in our two patients that a much higher proportion of the dose of clioquinol is absorbed.

Haskins, Luttermoser & Brady (1950) investigated the absorption and distribution of iodine after the oral administration of clioquinol to rabbits and suggested that this drug was absorbed, and eliminated, without degradation and without the liberation of inorganic iodine having occurred to any great degree. In human studies using clioquinol labelled with radio-active iodine, Liewendahl & Lamberg (1967) confirmed that a high proportion of the dose was absorbed from the gut. These workers also showed that, in rats, much of the drug was taken up by the thyroid gland in the unchanged form (Lamberg & Liewendahl, 1967). Iodine derived from the clioquinol was rapidly incorporated into the iodo-tyrosine precursors of thyroid hormone. This latter observation may explain why, although clioquinol interferes with the thyroidal uptake of iodine (Henderson Smith, 1964), no case of hypothyroidism attributed to clioquinol therapy has been recorded. Another possible risk of treatment with this drug is retinal damage (*Lancet*, 1968). The present cases suggest that very long-term application of clioquinol to extensive skin lesions should be embarked upon with caution.

The high levels of PBI found after clioquinol treatment are due in part to protein-binding of the drug as well as to contamination of the serum by inorganic iodine (Liewendahl & Lamberg, 1968). Although normal PBI levels were regained by our patients within 3 weeks of the cessation of treatment, the work of Thorén (1960), Levin *et al.* (1966), and Sonksen *et al.* (1968) suggests that this estimation is

probably valueless as a test of thyroid function for at least 2 months after oral administration of clioquinol.

References

- FIWEL, M. (1969) Percutaneous absorption of topical steroids in children. *British Journal of Dermatology*, **81**, suppl. 4, 113.
- HASKINS, W.T., LUTTERMOSER, G.W. & BRADY, F.J. (1950) The physiological disposition of Diodoquin, Vioform, and Chiniform in the rabbit as determined with radioiodine. *American Journal of Tropical Medicine*, **30**, 599.
- HENDERSON SMITH, S.L. (1964) Drugs and investigations. *British Medical Journal*, **2**, 1265.
- LAEMER, B.-A. & LIEWENDAHL, K. (1967) Transfer of the iodine of the iodo-chloroxyquinoline molecule (Vioform) to the iodo-amino acids of the thyroid gland. *Nuclear Medizin*, **6**, 16.
- LANCET (1968) Annotation—Clioquinol and other halogenated hydroxyquinolines. **i**, 679.
- LEVIN, K., JOSEPHSON, B. & GRUNEWALD, G. (1966) The effect of iodo-chloroxyquinoline and iopanoic acid on the determination of PBI and BEI. *Acta endocrinologica Copenhagen*, **52**, 627.
- LIEWENDAHL, K. & LAEMER, B.-A. (1967) Metabolism of iodo-chloroxyquinoline in man. *Nuclear Medizin*, **6**, 20.
- LIEWENDAHL, K. & LAEMER, B.-A. (1968) Clioquinol and thyroid-function assessment. *Lancet*, **ii**, 979.
- SARKANY, I. & HADGRAFT, J.W. (1968) The influence of formulation on topical corticosteroid activity. *British Journal of Dermatology*, **81**, suppl. 4, 98.
- SCOGGINS, R.B. & KLIMAN, B. (1965) Percutaneous absorption of corticosteroids. *New England Journal of Medicine*, **273**, 831.
- SONKSEN, P.H., EKINS, R.P., STEVENS, H.G., WILLIAMS, E. & NABARRO, J.D.N. (1968) Serum-levels of protein-bound iodine and thyroxine after a course of clioquinol. *Lancet*, **ii**, 425.
- THOREN, A. (1960) The influence of iodide and iodized compounds on the PBI and the ¹³¹I tracer test with special reference to various biologic states of the thyroid. *Acta endocrinologica Copenhagen*, **35**, 351.

Metabolic alkalosis treated with intravenous hydrochloric acid

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IN CLINICAL practice, a severe metabolic alkalosis is found less frequently than a severe metabolic acidosis. In both disturbances the treatment consists of removing the cause and correcting the deficits or excesses in the body fluids. The severe metabolic acidosis of diabetic coma or that which follows cardiac arrest often needs urgent correction by giving sodium bicarbonate intravenously. In contrast, a metabolic alkalosis very rarely causes an immediate threat to life. In two patients recently admitted to

this unit, the metabolic alkalosis required specific treatment with intravenous hydrochloric acid.

