SALICYLATE INTOXICATION TREATED WITH INTERMITTENT POSITIVE- PRESSURE RESPIRATION

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The returns of the Registrar-General for England and Wales (1950-2) indicate that in this country aspirin and its derivatives remain an important cause of death from poisoning in children. During the three years 1950-2, 21 children lost their lives in this manner. In the United States of America in 1952 there were 86 deaths from this cause in children under the age of 5 years (Committee on Toxicology, American Academy of Pediatrics, 1955). Many such cases are the result of accidental ingestion of the drug. In the experience of Heymann *et al.* (1954), however, the danger of intoxication following therapeutic administration of the drug is much greater. Holt (1954) has shown that the dose of salicylate administered does not bear a constant relationship to the resulting blood level and, furthermore, that the blood level at which toxic symptoms appear varies greatly from patient to patient.

Various therapeutic measures have been recommended for the condition, but there appears to be no previous report of the use of intermittent positive pressure respiration. This paper is presented in order to show that this procedure may have an important place in the treatment of salicylate intoxication.

Symptoms

Among the more common and important symptoms of salicylism is hyperventilation. Graham and Parker (1948) have shown that this is due to reflex stimulation of the central respiratory mechanism through the afferent fibres of the vagus nerve, and is independent of the blood acid-base relationship. As the reaction of the blood, however, depends to a large extent on the proportion of bicarbonate to carbonic acid in the plasma, the rapid elimination of carbon dioxide which occurs in hyperventilation quickly causes a state of respiratory alkalosis. This is the first disturbance of the acid-base equilibrium that occurs in salicylism. Thus the hyperventilation is the cause of the acid-base disturbance and not vice versa. Singer (1954) has shown that later, probably owing to the accumulation of unidentified organic acids, a true metabolic acidosis may supervene. The gross hyperactivity of the respiratory musculature may play a part in this. Hyperpnoea may also be a factor in the production of various other phenomena occurring in salicylism, including tachycardia, and a reduction of the cerebral blood flow (Kety and Schmidt, 1946).

As stated above, the hyperventilation is responsible for the state of alkalosis, and this in turn may be clinically manifest as tetany. This is believed to occur independently of the level of diffusible calcium in the blood (Wright, 1952), and is, in our experience, not affected by the administration of calcium gluconate.

Treatment

Apart from immediate withdrawal of the drug and washing out of the stomach, treatment has usually been directed towards the correction of the biochemical changes when these have become established. Most authorities (Williams and Panting, 1937; Barnett *et al.*, 1942; Heymann *et al.*, 1954) have recommended the use of appropriate intravenous infusions. The difficulty and uncertainty of such therapy, however, have led Heymann *et al.* (1954) and Done and Otterness (1956) to use exchange transfusion, and Doolan *et al.* (1951) have gone so far as to recommend the use of the artificial kidney.

In view of the fact that the electrolyte disturbances are secondary to the hyperpnoea, it would appear more rational to direct therapy towards a reduction of the respiratory exchange and of the hyperactivity of the respiratory musculature. One obvious means of obtaining this end is the use of drugs known to have a depressant effect on the central respiratory mechanism. In their experimental studies, Rapoport and Guest (1945) were able to limit the hyperpnoea and the secondary biochemical changes with barbiturates and opiates. They found, however, that salicylates appeared to sensitize their animals to the action of these drugs, and that their administration in doses normally well tolerated resulted in prolonged coma or in death. This would seem to preclude the use of such drugs in salicylism.

In order to limit the output of carbon dioxide, Harvie and Singer (1955) proposed that the patient be made to breathe a gas mixture with a high carbon dioxide content. Obviously in a patient with an active central respiratory mechanism this raises the blood carbon dioxide tension only when the patient is already ventilating at his maximum breathing capacity, or when carbon dioxide is administered in such high concentrations as to produce depression of the central nervous system. Our experiences, described below, illustrate the limitations of this therapeutic measure, in that any reduction of tetany occurs only at the expense of accentuated respiratory dysfunction. These limitations led us to consider the value of neuromuscular block in overcoming the respiratory and biochemical effects of salicylate poisoning.

Therefore, when we were presented with a case in which a child, as the result of salicylate poisoning, was comatose, hyperpnoeic, suffering from tetany, and clearly *in extremis*, this method of treatment was applied and its value is shown by the following case report.

