THE EFFECT OF ACID, ALKALI, AND MEALS ON THE BLOOD LEVEL AND EXCRETION OF SULPHAPYRIDINE IN CHILDREN

BY

H. ELLIS C. WILSON, M.B., D.Sc., F.R.F.P.S.

Biochemist to the Royal Hospital for Sick Children, Glasgow

The effect of the sulphonamide drugs on the acid-base metabolism has received a certain amount of attention without, however, any clear-cut conception as to the nature or cause of the upset having been obtained. Beckmann *et al.* (1940) have shown in adults that with doses of about 6 g. a day there is a proportionate fall in the sodium and bicarbonate, with a rise in the chloride of the blood. These changes were associated with a temporary increase in the sodium excretion and a smaller one in the chloride excretion which shortly fell to the normal rate of output. They state that the electrolytic pattern of the blood resembles that observed after the administration of acid salts such as ammonium chloride and ammonium sulphate, except that the increase in the blood chloride is bound to sodium in the case of the acid salts, while after sulph-anilamide they assume that the extra chloride must presumably be bound to the serum proteins.

These authors hold that the primary effect of the drug is to cause an increased excretion of sodium bicarbonate, which produces secondarily a certain degree of hyperpnoea (i.e., an acidosis). Hartmann *et al.* (1938) also observed a hyperpnoea and a fall in blood CO_2 . They, on the other hand, consider the hyperpnoea to be the primary change which accounts for the excretion of bicarbonate to keep the pH of the blood normal (i.e., an alkalosis). Beckmann *et al.* (1940) maintain that this latter explanation is unlikely, as it would require a greater degree of hyperpnoea to cause the reduction in blood bicarbonate observed.

Whatever the explanation, the net result appears to be a reduction in the fixed base of the blood, and hence an acidosis. It is perhaps this belief which has led to the giving of alkali along with the drug in order to relieve acidosis. The possibility of increased excretion and absorption, and the alleviation of undesirable symptoms such as vomiting, also require consideration. The scope of the present investigation was as follows: (a) to test the effect of acid and alkali on the blood level and excretion of sulphapyridine in children; (b) to test the effect of the timing of meals on the blood level and excretion of sulphapyridine in children.

Effect of Acid and Alkali

The subjects chosen for investigation were between 4 and 12 years of age and had been admitted to hospital with diseases unlikely to interfere with the absorption and excretion of the drug—e.g., chorea and epilepsy. In a series of 15 cases each child was given a single dose of 50 mg. of sulphapyridine per kilo of body weight, and the blood level followed at one-, four-, and eight-hour intervals. The excretion in the urine for the first 24 hours was also estimated. Three separate tests were carried out on each case: (1) sulphapyridine alone; (2) sulphapyridine and 30 gr. of sodium bicarbonate; (3) sulphapyridine and 19 gr. of ammonium chloride (the acid equivalent of 30 gr. of sodium bicarbonate). The estimations were made according to the method of Bratton and Marshall (1939). Both total and free sulphapyridine estimations were made on the urine, but in the blood the free form only.

The average results obtained are given in Table I, A. The individual figures vary considerably, but the averages did not show that there was any advantage in giving or withholding either acid or alkali. The excretion of the drug (50% in 24 hours) was the same in the three modes of administration (Table I, B). On an average about 50% of the amount excreted was in the free form, leaving the remainder as a combined form, probably the acetyl derivative. The amount of the combined form varied between 17 and 68% in the different cases. The only relatively constant feature was the percentage amount of the combined form in each individual case in the three

modes of administration, even although the total excretion varied. As all the children had essentially the same diet it is unlikely that food was a factor in the detoxicating process. Further, there appeared to be no correlation between vomiting

TABLE I

A.—Average Concentration of Free Sulphapyridine in Blood at 1, 4, and 8 Hours (15 Cases)

