1959

Salicylate intoxication

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1959

Omaha, Nebraska

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INTRODUCTION

The problem of ingestion of toxic materials is well known to the physician. This is particularly true of the salicylates probably because of their availability in every home in America, and the innocuous attitude the layman has toward these drugs.

In my review of the literature dealing with salicylate intoxication, I wish to discuss the general aspects of this problem, trying to explain the clinical features seen in this condition. I wish to demonstrate the more serious complications and the pathological changes seen in severe salicylate poisoning to emphasize that aspirin is a lethal drug.

Finally, I will review the more recent forms of treatment including exchange transfusion and the artificial kidney. I will discuss the use of the artificial kidney, carefully demonstrating the great promise it offers in rapid removal of salicylate from the patient. Also an examination will be made of the criteria for use of the artificial kidney in salicylate intoxication.

INCIDENCE AND ETIOLOGY OF SALICYLATE INTOXICATION

Salicylates account for 4 per cent of all fatal poisonings in the United States due to solids or liquids. (1) The actual incidence of aspirin poisoning is much higher. Out of the first 500 poisoning cases reported to the Chicago Poison Control Program in 1952, 84 of the cases were aspirin poisoning. This indicates an actual incidence of aspirin poisoning nearly 16 per cent of all poison cases.

Greenberg in 1950 (2) reported that in one third of the reported cases of acetylsalicylic acid poisoning, the drug was taken in suicidal attempts. Other reasons for taking acetylsalicylic acid were rheumatic fever, 22.2%; analgesis, 23.6%; other medicinal use, 13.9%; and accidents accounting for only 5% of acetylsalicylic poisoning cases. It is probable that this 5% of accidental ingestions has increased in recent years with the development of attractively flavored infant's and children's aspirin. The accidental ingestion or therapeutic overdose causing salicylate poisoning is an important hazard to children. The highest death rate from salicylate poisoning is found in the age group 1 to 4 years. (1) Methyl salicylate (oil of wintergreen) and aspirin are forms of salicylates most often involved in childhood poisonings. Salicylate compounds are known to have caused 113 deaths in the United States in 1952. (3) Of these deaths, 86 occurred in children under

5 years of age. Twenty-one of these deaths were caused by methyl salicylate, 41 by aspirin, but in most of the cases the type of salicylate was not specified.

Another factor causing an increase in salicylate poisoning cases in recent years is the increasing use of salicylates in the treatment of diseases such as acute rheumatic fever and rheumatoid arthritis. In these diseases, the difference between a therapeutic and a toxic dose of salicylate often becomes difficult to recognize. For this reason physicians must be able to recognize the early signs and symptoms of salicylate intoxication.

INGESTION AND ABSORPTION OF SALICYLATE

There appears to be very little correlation between the ingested dose and the serum level of salicylate. Schreiner, et al. 1955 (4), demonstrated this with two cases. The first case, a 44-year old man, ingested 210 grams of aspirin in doses of five 3 gm. tablets every day, increasing to 50 tablets every day over an eight week period. His serum salicylate level was 91 mgm per cent 26 hours after ingestion of the last dose. The second case, a 19-year old woman, ingested 45 grams of aspirin in a single dose and showed a serum salicylate level of 90 mgm per cent 30 hours after ingestion. The first patient ingested only 15 grams the day his salicylate level was measured as compared to 45 grams for the woman, yet their serum salicylate levels were nearly the same. Thus we see

that many factors, some unknown, are involved in the absorption of large doses of salicylates. We will review the absorption of salicylates at this time in an attempt to understand some of these factors.

The salicylates are chiefly absorbed from the upper intestinal tract. (5) Sodium salicylate in particular is rapidly absorbed and appreciable blood levels can be detected within 30 minutes of its oral ingestion. Acetyl salicylic acid is absorbed more slowly, reaching a peak serum concentration in from 2 to 3 hours. (6) Methyl salicylate is absorbed very slowly and may be delayed for many hours; therefore, gastric lavage should be performed even in cases of poisoning which seem late.

A lowering of the gastric pH tends to facilitate the absorption of salicylates. This tends to correlate with the work of Smull et al. (7), who demonstrated that the simultaneous administration of equal amounts of sodium bicarbonate and enteric coated sodium salicylate prevents the establishment of as high a serum salicylate level as would be obtained with sodium salicylate alone. Some authors (5) believe that sodium bicarbonate hastens the intestinal absorption of aspirin and that the fall in serum salicylate level is due to the effect of sodium bicarbonate in facilitating renal excretion of salicylates. I would tend to favor this latter opinion because of the tremendous effect sodium bicarbonate has on the excretion of salicylates, which I will discuss later in this paper.

The individual variation in the absorption of salicylates makes it extremely difficult to designate an accurate ingested lethal dose. The usual adult lethal dose of aspirin is considered in excess of 10 grams although fatal cases have been reported in adults with as little as 2 grams of aspirin ingested. (8)

By reviewing the ingestion and absorption of salicylates I have attempted to show that there is very little correlation between the ingested dose and the serum salicylate level, especially when the large toxic doses are considered. Also that the absorption of aspirin is in some way affected by the pH of the stomach, and that sodium bicarbonate when given orally with aspirin will produce a lower serum salicylate level than would be expected by aspirin alone. These factors I believe important when considering salicylate intoxication and proper treatment.

