involvement of the optic nerve.

Optic neuritis following 2 small doses of tryparsamide in a patient with tuberculous meningitis successfully treated with dimercaprol.—S. Friedenkrig, J. Amer. med. Ass., 1947, 134, 1072.

**Uses.** Tryparsamide is highly effective in trypanosomiasis due to *T. gambiense* infection; it is less effective in infection due to *T. rhodesiense*, except when the nervous system has become involved. It also has some specific activity and has an unusual power of penetration especially into the central nervous system. For this reason it is employed in the treatment of neurosyphilis, the standard course being obtained in early dementia paralytica and tabes. It is not effective against the primary or secondary stages of syphilis. It is also extensively used as a follow-up treatment after malaria therapy in syphilis of the central nervous system. Tryparsamide is usually given by intravenous injection, the injection being freshly prepared. It should not be given by mouth. In the treatment of trypanosomiasis it is given in doses of 15 to 45 gr. (1 to 3 g.), depending on the weight and condition of the patient, for a course of 8 or 10 weekly injections. A similar course of injections is employed in the treatment of neurosyphilis and may be used in conjuction with penicillin therapy.

Intravenous drip in treatment of trypanosomiasis was used in 72 cases. About 2 g. to 2 pints of water was given daily for 5 to 9 days. Results appeared to be satisfactory—A. F. Fowler, Trans. Soc. trop. Med. Hyg., 1947, 40, 763.

**[P. 31] Injectio Tryparsamidii (B.P.).** Prepared by dissolving the contents of a sealed container in water for injection immediately before use.

**Bismaride (May & Baker).** Bismuth tryparsamide, containing 14.5% As and 10.5% Bi. Ampoules contain 2 ml. of 5% solution; for intramuscular injection in neurosyphilis.

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**Arsenum**

**Argentica (Fr. Cx., P.G. and others). Syn. ARSENOBENZENE, ARSENOBENZOL, ARSENOBENZOLIUM CHLORHYDRICUM, ARSENOBENZOLIUM, AMINO-ARSENIC PHYLOR, SALVASEAN, "606".** Dioxydiaminoarsenobenzenedihydrochloride, diaminohydroxyarsenobenzenedihydrochloride. \[ (\text{HO})_2 \text{C}_6 \text{H}_4 \text{NH}_2 \text{As}, \text{H}_2 \text{O} = 475 \text{. I.} \]

**Dose.**—1 to 10 grains (0.5 to 0.6 g.) by intravenous injection.

Light yellow, odourless or almost odourless, hygroscopic powder. If discarded—either grey or brownish—it must not be used.

**Soluble** 1 in 5 of water, forming a thick, syrupy liquid, acid to litmus, but not acid to candied red paper; 1 in 3 of methyl alcohol, 1 in 12 of alcohol, and in glycerin. Slightly soluble in chloroform and ether. It is distributed in sealed containers. Should be stored below 15°.

**Antidotes and Toxic Effects.** As for Neosarphenamine, see below.

**Uses.** Although arsenophenamine has been proved the more effective drug in the treatment of acute and early syphilis, because of the difficulty of its preparation for injection and its greater toxicity, it has been almost entirely replaced by neosarphenamine and the arsenoxides.
include flushing of the face, a burning taste, edema of tongue and eyelids, nausea, vomiting and perspiration; dyspnea, cyanosis and precordial distress sometimes occur, and, in severe cases, unconsciousness. These symptoms usually disappear within 30 minutes, and may be avoided or treated by injection of adrenaline. Later reactions, commencing 1 to 4 hours after the injection, and known as Herxheimer reactions, consist of fever and an exacerbation of the symptoms, especially an intensification of secondary skin rash. These reactions usually pass off in about 2 hours and are unlikely to be dangerous, except in tertiary syphilis. They may often be prevented by starting treatment with small doses of neosaphenamine.