	1 Hour (mg./100 c.cm.)	4 Hours (mg./100 c.cm.)	8 Hours (mg./100 c.cm.)
Sulphapyridine alone ..	4.5	5.1	4.8
Sulphapyridine + 30 gr. NaHCO_3	3.8	5.4	4.5
Sulphapyridine + 19 gr. NH_4Cl	3.8	5.5	4.6

B.—Average Output of Drug in Urine (15 Cases)

	Drug excreted in 24 Hours	Form of Drug	
		Free	Combined
Sulphapyridine alone ..	49.05	53.8	46.2
Sulphapyridine + 30 gr. NaHCO_3	51.0	54.4	45.6
Sulphapyridine + 19 gr. NH_4Cl	50.6	50.4	49.6

and the giving of acid or alkali. Several of the cases vomited at varying intervals after getting the drug. Such observations were discarded, the investigations being repeated a few days later. Had the diminution of fixed base of the blood been a contributory cause of vomiting one would have expected that the giving of alkali or acid would have respectively improved or aggravated the condition. Such was not found to be the case. In one particular child, who vomited within half an hour of receiving the drug, the blood level was above the average an hour later. The extreme variability of the blood curves and percentage excretion both from case to case and in the same individual has been noted by others for sulphapyridine (Brown, Thornton, and Wilson, 1939; Cullen and Wilson, 1940). Barlow and Climenko (1941), however, claim that with sulphapyridine the giving of alkalis such as sodium bicarbonate and magnesium carbonate increased the excretion of sulphapyridine. Their figures are, however, in our opinion and considering the variability, too few and probably not significant. Siebert and Loose (1940) observed no difference in the absorption of sulphanilamide when given with 30 gr. of sodium bicarbonate. They found, further, that gastric acidity did not appear to influence absorption, and in support of their claim instanced a case of achlorhydria in which the excretion was normal.

Effect of Meals

The second series of cases (Table II, A) was designed to test the effect of taking the drug two hours before and immediately after the midday meal. In all, 17 children were studied. One

TABLE II

A

	Mg./100 c.cm.	Standard Deviation
Average blood sulphapyridine 4 hours after dose taken between meals ..	5.3	d=1.54
Average blood sulphapyridine 4 hours after dose taken immediately after meal ..	5.8	d=1.73
Difference	0.5	

B

Average excretion of sulphapyridine in 24 hours: drug taken between meals ..	60.7%	d=15.4
Average excretion of sulphapyridine in 24 hours: urine: drug taken immediately after meal ..	66.2%	d=13.5
Difference	5.5%	

blood sample was taken four hours after administration and the urine was collected for 24 hours. The figures again were extremely variable. The average blood level was 0.5 mg. higher when the drug was taken after the meal.

The standard deviations were 1.54 and 1.73, and the probable error of the difference of the means was 0.2716. The ratio of the difference of the means is hence $0.2716:0.5=1.8$. When this

is less than 3 it is usually considered not to be significant. When the drug was administered immediately after a meal the percentage excretion in urine was 5.5 greater than when taken between meals. The standard deviations were 15.4 and 13.5 respectively. The above-mentioned ratio in this case is 6.5, and hence the difference can be considered to be statistically significant, although from the clinical point of view it is scarcely of importance.

Conclusions

The data presented here would appear to show that there is no advantage with respect to the blood concentration or urinary excretion, and hence absorption, in giving acid or alkali with sulphapyridine. Nor was any significant effect observed on the blood concentration by timing the administration of the drug in relation to meals. The excretion of the drug was greater when taken immediately after as opposed to two hours before a meal. This difference was statistically significant, but clinically can scarcely be of much importance.

I desire to thank Dr. Stanley G. Graham for his advice and criticism in the preparation of this paper.

