TABLE III—*High-rise Bicycle Injuries in Relation to Ownership*

	Own (n = 30)		Borrowed (n = 37)		Significance of Difference (χ^2 test)
	No.	%	No.	%	
Abrasion ..	12	40·0	27	73·0	P<0·01
Laceration ..	11	36·7	9	24·3	N.S.
Fracture	11	36·7	9	24·3	N.S.
Head injury ..	5	16·7	18	48·6	P<0·01
Other	6	20·0	7	18·9	N.S.
Admitted ..	6	20·0	10	27·0	N.S.

Discussion

The results show that in this group of children injured in bicycle accidents there was a higher incidence of abrasions, fractures, and head injuries among those riding high-rise models compared with those on conventional machines. Furthermore, admission to hospital as a result of injury was commoner after high-rise cycle accidents. There is a variety of possible explanations for these differences but attention is drawn to the fact that surprisingly many high-rise accidents occurred when on borrowed machines and in these the injuries tended to be more severe (table III). Also, a fifth of the children injured while riding their own high-rise bicycle had recently acquired it, and this figure was even higher in our earlier study, which covered the Christmas period. These facts suggest that unfamiliarity with the high-rise type of cycle may be responsible for many of the accidents which appear to cause more severe injury to inexperienced riders.

Many activities in childhood carry some risks of injury and the results of this study must be seen in perspective. All bicycles are potentially dangerous and the figures presented here are not necessarily a condemnation of the high-rise type. So far as this study goes the style has shown itself to carry some extra hazard and parents should clearly be informed of the safety factor whether relating to toys, bicycles, or other articles which they buy for their children. One important point to emerge is that unfamiliarity with the machine is a factor in high-rise accidents.

We are greatly indebted to the Newcastle Regional Hospital Board for its support of our studies in head injury, including the provision of a research registrarship for A.W.C. We thank all the casualty officers and heads of accident departments for their willing co-operation, and we are grateful to Dr. Hugh Jackson for his interest in this study. Finally, we are indebted to Mrs. D. Weightman for statistical help.

References

Craft, A. W., Shaw, D. A., and Cartlidge, N. E. F. (1972). *British Medical Journal*, **4**, 200.
Howell, T. R. (1968). *Pediatrics*, **42**, 214.
National Safety Council (1970). *National Commission on Product Safety. Final Report*. Washington D.C., Government Printing Office.
Rice, R. S. (1970). Technical Report No. CAL. VJ-2888-K. Buffalo, New York, Cornell Aeronautical Laboratory.
Waller, J. A. (1971). *Pediatrics*, **47**, 1042.

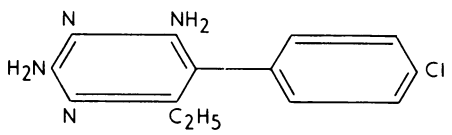
MEDICAL MEMORANDA

Pyrimethamine Poisoning

OLU AKINYANJU, J. C. GODDELL, I. AHMED

British Medical Journal, 1973, **4**, 147–148

Pyrimethamine (Daraprim) is an amyl analogue of 2,4-diaminopyrimidine which binds dihydrofolate reductase and acts as a folate antagonist, thus preventing nuclear division (Hamilton *et al.*, 1952). It has been used for the treatment of malaria



Formula of pyrimethamine (Daraprim).

(Covell, 1953), toxoplasmosis (Grisham, 1962), and polycythaemia vera (Isaacs, 1954). Its efficacy when administered in a once-weekly dose of 25 mg for adults and its tastelessness and relative freedom from toxic allergic reactions, have commended it for wide use as a malarial prophylaxis drug in Nigeria. It is not commonly regarded as a dangerous drug, and is publicly advertised and easily obtained without a prescription. In spite of its widespread use we are not aware of reports of its toxicity from Nigeria. We report two cases of successfully treated pyrimethamine poisoning and discuss the treatment.