Dermatitis or other skin eruptions may develop in from 1 to 14 days; these generally subside within a day or two, but the more dangerous exfoliative dermatitis may sometimes occur, often in conjunction with severe nephritis. Development of dermatitis may often be prevented by discontinuation of the drug at the first sign of itch or rash, and the immediate withdrawal of about 1/2 pint of blood. The most effective treatment for an established dermatitis is injection of dicyclopiro. Occasionally, severe, and even fatal, reactions set in from a few days to several weeks after administration; these include jaundice, acute yellow atrophy of the liver, acute purpura, aplastic anemia, and agranulocytosis. Severe nervous manifestations may occur after an interval of weeks or months of treatment; these include cranial nerve palsy and neuritis of the auditory, optic and facial nerves; these are generally regarded as being of syphilitic rather than of arsenical origin and their occurrence calls for more vigorous arsenical medication.

**Agranulocytosis** in 6 cases after neosaphenamine treatment of syphilis. One patient showed depression of all marrow elements. An increased absolute number of monocytes was found in 3 cases which recovered, but not in 2 fatal cases. Pneumonitis appeared in 3 cases of which 2 died, the 3rd patient recovered. Recovery followed treatment with ampicillin and bismuth. Recovery followed treatment with penicillin and streptomycin. Treatment cases included 10 ml. 3 times a day. Increased 50 ml. daily.

**Hemorrhagic Encephalopathy** occurring in 4 cases as a complication of treatment with arsenic in syphilis; 2 of these were pregnant women. Although it is impossible to determine in advance the type of individual who will develop this rare complication, the pregnant woman with syphilis should be regarded as a potential reactor. Clinical symptoms of cerebral hemorrhage may vary from headaches and visual disturbances to coma and death. The condition is rapidly fatal unless diagnosis is prompt and treatment instituted. 

**Thrombocytopenic Purpura**. A case of severe and acute symptoms and great reduction in the platelet count following injection of neosaphenamine in a congenital syphilitic. G. M. Lewis, Brit. med. j., 1944, 12.

**Contraindications**. Addison's disease and hemophilia. Small initial doses and extracutaneous injections are necessary in alcoholism, cachexia, renal and cardiac lesions and where there is a tendency to eczema.

**Uses**. Neosaphenamine has almost entirely replaced arsphenamine in the treatment of syphilitic infections owing to its relatively high doses and extracutaneous injections. It is used in the treatment of syphilitic infections owing to its relatively high doses and extracutaneous injections. It is found to have about two-thirds the activity of arsphenamine and it is given intravenously, since intramuscular injections are painful, although the pain is reduced by using as solvent a solution of guaiacol 1, dextrose 50, sterile water to 100. For intramuscular injection, sulfaphenamine is preferable.

In a case of early syphilis the initial dose of neosaphenamine for a man of average weight is 0.45 g., increasing to 0.6 g., to a total of 1 ounce of arsenicaceous. The injections are given at weekly intervals, and the interval between doses varies from 4 to 12 weeks. The number of courses required is determined by the serological reaction. The neosaphenamine treatment is used in conjunction with penicillin, or with bismuth or mercury preparations, and these may be given at the same time (the alternating method) or in the intervals between courses (the intermittent method).

The standards of treatment laid down by the League of Nations Committee in 1934 are now almost universally accepted. They include:—(1) a loading dose; (2) preliminary physical examination to determine the absence of any indication for caution in dosage; (3) strict supervision of the patient, skin, kidneys, and liver to avoid toxic effects; (4) a comprehensive and continuous examination of the arsenic and mercury compounds to be given, the doses being administered in comparatively rapid succession, especially at the commencement; (5) persistent attack on the disease, avoiding intervals of such length as to afford the parasite an opportunity of recovery; (6) approximately as rapidly as possible, clinical and serological, after completion of treatment should be for at least before dismissal from observation.

In addition to its use in syphilis, neosaphenamine is successfully employed in the treatment of other treponemal diseases. The treatment is not as effective as for syphilis. Vincent's angina and gangrenous ulcers are arrested by a single intravenous injection, the pain subsiding within a few hours and the inflammation subsiding within a few days; alternatively, daily applications of a 5 or 10% solution in glycine may be employed. Relapsing fever and rat-bite fever also respond well to neosaphenamine. In anthrax, one injection of neosaphenamine is often sufficient to effect a cure, though it is preferably given as an adjunction to serum treatment.