Case History

A 6-year-old boy complained of sore throat early in January, 1956. One week later he developed painful swellings of both knees, and a patchy erythema with well-defined margins was noted on the upper parts of both arms and on the thighs. He was thought to be suffering from rheumatic fever, and sodium salicylate, 7½ gr. (0.5 g.) was prescribed, to be given two-hourly, the total daily dose being 75 gr. (5 g.). He was not given any alkali. This was taken regularly up to the time of his admission to Alder Hey Children's Hospital 11 days later, on January 20. On the day preceding admission he had become a little drowsy and seemed somewhat irrational. That evening he vomited once and had two nose bleeds. The following afternoon his respiratory rate increased and he was admitted the same evening.

On admission he weighed only 35 lb. (15.9 kg.); he had thus received a little over 2 gr. of salicylate per pound (280 mg. per kg.) body weight per day for 11 days. He was conscious and co-operative and did not appear to be particularly ill, although his respiration was somewhat increased

in both amplitude and rate (50 a minute). The temperature was 97.8° F. (36.5° C.) and his pulse rate 148 a minute. There was no evidence of carditis or of any other manifestation of rheumatic fever.

He was given 10 mg. of vitamin K intramuscularly in view of the epistaxis and known capacity of salicylate to induce hypoprothrombinaemia. Drinks of orange juice with added sodium bicarbonate were offered and he was kept under observation overnight. No marked change was noticed during the night, but the next morning, January 21, it became obvious that he was deteriorating. He became deeply unconscious and began to sweat profusely. Muscular tetany then appeared; there was spasmodic arching of the back accompanied by marked stiffness of the limbs, the arms being extended at the elbows, the forearms pronated, the wrists flexed, the fingers flexed at the proximal interphalangeal joints, and the thumbs adducted; the hips and knees were extended and the feet plantar-flexed; the jaw was tightly clenched.

At this stage a report was received showing that the blood salicylate concentration of the previous evening had reached the extraordinarily high level of 66 mg./100 ml. Blood taken at 9.30 a.m. on January 21 showed the level of salicylate to have fallen to 40 mg./100 ml. while the alkali reserve was 30.9 vols./100 ml. (13.8 mEq/l.); serum chlorides, 529 mg./100 ml. (90.3 mEq/l.); blood urea, 36 mg./100 ml.; serum protein, 6.8 g./100 ml. (16.3 mEq/l.); serum potassium, 13.1 mg./100 ml. (3.3 mEq/l.); serum calcium, 9.3 mg./100 ml. (4.6 mEq/l.); serum calcium ions, 4.2 mg./100 ml. (2.1 mEq/l.); unfortunately neither serum pH nor carbon dioxide tension was estimated.

Despite the falling plasma salicylate concentration the patient's clinical condition continued to worsen during the day. Therapy at this stage consisted of an intravenous infusion of N/5 sodium chloride with 5% dextrose, given at the rate of 30 ml. an hour, and a gastric milk drip, containing 50 g. of glucose to the pint, at the rate of 1 pint (570 ml.) in 24 hours. Alkalinizing solutions were not used at this stage because the patient was still tetanic and therefore presumably still alkalotic. Intravenous injections of 0.3 g. and 0.4 g. of calcium gluconate failed to affect the tetany.

By 7 p.m. he was still comatose, tetanic spasm was almost constantly present, the temperature had risen to 102° F. (38.9° C.), and the respirations had increased to 70 a minute and were extremely deep.

In view of the gross clinical tetany, presumably due to respiratory alkalosis, it was decided to try to conserve and increase the patient's serum carbon dioxide concentration. Initially an attempt was made to encourage rebreathing through a length of corrugated rubber tubing, and after several minutes there was a slight fall in the respiratory rate and slight lessening of limb rigidity, but no notable beneficial effect. With a mixture of 5% carbon dioxide in oxygen the respiratory rate again fell somewhat after several minutes, but the respiratory effort was still very great. The respiratory rhythm changed, his expirations becoming more forceful. Within four minutes the limb rigidity had diminished until the arms were quite flaccid and convulsive spasms became infrequent. After 20 minutes, however, the limbs again became rigid and the spasms increased. The raising of the concentration of carbon dioxide to 10% produced a similar transient effect. Despite these manoeuvres respiration remained violent and exhausting and the severe tetany recurred.