Laboratory methods

pH was determined electrometrically using a capillary electrode (Siggaard-Andersen *et al.*, 1960). The electrode was calibrated with two phosphate buffers of pH 7.416 and 6.839 at 38° (Semple, Mattock & Uncles, 1962). The normal range was taken as 7.35–7.45.

PaCO_2 was measured directly with an electrode (Severinghaus & Bradley, 1958), calibrated with two gas mixtures, the CO_2 contents of which were determined on the Haldane apparatus (Douglas & Priestley, 1948). Normal values were taken as 33–44 mmHg. An aliquot of the arterial sample was centrifuged in a tube sealed by a thin layer of neutral mineral oil (Van Slyke, Weisiger & Van Slyke, 1949) and a rubber vaccine closure. The plasma was quickly separated for the determination of sodium, potassium, chloride and total CO_2 . The latter was measured in duplicate on the AutoAnalyzer by the method of Skeggs (1960). The plasma bicarbonate was calculated from the total CO_2 . The normal value for healthy subjects at rest was found to be 22.4 ± 1.86 mEq/l. When it was impossible to measure the plasma bicarbonate this was calculated from the Hendersen-Hasselbalch equation using a nomogram of Siggaard-Andersen (1963). We have used the acid-base terminology of Peters & Van Slyke (1931). Sodium and potassium were measured on an internal-standard flame photometer and chloride electrometrically. The 95% confidence limits for healthy subjects were: serum sodium 136–147 mEq/l, potassium 3.7–4.6 mEq/l, chloride 100–110 mEq/l (Thompson & Jones, 1965).

Fluid therapy, acid therapy and nutrition

Intravenous infusions containing sodium, potassium and chloride were used to correct the deficits of electrolyte. Calories and nitrogen were given as dextrose, fructose, ethanol, amino acids and fat emulsion (Peaston, 1966). An ampoule of Analar hydrochloric acid (British Drug Houses Concentrated Volumetric Solution No. 18005) was diluted in water for injection BP to give a normal solution.

Fifty millilitres of this solution was substituted for 50 ml of 5% dextrose removed from a litre container. The dextrose solution containing 100 mEq of hydrochloric acid/l was given by slow infusion through a peripheral vein as detailed in Table 2.

Case 1

A man aged 61 developed pancreatitis after cholecystectomy. There was shock and 18 l of fluid were aspirated from the stomach during 3 days. The serum amylase was 1200 Somogyi units/100 ml. During the first 5 postoperative days the patient was given the following intravenous fluid therapy: water 16.7 l, sodium 2933 mEq—as chloride except for 80 mEq as bicarbonate, potassium 130 mEq; but only 300 calories were available and no nitrogen was given. The patient was critically ill when transferred on the fifth day to our Intensive Care Unit. He showed dehydration, hypotension, cyanosis, shallow breathing and a minute volume of less than 5 l. The chest radiograph and electrocardiogram were normal.

The arterial blood (Table 1) and a pH of 7.55, high bicarbonate and hypercapnia, that is the metabolic alkalosis was incompletely compensated. There was hypochloraemia, hypokalaemia, uraemia and a small increase in plasma sodium. The urine was alkaline due to a high concentration of bicarbonate, the concentrations of sodium and potassium were normal but the urea content was low and the U/P ratio for urea was 6.0.

The initial fluid therapy consisted of solutions containing hydrochloric acid, sodium, potassium, chloride, dextrose, fructose, ethanol, amino acids and a fat emulsion. The amounts of each given during the first few hours are shown in Table 2. Oxygen therapy was given by means of an MC mask.

