TREATMENT OF ASPIRIN POISONING BY INTRAVENOUS SODIUM LACTATE SOLUTION

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Aspirin, or acetyl-salicylic acid, is formed by the action of acetic anhydride upon salicylic acid. It is not a completely stable substance, and samples often have the odour of acetic acid. In the commercial preparation certain impurities may be present in the form of ortho-cresotic acid and acetic acid, as well as free salicylic acid.

A solution of aspirin yields a buff-coloured precipitate with ferric chloride. In the presence of free salicylic acid a violet colour is formed, although the colour due to a small amount of salicylic acid can be masked by the addition of tartaric, citric, or other oxyacids. The limit of free salicylic acid has been suggested as 0.2 per cent. in the tablet form (Martindale and Westcott, Vol. 2).

Large single doses are usually required to produce symptoms of intoxication, and very large doses may be fatal. A patient recently reported by A. V. Neale (1936) recovered with intensive treatment after taking 500 grains (32.4 grammes), and a patient of S. C. Dyke's recovered with treatment after taking 435 grains (28.8 grammes) (Dyke, 1935). Dyke also quotes from the literature a series of fatal cases: Hitché's patient, who died after taking 1,000 grains (64.8 grammes); five cases of Janoviche's, in whom the average fatal dose had been about 500 grains (32.4 grammes); and a series of cases studied by Balázs, who considered the minimum fatal dose to be in the neighbourhood of 450 to 600 grains (29.8 to 38.9 grammes).

We have found no mention, however, of the dose which may prove fatal in children. One child whose case we are here reporting was 14 months old, and took a dose of about 30 grains (1.944 grammes), which would probably have proved fatal but for intensive treatment.

Poisoning may also occur where salicylate is administered therapeutically in divided doses. M. Odin (1932) reports fourteen cases in which poisoning occurred after doses of 90 grains (5.8 grammes) a day, and two cases in which only 45 grains (2.9 grammes) per day were administered.

Metabolism of Aspirin

The solubility of aspirin in water is very slight—only 1 in 400—and the rate of hydrolysis is minimum in a neutral solution. It is markedly increased by the presence of acid or alkali. Martindale showed that the percentage hydrolysis in water after four hours was only 2.9 per cent.; in 0.2 per cent. hydrochloric acid it was 4.7 per cent. Thus hydrolysis with physiological acid is very slight, which means that the amount split up while passing through the stomach does not exceed 5 per cent. of the total amount taken. The bulk of the ingested aspirin is decomposed by the alkaline intestinal juices to salicylate, while a small amount is absorbed unchanged as aspirin, and may be excreted in this form. The total excretion in the urine of ingested salicylate is normally between 60 and 75 per cent. The total excretion of unchanged aspirin varied from 8 to 36 per cent. in a series investigated by Hanzlik (Martindale and Westcott, Vol. 2).

Potassium citrate increases the water solubility of the aspirin, two volumes of potassium citrate rendering it

soluble 1 in 20 (Martindale and Westcott, Vol. 1). When prescribed with potassium citrate "there may be a notable difference in physiological effect, as apart from the independent action of the potassium citrate the speed, and even the locus of absorption in the system, may give enhanced effect. A larger proportion may perhaps be absorbed in the stomach, and in consequence less would be carried forward to the duodenum, where alone aspirin is thought to be assimilated." Sodium bicarbonate has a similar action in hastening the decomposition of aspirin and leads to the formation of acetate and salicylate of sodium. These pharmacological factors have an important bearing on the treatment of aspirin poisoning. For example, a stomach wash-out will probably be of value only if performed within the first hour or two after the ingestion of the aspirin, when the bulk of the aspirin has not yet passed on to the duodenum. Also, the oral administration of sodium bicarbonate as an antidote, which is so popularly favoured, is contraindicated in the early stage when the absorption of aspirin may be increased.