REFERENCES

- Barlow, O. W., and Climenko, D. R. (1941). *J. Amer. med. Ass.*, **116**, 282.
Beckmann, W. W., Rossmessl, E. C., Pettengill, R. B., and Bauer, W. (1940). *J. clin. Invest.*, **19**, 635.
Bratton, A. C., and Marshall, E. K. (1939). *J. biol. Chem.*, **128**, 537.
Brown, W. H., Thornton, W. B., and Wilson, J. S. (1939). *J. clin. Invest.*, **18**, 803.
Cullen, G. E., and Wilson, A. T. (1940). *Amer. J. Dis. Child.*, **60**, 891.
Hartmann, A. F., Perley, A. M., and Barnett, H. L. (1938). *J. clin. Invest.*, **17**, 465.
Siebert, W. J., and Loose, F. (1940). *J. lab. clin. Med.*, **26**, 371.

Medical Memoranda

Encephalitis after Measles with Severe Parkinsonian Rigidity: Recovery

Although variability in the signs and symptoms produced by encephalitis is notorious, the following case which followed upon an attack of measles is of interest on account of the predominance of the Parkinsonian syndrome from the onset.

CASE HISTORY

The patient, a boy aged 6, was admitted on Sept. 10, 1942, with a history that nine days previously he had developed a typical mild attack of measles. This was treated at home by his medical practitioner, who confirms that the illness had every appearance of ordinary measles. Seven days later the doctor was called in again on account of some stiffness in the limbs and the fact that for the last day or two the boy failed to answer when spoken to. When he was brought to the hospital two days later he had during the interval uttered only one or two short spontaneous remarks, and, as he did not speak and had a strange expressionless face, the mother thought he was suffering from some kind of mental derangement.

On examination the patient showed a typical Parkinsonian facies, emotional as well as voluntary facial movements being absent. The tongue could not be protruded, and there was some dribbling of saliva from the corners of the mouth. Crying resulted in a peculiar whining noise. There was some difficulty in swallowing, but fluids could be taken fairly well. Drowsiness was not apparent. The eyes were unaffected, and when asked to follow a moving object he responded promptly. All limbs showed well-marked Parkinsonian rigidity and tremor, and were affected almost equally; but with a little assistance he was able to get off the couch and walk round the room. At this stage tendon jerks were brisk, plantar reflexes normal, and the lower abdominal reflexes absent. The fundi were normal, and remained so throughout the illness. There was no nystagmus or strabismus, and the pupils reacted normally. During the illness the C.S.F. was normal on two occasions in respect of sugar, chlorides, and leucocytes, but contained a few red cells (probably contaminants) and a total protein of 0.06% and 0.05%. The blood W.R. was negative and the blood count normal. During the first two weeks the temperature was 100° F. on a few occasions, but was later normal.

During the first ten days in hospital the condition became progressively worse. The arms, particularly the right arm, became fixed in a position of flexion, tremor was very pronounced, and the knees tended to become flexed. Voluntary movements had practically disappeared. For a short period a transient left internal strabismus occurred, and the left plantar response became extensor. There were also at this stage frequent attacks of restlessness with increased tremor and flexion of the arms and knees. There was no inversion of sleep rhythm. Sphincters were unaffected, and he continued to be able to swallow. On the eighteenth day of the illness the patient spoke a few words, and within a week posture was almost normal. At about this time he was emotionally labile and his speech rather confused. He was discharged from hospital, apparently completely normal, on Oct. 12, 42 days after the onset of the measles rash.

Treatment consisted of general measures and the administration of large doses of pot. brom. and tinct. hyoscyami, and frequently chloral

at night. Somewhat empirically, three injections of liver extract were also given intramuscularly.

Since leaving hospital the boy has been in good health, and attends school, where he also plays games. In a recent examination no abnormality could be found in his central nervous system. The fundi were normal; there was no strabismus or tremor. Vision was 6/6 and hearing normal. No character change has been noted by his mother, and at school he is well up to the average. There is no relevant family history.

It appears that in spite of the prominence of Parkinsonism a diagnosis of post-measles encephalitis rather than of a lethargic type of the disease should be made in this case. This is supported by the history of measles and by the completeness and rapidity of recovery.