TABLE 1. Biochemical findings on admission to the Intensive Care Unit

	pH	PaCO_2 (mmHg)	Electrolytes (mEq/l)				Urea (mg/100 ml)	Specific gravity
			Bicarbonate	Sodium	Potassium	Chloride		
First patient								
Blood or plasma	7.55	68	48	150	3.2	84	150	
Urine	7.42		75	58	72		1600	1.015
Second patient								
Blood or plasma	7.44	70	50	155	4.5	61	350	
Urine				70	55	24		1.010

TABLE 2. Initial fluid therapy and nutrition

	Time	Water (l)	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Hydrion (mEq)	Calories	Nitrogen (g)
First patient	Day 1, 4 p.m. to 10.30 p.m.	1.68	96	44	166	40	787	1.1
	4 p.m. of Day 1 to 10 a.m. of Day 2	4.45	326	139	556	100	2074	7.1
Second patient	5 p.m. of Day 1 to 8 p.m. of Day 2	4.63	181	40	367	150	3304	2.1

After 6½ hr the general state of the patient had improved. The minute volume was then 8 l and the Paco_2 and plasma bicarbonate had fallen by 15 mmHg and 12 mEq/l respectively. (Table 3) During this time the patient was given 40 mEq hydrochloric acid. After 18 hr of fluid therapy 100 mEq hydrochloric acid had been used together with the other electrolytes and food shown in Table 2. The blood then showed a normal pH but raised Paco_2 and bicarbonate. During the evening of the second day of intensive care (postoperative Day 6) there was deterioration and shock recurred. Improvement followed infusions of 'Macrodex' 6% given to restore the blood pressure and central venous pressure, together with hydrocortisone. During Days 3 and 4 the patient was better and well enough to sit out of bed for a short time. The temperature fell to normal and the gastric aspirate decreased. On Day 3 the arterial blood showed a mild metabolic alkalosis with moderate hypercapnia. The alkalosis was still present on Day 4 but the Paco_2 was then normal (Table 3). The intakes of water, sodium, potassium and chloride and the losses of water, sodium and potassium are given in Table 3.

The good progress was not maintained and fever, hypotension and a large gastric aspirate recurred. The patient died on the eleventh postoperative day when the blood findings were: pH 7.48, Paco_2 36 mmHg and bicarbonate 27 mEq/l, plasma sodium 161 mEq/l, plasma potassium 5.8 mEq/l, blood urea 232 mg/100 ml, blood sugar 1000 mg/100 ml, serum amylase 800 Somogyi units/100 ml, haemoglobin 50%. Acute pancreatitis and generalized peritonitis were found at necropsy.

Case 2

A man aged 48 with a chronic peptic ulcer developed persistent vomiting due to pyloric obstruction. His habit was to take 800–1000 mEq of alkali each day as magnesium hydroxide and carbonate. The patient was restless and confused, emaciated and dehydrated. Respirations were slow and shallow. The blood pressure was 100/60 and the ECG showed atrial fibrillation. Radiographs of the chest and abdomen were normal. The blood (Table 1) showed a fully-compensated metabolic alkalosis with severe hypercapnia. There was hypernatraemia, severe hypochloraemia and uraemia. The urine had a normal specific gravity, normal concentrations of sodium and potassium but a low chloride content.

During the first 27 hr the patient was given 150 mEq of hydrochloric acid together with the other electrolytes and food shown in Table 2. Oxygen therapy was given by means of an MC mask. During this period the patient improved generally and alveolar ventilation increased, the Paco_2 falling by 10 mmHg. The plasma bicarbonate fell from 50 to

34 mEq/l and there was a small increase in the plasma chloride, which remained low. The plasma potassium was normal. By the third day the patient was greatly improved and was able to sit out of bed. The blood showed a normal pH and Paco_2 and the plasma bicarbonate was only slightly raised. The intakes of water, sodium, potassium and chloride and the losses of water, sodium and potassium are given in Table 3. Persistent uraemia attributed to tubular damage was treated by 5 days of peritoneal dialysis.

Pyloroplasty and vagotomy (Mr R. Brearley, F.R.C.S.) was carried out on the thirteenth day and convalescence was trouble-free. Three months later the patient was symptomless. The blood urea was 32 mg/100 ml, creatinine clearance 125 ml/min and the acidification test of Wrong & Davies (1959) gave a urinary pH of 5.2. Spirometry, lung volumes and transfer factor (Dr C. M. Ogilvie) were normal.

Discussion

In the first patient, who had severe pancreatitis, the alkalosis was probably due to loss of chloride as gastric acid and sodium chloride together with potassium depletion and the administration of sodium bicarbonate. In the patient with pyloric obstruction, the alkalosis was caused by loss of gastric acid, a large intake of alkali and potassium depletion due to starvation.