Clinical Picture

The clinical features of aspirin poisoning may best be described by the report of a case from the literature. S. C. Dyke's patient (1935) was a woman who recovered after taking 435 grains (28.8 grammes). In the first few hours of illness the main symptoms were nausea and buzzing in the ears. During the night she appeared to be mentally confused, and became deaf. Next day she became stuporous, disorientated, and extremely restless, and resisted all interference. Severe vomiting produced dehydration, but sweating was not specially noted. Her respirations were deep and slow, and she presented the picture of acidosis, the urine showing acetone by Rothera's test and a deep purple colour with ferric chloride. This latter reaction was out of proportion to the amount of acetone present, and was best explained by the probable presence of aspirin in the urine. Visceral damage was indicated by the presence in the urine of bile salts and traces of urobilin. The urine also reduced Fehling's solution. Treatment consisted mainly in the administration of fluid and glucose by the bowel and mouth, and in repeated lumbar punctures, which appeared to have a very beneficial effect. By the third day the patient had improved, although she was still drowsy and complained that her head felt large and that her vision was blurred. She made a complete recovery.

A. V. Neale (1936) described a patient who rapidly developed symptoms after taking 500 grains (32.4 grammes) of aspirin. Vomiting occurred after two and a half hours, and four and a half hours later she became semi-comatose. She was very pale and sweated profusely, and her respirations were quick and shallow, later becoming deeper. The alkali reserve in this patient was 40 volumes per cent. (the normal is from 50 to 60 volumes per cent.). Treatment consisted chiefly of a stomach wash-out and lumbar puncture. In twenty-four hours there was improvement, but she complained of deafness and tinnitus. A reactionary pyrexia up to 100° F. (38° C.) followed forty-eight hours later. The urine was free from salicylic acid four days after admission.

Report of Patients at the Children's Hospital, Melbourne

CASE I

A male infant, 14 months old, was admitted to the Children's Hospital, Melbourne, under the care of Dr. Stewart Ferguson, at 4 p.m. on September 16, 1936, with the history that two and a half hours previously he had eaten six or

seven aspirin tablets—that is, at least 30 grains (1.944 grammes). Half an hour later he had vomited white frothy material freely mixed with pink blood, and the vomiting had been repeated three or four times. He was now looking a little paler than normal, but was otherwise well. At 6 p.m. he had a temperature of 98.5° F. (36.8° C.), a good pulse of 128, and the respirations of 28 per minute were quiet and easy. When seen again at 11 p.m. he was sitting up and looking very wideawake, but seemed quite comfortable, with a good pulse and colour. During the night his respirations increased in frequency and depth, and he became agitated and noisy, passing a sleepless night. Five ounces (142.1 c.cm.) of 10 per cent. glucose and saline were taken orally by the child. When seen next morning he showed extreme mental and physical restlessness and great thirst. He drank liberal amounts of fluid, but most of it was vomited. His respirations were rapid and gasping, at 56 per minute. Circulatory depression was present, the pulse being 162 per minute and of very poor volume, and the child's colour was slightly grey and cyanotic. He was also dehydrated and hollow-eyed. A specimen of blood was taken from the superior longitudinal sinus through the anterior fontanelle for an estimation of the alkali reserve, which was 22 volumes per cent. The temperature was 102° F. (39° C.). His general condition rapidly became worse and the respiratory distress was greater, making the outlook extremely grave.

A continuous intravenous infusion of a buffer solution of isotonic sodium lactate, as described by Hartmann (1934), was commenced, and 15 ounces (85.6 c.cm.) were run in by the slow-drip method. This was followed by 30 ounces (170.52 c.cm.) of 10 per cent. glucose and saline solution. Two units of insulin were given four-hourly with the glucose. Chloral hydrate and potassium bromide, 4 grains, were administered as a sedative, and large amounts of sodium bicarbonate solution and glucose were given by mouth.

Two hours after the intravenous solution had been running his general condition commenced to improve. His colour and circulation were better, and the respirations, though deep and rapid, were less distressed. His temperature remained elevated, and he fell into a light, restless sleep. By the next morning he had become peaceful, and the respirations, while remaining rapid, were shallow and easy. Another estimation of the alkali reserve showed that it had risen to 55 volumes per cent. On the following day the alkali reserve had fallen again to 38 volumes per cent., but the general improvement was sufficiently established to allow the intravenous infusion to be discontinued.

From the third day until the tenth day he continued to vomit several times daily; he was looking pale and sick, running an irregular temperature, and losing weight. The urine showed occasional hyaline and granular casts. The alkali reserve on the seventh day was 42 volumes per cent. From the tenth day onwards he commenced to improve and to gain in weight, and became a normal cheerful baby once more, making a complete recovery.

