ARSENOBENZENE ENCEPHALOPATHY WITH RECOVERY

G. D. CAMPBELL, M.B., M.R.C.P. (EDIN.), *Physician, Durban*

Severe toxic reactions following the use of organic arsenicals used to be fairly common. Glaser,[1] in 1935, reported 1 death in every 2,700 patients treated with these preparations in a series of 170,000: half these deaths were due to involvement of the central nervous system. A particularly severe encephalopathy, 'fortunately rare',[2] is among the neurological reactions described.[1-7] Organic arsenicals are still widely used in non-specific conditions and, to emphasize the severity of

reaction that sometimes occurs after their use, the following case of 'arsenobenzene encephalopathy' (Brain[6]) due to intravenous Novarsenobillon (NAB) is recorded.

CASE REPORT

A 16-year-old schoolgirl was admitted to hospital on 20 November 1957. She had been quite well until 9 days before admission, when she had been given 'an injection for acne into the vein'. About 10 minutes after this she collapsed in the street, but recovered quickly, having been unconscious for less than half a minute. During the next week she felt a little unwell, but did not have any particular complaints. She was noted to have taken 'a lot of aspirins' during that time.

Two days before admission, and exactly 1 week after the first injection, she was given another intravenous injection, this time the injection being 'covered by cortisone'. She had no immediate ill-effects from this, and felt quite well until 48 hours after, when she woke in the morning feeling a little off colour, ate her breakfast with reluctance, and against the wishes of her father insisted on going to school. On her arrival there she looked so unwell that her teacher put her into the 'sick room', where she lay until she was sent home at 3 o'clock in the afternoon. On reaching home she complained of a headache, and said she was dizzy. She felt nauseated and her speech became confused. Shortly after this she suddenly lost consciousness and was seized by the most violent generalized convulsions. Each fit lasted for about 10 minutes, and they succeeded one another after intervals of about 20 minutes, until she was seen by her doctor, who gave her an intramuscular injection of 5 gr. of sodium luminal. She vomited with the first 3 fits, but not again after this. There was no previous history of epilepsy or of drug idiosyncrasy. Soon after admission it was found that the injections had in fact been NAB, the first of 0·15 mg. and the second of 0·30 mg.

When first seen the patient was unconscious and appeared to be gravely ill; she did not respond to painful stimuli otherwise than by having more seizures, which became more frequent as the examination proceeded. Her pupils were dilated in the extreme and did not respond to light. The retinae were normal. There was no evidence of neck retraction or other sign of meningeal irritation. The blood pressure was 125/65 mm. Hg, and the heart and abdomen were normal. There was no evidence of aspiration pneumonia. The skin was normal, no rash or purpura being seen.

Urine: Sugar 0·5%. Acetone +. Albumin +. Red cells—a few present.

Blood: Haemoglobin 13·2 g.%. Red cells 4·5 million per c.mm. Blood sedimentation rate (Wintrobe) 34 mm. in the 1st hour. White cells 16,000 per c.mm. (polymorphs 92%, lymphocytes 3%, mononuclears 5%). Red cells showed anisocytosis and polychromasia, and basophilic stippling was present. The platelets appeared to be increased, and there was a shift to the left in the myeloid series, with toxic changes.

Lumbar puncture: Pressure 140 mm. of water. Total cell-count less than 1 per c.mm. Globulin markedly increased. Sugar 87 mg.%. Protein 100 mg.%. Chlorides 730 mg.%.

A tentative diagnosis of arsenical encephalopathy was made, and treatment started on that supposition. In all the patient was unconscious for 5½ days, and *in extremis* for the first 2 days. The fits were well controlled at first by intramuscular paraldehyde, in doses of up to 4 ml. 4-hourly; although this was given by deep injection, it raised some large urticarial wheals on each occasion it was given. BAL (dimercaptol) therapy was started forthwith, in a dosage of one 2 ml. ampoule (100 mg.) every 6 hours, and this was kept up for 2 days. Intramuscular prednisolone was given, in an initial dosage of 20 mg., and 10 mg. 12-hourly after this for the first 3½ days. Soluble penicillin (500,000 units 12-hourly) was given for the whole period of unconsciousness and for a day after. An artificial airway was inserted soon after admission, and oxygen administered through it during an episode of cyanosis on the second day; this airway was kept in position, with frequent changes, until the cough reflex was recovered. An indwelling urethral catheter was inserted with the usual sterile precautions, and the bladder emptied at regular intervals, until she regained consciousness.

On the 2nd day, in spite of heavy paraldehyde dosage, the fits became more frequent and severe; the pulse rate rose to over 130 per minute and the respiration rate to 60 per minute. There was only slight pyrexia, to 99·0°F, and no signs of aspiration pneumonia were seen. It was thought that the rise in heart rate and respiration rate might be due to extreme brain-stem stimulation which was not being affected by the paraldehyde, and so morphia was cautiously substituted, in an initial trial dose of 1/6th gr. The response was most gratifying; the pulse rate dropped to 100 per minute and the respirations to 24 per minute, and the fits were well controlled. The dose of 1/6th g. of morphine was repeated 6-hourly for the next day and 8-hourly for the 4th day; it was discontinued on the 5th day.

