

fering with extracellular lipases before killing the bacteria.

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Coma Associated with Vincristine Therapy

J. A. WHITTAKER, D. H. PARRY, C. BUNCH, D. J. WEATHERALL

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Summary

Three cases of coma after vincristine therapy are described. One patient had hyponatraemia and other features of inappropriate secretion of antidiuretic hormone. The effects were temporary, and full recovery occurred in all three patients.

Introduction

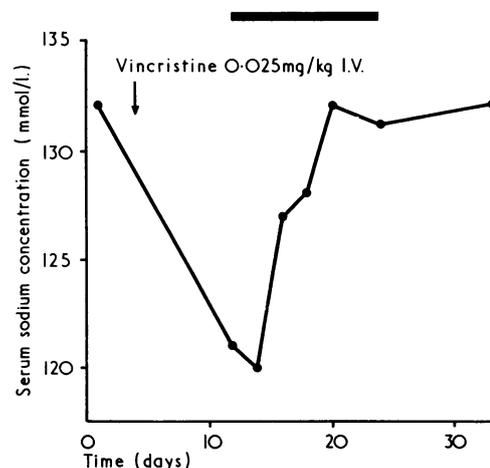
Though vincristine therapy is commonly complicated by a peripheral neuropathy (Finkel, 1967) central nervous system effects have been less frequently reported. Coma is particularly uncommon (Kleinknecht *et al.*, 1967; Loo and Zittoun, 1969; Johnson *et al.*, 1973) and in some patients it has been associated with hyponatraemia ascribed to inappropriate secretion of antidiuretic hormone (Fine *et al.*, 1966; Slater *et al.*, 1969). We report here three further patients with reversible coma after vincristine therapy, one of whom was also noted to have hyponatraemia during the period of unconsciousness.

Case 1

A 65-year-old man was admitted to the University Hospital of Wales on 24 April 1973 with a one-month history of increasing shortness of breath. On examination he was pyrexial (temperature 38.5°C) and a pleural rub was audible at the left base. There was mod-

erate hepatosplenomegaly but no purpura or lymphadenopathy, and a full examination of the central nervous system showed nothing abnormal. Investigations were Hb 9.3 g/100 ml, W.B.C. 15,600/mm³ (23% blasts, 55% atypical monocytes), and platelets 42,000/mm³. A chest x-ray picture showed diffuse bilateral nodular opacities and a small pleural effusion at the left base. Blood and sputum cultures were sterile. Bone marrow examination confirmed a diagnosis of acute leukaemia of undifferentiated cell type.

Treatment was started on the third hospital day with cyclophosphamide (200 mg/m² given intravenously). Next day he was given vincristine intravenously (1.0 mg/m², total dose 1.75 mg) and started on cytosine arabinoside (280 mg/m² given intravenously 12-hourly for two days) and prednisone (40 mg/m² by mouth for five days). He remained well until the 12th hospital day when he became comatose. Next day he was just rousable, but incoherent and disorientated; he remained in this state for 11 days, when consciousness fully returned. Throughout this period there was no clinical evidence of focal neurological abnormality and cerebrospinal fluid examination showed nothing abnormal. An electro-



Serum sodium concentration in case 1. Solid line represents period of unconsciousness.

Department of Haematology, Welsh National School of Medicine, Cardiff CF4 4XW

J. A. WHITTAKER, M.D., M.R.C.P., Senior Lecturer
 D. H. PARRY, M.B., B.S., Senior Registrar

Department of Haematology and Nuffield Unit of Medical Genetics, University of Liverpool, Liverpool L69 3BX

C. BUNCH, M.B., CH.B., M.R.C. Research Assistant
 D. J. WEATHERALL, M.D., F.R.C.P., Professor

encephalogram showed some preponderance of slow waves in the left frontal region. His platelet count ranged from 11,000/mm³ to 77,000/mm³, but there was no overt evidence of bleeding. Hyponatraemia was noted throughout the period of unconsciousness (see graph).