DISTRIBUTION AND EXCRETION OF SALICYLATE

After the absorption of salicylate the drug is distributed rapidly throughout all body tissues. Salicylate has been detected in synovial, spinal and peritoneal fluid, saliva, bile and milk. The concentration of salicylate in different tissues is directly dependent upon the serum concentration. This results from the equilibrium maintained between tissue water and serum. However, the concentration of salicylate in muscle and brain is considerably lower than that to be anticipated on the basis of water content. (9)

This indicates that factors other than molar equilibrium play a part in the distribution of salicylate to these tissues. Some authors (5) believe that salicylate becomes bound to plasma protein upon entering the blood stream. This seems unlikely with the demonstration of dialysis of salicylate readily across a semipermeable membrane. If such a bond does exist, it is readily broken upon exposure to an osmotic gradient.

The concentration of salicylate in nervous tissue becomes important when describing the toxic effects of excessive salicylate. Many of the toxic effects of salicylate are apparently caused by the direct action of salicylate upon nervous tissue.

Salicylates are excreted from the body mainly by the kidneys. Of a given dose, approximately 70 to 80 per cent can be recovered in the urine in the form of salicylate and its metabolites. The actual excretion of salicylate by the kidneys is relatively slow. Salicylate can be demonstrated in the urine within a few minutes after its administration, but only 50 per cent of a given dose is eliminated in 24 hours. Traces of salicylate can be found in the urine up to 48 hours or longer. (5) The renal clearance of salicylate is dependent largely upon the pH of the urine. When the urinary pH is above 7 the renal clearance of salicylate increases rapidly. So dependent is the renal clearance of salicylic acid on the pH of the urine that an increase in pH from 6.0 to 7.7 causes approximately a tenfold increase in excretion. (5) Exactly why

this occurs is questionable. Some authors (10) believe that the dissociation of salicylic acid varies with the pH so as to affect excretion of the acid. Others (11) have shown that the renal tubules actively secrete conjugated metabolites of salicylate and that the rubular reabsorption predominates when the urine is acid and tubular excretion is ascendent when the urine is alkaline. The exact mechanism as to how the pH of the urine alters the secretory and reabsorptive processes of tubular cells is not clear at present. This problem deserves further exploration. The enhancement of renal excretion of salicylate by raising the pH of the urine is the reason sodium bicarbonate is often given in treatment of salicylate intoxication. This also explains why ammonium chloride is given to some patients with rheumatic fever receiving salicylates. In these cases the ammonium chloride elevates the serum salicylate level to therapeutic levels. The excretion of salicylate by the kidneys becomes very important in salicylate intoxication. Enhancing the excretion of salicylate by the kidneys or providing other methods of removing salicylate from the body make up the treatment of salicylate intoxication.

SIGNS AND SYMPTOMS OF SALICYLATE INTOXICATION

The toxic manifestations of salicylate overdose fall into three groups. In the first group are those which are relatively

unimportant but common. These are tinnitus, headache, deafness, nausea, sweating and transient vomiting. The aural disturbances are apparently due to a functional impairment of the eighth cranial nerve, the same as described with quinine intoxication. (5)

The second group of symptoms are those that are uncommon though individually they may be serious. They are vertigo, drowsiness, mental upsets, pulmonary edema and hemorrhage. The central nervous system disturbances are apparently due to direct action of the salicylates on the central nervous system. (5) The bleeding tendency noted in patients or animals receiving toxic doses of salicylate are believed due to multiple defects in the coagulation mechanism. Salicylates exert an antivitamin K effect in liver metabolism so that the production of prothrombin is impaired. This effect can be somewhat overcome by the administration of large doses of Vitamin K. In addition the level of circulating fibrinogen falls in subjects poisoned with salicylate, probably because of the failure of synthesis by the liver. (1)

The third group of symptoms are both common and alarming. They are hyperventilation and severe vomiting. The hyperventilation is now generally believed caused by the central stimulatory effect of salicylate on the respiratory center. (5) The severe vomiting is one of the most disturbing features of salicylate intoxication and if persistent results in dehydration and may interrupt treatment. This vomiting was formerly believed due to local

gastric irritation by the salicylate, but the demonstration of vomiting after intravenous administration of sodium salicylate in the absence of salicylate in the stomach contents indicates that the main cause is central rather than local. (13, 14)

The signs and symptoms of salicylate intoxication are easily recognized when a history of salicylate ingestion is available. It is in the cases which present no clear history of salicylate ingestion in which recognition of these toxic manifestations becomes important. A patient may be actually taking aspirin in an effort to relieve some of the symptoms produced by overdose of the drug. This emphasizes the danger of a drug which is so readily available to the public.

THE ACID-BASE DISTURBANCE IN SALICYLATE INTOXICATION

The acid-base disturbance in salicylate intoxication as recently reviewed by Singer, 1954 (12), is described as an initial primary respiratory alkalosis produced by the hyperventitory effect of salicylate upon the central respiratory center. In severe intoxication, especially in infants, the initial stage is succeeded by a mixed disturbance, a combination of primary CO_2 deficit and primary alkali deficit, with marked reduction of both CO_2 pressure and buffer base and the pH shifting from the alkaline to the acid side of normal. The cause of the primary metabolic acidosis is unknown. It may be due to accumulation of unidentified organic acids as a

result of toxic effects of salicylate on cellular metabolism.

Some authors (15) believe the development of metabolic acidosis is started by a specific action of salicylate on carbohydrate metabolism in the liver, with resultant rapid depletion of glycogen. This results in ketosis which becomes rapidly severe because of the already diminished bicarbonate supply. This acidosis provides further stimulus for hyperventilation which increases the respiratory alkalosis.

