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Miscellanea

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Mel B Toxicity in Human Trypanosomiasis in the Gboko Endemic Area of Nigeria

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Abstract

Nine cases of Mel. B (a melaminyl arsenical used in treating sleeping sickness patients who have developed central nervous system involvement) treated patients who developed reactions to the drug are described. They all developed high temperatures, pyrexia, diarrhoea, vomitting or itching and some had convulsions. Three of the nine described patients died. It is recommended that extra care and caution is needed while treating patients with Mel B.

Introduction

At present chemotherapy of African trypanosomiasis is dependent on a relatively small number of synthetic drugs. Suramin and pentamidine are used for prophylaxis and treatment of early stages of the disease in man; organic arsenicals such as tryparsamides and melaminyl compounds for advanced cases, when trypanosomes have invaded the central nervous system.

Resistance has been reported to occur against all these drugs and development of resistance to one compound is often accompanied by cross-resistance to others.

This brief communication describes the occurrence of reactions and idiosyncrasies to the drug Mel B that is currently being used in our retaining Ward in the Gboko endemic area of Nigeria.

History of Mel B

Mel B (melarsoprol B. P.) (Arsobal; RP3854) (C1 2H15As N6 OS2; Mol. Wt. 398.3) (2-p-(4, 6-diamino-1, 3, 5-triazin-2-ylamino) phenyl-4-hydroxy-methyl-1, 3, 2-dithiar solan) is a pale creamy powder insoluble in water, alcohol or ether, but soluble in propylene glycol (in which it is usually administered as a 3.6% solution); propylene glycol solutions are stable to autoclaving (see diagram of drug).

This drug was first tested by FRIEDHEIM (1949) on sleeping sickness patients in French West Africa and he recommmended a treatment course of daily intravenous injections of 3.6 mg/kg for four days followed by an interval of one week and a further course of four similar injections. A 3–4 days interval between injections was advised for very advanced cases, to avoid herxheimer type reactions due to sudden massive destruction of parasites in the central nervous system.

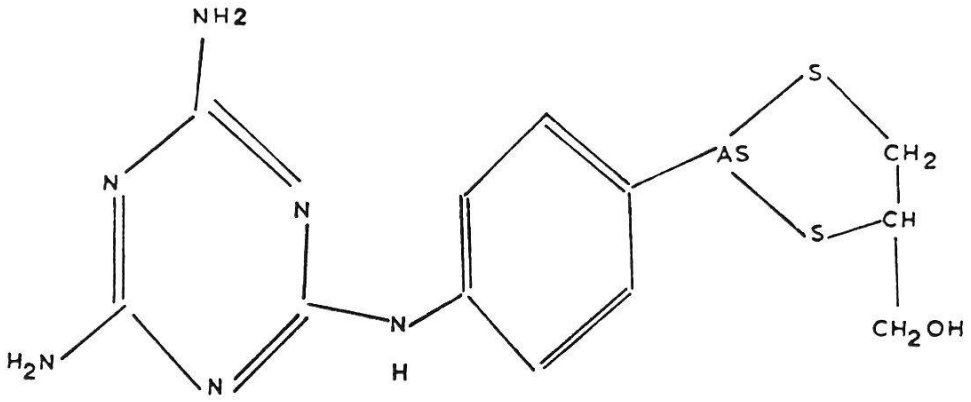
Procedure

Histories from all the patients were taken first. Blood was then collected for capillary-tube agglutination test, haemoglobin estimations and stained thick blood

Table 1. Details of patients with reaction to Mel B

Patient No.	Sex and Age	Weight (Ib)	Diagnosis	CSF. before treatment		Reactions	Remarks
				Cells per c.mm	Proteins mg per 100 ml		
1/72	M: 29	130	Relapsed	68	58	Had 3 courses of Mel B. Rise in temperature and inflammatory reaction on right arm due to leakage of Mel B.	Recovered
2/72	M: 20	130	Relapsed	6	35	Had microfilaria in skin snip, 3 courses of Mel B pyrexia and diarrhoea. Had Tetracyclines and Thalazole.	Recovered
3/72	M: 42	120	Clinical	116	52	3 courses of Mel B. Rise in temperature, diarrhoea.	Recovered
1/73	M: 25	110	G.P. + ve. advanced	688	152	3 courses of Mel B. Rashes and itching, vomitted, high temperature.	Recovered
2/73	M: 40	115	G.P. + ve. early	146	80	Diarrhoea, 2 courses of Mel B, given Thalazole and Creta Aroma.	Recovered
3/73	M: 20	120	G.P. + ve. advanced	661	162	Microfilaria in skin snip, 3 courses of Mel B, diarrhoea, high temperature.	Recovered
1/74	M: 18	110	G.P. + ve. advanced	448	86	2 courses of Mel B. Had fits of convulsions, vomitted, Paraldehyde given.	Died
2/74	F: 11	85	G.P. + ve. advanced	436	50	1 course of Mel B. Convulsions, vomitted, pyrexia, given BAL, Paraldehyde and Sodium Gardener.	Died
3/74	F: 29	120	Clinical	1441	141	3 courses of Mel B, pyrexia in second dose, skin eruptions, itching, septic, given triplopen, high temperature stiff neck, hands and leg; Solumethazine, suta, Asprin administered.	Died

GP + ve: patients with live trypanosomes in their cervical gland juice examined under the microscope



Mel B

films, and serum protein estimations. Non-catheter specimens of urine were tested for the presence of albumin. Positive diagnosis by gland puncture had been made by the survey team and confirmed in the laboratory.