In both patients respiratory compensation of the alkalosis was complete or nearly so. This extreme compensation caused severe respiratory failure, which of itself, was a serious threat to life. The laboratory measurements show that, to determine the effects of an alkalosis, it is necessary to measure pH and Paco_2 . It is also preferable to measure bicarbonate rather than calculate this value from the Henderson-Hasselbalch equation. In a separate study we have confirmed that, in disease, large differences exist between the plasma bicarbonate measured and the value calculated from the Henderson-Hasselbalch equation. The finding of severe hypercapnia in the blood of a 'surgical' patient is a pitfall because the hypercapnia could be wrongly interpreted as the prime disorder of acid-base balance. It would be illogical and dangerous to lower the Paco_2 by artificial respiration. We believe that the respiratory failure caused by the metabolic alkalosis required specific treatment with hydrochloric acid. The acid therapy was included in the fluid therapy and nutrition used to replace deficits of water, sodium and potassium and to provide calories and nitrogen. This made it impossible to prove that hydrochloric acid alone improved alveolar ventilation; the observations do however, strongly suggest that hydrochloric acid increased ventilation.

TABLE 3. Biochemical results, fluid therapy and nutrition during the first 4 days of intensive therapy. The recording of intake and output started at 8 a.m. of each day

Day and time	Arterial blood		Plasma electrolytes				Blood urea (mg/100 ml)	Water (l/day)		Sodium (mEq/day)		Potassium (mEq/day)		Chloride (mEq/day)		Intra-venous HCl (mEq)	Diet	
	pH	PaCO ₂ (mmHg)	Sodium (mEq/l)	Potassium (mEq/l)	Chloride (mEq/l)	Intake		Output	Intake	Output	Intake	Output	Intake	Output				
							Day								time			
First patient																		
Day 1, 4.00 p.m.	7.55	68	48	150	3.2	84	140	43	u 1.3	u 36	u 100	549	†	100	1942	6.5		
10.30 p.m.	7.53	53	36					a 2.3	a 209	a 30								
Day 2, 10.00 a.m.	7.44	62	36	169	3.7	100	212	7.22	u 2.6	u 75	u 169	552	†	0	4132	15.4		
8.00 p.m.	7.47	43	30*			109	272	a 1.0	a 116	a 11								
Day 3, 11.45 a.m.	7.47	56	27			109	176	4.37	u 1.45	u 29	u 96	318	†	0	3508	8.1		
								a 0.85	a 51	a 31								
Day 4, 11.00 a.m.	7.50	40	21	150	4.3	112	94	5.21	u 1.15	u 32	u 71	273	†	0	4028	8.7		
								a 0.6	a 65	a 8								
Second patient																		
Day 1, 5.00 p.m.	7.44	70	50	155	4.5	61	350	2.0	u 1.0	u 70	u 58	140	u 24	100	615	0		
10.00 p.m.	7.44	68	42															
Day 2, 1.00 p.m.	7.39	65	38	149	5.0	68	280	4.93	u 1.3	u 78	u 47	338	u 39	50	3904	12.9		
8.00 p.m.	7.38	60	34*															
Day 3, 11.00 a.m.	7.46	43	30*			81	300	3.49	u †	u †	u †	263	u †	0	3474	12.9		
Day 4, 11.15 a.m.	7.35	43	28			85	345	3.28	u 2.5	u 172	u 60	263	u 113	0	3474	12.9		

u, Urine; a, gastric aspirate; *, calculated result; †, no data.

TABLE 4. Acid therapy used to treat metabolic alkalosis

References	Cause of alkalosis	Intravenous hydrochloric acid (mEq)	Patients treated	
			Number treated	Number survived
Elkington & Danowski (1955)	Ileus and acute renal failure	50 700	1	0
Frick & Senning (1963)	Ileus	765 500	3	2
Rampini & Frick (1964)	Ileus and acute renal failure	150	1	1
Girardet (1967)	Pyloric stenosis	No data	1	1
Bradham (1968)	Trans-lumbar amputation	No data	1	1

In other patients admitted to this unit with a metabolic alkalosis, respiratory compensation has been slight or absent. These patients showed tetany which, when associated with coma and convulsions, was an immediate threat to life. We suggest that when a metabolic alkalosis causes either severe respiratory failure or severe tetany, intravenous hydrochloric acid is a valuable and safe addition to conventional fluid therapy. We found no reference to these indications for using hydrochloric acid therapy. Frick & Senning (1964) advise hydrochloric acid therapy to treat a metabolic alkalosis when intravenous sodium chloride was contra-indicated because of acute renal failure with oliguria; a situation in which we would use dialysis. The scanty literature on the use of intravenous hydrochloric acid is shown in Table 4. Intravenous ammonium chloride has been used more often than hydrochloric acid but has the serious disadvantage of ammonium toxicity (Zintel, Rhoads & Ravdin, 1943; Moore, 1959). Peritoneal dialysis has been successfully used to correct the metabolic alkalosis of pyloric obstruction (D. M. Morrison, personal communication).