There are many interesting features in this case on which we should like to comment. There are several symptoms in common with those seen in adult patients, such as the vomiting, mental restlessness, thirst, dehydration, and respiratory changes. The long latent period may be very misleading in assessing the seriousness of the intoxication. There is also the very critical level of 22 volumes per cent. to which the alkali reserve had fallen; this is the lowest figure we have seen reported in literature in which recovery occurred.

With regard to treatment it would have been advisable to wash out the stomach in spite of the fact that copious vomiting had occurred. The dose of sodium lactate solution required to raise the alkali reserve 25 to 30 volumes per cent. is 10 c.cm. of the molar sodium lactate per kilogramme of body weight diluted with five volumes of distilled water (Williams and Panting). We can find no previous record of the treatment of aspirin poisoning with this solution.

Discussion

It is of interest to consider what is the pathological and biochemical basis underlying these clinical manifestations of profound toxæmia in aspirin poisoning. A necropsy of the case described by Andrew Wyllie (1935) revealed blood in the stomach and petechial haemorrhages on the serous surfaces of the lungs and heart. The kidneys were in a condition of glomerulonephritis, and the liver showed fatty degeneration. Paisseau, Friedmann, and Vaille (1934) describe the anatomical changes as being discrete in the case of the kidneys, but of great intensity in the liver, which was in a state of fatty degeneration. The anatomical changes are well established, but the mechanism of the production of the clinical syndrome is not so universally agreed upon.

Almost everywhere in the literature salicylate poisoning has been regarded as an acidosis due to poisoning by the acid radical, either that contained in the salicylate itself, the view most commonly held, or by some other acid formed in the body as a result of disturbed metabolism, a view held by Balázs (1930). In 1928 opposition had been raised by Veil and Graubner against the view that salicylate poisoning was due to an acidosis, and more recently by Martin Odin, who regards the symptoms of deep respiration as being due to a specific toxic action of the salicylate on the respiratory centre.

As early as 1882 Quincke described the hyperpnoea so frequently found in salicylate poisoning, and regarded it as being due to the action of the acid radical on the respiratory centre. This was again regarded as being analogous to the deep breathing found regularly in the acidosis of diabetic coma. Further support for this conception is the fact that there is always a fall in the alkali reserve of the blood. Also, it is thought that a favourable result could be observed from the administration of sodium bicarbonate. G. Paisseau notes further points in favour of this interpretation in the acidity of the urine with a constantly lowered pH, the resistance to alkalization, and the raised ammonia excretion.

Veil and Graubner base their opposing theory partly on certain theoretical calculations showing disproportion between the fall of the alkali reserve and the quantity of salicylic acid ingested. They regard the deep breathing as due to a specific action on the respiratory centre.

Martin Odin (1932) compares the biochemical findings in salicylic intoxication and diabetic coma. He finds in the first instance an average alkali reserve of 38 volumes, a salicylic acid content of the blood of about 0.3 gramme per litre of blood, the pH of the blood being normal or slightly raised. In diabetic coma where deep breathing was present the alkali reserve was usually about 26 volumes, the total acids in the blood 0.75 gramme per litre—double the amount of salicylic acid—and the pH of the blood lowered. He draws the conclusion that the salicylic acid must be considerably more toxic than diacetic acid, seeing that the symptoms of poisoning in diabetic coma arise only when the content of the latter acid in the blood is considerably higher. And so one can hardly speak of salicylic poisoning as an acid poisoning pure and simple; it is a more specific toxic action.

Investigation of a second child treated at the Children's Hospital, Melbourne, for aspirin poisoning lends support to the view of a specific action of salicylate on the respiratory centre, at least in the earlier stage of the toxic effect.

CASE II

A girl, aged 2 years and 8 months, swallowed approximately 60 grains (3.89 grammes) of aspirin, and it was not until twelve hours later that her parents became worried

about her condition. At first irritable, while mentally very alert, with rapid breathing and fits of screaming, she was admitted to hospital twenty-four hours after the ingestion of the aspirin. Her clinical picture, with deep rapid respirations 48 per minute, flushed face, and vomiting, was compatible with a diagnosis of acidosis; yet this was not confirmed by investigation. The alkali reserve was 50 volumes per cent., and the urine gave negative reactions to Gerhardt's and Rothera's tests. The treatment given was 8 ounces (227 c.cm.) of 2 per cent. glucose and saline solution intravenously, and 1 pint (568 c.cm.) of 10 per cent. glucose and 0.9 per cent. sodium bicarbonate solution orally during the first twelve hours. The child's breathing remained deep, and the rate was 40 per minute; she was still irritable. The alkali reserve had fallen to 29 volumes per cent. and the urine gave positive reactions to Gerhardt's and Rothera's tests, showing that a state of acidosis had developed.