Singer (12) emphasizes that the dual acid-base disturbance makes it necessary to obtain CO_2 concentration and blood pH measurements before proper clinical evaluation of such a patient can be made. Both respiratory alkalosis and metabolic acidosis produce lowering of the CO_2 concentration and there is no certain way to differentiate them without the additional determination of a blood pH or its equivalent.

THE PATHOLOGICAL CHANGES SEEN IN SALICYLATE INTOXICATION

The pathological changes seen in salicylate intoxication, although rare, appear to be striking when seen. Krasnoff and Bernstein, 1947 (8), describe pathological changes in the brain, kidneys, and liver of a patient who died of acetylsalicylic acid intoxication. Examination of this brain revealed cerebral atherosclerosis, cortical and subcortical degeneration, areas of necrosis

and fatty degeneration of the cells of the medulla. A case of toxic encephalopathy has been reported in a patient treated with salicylates for rheumatic fever. (16)

The kidney changes seen in salicylate intoxication are usually the changes most clearly demonstrated. These changes consist of renal congestion, glomerular degeneration and tubular degeneration. (8) The arterioles show a definite degeneration of their walls. Campbell and McClaurin, 1958 (17), describe a case of acute renal failure probably due to tubular necrosis following salicylate poisoning. They suggest that renal damage in salicylate poisoning is commoner than is generally appreciated and may play a part in the acid-base disturbance.

The liver changes described consist of sinusoidal congestion, many large and small vacuoles, hydropic and fatty degeneration and beginning necrosis. The changes seen in the liver are apparently not very common or clear. Only one report (8) in my review of the literature mentioned liver damage in salicylate intoxication.

Other pathological changes apparently result from the hypoprothrombinemia sometimes seen in salicylate poisoning. These changes consist of petechial hemorrhages in the skin, mucous membranes and often through the serosal surfaces of the viscera. (8) This condition may produce severe hemorrhaging and even hematuria, (1) in affected patients. A clinical picture not unlike that seen in the blood dyscrasias is sometimes seen.

Certain authors report gastric ulceration in salicylate poisoning. They have demonstrated this both with gastroscopy and on section of biopsy material. The process seems to be a necrosis of the neck cells in the foveola, with sloughing and superficial ulceration.

The pathological changes seen in salicylate intoxication, although rarely seen, point out the toxic systemic effects that an overdose of aspirin may have.

COMPLICATIONS OF SALICYLATE INTOXICATION

The nephrotoxic and hemorrhagic complications have already been discussed. Other complications frequently noted in salicylate toxicity are glycosuria and hyperglycemia. Often the report of glycosuria may have been due to the presence of salicylate in the urine, since salicylate is a reducing substance for copper-containing reagents. In other instances care has been taken to make sure that the reducing substance was glucose. Sevringhaus and Meyer, 1930 (18), reported hyperglycemia in an adult patient poisoned by methyl salicylate whose glucose tolerance curve remained definitely abnormal eight days after recovery, but was normal again two weeks later. Schadt and Purnell, 1958 (15) published a case of permanent diabetes mellitus following severe salicylate poisoning in a 59-year old man. They believe the development of diabetes mellitus in this patient is most likely coincidental to the salicylate

poisoning episode but it is of interest because of the known hyperglycemic effects of salicylates. Silverman and Piccolo, 1942 (19), speculated that the hyperglycemia may be due to damage to the hypothalamic region by the salicylate.

In a number of reports of salicylate toxicity, scalp paresthesias and pain have been mentioned as prominent features. It might be possible that the toxicity increased the pain through its neurotoxic action. This would lead the patient to take more salicylate, thus forming a vicious cycle. In at least one instance, the pain, herpetic in nature, disappeared after recovery from salicylate toxicity. (15)

PROGNOSIS IN SALICYLATE INTOXICATION

Recovery from salicylate intoxication is usually complete when none of the more severe symptoms or complications are present. With the development of bleeding tendencies, severe vomiting, coma or renal disease the prognosis becomes more guarded. There is a poor correlation between the serum salicylate level and the clinical condition of the patient so that a serum salicylate level should not be used as a prognostic tool.

TREATMENT OF SALICYLATE INTOXICATION

Until recently the treatment of salicylate poisoning has been largely symptomatic. Gastric lavage should always be performed in hope of recovering some of the ingested salicylate. Before beginning more definitive treatment a blood CO_2 concentration and pH should be performed to determine the exact acid-base condition of the patient. In the alkalotic stage fluids should be administered in the form of glucose in water. Some authors recommend small doses of sodium bicarbonate so as to increase the renal excretion of salicylate and also prevent too great a lowering of the bicarbonate reserve. Other authors recommend that no bicarbonate be given so as not to aggravate the alkalotic state. I believe that the marked effect sodium bicarbonate has upon increasing renal excretion of salicylate would justify its use even in this alkalotic state.

Once the patient has become acidotic, intravenous injection of sodium lactate is the preferred form of fluid therapy. Williams and Pauling, 1937 (20) first recommended this treatment and it has become standard treatment since that time. This solution replaces the fixed cation lost through the kidneys or bound to ketone acids in the acidotic state. Schadt and Purnell, 1958 (15), showed dramatic improvement in the condition of their patient following intravenous administration of M/6 sodium lactate. They began therapy

with 1000 cc of the solution intravenously at a rate of 80 drops per minute. They followed the condition of their patient with CO_2 combining power determinations and clinical observations. Four hours after the start of the first infusion their patient was no longer comatose and responded to simple questions. Diaphoresis and hyperpnea had also diminished greatly after the first 4 hours of treatment. The dramatic improvement produced in this comatose patient would certainly emphasize the importance of proper fluid therapy in treatment of salicylate intoxication.