On the 3rd day after admission the patient developed a widespread blotchy erythematous rash, confined mostly to the body but which was also seen on the arms and legs; this disappeared within 2 days, no purpura being seen. At this time she was showing definite signs of improvement in that smaller doses of morphine were needed to stop the fits. Intravenous therapy was cautiously started that day and 500 ml. of 5% dextrose in saline run in. This was followed by 1,500 ml. on the 4th day; and on the 5th she woke up after 500 ml. had been given, and intravenous fluids were discontinued soon after, because she was able to take sips of fluid by mouth almost at once. She had no other complaints other than of being tired and thirsty and of having a headache. Her recovery was complicated by a mild degree of nausea and vomiting, and she was discharged from hospital 10 days after admission without any evidence of neurological sequelae. Her urine was normal and has remained so. Six months later, she says that she has had lapses of memory, which have lasted up to a few hours on 2 occasions; there has been no headache or weakness, and she is progressing satisfactorily at a shorthand-typing school. Neurological examination is normal.

DISCUSSION

This syndrome seems to be clear cut: between 12 hours and 6 days after an intravenous injection of NAB, generally the 2nd or 3rd of a course,[5,2] the patient begins to feel ill. Headache and drowsiness come on, and there may be vomiting. Confusion and coma set in, and in three-quarters of the cases generalized convulsions occur.[4,5] Variable and diffuse signs are seen.[4] A scarlatiniform rash turning into a haemorrhagic purpura was noted by one observer.[3] The ultimate mortality has not been determined but one-quarter of the cases die within 24 hours of the onset of the illness.[4] All the 4 cases of Nelson *et al.*[3] died. Three of them were pregnant. In their article Nelson *et al.*[3] added that 'most cases' die, though recovery had been reported in 'several instances'. Recovery, when it occurs, is generally complete,[4] though residual disability has been noted.[5] 'Good results' are said to have been obtained by nursing the patients in an upright posture.[7] A raised cerebrospinal-fluid protein was considered unusual by one observer,[2] though we noted it in our case.

The actual cause of the syndrome is unknown; it has been seen after only one injection, but it occurs more commonly after the second or third.[2,3,5] It is not seen invariably in syphilitic patients,[4,5] and this would tend to rule out a Herxheimer reaction. Neither the dosage[3] nor the nature of the radical[2] appears to play any part in the genesis of the syndrome. It probably represents an antigen-antibody reaction, the brunt of which is borne by the nervous system—a 'neuro-allergy'; even myelitis has been reported.[5] A 'direct toxic action on the capillaries' has been suggested by the results of the post-mortem examinations.[3] The brain shows oedema and perivascular haemorrhages.[2] There is endothelial swelling of the vessels with ante-mortem thrombus formation and occasional vascular rupture.[2] Gross cerebral haemorrhage has also been reported.[5] The basal nuclei seem to be particularly affected.[3]

NAB is still used fairly widely in practice in non-specific conditions, notably stubborn mouth ulceration, in acne vulgaris, and to induce remissions in disseminated sclerosis. In view of this it is important to remember that its use sometimes causes severe illness and even death, and it should be reserved for those few cases of syphilis in which it is specifically indicated. When it is used, one should remember that it is rapidly oxidized by atmospheric oxygen to a toxic substance,[10] and it should be injected as soon as the ampoule is opened.

If a case of encephalopathy is encountered, early use should be made of BAL, and it would appear that treatment should include prednisone or an allied drug in full doses and an efficient anti-convulsant drug. With these drugs, and the withdrawal of as much cerebrospinal fluid as possible with the first lumbar puncture (if papilloedema is absent), mere fluid restriction would seem preferable to repeated lumbar punctures and the nursing of the patient in the upright position,[7] since this must be a difficult measure to introduce with patients as restless as these. Attention has recently been drawn to the fact that the Landry-Guillain-Barré syndrome may be a 'neuro-allergy', and impressive results are said to have been obtained by the use of large doses of cortisone.[11] Arsenobenzene encephalopathy, being almost certainly a neuro-allergy, should probably be treated with the same dosage; the doses used in this case (prednisolone, 20-30 mg. daily intramuscularly), though adequate, were probably smaller than those needed for a maximum margin of safety.

SUMMARY

To emphasize the need for restricting the indiscriminate use of Novarsenobillon (NAB), a case of 'arsenobenzene encephalopathy' is described in a 16-year schoolgirl who had been given 2 intravenous injections for acne vulgaris. The extreme severity of the illness, the clinical features, the laboratory findings and the method of treatment are described. The patient made a complete recovery. The condition is believed to be an allergic response. Its high mortality rate is discussed and a plea made that NAB should be used only in those cases of syphilis in which it is indicated. Attention is drawn to the fact that NAB is rapidly oxidized by atmospheric oxygen to a toxic substance, and should be injected as soon as the ampoule is opened.

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