Vincristine was omitted from two further courses of chemotherapy; these were well tolerated, and no further fall in serum sodium occurred. Unfortunately a repeat electroencephalogram was not obtained. He did not have any fits or any further disturbances of consciousness. On the 36th hospital day he died suddenly after a massive pulmonary haemorrhage. At necropsy there was no evidence of abnormality in the brain or central nervous system.

Case 2

A 15-year-old boy was admitted to Liverpool Royal Infirmary on 24 May 1971 with a two-week history of tiredness, loss of weight and pallor. On examination he was very pale, there was right axillary lymphadenopathy and a massive spleen extending below the umbilicus. There were bilateral fundal haemorrhages but no papilloedema, meningism, or other abnormal signs in the central nervous system. Investigations were Hb 5.7 g/100 ml, W.B.C. 500,000/mm³, mostly lymphoblasts, and platelets 22,000/mm³. A chest x-ray picture showed mediastinal widening consistent with lymphadenopathy. The blood urea was 36 mg/100 ml, serum sodium 135 mEq/l., serum potassium 4.4 mEq/l., and uric acid 5.7 mg/100 ml.

On the first hospital day he was transfused, and treatment was started with vincristine (1.4 mg/m² given intravenously total dose 2.25 mg), prednisolone (40 mg/m² by mouth daily), and allopurinol (100 mg three times a day). On the fourth day he became very drowsy, but on examination no obvious cause for this was found. There were extensive fundal haemorrhages, generalized hypotonia, normal reflexes, and flexor plantar responses. There was no meningism or any localizing neurological signs, and he remained apyrexial. His W.B.C. had fallen to 257,000/mm³ and the size of his spleen had reduced markedly. His blood urea was 40 mg/100 ml, serum sodium 134 mEq/l., serum potassium 4.9 mEq/l. and blood sugar 122 mg/100 ml. The episode was thought to be most likely due to intracranial haemorrhage, and multiple platelet transfusions were given over the following week.

On the seventh day there had been no improvement, and cerebrospinal fluid examination showed nothing abnormal. Later that day his consciousness returned, and he became quite rational. No neurological signs were found on clinical examination. After 14 hours of normal consciousness he lapsed into coma again, and remained in this state for a further two days, during which time he was noted to have absent reflexes, extensor plantar responses, and unequal pupils. A brain scan carried out on the 10th hospital day showed nothing abnormal. Recovery was complete and treatment was resumed with vincristine (10 further doses of 2.25 mg given intravenously at intervals of from two to four weeks) and prednisolone. No further problems were encountered, and a haematological remission was eventually obtained. No epileptic fits were known to have occurred. One year later, however, he relapsed and died with evidence of meningeal leukaemia. Postmortem examination was refused.

Case 3

A 71-year-old woman was admitted to the University Hospital of Wales on 31 January 1973 complaining of generalized abdominal discomfort and a productive cough. On examination there was moderate congestive cardiac failure, lymphadenopathy involving the neck, both axillae and groins, and coarse crepitations at both lung bases. Investigations were Hb 10.7 g/100 ml., W.B.C. 14,600/mm³ (normal differential), and platelets 85,000/mm³. A chest x-ray picture showed patchy consolidation of both lung bases, and a streptococcus was grown on sputum culture. The cardiac failure was treated with digoxin and frusemide, and her chest infection with erythromycin. A diagnosis of Hodgkin's disease was made on lymph node biopsy, and on the third hospital day treatment was begun with vincristine (1.4 mg/m², total dose 2.10 mg) and prednisone (25 mg/m² daily).

Ten days later she became comatose and remained so for five days. For a further 10 days she was drowsy but easily roused, with eventual full recovery. She had no epileptic fits and at no time were focal neurological abnormalities detected, and cerebro-

spinal fluid examination showed nothing abnormal. Serum electrolytes were estimated on several occasions, but were always normal. Her improvement was maintained, but one month later she developed a fatal bronchopneumonia. At necropsy there was atheroma in the main cerebral vessels, but the brain and central nervous system were otherwise normal.