**Abacterial Pyuria**. Neosaphenamine has proved of value, 0.2 to 0.3 g. being given intravenously, at five-day intervals. E. N. Cook, Proc. Mayo Clin., 1944, 1937. Three cases responded promptly; cases of 100 with a single injection of neosaphenamine, 1938, 1939, 1940, 1941.

**Typhus**. Nine patients with pustular anthrax were successfully treated with neosaphenamine only. Eight of the 10 aged 1 and 5 years died. The results were, however, less than satisfactory. The only significant side-effects were those attendant on intravenous arsphenamine therapy, such as fever and general malaise, which may persist for a few weeks. The results were, however, less than satisfactory. The only significant side-effects were those attendant on intravenous arsphenamine therapy, such as fever and general malaise, which may persist for a few weeks. The results were, however, less than satisfactory. The only significant side-effects were those attendant on intravenous arsphenamine therapy, such as fever and general malaise, which may persist for a few weeks. The results were, however, less than satisfactory. The only significant side-effects were those attendant on intravenous arsphenamine therapy, such as fever and general malaise, which may persist for a few weeks. The results were, however, less than satisfactory.
unsatisfactory. A course of 3 or 4 injections at intervals of 5 to 7 days brought the relapse rate down to 17-4% (29 cases). Two injections produced a relapse rate of 38-8% (13 cases) while one injection given during the fever, produced a relapse-rate of 33% (34 cases). Dosage was 0-6 g intravenously. — N. F. Coghlin, Lancet, 1/1951, 604.

Tropical Eosinophilia. In 58 cases arcainols were found to be specific and rapid affecting patients with eosinophilia in every fourth day for 6 doses. Acellular arsanil Stavudini was also used successfully. — R. J. Weiniger, Lancet, 1/1943, 315.

Five cases of eosinophilia, combined with pulmonary disease, all responded by complete resolution of eosinophilia and fall of blood eosinophils, to a course of neoparsenic acid injections, 3 of 0-5 g followed by 3 of 0-5 g given intravenously with saline and calcium glucosate, at 3- to 10-day intervals. — J. Apley and G. H. Grant, Lancet, 1/1943, 312.

High eosinophilia with bronchitis and asthma in 25 patients, was treated with arsenical arsanil; all but one patient responded rapidly, with a great reduction in eosinophilia and cessation of clinical symptoms. — H. F. Carter and V. St. E. D'Aubra, Trans. R. Soc. trop. Med. Hyg., 1948, 35, 573.

Six of 9 cases of eosinophilia were successfully treated with arsenic and the seventh responded spontaneously. — H. T. H. Wilson, Brit. med. J., 11/1947, 801.

Vincent's Angina. The condition responds to local treatment with neoparsenicum 0.1% in 29.4 ml of water, or arsanil solution and glycerin in equal parts. R. G. Evans, Practitioner, 1948, 161, 140.

[PI-11] Injectio Neoparsenicum (B.P., N.F. 1952). Prepared by dissolving the contents of a sealed container in water for injection and should be used within 5 minutes of preparation.


[PI-12] Oxeparsenic Hydrochloridum (B.P. Add.). Syn. ARSENIBENOXID. HYDROCHLORIDUM

The hydrochloride of 3-amino-4-hydroxybenzenesulfonate oxide,

\[ (\text{NH}_2)_2\text{C}_6\text{H}_4\text{(OH)AsO}_2\text{HCl} = \text{235.5 g/mol}. \]


Dose — 1 to 1 gram (20 to 60 mg) by intravenous injection.

White or nearly white, colourless, deliquescent powder, containing 29-5 to 32% of trivalent arsenic.

Very soluble in water, solutions of alkalis, and mineral acids; sparingly soluble in alcohol; almost insoluble in acetone, chloroform, and ether. Distributed in closed containers, usually mixed with alkalis and buffers to increase the pH and make it physiologically compatible with human blood. Should be stored in sealed containers at a temperature below 20°.

When sodium carbonate or bicarbonate is added to the aqueous solution, carbon dioxide is evolved and the base precipitated, but the precipitate dissolves on shaking.

Toxic Effects. The toxic effects following the use of oxeparsenic hydrochloride are similar to those arising from neoparsenicum but the effective dose is much less than they are usually milder and of less frequent occurrence. The acute toxic effects are treated with dmercaprol.