There is no specific antidote for salicylates. For this reason after the absorption of large doses of salicylate the only effective form of treating this intoxication must be by increasing the excretion of the drug. One of the most recent methods of elimination of salicylate has been with exchange transfusions. Most of this work has been done in methyl salicylate poisoning cases because of the apparently small amount of this substance ingested required to produce a rapid fatal outcome. Done and Otterness, 1956 (21), were the first to successfully treat a patient with salicylate intoxication with exchange transfusion. Adams et al., 1958 (22), treated a 20-month old male, who had ingested approximately 5 ml. of methyl salicylate, with exchange transfusion. The child was in acute critical condition before transfusion with very little chance for survival. The blood salicylate level on admission had been 72.7 mg per 100 ml and was reduced by only 42% after the exchange trans-

fusion of 1200 ml. of whole blood. This was the equivalent of the child's total blood volume. After the exchange of 2035 ml. of whole blood, the salicylate level was reduced by a total of 59%. The child tolerated the procedure well and was considered entirely normal 10 days after the exchange transfusion. However, directly following the exchange the respirations continued to be rapid 48 to 50 per minute. The patient was comatose prior to the transfusion but did respond by crying out to any type of motion of his arms, legs or head directly following the transfusion. Approximately four and one half hours after completion of the exchange, the patient began to urinate small amounts of urine. The respiration slowed to 30 to 32 per minute. However, it was not until 24 hours after transfusion that the patient was responsive to his name and began to take fluids by mouth.

The presentation of this case indicates that this form of treatment may be life-saving in certain cases. However, it does not produce the dramatic reversal of symptoms we would like to see in treatment of this condition. Only by dramatic reversal of clinical state can we hope to avoid the serious complications of salicylate intoxication. This case presentation also indicates that this form of treatment may be restricted to smaller children for technical reasons. It would require approximately 20 units of whole blood to exchange transfuse an average adult and get the same results as above.

An exchange transfusion is also limited because tissue pools

rapidly replete blood salicylate following exchange transfusion and reintoxication (endogenous) may occur.

Thus we see that although this form of treatment can be life-saving in certain cases, it does not answer completely the problem of salicylate intoxication therapy.

Although only recently popularized, the dialysis of salicylic acid was performed as early as 1914. Abel, Rountree and Turner, 1914 (23), used their vividiffusion apparatus in removing an ingested amount of salicylic acid from dogs. Their vividiffusion apparatus consisted of a series of collodion tubes connected with glass tubing which then were submerged in normal saline. With this apparatus they were able to remove 24.35 per cent of the amount of salicylic acid they had injected into a dog. They recognized as early as 1914 the importance of being able to remove such a toxic substance as salicylic acid from the body.

This early work prompted Doolan et al. (24) in 1951 to attempt the dialysis of an adult man who had ingested 140 five-grain tablets the day of admission to the hospital. This man came to the hospital in coma, hyperventilating and drenched with perspiration. He was dialysed using a modified Kolff artificial kidney. The dialysis had to be interrupted after one hour for technical reasons, but during the one hour of dialysis 1.3 grams of salicylic acid were removed in the bath. His blood salicylate level was 55 mgm per cent following dialysis. This patient continued to degenerate and died the day after

dialysis of apparent respiratory failure. Necropsy disclosed petechial hemorrhages throughout the cerebrum, brain stem, visceral peritoneum and mesentery. This dialysis, although not successful in saving the patient's life, proved the value of dialysis in removing salicylate from the human bloodstream.

Leonard in 1955 (25) dialysed two patients with salicylate poisoning with excellent results. Details are given for only one patient. This patient had taken a large dose of methyl salicylate and on admission to the hospital had a blood concentration of 130 mgm per 100 ml. salicylate. It was possible to remove 9.5 gm salicylate by hemodialysis, reducing the serum salicylate concentration to 30 to 40 mgm per 100 ml. The patient recovered from coma and the respiratory rate fell very quickly.

Schreiner et al., 1955 (4), reported two cases of salicylate intoxication, one treated using hemodialysis and the other treated conservatively. I wish to describe these cases carefully as they point out differences in the treatments and demonstrate the rapid recovery possible through hemodialysis.

Case I is a 44-year-old man who entered Georgetown University Hospital in a comatose condition after taking 7 bottles of aspirin over the preceding 8 weeks. He had been taking 5 aspirins per day, increasing to 50 tablets per day for a headache. The day before admission to the hospital, he had taken his usual dose of aspirin but had combined it with coca-cola to synergize their effect. On ad-

mission he was breathing deep and regular at 22 per minute. His pulse was 120 and his blood pressure 120/75. Urinalysis revealed a clear yellow urine with a pH of 5.5 and specific gravity of 1.018. The urine was 1+ for albumin and negative for sugar but 4+ for acetone. The carbon dioxide combining power was 9 milliequiv/liter. The ferric chloride test for urine salicylate was strongly positive both before and after the urine was boiled. The pH of arterial blood was 7.15 and the blood salicylate level was 90 mgm per 100 ml. This patient was dialysed on a Kolff artificial kidney $7\frac{1}{2}$ hours after admission. It was decided to begin dialysis on this patient because of his poor clinical condition. The clinical improvement after dialysis had begun was remarkable. See Figure 1. After 3 hours the patient was speaking rationally. The dialysis was discontinued after six hours with a mild hypotension (blood pressure of 80/60) as the only untoward effect. The serum salicylate level had fallen 57 mgm per cent during these 6 hours with 9.4 gm of salicylate recovered from the bath. The patient continued to improve after dialysis and was dismissed 12 days after admission asymptomatic.