Discussion

Since its introduction vincristine has been used extensively and successfully in the treatment of malignant diseases, particularly lymphomas and acute leukaemia. Side effects are common but are usually transient or reversible, and are regarded as acceptable in view of the drug's undoubted efficacy in situations of grave prognosis. The peripheral neurotoxicity of vincristine is well described: in most patients a mild reversible peripheral neuropathy occurs, with loss of deep tendon reflexes, muscular pains, and parasthesiae. Objective sensory loss (Whitelaw *et al.*, 1963), muscular weakness (Costa *et al.*, 1962), and autonomic dysfunction (Finkel, 1967) are somewhat less frequent, and irritability (Council on Drugs, 1965), mental depression (Karon *et al.*, 1962), convulsions (Kleinknecht *et al.*, 1967; Grobe and Palm, 1972; Johnson *et al.*, 1973), and coma (Kleinknecht *et al.*, 1967; Loo and Zittoun, 1969; Slater *et al.*, 1969) are rare.

In several ways the cases reported here resemble other reported cases of coma or convulsions after vincristine therapy. The onset is usually a few days after an injection of vincristine recovery seems to be complete and, as shown by case 2, further treatment with vincristine may be tolerated without recurrence (Johnson *et al.*, 1973). Furthermore in a proportion of patients coma or convulsions have been associated with hyponatraemia (Fine *et al.*, 1966; Loo and Zittoun, 1969; Slater *et al.*, 1969) and this has been ascribed to inappropriate secretion of antidiuretic hormone (Slater *et al.*, 1969).

The mechanism of coma after vincristine therapy remains obscure. In no patients so far described have focal neurological lesions been substantiated, and though no deaths have occurred from this complication, postmortem examination of patients who have died subsequently has been consistently unhelpful. Indeed vincristine has been implicated as a cause of coma and convulsions as much through a lack of other demonstrable cause as through an appreciation of its other, more substantiated, neurological side effects.

The suggestion that inappropriate antidiuretic hormone secretion occurs in a proportion of patients suggests either that two separate mechanisms are involved or that a single mechanism may be operative at the cellular level producing different clinical effects depending on the susceptibility of the various cells involved. This latter possibility may explain the development of coma in some and convulsions in others, and hyponatraemia in some patients from both groups. The duration of hyponatraemia is much shorter than that associated with inappropriate secretion of antidiuretic hormone from other causes (Haden and Knox, 1965) and this would be in keeping with the removal of a causative agent. The observation that recurrence does not inevitably follow reintroduction of vincristine remains to be explained. In case 1 inappropriate antidiuretic hormone secretion was suspected because the patient showed most of the important features of this syndrome (Haden and Knox, 1965)—hyponatraemia in association with a urine hypertonic with respect to plasma, in the presence of normal renal function and in the absence of hypotension, dehydration, uraemia, and clinical oedema. Serum osmolality was not measured directly in this patient, but it can be approximated closely by doubling the sum of the serum sodium and potassium concentrations (Haden and Knox, 1965).

Inappropriate antidiuretic hormone secretion could be caused by interference with the function of hypothalamic cells controlling the secretion of the hormone, or by a direct action on the neurohypophyseal tract or the posterior pituitary itself. In cases where coma or convulsions occur without electrolyte abnormalities some other site of action must be involved.

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MEDICAL MEMORANDA

Candida albicans Septicaemia during First Half of Pregnancy Successfully Treated with 5-Fluorocytosine

J. SCHÖNEBECK, E. SEGERBRAND

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Cases of intrauterine candida infection during pregnancy are probably very grave and not too rare. They are likely to result in a dead fetus and a spontaneous abortion (Albarracin *et al.*, 1967; Aterman, 1968; Lopez and Aterman, 1968; Ho and Aterman, 1970). In these cases the infection is generally believed to ascend from the vagina. Cases of yeast fungus septicaemia during pregnancy are probably extremely rare. However, they present great therapeutic problems, as the antimycotic drugs available—above all amphotericin B—are so toxic that their use involves a great risk for the patient and probably an even greater risk for the fetus.

We recently treated a case of *Candida albicans* septicaemia during pregnancy successfully with 5-fluorocytosine (5-FC).