Twenty-six ounces (738 c.cm.) of sodium lactate solution and 17 ounces (447 c.cm.) of 10 per cent. glucose and saline solution were given by the slow-drip method intravenously in twenty hours, the patient showing considerable improvement. She was able to take a normal light diet, and appeared quite well after a further three days.

Conclusion

In our cases the weight of evidence seems to be in favour of the intoxication being possibly a toxic action on the respiratory centre, but chiefly due to an acidosis. This is borne out by the rapid improvement in the clinical condition which accompanied the rise in the alkali reserve following the administration of sodium lactate solution. Odin (1932) warns us to be careful in using salicylate in nephritic patients. In two of his cases already quoted albumin was present in the urine before treatment was commenced, and both patients developed symptoms of poisoning with so small a dose as 45 grains a day. All of his cases had a moderate number of red blood cells in the urine, five had albuminuria, and two had some casts. This, considered with the necropsy findings of acute nephritis, indicates that it is difficult for nephritic patients to excrete salicylic acid.

Summary

1. A survey of the reported cases of aspirin poisoning is given, showing that large doses are necessary in adults to produce toxic effects.

2. Alkalis increase the absorbability of aspirin.

3. Two infants, who developed severe toxic symptoms after the ingestion of 30 grains (1.944 grammes) and 60 grains (3.89 grammes) of aspirin respectively, are described; both recovered after sodium lactate (Hartmann's solution) had been injected intravenously.

4. It is considered that the toxicity of aspirin is due to an acidosis, and possibly to a direct action of salicylic acid on the respiratory centre.

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CONTINUOUS INTRAVENOUS SALINE INFUSION

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Continuous intravenous saline infusion is now being used more extensively in this country; unquestionably it has helped to save many lives. We feel that a time has been reached when it would be well to review its advantages, to try to enumerate its indications and contraindications, and particularly to dwell upon the dangers connected with its use.

Indications

1. *Dehydration* from any cause, such as starvation, vomiting, diarrhoea, or excessive sweating.—In acute intestinal obstruction the combination of continuous gastric aspiration and continuous intravenous saline infusion both before and after operation is a marvellous therapeutic advance.

2. *Prevention of Post-operative Shock*.—A typical indication is at the close of the operation of partial gastrectomy, especially when it has been performed on a poor subject.

3. *Shock*.—Here we appear to have a helpful method of combating shock. In these cases we have added one ampoule of coramine to each pint of saline solution with advantage. French observers have reported favourably on the results of adding adrenaline to the solution in doses of about 5 minims of 1 in 1,000 solution to each pint.

4. *Diabetic Coma*.—This is probably the best method of introducing large quantities of glucose and insulin, a measure which is so necessary in this condition.

5. *Post-operative Thyrotoxicosis*.—It has long been recognized that a copious fluid intake is beneficial in these cases. If administered early enough continuous intravenous saline infusion will often tide the patient over a crisis. If hyperpyrexia and other signs indicate that the patient is being flooded with the toxin, the injection of 50 minims or more of Lugol's solution into the delivery tube, associated with the application of an ice-pack to the limbs and precordial region, and, above all, the employment of an oxygen tent, is the best possible course to adopt in these anxious, but now fortunately rare, catastrophes.

6. *In profound jaundice, after the obstruction has been removed*, it is often remarkable how quickly the jaundice clears when continuous intravenous saline treatment is administered (see also Contraindications).

7. *Septicaemia*.—That benefit accrues from continuous intravenous medication in septicaemia is not generally agreed. In our experience in some cases continuous intravenous saline therapy, by diluting the circulating toxin and stimulating the excretory activity of the kidneys, appears to have done good. The addition of a capsule of intravenous mercurochrome to each filling of the reservoir definitely has done no harm, and we believe that in several cases of septicaemia it has helped the patient to combat the infection.