Case 2 is a 19-year-old woman who disolved 1 bottle (83 gm) of aspirin in a glass of water and drank about "half" in a suicidal attempt. A gastric lavage was performed 4 hours after ingestion, but she was still asymptomatic. Later the same day she was admitted to Georgetown Hospital in a drowsy but orientated condition. She was hyperpneic, restless and partially deaf. The CO_2 combining power

was 24 milliequiv. per liter and the prothrombin time was 50 per cent of normal. She was treated with vitamin K, sodium bicarbonate by mouth and fluids intravenously. She became more drowsy, had slurred speech, and complained of "roaring" in her ears. Physical examination revealed flushed facies, a hot dry skin and deep irregular respirations at 36 per minute. The blood pressure was 110/50, the pulse was 100 and the neurological signs were not remarkable. Laboratory data revealed urine to be negative for sugar, acetone, albumin or salicylates. The serum salicylate level was 91 mg. per 100 ml. This patient was continued on conservative management because approximately 30 hours had elapsed since ingestion of the aspirin without loss of consciousness and close observation was possible. Intravenous fluids and sodium lactate were started. The patient's course over the next six days was one of progressively severe mental disturbances including visual hallucinations and maniacal behavior which reached their peak on the fourth day. She abruptly reverted to normal behavior on the fifth day and was dismissed asymptomatic one day later to the care of her family and psychiatrist. The serum salicylate had slowly declined and had disappeared by the sixth day. The recovery from the urine totaled 8.4 gm.

These two cases are very similar in onset both presenting with many of the common symptoms seen in salicylate intoxication. They both had serum salicylate levels near 90 mg per cent yet Case I

was comatose whereas Case 2 was only drowsy yet orientated. This again demonstrates the poor correlation between clinical state and serum salicylate level.

The shortened morbidity and rapid reversal of coma in Case 1 following dialysis certainly decreased the possibility of cerebral and pulmonary complications. Schreiner et al. in comparing the salicylate recovery from the two patients showed that the artificial kidney removed salicylate about twenty times faster than normal urinary excretion. See Figure 2.

These two cases represent borderline cases as to the decision to use the artificial kidney. Some might question the hesitancy of the author to dialyze Case 2 with her high serum salicylate level and no improvement in her clinical course. The decision in favor of conservative treatment after 30 hours without coma may be a valid one. Acetyl salicylic acid in 1 gram doses reaches a peak of absorption at 2-3 hours (6) so even with this much larger dose (45 gm) absorption should be complete at 30 hours remembering gastric lavage was done 4 hours after ingestion of the aspirin.

Thomas and Dolgard, 1958 (26), reported a case of acetylsalicylic acid which they treated with hemodialysis. They have also attempted to formulate the indications for hemodialysis in salicylate poisoning.

The Thomas and Dolgard indications for hemodialysis in salicylate poisoning are: Cases of poisoning in which

(1) the elimination of salicylate is slow as a result of acute or chronic renal insufficiency, or

(2) coma or signs of respiratory and circulatory depression are present.

Their first indication was apparently stimulated by their case of a 41-year-old man who consumed 150 gm. of acetylsalicylic acid with the development of classic signs and symptoms of salicylate poisoning, with superimposed renal insufficiency. This patient was dialysed for $5\frac{1}{2}$ hours with the serum salicylic acid concentration reduced from 51.0 mg to 24.8 mg per 100 ml. Following this, renal function returned to normal and clinical condition was dramatically improved.

In considering indications for dialysis we must remember that amount ingested and serum salicylate level in no way reflect the clinical state. Schreiner (27), in a recent review of their salicylate poisoning cases treated with hemodialysis, emphasizes that one cannot predict survival or death accurately from the estimated ingested dose or the blood concentration. He believes this is due to the wide range of tolerance to salicylates in different individuals. In general, he believes that more than 20 gms. of acetylsalicylic acid ingested or blood salicylate level over 50 mg. per 100 ml. are often associated with severe toxicity.

Experienced clinical judgment is necessary to select patients for hemodialysis. Also we must remember that hemodialysis is not