Lagos University Teaching Hospital, Lagos, Nigeria
OLU AKINYANJU, M.B., M.R.C.P., Consultant in Clinical Haematology
J. C. GODDELL, F.R.C.P. (CAN.), Consultant in Paediatrics
I. AHMED, M.R.C.P., F.M.C.PAED.(NIG.), Consultant in Paediatrics

Case 1

A 14-month-old male Caucasian child weighing 10·4 kg was admitted to this hospital about two hours after ingesting 450 mg of pyrimethamine tablets. Half an hour after ingestion his parents observed an unsteady gait and a vacant expression on his face. During the next half hour he vomited several times, lost consciousness, and began to convulse every few minutes.

On examination he was unconscious, cyanosed, and had almost continuous generalized convulsions and a hyperpyrexia of 40·6°C. He had a tachycardia of 146/min, tachypnoea, and dyspnoea, with bilateral rales heard over both lower lung fields.

Oxygen was administered, and the convulsions were controlled by giving intravenous diazepam 5 mg.

Intramuscular liver extract 2 ml and folic acid 10 mg were also given. An intravenous drip containing 100 ml of 10% mannitol was given within 30 minutes and then 4·3% dextrose and 0·18% saline were continued at the rate of 1·2 l. a day. Sodium bicarbonate and potassium chloride were added to correct acidosis and electrolyte imbalance. The child was put on broad spectrum antibiotics, intramuscular diazepam 3 mg eight-hourly, folic acid, and liver extract.

Investigations on admission were: packed cell volume (P.C.V.) 35%; W.B.C. 10,500/mm^3; blood urea 44 mg/100 ml; sodium 125 mEq/l.; potassium 3·2 mEq/l.; chloride 100 mEq/l.; bicarbonate 8 mEq/l.; bilirubin 0·6 mg/100 ml; alkaline phosphatase 28 units; SGOT 122 units; and SGPT 32 units. Cerebrospinal fluid was normal. An *x*-ray picture of the chest showed patchy opacities at both lung bases, and *x*-ray appearances of the skull were normal.

During the next 24 hours the child's condition continued to cause anxiety. The respiration remained hurried and laboured with bilateral rales; fever ranged from 40-40·6°C, and he remained unconscious and

spastic but convulsions did not recur. He improved over the next few days, however, and became more responsive, and his respiration and fever settled down. Neurological examination on the fourth day showed blindness and deafness but normal fundi and discs. Eye movements were conjugate and the pupils were fairly dilated and did not react to light. An electroencephalogram showed slow amplitude waves and no response to visual or auditory stimuli. Other cranial nerves were intact. There was generalized motor weakness and an inability to hold up his head and sit up. The muscle tone in both upper limbs was increased and deep reflexes were abnormally brisk. From, then on he steadily improved, became conscious, and by the ninth day, when he was discharged from hospital, he was able to feed by mouth. He was discharged on diazepam 3 mg eight-hourly, folic acid 5 mg three times a day, and phenobarbitone 15 mg twice a day, which was continued for three months, and chloroquine sulphate 100 mg weekly as malarial prophylaxis. Physiotherapy was given at regular intervals, and he was followed in outpatients.

By six weeks he could hold up his head and by the eighth week could sit unsupported. By the 12th week he was able to stand. Vision and hearing also improved so that by the fourth week he was following objects with his eyes, and by the eighth week reacted to sounds.

Three months after his accident the Denver developmental screening test showed that his gross mental age was equivalent to that of a 13-month-old child, with fine motor adaptation of a 10-month-old.

Two years after the accident he has perfect vision and hearing, and normal physical development, but his speech development is slow and he is slightly mentally retarded.

Case 2

A 4½-year-old British girl was first observed to be very pale by a neighbour. She was asymptomatic but her mother took her to the family doctor, who diagnosed anaemia and admitted her to a private hospital for blood transfusion. She was admitted to this hospital next day. There was no history of bleeding, purpura, fever, or previous illness, and her diet was normal. Her mother revealed that she had given her 25 mg of pyrimethamine twice weekly over the preceding six months as malaria prophylaxis. On examination her physical development was normal, there were pronounced pallor and a smooth-edged tongue, but no jaundice or oedema. Examination of the cardiovascular system showed a regular tachycardia (140/min), but no evidence of cardiac failure. The respiratory system, the abdomen, and the central nervous system were normal.