I wish to thank Dr. W. E. Crosbie, medical superintendent of the hospital, for permission to publish this case; and Dr. Norman B. Capon, visiting consultant physician, for his advice and supervision.

Alder Hey Hospital, Liverpool.

B. MEYER, M.B., B.S., D.C.H.

A Case of Malignant Tertian Malaria

Malignant malaria is seldom seen in this country, though Murray and Shute (1942) have recently reported a case. The following case is remarkable for its benign clinical course and for the manner in which it responded to small doses of quinine.

CASE RECORD

The patient, a ship's steward, was admitted to the General Hospital, South Shields, on Aug. 27, 1942, with a history of "malaria." He had been torpedoed off the West African coast in March, 1942, and after two days at sea was interned in French West Africa. He was kept in insanitary conditions, on a poor diet, until his release at the end of June. During this period he is said to have contracted "malaria" and "dysentery." During July and August he had regular attacks with rigors at intervals of 3 to 4 days. The last rigor occurred the night before admission. He had had no systematic treatment, but had taken "a few quinine tablets now and then."

On admission to hospital he was noted to be thin and pale, but not emaciated. Clinical examination was negative apart from some tenderness in the left epigastrium. The liver and spleen were not palpable, the conjunctivae were pale, there was no jaundice, and urine analysis proved negative. Temperature on admission was 99.4° and pulse 104. Next morning the temperature was subnormal; it rose again in the evening, to 100°, and returned to normal the following morning. There has been no subsequent rise in temperature.

Blood films taken on Aug. 29 showed large numbers of malaria parasites, chiefly the gametocyte stage of *P. falciparum*, together with some ring forms. Although the films were only ordinary thin ones, parasites were so numerous that some fields showed two crescent forms. A further film on Sept. 8 contained crescent forms in fair numbers. On Sept. 23 only a single ring form was seen. Subsequent films have been negative.

Treatment.—The patient was put on quinine sulphate gr. 5 t.d.s. on admission, before the blood had been examined. This was discontinued on Sept. 2. On Sept. 6 he had one dose of 10 gr., and on Sept. 8 quinine sulphate gr. 5 t.d.s. was reinstituted. On Oct. 3 the patient was discharged apparently well, having then been afebrile for 36 days. He was gaining weight and the signs of anaemia noted on admission had largely disappeared, although he had had no specific treatment to combat the anaemia. At the end of October he was still taking 5 gr. of quinine thrice daily, and, while that was too soon to speak of cure, there had been no recurrence of symptoms and films remained negative.

It should be mentioned that the patient gives a history of having contracted malaria ten years ago and having had subsequent attacks at intervals of a few months up to the onset of the present illness. It is most improbable that he has been suffering from malignant malaria for ten years, particularly in the absence of splenic enlargement. That he contracted any form of malaria ten years ago is doubtful: there is no medical confirmation, and seafaring men commonly refer to any pyrexial illness as "malaria."

The presenting symptoms in Murray and Shute's case were gastro-intestinal, and it is interesting to note that diarrhoea ("dysentery") had been an early symptom in our case, but had subsided before admission. Manson-Bahr (1942) states that malaria is often accompanied by diarrhoea, and mentions "malarial dysentery" with blood and mucus in the stools.

Our thanks are due to Dr. D. J. Mackinnon (late R.A.M.C., East Africa), who confirmed the diagnosis, and to Dr. W. Campbell Lyons, medical officer of health, South Shields, for permission to publish this note.

W. L. ANDERSON, M.B., Ch.B. Glasg.,

R.A.M.O., General Hospital, South Shields.

D. B. BRADSHAW, M.B., Ch.B., D.P.H. Dubl.,

Deputy Medical Officer of Health, South Shields.

REFERENCES

- Manson-Bahr, Sir P. H. (1942). *British Medical Journal*, **2**, 489.
Murray, J. E., and Shute, P. G. (1942). *Lancet*, **2**, 365.