In theory acetazolamide should accelerate removal of excess bicarbonate from the extracellular fluid into the urine but we have no information on this treatment. On the treatment of alkalosis, Black (1964) wrote 'I am doubtful if direct attack on alkalosis by giving acids (or potential acids such as ammonium chloride) is ever called for.' We think that there are rare exceptions to this opinion.

References

- BLACK, D.A.K. (1964) *Essentials of Fluid Balance*, 3rd edn. Blackwell Scientific Publications, Oxford.
- BRADHAM, G.B. (1968) The intravenous use of hydrochloric acid in the treatment of severe alkalosis. *American Surgery*, **34**, 551.
- DOUGLAS, C.G. & PRIESTLEY, J.G. (1948) *Human Physiology*, 3rd edn. Oxford University Press, London.

- ELKINGTON, J.R. & DANOWSKI, T.S. (1955) *The Body Fluids*. Baillière, Tindall & Cox, London.
- FRICK, P.G. & SENNING, A. (1963) The treatment of severe metabolic alkalosis with intravenous N/10 or N/5 hydrochloric acid. *Deutsche medizinische Wochenschrift*, **88**, 1924.
- GIRARDET, P. (1967) Intravenous injection of hydrochloric acid in a case of serious metabolic hypochloreaemic alkalosis. *Rev. Med. Suisse, Rom.* **87**, 278.
- MOORE, F.D. (1959) *Metabolic Care of the Surgical Patient*. W. B. Saunders, Philadelphia.
- PEASTON, M.J.T. (1966) Design of an intravenous diet of amino-acids and fat suitable for intensive patient care. *British Medical Journal*, **2**, 338.
- PETERS, J.P. & VAN SLYKE, D.D. (1931) *Quantitative Clinical Chemistry*. Baillière, Tindall & Cox, London.
- RAMPINI, S. & FRICK, P.G. (1964) Intravenous hydrochloric acid in the treatment of hypochloreaemic alkalosis. *Helvetica paediatrica acta*, **19**, 391.
- SEMPLE, S.J.G., MATTOCK, G. & UNCLES, R. (1962) A buffer standard for blood pH measurements. *Journal of Biological Chemistry*, **237**, 963.
- SEVERINGHAUS, J.W. & BRADLEY, A.F. (1958) Electrodes for blood PO_2 and PCO_2 determination. *Journal of Applied Physiology*, **13**, 515.
- SIGGAARD-ANDERSEN, O. (1963) Blood acid-base alignment nomogram. *Scandinavian Journal of Clinical and Laboratory Investigation*, **15**, 211.
- SIGGAARD-ANDERSEN, O., ENGEL, K., JØRGENSEN, K. & ASTRUP, P. (1960) A micro method for the determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. *Scandinavian Journal of Clinical and Laboratory Investigation*, **12**, 172.
- SKEGGS, L.T. (1960) An automatic method for the determination of carbon dioxide in blood plasma. *American Journal of Clinical Pathology*, **33**, 181.
- THOMPSON, G.S. & JONES, E.S. (1965) Errors in the measurements of serum electrolytes. *Journal of Clinical Pathology*, **18**, 443.
- VAN SLYKE, D.D., WEISIGER, J.R. & VAN SLYKE, K.K. (1949) Photometric measurement of plasma pH. *Journal of Biological Chemistry*, **179**, 743.
- WRONG, O. & DAVIES, H.E.F. (1959) The excretion of acid in renal disease. *Quarterly Journal of Medicine*, **28**, 259.
- ZINTEL, H.A., RHOADS, J.E. & RAVDIN, I.S. (1943) The use of intravenous ammonium chloride in the treatment of alkalosis. *Surgery*, **14**, 728.