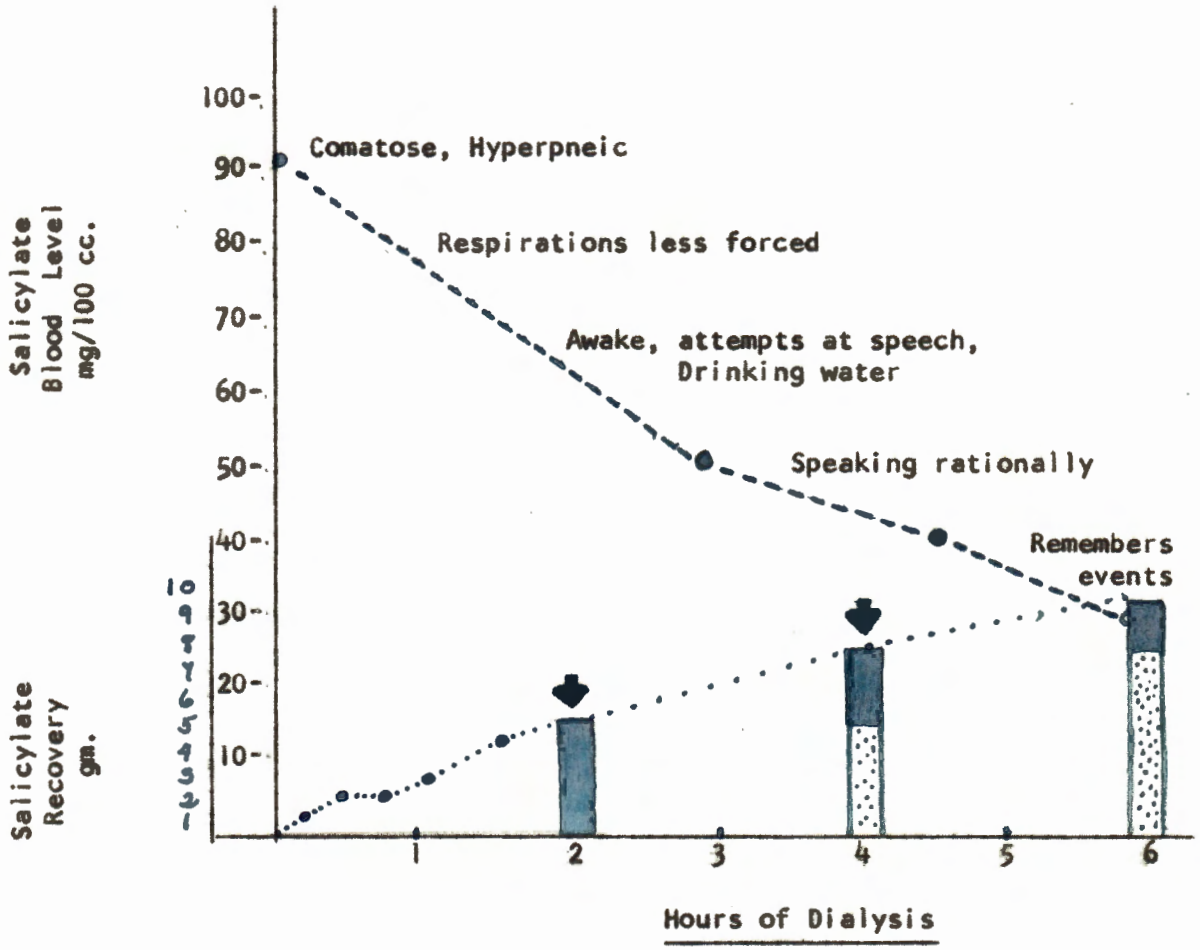
done without risk to the patient. Therefore, we must not submit patients to hemodialysis who would survive under conservative therapy.

I believe that the Thomas and Dolgard indications for hemodialysis, although not precise as to when to do hemodialysis during the clinical course of the patient, cover the general indications for hemodialysis. Certainly any patient with impaired renal function and salicylate poisoning deserves dialysis with the artificial kidney. Also coma and depression of the vital centers would certainly alert you that it is time for hemodialysis.

Here again we have reserved for the artificial kidney the role of the "last chance" for the survival of the patient. Schreiner (27) suggests that earlier use of dialysis in patients with high blood levels may reduce the severity of subsequent pathology. He suggests this after describing two cases of salicylate poisoning which ended fatally. One case with irreversable brain damage and one with irreversable liver necrosis. Perhaps our criteria should be lowered to allow less moribund patients to be dialysed. The thing that must be remembered in considering indications for hemodialysis is that each patient must be analysed and treated individually. For this reason we must adhere to the broad indication as listed above and determine individually the optimal time and duration of dialysis for each patient.

Figure 1.

---- Blood Salicylate Level, Case I
.... Salicylate present in bath
Total Salicylate in previous baths
Amount Salicylate in bath
Bath change



This clearly demonstrates the rapid clinical improvement in Schreiner's Case I during hemodialysis.

Figure 1, page 214
(New England J. of Med. August 11, 1955)

Clinical Dialysis of Salicylate (Case 1)

Figure 2.

---- Case I Dialysed
.... Case II No Dialysis
Urine Salicylate Excretion
Salicylate Extraction
6 hours Hemodialysis