When neoparsenicum was used, approximately 1 patient in 3 developed polyneuropathy. In addition there was a high percentage of toxic symptoms, fever, and reactions referred to the gastrointestinal tract. Since Maprasin has been substituted in the incidence to the gastrointestinal tract. Since Maprash has been substituted in the incidence of the reactions has markedly diminished, but (as with neoparsenicum) there have been several cases of hemolytic anaemia, with 2 deaths to date. — F. E. Cornish, Canad. med. Ass. J., 12/1941, 187.

Toxic phenomena occurring during the treatment of 74 patients included pruritus, dizziness, nausea, vomiting, purpura, urticaria, and secondary anaemia. None of these gave cause for alarm. Therefore secondary anaemia and peripheral neuritis. One of these cases was of motor neuritis and jaundice. — B. Craigie and J. F. Sadusky, New Engl. J. Med., 1944, 230, 314.

AGRAVATION. Twelve cases of severe agranulocytosis occurring among some 3000 patients treated with intravenous meparsamine therapy for syphilis. All the patients recovered. — S. Fisher et al., Ann. Intern. Med., 1947, 26, 314.


Contraindications. As for Neoparsenicum, p. 212.

Uses. Oxeparsenic hydrochloride is employed in the treatment of syphilis, and is particularly effective in the early stages, causing the disappearance of spirochaetes, healing of lesions, and reversal of positive Wassermann reactions in a large percentage of cases. As it is effective in much lower dosage than neoparsenicum, it is less liable to give rise to severe reactions. It is administered by rapid intravenous injection of a solution of the required dose in 10 ml of water for injection, the initial dose being 45 mg for men and 30 mg for women. These doses may be increased to 60 mg and 45 mg, respectively at the second dose. For children the dose should not exceed 0.5 mg per kg body weight. As the drug is rapidly excreted by the kidneys injection may be repeated every 3 or 4 days.

Oxeparsenic hydrochloride may also be employed in the treatment of yaws and relapsing fever, and as a local application in the treatment of Vincent's angina.

As the result of administration of 15,000 intravenous injections of Mapharsen to 1400 patients with syphilis it was concluded that Mapharsen is as efficient as the arsphenamines, but the dermatitis was seen. — E. Schmidt and G. G. Taylor, Amer. J. Syph., 1927.

The use of Mapharsen in the treatment of congenital syphilis has much to recommend it, and it is easier to administer and reactions are milder and can be completely avoided. However, the drug is more expensive than the others and it is not recommended for use in treating the severe cases. — R. F. Morgan, Canad. med. Ass. J., 1938, 53.

In all cases of early syphilis the percentage of unsatisfactory results with the arsphenamines in primary syphilis was the percentage of unsatisfactory results with Mapharsen was the percentage of unsatisfactory results with syphilis and neoparsenicum being 39, 49, 203.

A series of 100 cases of syphilis were treated with multiple daily injections of Mapharsen giving a total of 1 g. During this period, the reactions being combated with the primary syphilis, the secondary and tertiary lesions heal very quickly. It has been found that on an average it takes 10 months. In the series of 300 cases there were three serological and clinical reactions — 1944, 69.

In 150 cases of early syphilis Mapharsen was substituted for neoparsenicum in a test patient, and in efficient dosage it is considerably less toxic than neoparasenicum.

Forty-eight patients, and 3 serious complications out of 100 cases of early syphilis were treated. Weekly injections were given at the control; Mapharsen 0.5 mg, 3 times a week for the first month, combined with bismuth injections should be the maximum. — E. R. Ross, Lancet, 1943, 704.

At 12 hours for five days by intravenous drip (total Mapharsen 1.2 g). Satisfactory results were obtained in 75% of cases observed for six months or more. Re-treatment in cases of secondary syphilis is feasible. — H. Craigie and J. F. Sadusky, New Engl. J. Med., 1944, 230, 314.

In 90 days (1800 mg total). Clinical reactions observed in 2 to 3 weeks, and of 56 with glomerular lesions, 4 cases of threatened malignant granulopoiesis, of which returned treatment J. Med., 1944, 230, 314.