Neuromuscular Block and Control of Respiration

It was then decided to try to reduce the respiratory excursion and effort by neuromuscular block. Five milligrams of suxamethonium was injected intravenously. The respiratory excursion diminished greatly and a "see-saw" type of rhythm developed, there being no change in respiratory rate. Two further injections of 5 mg. were given at intervals of five minutes. With these the respiratory excursion diminished until ventilation became quite ineffec-

tive. Despite this, however, the trismus persisted and difficulty was experienced in maintaining an airway. It was apparent that incomplete myoneural blockade would not be effective as a means of controlling hyperventilation. Therefore, at 11 p.m. on January 21, 27 hours after the patient's admission to hospital, the decision was taken to curarize the patient fully and to control his respiration.

The head was lowered and 10 mg. of D-tubocurarine was injected intravenously, while the patient was made to breathe oxygen. As the jaw relaxed accumulated secretions were aspirated from the pharynx. A No. 3 uncuffed McGill endotracheal tube was inserted and copious yellowish mucoid secretion aspirated from the trachea and bronchi. The tube was then connected to an Ayre T-piece and controlled intermittent positive-pressure respiration was instituted, with 3 litres a minute each of oxygen and nitrous oxide.

Progress

With this treatment sweating soon ceased, his pulse rate fell from 140 to 100 beats a minute and the temperature from 101 to 99.4° F. (38.3 to 37.4° C.). The patient was carefully observed and 3 to 6 mg. of D-tubocurarine was given intravenously at intervals as required, a total of 36 mg. being administered within the next 12 hours. One and a half hours after the last dose of D-tubocurarine artificial respiration was discontinued and the endotracheal tube was removed. A bronchoscope was passed and bronchial secretions were aspirated. He was then placed in an oxygen tent.

Soon after the cessation of intermittent positive-pressure respiration the patient's breathing was normal in rhythm and depth and settled at a rate of 24 a minute. His pulse was 110 a minute and the temperature had fallen to normal. His coma, however, persisted and the tone of his limbs was still slightly increased, but there were no further tetanic spasms. On examination of his eyes it was noticed that the arteries in the left fundus were constricted.

At this time (10 a.m. on January 22) his blood salicylate level was 29.5 mg./100 ml. Other values were as follows: alkali reserve, 32.8 vols./100 ml. (14.8 mEq/l.); serum chloride, 542 mg./100 ml. (92.4 mEq/l.); serum potassium, 10.2 mg./100 ml. (2.5 mEq/l.); serum sodium 310 mg./100 ml. (134 mEq/l.); blood urea, 39 mg./100 ml.; serum protein 7 g./100 ml. (16.8 mEq/l.); blood sugar, 120 mg./100 ml.

At 11.30 a.m. his intravenous infusion was changed from N/5 saline to 1/6 molar lactate, as at this stage he was thought to have entered the phase of metabolic acidosis. He was given a total of 300 ml. in the space of 10 hours. His gastric drip was continued at the rate of 1 pint (570 ml.) per 24 hours, and 2 g. of potassium was added to it in order to correct the deficiency of this electrolyte.

At 7 p.m. on that day his alkali reserve had risen to 53.8 vols./100 ml. (24 mEq/l.); his serum salicylate level was 24 mg./100 ml. Other blood levels estimated at this time were: serum chloride, 538 mg./100 ml. (93 mEq/l.); serum sodium, 326 mg./100 ml. (142 mEq/l.); serum potassium, 10.5 mg./100 ml. (2.64 mEq/l.); red-cell sodium, 64 mg./100 ml. (28 mEq/l.) (normal 36–58 mg./100 ml., 15.7–25.3 mEq/l.); red-cell potassium, 330 mg./100 ml. (84.6 mEq/l.) (normal 358–390 mg./100 ml., 98.1–100 mEq/l.).

On the following morning, January 23, 24 hours after the end of controlled respiration, consciousness returned, though he was still very listless and drowsy. His temperature had remained normal; his pulse rate was 100 a minute and his respirations 30 a minute. By then his blood salicylate level had fallen to less than 5 mg./100 ml.; serum chlorides were 542 mg./100 ml. (93 mEq/l.); serum potassium, 11.6 mg./100 ml. (2.9 mEq/l.); and alkali reserve 55.7 vols./100 ml. (25 mEq/l.). Thereafter he rapidly improved, and he was discharged home eight days after admission, having made a complete recovery from his salicylate intoxication. Clinically and radiologically his lungs were normal. The mixture of salicylate which he had been taking was analysed and found to contain the prescribed dose of the drug.