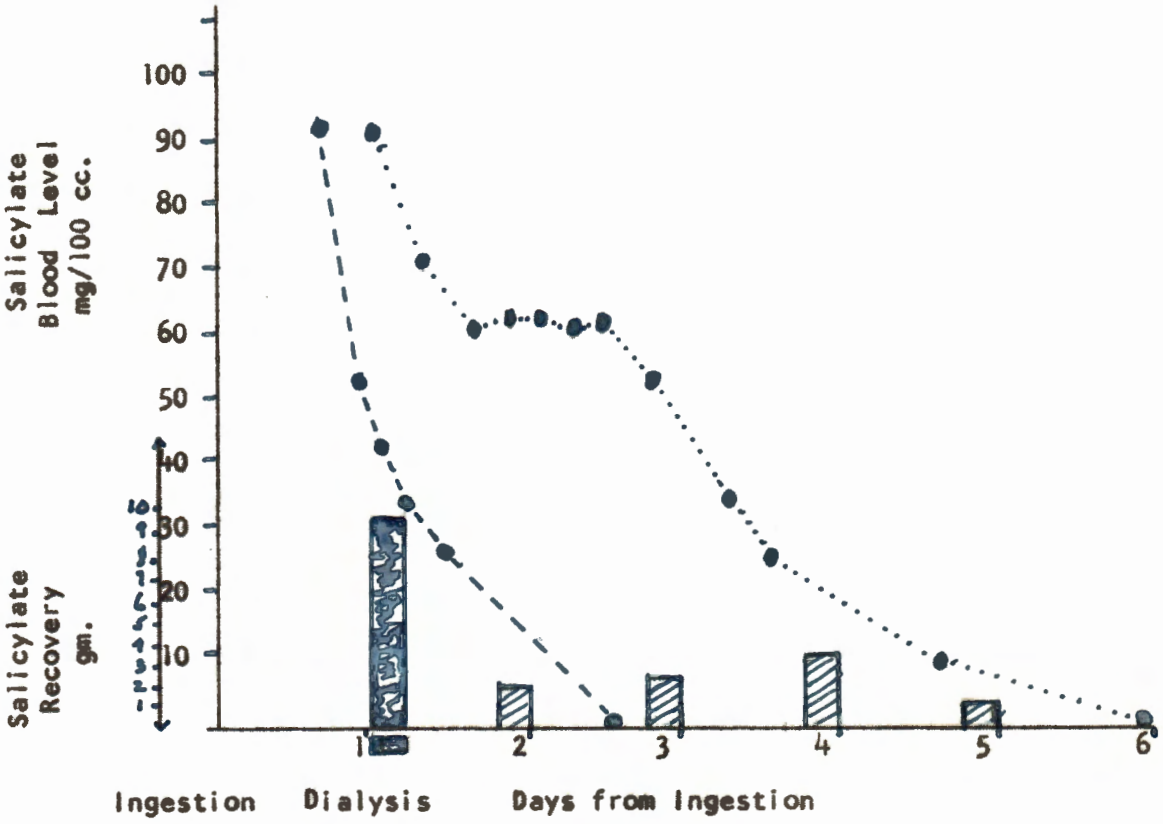


Figure 2. Efficiency of Hemodialysis in Salicylism (Cases 1 & 2)

A comparison is made between Case 1 and 2 of the excretion of salicylates. This demonstrates the efficiency of hemodialysis in rapid removal of salicylates as compared to normal urinary excretion.

SUMMARY AND CONCLUSIONS

Salicylate intoxication has become one of the most common causes of fatal poisonings. Fatalities from salicylate intoxication occur most commonly from accidental ingestion in the 1-4 age group. Fatalities also commonly occur with therapeutic administration of salicylates in this younger age group.

The amount of salicylate ingested does not appear to correlate with the serum salicylate level or the clinical state of the patient.

Absorption of salicylate is controlled by many factors, some unknown. An increase in gastric acidity tends to increase absorption of salicylate.

The excretion of salicylate by the kidney is controlled mainly by the pH of the urine. An increase in the pH of the urine causes up to a tenfold increase in the excretion of salicylate. This becomes important in treating salicylate intoxication.

Signs and symptoms of salicylate are easily recognized when a history of salicylate ingestion is known. Salicylate intoxication should always be suspected in a patient with hyperventilation, persistent vomiting, tinnitus and central nervous system symptoms. Bleeding tendencies, acid-base disturbance and coma are usually seen late in this condition.

The acid-base disturbance often seen is in initial primary respiratory alkalosis produced by the hyperventitory effect of

salicylate upon the central respiratory center. Later a metabolic acidosis is seen, believed to be caused by accumulation of organic acids or due to the depletion of glycogen by the specific action of salicylate on carbohydrate metabolism in the liver. This dual acid-base disturbance emphasizes the need for both serum carbon dioxide concentration and pH determinations before definitive treatment.

The pathological changes of salicylate have been described in the brain, kidneys, liver, mucous membranes and stomach. These pathological changes are rarely seen, but are believed present more than is presently recognized. These pathological changes demonstrate the toxic systemic effects which an overdose of aspirin may produce.

Complications of salicylate intoxication include bleeding tendencies, hyperglycemia, glycosuria and scalp paresthesias. The hypoprothrombinemia is believed caused by an antivitemin K effect exerted by salicylate in liver metabolism. Salicylate also impairs the production of fibrinogen by the liver. The hyperglycemia may be due to demage to the hypothalamic region by the salicylate. Scalp paresthesias are believed caused by a neurotoxic effect of salicylate.

The treatment of salicylate intoxication has long consisted of immediate gastric lavage and fluid therapy only. Sodium lactate is the preferred fluid of choice in treating the acidotic patient.

Sodium bicarbonate may be of definite value in increasing the urinary excretion of salicylate but must be used with caution especially in the alkalotic state.

Recent treatment has been concerned with the rapid removal of salicylate with exchange transfusion and the artificial kidney. Exchange transfusion appears to be of value in treating smaller children and has been life-saving in several cases. believe that exchange transfusion must be limited to use on smaller children because of mechanical reasons.

The use of the artificial kidney provides a rapid removal of a large amount of salicylate from the blood stream. In the two cases described, the artificial kidney removed salicylate about twenty times faster than normal urinary excretion. A criteria for use of the artificial kidney must depend upon the clinical state of the patient and not upon serum salicylate levels or the amount of salicylate ingested.