Investigations before transfusion were: Hb 2·5 g/100 ml, and P.C.V. 8%; W.B.C. 5,000/mm³ (normal differential). The blood film showed severe anisocytosis, macrocytosis, moderate poikilocytosis, a few megaloblasts, many multilobed neutrophils, and thrombocytopenia. Post-transfusion Hb was 8·3 g/100 ml, W.B.C. 4,300/mm³, platelets 56,000/mm³, and there was reticulocytopenia. A bone marrow aspiration smear showed severe megaloblastic erythropoiesis with giant band granulocytes. Xylose absorption test showed nothing abnormal. She was diagnosed as a case of folic acid-deficient megaloblastic anaemia. The pyrimethamine was stopped and she was treated with folic acid 10 mg daily by mouth. A day after folic acid was started her P.C.V. was 21%, dropped to 20% the next day, then gradually rose to 28% on the sixth day. Reticulocyte response was absent until the sixth day when it suddenly jumped to 43%. From then on her P.C.V. rose steadily to normal. Her platelet count also increased gradually to normal three weeks after the commencement of folic acid. The folic acid was stopped after two months and she remained well eight months after discovery of her anaemia.

Comment

The first case illustrates the danger of acute poisoning after ingestion of a large number of tablets. This patient had the well-known toxic effects of pyrimethamine poisoning (Guignard, 1965; Grisham, 1962), but ataxia, hyperpyrexia, blindness, deafness, and residual mental retardation have not been reported so far as we know. The speed of onset of the neurological symptoms suggest that the drug has a direct toxic action on the central nervous system rather than a metabolic one due to folate antagonism. It also suggests that the drug is rapidly and well absorbed from the gastrointestinal tract, though variable absorption of the drug after oral administration has been reported (Covell, 1953; Kaufmann and Caldwell, 1959).

Routine measures are effective in treating the acute intoxication—that is, maintenance of a clear airway, suppression of convulsions, and forced diuresis. Gastric lavage has not been reported as useful, and unless it is done very soon after ingestion of the drug and before vomiting starts it would appear to be pointless to attempt it. On theoretical grounds at least, the administration of large doses of folinic acid is justified because this drug will bypass the block caused by pyrimethamine on the conversion of folic acid to folinic acid and thus minimize the metabolic insult to the tissues.

The second case with slowly developing megaloblastic anaemia illustrates the result of chronic pyrimethamine poisoning. This patient had been on four times (50 mg) the usual weekly dose (12·5 mg) for her age for over six months. The development of the anaemia appears to depend not only on the dose of the drug, but also on the duration of administration and on the available dietary folic acid, provided there was no malabsorption. Laing (1957) reported the development of megaloblastic anaemia in adult Asians who were on only 25 mg weekly but were also on a rather low folic acid diet. Withdrawal of the drug and administration of folinic acid would be the logical treatment. In our own case folinic acid was not available, and folic acid produced the desired effect after one week of stopping pyrimethamine. It is obvious that pyrimethamine is a very dangerous drug, and we feel that its packages should carry strict instructions about not exceeding the recommended dose.

Perhaps the addition of a bitter tasting substance to the tablets will deter children from unsupervised ingestion.

We are grateful to Mr. S. Ahaiwe for typing the manuscript.

Requests for reprints should be addressed to: Dr. O. Akinyanju, Lagos University Teaching Hospital, P.M.B. 12003, Lagos, Nigeria.

References

Covell, G. (1953). *British Medical Journal*, **2**, 285.
Grisham, R. S. C. (1962). *American Journal of Ophthalmology*, **54**, 1119.
Guignard, J. (1965). *Annales de Pediatrie*, **12**, 120.
Hamilton, L., Phillips, F. S., Clarke, D. A., and Sternberg, S. S. (1952). *Federation Proceedings*, **11**, 225.
Isaacs, R. (1954). *Journal of the American Medical Association*, **156**, 1491.
Kaufmann, H. E., and Caldwell, L. (1959). *Archives of Ophthalmology*, **61**, 885.
Laing, S. R. S. (1957). *Journal of Tropical Medicine and Hygiene*, **60**, 131.