Comment

Apart from the successful control of hyperpnoea, the following points in the above case history are considered to be significant.

At the time when intermittent positive-pressure respiration was instituted copious mucopus was present in the trachea. With our form of treatment, however, tracheo-bronchial toilet could be performed with ease, and bronchial aspiration was prevented. Thus one of the major hazards of coma was eliminated. Another advantage was that intra-gastric feeding could be continued in safety.

Following the institution of our form of treatment, the raised temperature and pulse rate moved rapidly towards normal, suggesting that they were caused by the heightened respiratory muscular activity.

The response of this boy to the inhalation of carbon dioxide shows that it has no place in the treatment of salicylate intoxication.

Tetany in our patient was a manifestation of alkalosis, and was not related to the level of ionized calcium in the blood, as this was within normal limits. It is therefore not surprising that the administration of calcium gluconate had no beneficial effect.

Summary

Salicylate intoxication causes an appreciable number of deaths among children. Gross hyperpnoea is one of the more serious toxic effects of salicylate poisoning; it is caused by reflex stimulation of the respiratory centre through the afferent fibres of the vagus nerves. The hyperpnoea gives rise to respiratory alkalosis and this may be accompanied by tetany and convulsions.

A case is described in which the hyperpnoea of salicylate poisoning was treated successfully by neuromuscular block and manually controlled intermittent positive-pressure respiration. It is believed that this method of treatment contributed materially to the patient's recovery. In addition, the administration of intravenous fluids is essential in order to conserve the body's water balance; milk can be given by gastric drip with impunity, as aspiration of fluid is prevented by a cuffed endotracheal tube.

The inhalation of carbon dioxide and the administration of calcium gluconate were not found to be effective therapeutic measures.

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USE OF HYPOTHERMIA IN NON-VASCULAR INTRACRANIAL TUMOURS

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During recent years the value of hypothermia as an aid to certain types of surgery has become established. In cardiac surgery when temporary occlusion of one or more of the great vessels is required, and in cerebral surgery when the main arteries supplying vital structures are occluded, or when a period of prolonged induced hypotension is desired, hypothermia has been found to be of undisputed value (Lougheed *et al.*, 1955; Botterell *et al.*, 1956).

One mechanism by which reduced body temperature safeguards vital organs is known to be that of metabolic depression with resulting reduced vulnerability to anoxia, and where arterial occlusion is practised this mechanism is clearly the prime one (Ralston *et al.*, 1955; Rosomoff, 1956). Where no deliberately induced ischaemia of this type is involved, however, hypothermia would still appear to have certain benefits, the exact mechanism of which is less clearly understood, although the basic theory of reduction of susceptibility to anoxia is still no doubt a major consideration (Lundberg *et al.*, 1956).

The use of hypothermia in the management of head injuries has had recent publicity and is an example of this "non-vascular" indication for a lowered body temperature. We have recently gained the impression that reduction of temperature is also of value when operative procedures involving the hypothalamus, diencephalon, and brain stem are contemplated, even though neither carotid occlusion nor prolonged hypotension is to be employed as part of the technique. Operative intervention in the brain-stem region is known to carry a high post-operative mortality, and the reasons for such deaths are not always clear. It is suggested that the commonly seen post-operative coma and hyperpyrexia are due, in part at least, to tissue-swelling resulting from trauma with consequent cellular damage, in which case it is probable that anoxia plays a not unimportant part. Indeed, such anoxia might conceivably result from operative retraction itself, as the arteries supplying the midline structures are often end arteries. It is not at all unknown for an actual thrombosis of the lenticulostriate artery to occur on one or other side during the course of such an operation.

Whatever the causes of such injury may be, however, whether they be anoxia or indirect or direct trauma, we have come to the opinion that hypothermia protects cells of the brain stem and diencephalon during operative procedures.

This is obviously a point which would require statistical proof, and such will not be possible until large numbers of cases are available; even then advances in other directions render a control series almost impossible. No further comment can therefore be made than to say that it is now our routine to use hypothermia in all cases