The Thomas and Dolgard criteria appears to be valid for determining indications for hemodialysis. This criteria includes cases of salicylate poisoning in which (1) the elimination of salicylate is slow as a result of acute or chronic renal insufficiency, or (2) coma or signs of respiratory and circulatory depression are present. It is suggested that earlier use of dialysis in patients with high blood levels may reduce the severity of subsequent pathology. It remains that sound clinical judgment is necessary to select

patients for hemodialysis and to determine the optimal time and duration of dialysis. With the increasing use of hemodialysis in these types of cases, the artificial kidney may become an important tool in the treatment of salicylate intoxication.

Acknowledgements

I wish to thank Doctor George W. Loomis for his aid in the preparation of this thesis.

BIBLIOGRAPHY

1. Winter, R. W.: Salicylate Intoxication in Infants and Children, Gen. Practitioner 10:67-72, 1942.

2. Greenberg, L. A.: An evaluation of reported poisonings by acetylsalicylic acid, New England J. Med. 243:124, 1950.

3. J. A. M. A. Council on Pharmacology and Chemistry: Precautions regarding Salicylates, including Aspirin, J.A.M.A. 158:831, (July 9) 1955.

4. Schreiner, G. E., Berman, L. B., Griffen, John and Feys, Jean; Specific Therapy for Salicylism, New England J. of Med. 253:213, 1955.

5. Goodman,L. S. and Gilman, Alfred: The Pharmacological Basis of Therapeutics: A textbook of Pharmacology, Toxicology and Therapeutics for physicians and medical students, New York, Macmillan, 1956.

6. Weikel, J. H. Jr.: A comparison of human serum levels of acetylsalicylic acid, salicylamide and n-acetyl-p-aminophenol following oral administration, J. Am. Pharm. Assn., Sc. Ed. 47 (7) July, 1958, pp. 477-479.

7. Smull, Katherine, Wegria, R., and Leland, Jessica: The effect of sodium bicarbonate on the serum salicylate level, during salicylate therapy of patients with acute rheumatic fever, J.A.M.A. 125:1173-75, 1944.

8. Krasnoff, S. O. and Bernstein, M.: Acetylsalicylic acid poisoning, J.A.M.A. 135:712-714, 1947.

9. Smith, P. K., Gleason, H. L., Stoll, C. G. and Ogorzalek, S.: Studies of the Pharmacology of Salicylates, J. Pharmacol. and Exper. Ther. 87:237-255, 1946.

10. Smith, P. K.: Certain aspects of the Pharmacology of the Salicylates, Pharmacol. Rev. 1:353-382, 1949.

11. Dalgaard-Mikkelsen, S.: On the renal excretion of salicylate, Acta Pharmacol. et Toxicol.7:243-258, 1951.

12. Singer, R. B.: The Acid-Base Disturbance in Salicylate Intoxication, Medicine 33:1-15, 1954.

13. Caravate, C. M. and Cosgrove, E. F.: Salicylate Toxicity: The probable mechanism of its action, Ann. Int. Med. 24: 638-642, 1946.

14. Graham, J. D. P. and Parker, W. A.: Toxic manifestations of sodium salicylate therapy, Quart. J. Med. 17:153-163, (April) 1948.

15. Schadt, D. C. and Purnell, D. C.: Salicylate Intoxication in an Adult, A. M. A. Archives of Int. Med. 102 (August) 1958.

16. Ryder, H. W., Shaver, M., and Ferris, E.: Salicylism accompanied by respiratory alkalosis and toxic encephalopathy: report of a fatal case, New England J. Med. 232:617-621, 1945.

17. Campbell, E. J. and Maclaurin, R. E.: Acute Renal Failure in Salicylate Poisoning, British Med. J. 5069:503-505, (March 1) 1958.

18. Sevringhaus, E. L., and Meyer, O. O.: Glycosuria and Recovery following Methyl Salicylate Poisoning, Ann. Int. Med. 3: 1147-1148, (May) 1930.

19. Silverman, II, and Piccolo, P. A.: Oil of Wintergreen Poisoning, Bull. New England Med. Center, 4:172-176, (August) 1942.

20. Williams, S. W., and Panting, R. M.: Treatment of Aspirin Poisoning by Intravenous Sodium Lactate Solution, Brit. Med. J. 1:550-552, (March 13) 1937.

21. Done, A. K., and Otterness, L. J.: Exchange Transfusion in Treatment of Oil of Wintergreen (Methyl Salicylate) Poisoning, Pediatrics 18:80, 1956.

22. Adams, J. T., Bigler, J. A., and Green, O. C.: A Case of Methyl Salicylate Intoxication Treated by Exchange Transfusion, J.A.M.A. 165:1563, 1957.

23. Abel, J. J., Rowntree, L. G. and Turner, B. B.: On Removal of Diffusible Substances from Circulation Blood of Living Animals by Dialysis, J. Pharmacol. and Exper. Therap. 5: 275-316, 1914.

24. Doolan, P. D., Walsh, W. P., Kyle, L. H., and Wishinsky, H.: Acetylsalicylic Acid Intoxication: A Proposed Method of Treatment, J.A.M.A. 146:105, 1951.

25. Leonards, J.: Use of the Artificial Kidney for Purposes other than Treatment of Uremia, Tr. Am. Soc. Artific. Int. Organs 1:46, 1955.

26. Thomsen, A. C. and Dolgard, O. Z.: Haemodialysis in acute acetylsalicylic acid poisoning, Amer. J. of Med. 25: 484-486, (September) 1958.

27. Schreiner, G. E.: The Role of Hemodialysis (Artificial Kidney) in Acute Poisoning, A.M.A. Archives of Int. Med. 102:896-913, (December) 1958.