Treatment

Assessment of the stage of the disease was made by a cell count and an estimation of the protein of the cerebrospinal fluid obtained by lumbar puncture. The upper level of normality was taken as 3 cells/mm^3 and 26 mg of protein per 100 ml of C.S.F. (WATSON, 1972). The choice of drug was made when this information was available. When the CSF was abnormal in respect of either the cell count, high level of IgM or the protein content or when the illness has started to show clinical signs, the drug of choice was Mel B.

The course of treatment used was as follows: Mel B: This drug is supplied as a 3.6% solution in 5ml ampoules. The dosage is at the rate of 3.6 mg per kg body weight, but a 5 ml ampoule (which is the dose at the above rate for a 50 kg man) is required at the maximum dose for any single injection, usually in the morning before food. The course consists of 3 or 4 daily intravenous injections followed after an interval of 7–14 days by a second course. The first course, especially in severely ill cases may be reduced and 4 daily injections such as 2.5, 3.5, and 5 ml given to a man of 50 kg or over. Since Mel B can cause renal damage, the urine should be examined for albumin before injection.

Results

Most advanced cases of sleeping sickness with marked central nervous system involvement, who look very weak and inactive rarely have violent reaction to Mel B. Patients who had earlier been treated with any of the available trypanocides such as Melarsen Sodium or Antrypol Tryparsamide mixture (ATm) and have relapsed, usually respond well to Mel B treatment without any serious reactions.

In some cases, patients who have been treated with Mel B (and probably received an under dose) usually fall into relapse. In such patients, when Mel B is used (the correct dosage according to body weight) they tolerate the Mel B very well.

The patients who have developed violent reactions to Mel B include: very early cases, intermediate, that is slightly advanced cases. These reactions also depends on the individuals tissue acceptance to the Mel B. Sometimes, these patients have demonstrable trypanosomes in the cerebro-spinal fluid (CSF), a high cell and protein counts but have no noticeable signs of central nervous system (CNS) involvement.

In all the cases that we have seen, reactions usually occur in the second or third course of the Mel B. Very few cases were recorded that had adverse reactions to Mel B in the 1st course after the first injection. An example was a small girl aged 4 years who developed reaction after the 1st test dose of Mel B. Her temperature went up 104.4°F. Although she ran temperatures on admission but this went down after pretreatment with antrypol.

Table 1 describes in details some of our patients who have developed reactions to Mel B.

Reaction

When reaction occurs, the patients body temperature goes up. He becomes toxic with a thickening of the skin, reddish eyes with complaints of headache, waist pain or pain in the loins. The patient in most cases develop diarrhoea, may vomit, thus becoming drowsy and may pass into convulsions, comma and may die.

Treatment and care of patient

A special watch is always kept on those who start Mel B treatment. Four hourly temperature is always maintained. If the reaction does occur, the patients foot of bed or the head of the patient is kept low to allow saliva to drain in order that the patient does not get chocked. Usually there is rise in body temperature. Cold sponging is performed and the temperature assessed with a clinical thermometer to determine improvement. BAL 2 ml 4 hourly is started at once. Paraldehyde 5 ml intramuscular is given at interval as muscle relaxant.

Toileting of the patients mouth and applying glycerine borax to lips to keep them moist is often done. An in-take and out-put chart is kept. Hartman's solution or glucose saline is given at regulated rate of 30 to 40 drops per minute or more, depending on the severity of the diarrhoea.

Eye ointment is applied to eyes morning and evening. Pressure areas are attended to prevent pressure sores.

The patients that would survive are usually up in two or three days. Others may continue in the state of unconsciousness and die eventually.

Discussion

This short communication is intended to highlight the urgency of the requirement for new prophylactic and curative drugs to combat all forms of trypanosomiasis. Without exception the drugs used at present result from the empirical approach of the chemist to the problem of selective toxicity, and it has to be recognised that this approach has yielded more useful drugs than any other. However, no effective new compound has been introduced recently and many of the drugs developed in the last 20 years were produced by combining portions of known trypanocides (a procedure termed 'hybrid synthesis' by WILLIAMSON, 1962). WHITESIDE (1962) has observed that development of resistance to quartenary ammonium drugs is frequently accompanied by cross-resistance to structurally related substances. This demonstrates the danger of continuing to produce new drugs by 'hybrid synthesis'.

The nine cases described in the table shows the type of reactions that accompanies the treatment and care of trypanosomiasis patients. In 1972, 1973 and 1974, the cases that had Mel B toxicity or reactions were 5.3 and 3 respectively. The majority of the patients recovered from the reactions and the 3 of them died in 1974. The number of patients with the reactions is small compared with the overall cases detected in the Gboko endemic area during the three years under review (1972 had 161 cases, 1973 had 143 and 1974 had 132 cases). This paper demonstrate that care and caution are needed when treating sleeping sickness patients with Mel B.

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