Case Report

A 22-year-old woman suffered from hyperemesis gravidarum during her first pregnancy in 1970 which ended in spontaneous abortion. In 1971 she was again pregnant, having had her last menstruation on 3 November 1971. At the end of December she suffered from a pronounced hyperemesis gravidarum, which necessitated admittance to hospital. Her symptoms grew worse and intravenous nutrition had to be given. A central venous catheter was placed in the superior vena cava and remained there until 22 February 1972. At the end of January 1972 she got septic fever. Ampicillin was given intravenously, and the temperature was temporarily reduced. On 9 February, however, she got chills and rising septic fever. Cloxacillin treatment was then instituted. Blood culture at that time showed a pure culture of *C. albicans*, and oral nystatin treatment, 1,000,000 I.U. three times daily, was started. The fever was slightly reduced, but on 16 February the patient again got chills and her general condition was strongly affected. Again blood culture showed a pure culture of *C. albicans*. The nystatin administration was stopped, and on 16 February 600 mg of 5-FC was given as an intravenous infusion. On 17 February this treatment was substituted by oral administration of 5-FC, 2 g four times daily. Next day she was free from fever. Her general condition improved rapidly,

and she was able to take food per os. The central venous catheter was removed on 22 February. Culture from the tip of the catheter showed growth of *C. albicans*. The patient recovered completely and was discharged on 17 March. She had received a total dose of 52.6 g 5-FC.

Even before the institution of 5-FC therapy the patient's SGPT values were increased. After stopping the treatment they returned to normal. The complement fixation test for *Candida* was positive. On 21 February the serum concentration of 5-FC was 25 µg/ml.

Subsequently the patient's pregnancy advanced quite normally, and on 25 July 1972 she gave birth to a normally developed girl (birth weight 2,940 g, length 48 cm). The child's progress was followed in the usual manner during the first seven months after delivery and was completely normal.

Comment

There is no doubt that the central venous catheter was the cause of the patient's candida septicaemia. It was removed during the course of treatment, and on culture from the tip of the catheter there was growth of *C. albicans* in spite of adequate serum concentration of 5-FC (25 µg/ml). The reason for this is that the antimycotic drug does not reach adequate concentration on the surface of a foreign body. Thus, in intravenously nourished patients who develop yeast fungus septicaemia, the first step to be taken should be to remove or exchange the central venous catheter.

Yeast fungus septicaemia during early pregnancy is probably not a common condition. In reviewing the literature we have found only one similar case. This also occurred in connexion with a severe hyperemesis which necessitated intravenous nutrition. To save the patient first an abortion was induced and then amphotericin B treatment given. In this case the fungus was *Torulopsis glabrata* (Hahn *et al.*, 1968).

In these cases the problem of appropriate treatment is a very difficult one. Until now there has been nothing but amphotericin B treatment to be given. This preparation is effective against the fungus, but it is so toxic that many physicians hesitate to give it to children (Holt and Newman, 1972). If it has to be given to a pregnant woman it therefore seems reasonable to induce an abortion because of the toxicity of the drug. This should be done when the patient's fungus septicaemia has been cured and her general condition has improved.

5-FC has proved to be an excellent antimycotic drug (Scholer, 1970; Schönebeck, 1971, 1972) with few and as a rule not serious side effects. However, Bennett (1971) and R. Y. Cartwright (personal communication, 1972) have reported bone marrow and liver toxicity. The teratogenic effects of 5-FC have been studied by Chaube and Murphy (1969). They found that intraperitoneal administration of 500-4,000 mg/kg body weight to rats on the 11th or 12th day of gestation resulted in fetal deformities—mostly cleft palates, micrognathia, and short, kinky tails. If the drug was administered on the 9th or 10th day there were no deformities. The lowest teratogenic dose was 700 mg/kg body weight. The therapeutic dose of 5-FC in normal kidney function is about 50 mg/kg body weight every

Departments of Urology and of Obstetrics and Gynaecology, University of Umeå, Umeå, Sweden

J. SCHÖNEBECK, M.D., Assistant Surgeon
E. SEGERBRAND, M.D., Assistant Surgeon