SALICYLATE THERAPY IN CHILDREN

BY
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For more than half a century salicylate compounds have been used empirically in the treatment of rheumatic fever. Although there is almost general agreement (Griffith, 1947) that they have analgesic and antipyretic properties, inducing symptomatic relief, especially in the presence of polyarthritis, yet the mechanism underlying their effect is still unsolved and there is no satisfactory explanation of their action on the rheumatic process. In the last few years the question has once again been raised following Coburn’s statement (1943) that high doses of sodium salicylate (0·19 g. to 0·14 g. per kilo of body weight, sufficient to raise blood levels to 35 or 45 mg. per 100 ml. of plasma) would be able ‘to modify the sterile inflammatory reaction which occurs during activity of rheumatism,’ thus preventing the subsequent development of cardiac disease. His advice to use high doses of sodium salicylate is not original, since many authors in the past have emphasized the necessity of such massive or even larger doses to obtain the best results rapidly (Lees, 1903; Clarke, 1906; Peters, 1929; Wilkinson, 1935). Coburn achieved a correlation between salicylate therapy and concentration of the drug in the circulating blood, and considered that information about the salicylate plasma concentration was essential for a rational therapeutic scheme.

Coburn’s opinion was partly supported by Taran and Jacobs (1945), Manchester (1946), and Peters (1947), while other authors emphasized the inefficiency and even the dangers of such massive therapy (Wégréia and Smull, 1945; Murphy, 1945; Harris, 1947). In the meanwhile new and simpler methods of estimating the salicylate, both in blood and urine, have been developed, thus making it possible to review the clinical pharmacological work of Baldoni (1908 and 1914), Hanzlik (1926), and Quick (1932a, b, and c, and 1933). New and interesting observations have also been reported by Kapp and Coburn (1942), Smith et al. (1946), Lester et al. (1946), and other authors on the absorption, excretion, and the metabolism of the salicylate compounds, and on the blood levels, especially in adults.

Considering the frequency of the beginning of rheumatic disease in childhood (Cohn and Lingg 1943), a study of the salicylate levels in blood and urine during salicylate treatment is of particular interest in that age group. Some observations are presented in this paper on the fate of salicylate drugs in normal and rheumatic children, but without any attempt to discuss the efficacy and specificity of this therapy. No restrictions were placed on food or liquid intake during these observations.

Methods of Estimation

Salicylates in blood. A very extensive literature exists on the quantitative and qualitative estimation of salicylates (Beilstein, 1932; Allport, 1945). For the estimation in blood we have employed the method of Brodie et al. (1944), now used in routine practice, with some modifications as follows, using the Evelyn photo-electric colorimeter to measure the colour density of the solutions.

To 1 ml. of plasma, collected over heparin (potassium or sodium oxalate influences the colour reaction) or 1 ml. or less of serum, add 0·5 ml. of 6 N HCl and 30 ml. ethylene dichloride in a small separating funnel. The use of ethylene dichloride for extracting salicylates was first advised by Stoecklin in 1912. Shake vigorously for five minutes and allow to separate. Run the ethylene dichloride layer into another funnel through a small cotton-wool plug. Treat the ethylene dichloride solution twice with 10 ml. of water and 0·2 ml. of 1 per cent. ferric nitrate in 0·07 N HNO₃. Separate and run the coloured water layer into the colorimeter tube and compare with a standard curve prepared in the same way.

Total salicylates in urine. As pointed out by Brodie et al. (1944), free salicylate in non-hydrolysed urine cannot be determined by their method, but we have confirmed the statement of Lester et al. (1946) that it can be used for the estimation of total salicylate in hydrolysed urine if the pH is adjusted to 4·6. We have therefore used Lester’s method for the estimation of total salicylate in urine, acidifying with hydrochloric (Galmard, 1944) instead of sulphuric acid. The details are as follows:
To 5 ml. of urine add 1 ml. concentrated HCl and hydrolyse for one to one and a half hours under a reflux condenser. Cool, and make to 50 ml. with water. Extract 2 ml. twice with ether, transferring the ether solution to a colorimeter tube. Warm the ether slightly in a warm water bath and blow air through it to evaporate off the ether. Dissolve the residue in water (5 or 6 ml.), adjust the pH if necessary to 4-6, and add 0·2 ml. of the ferric nitrate reagent as for blood, etc.

All estimations in this paper are expressed in terms of salicylic acid.

Drugs. The intravenous administration of salicylate is not used in this hospital, having no practical advantage. The drugs used orally in the routine treatment of rheumatic fever in this hospital are:

(a) sodium salicylate with sodium bicarbonate (1:2) in liquid mixture of which 0·5 oz. is said to contain 20 gr. (=1·3 g.) of the drug; (b) aspirin, 5 gr. (=0·325 g.) per tablet; (c) calcium aspirin, 5 gr. per tablet (=0·325 g.).

Specimens of these compounds were collected from different wards and from different nurses and estimated for their actual content of the drug. Four specimens of sodium salicylate mixture contained 15·0, 15·7, 15·7, and 14·7 gr. of sodium salicylate instead of 20 gr. The aspirin tablets gave an average of 6 gr. of aspirin per tablet instead of 5.

A child of nine years, therefore, will receive daily 96-100 gr. instead of 120 gr. of sodium salicylate, and 72 gr. instead of 60 gr. of aspirin. We were also able to show that with time the sodium salicylate solutions deteriorate. A diminution of 13 per cent. in one month was observed. Moreover, traces of the drug were usually left in the medicine glass.

On the whole the difference between the theoretical and actual therapy may amount to a loss of about 20 per cent. Therefore it is advisable to use sodium salicylate in tablet form or in freshly prepared solutions, and the importance of shaking the bottle at the time of administration and of not leaving residue in the medicine glass needs emphasis.

Absorption and Excretion

The intake by mouth of sodium salicylate in water is followed rapidly by its absorption, and its presence can be detected after fifteen or twenty-five minutes in blood and urine. The peak in the blood level is reached in from one and a half to two hours, and decreases slowly. It is not a new discovery that in children aspirin and calcium aspirin are absorbed at a slower rate, as shown in fig. 1, and that the peak in the blood remains at the same level longer, falling more slowly (Smith et al., 1946).

There is a relation between the doses of salicylate intake and the duration of excretion, the latter being proportionally longer with a larger dose. In a child convalescent from an acute disease other than rheumatic fever, we found that the time required for the complete excretion of a single dose of 1 g. of sodium salicylate was from thirty to thirty-six hours, whereas with 0·5 g. no salicylate was detected in the urine after twenty-four hours.

In figs. 2 and 3 are shown the hourly excretions after different doses of sodium salicylate or aspirin in the same subject. These data are in accord with the findings of Lester et al. (1946) for adults after taking aspirin. After oral sodium salicylate, practically no differences were observed between the free salicylate of plasma and total salicylate after hydrolysis of plasma. The possibility that some acetyl salicylic acid is absorbed without alteration or is present in conjugated form is supported by the observation that either after a single dose or after continuous treatment differences were discovered between total "salicyl" and free "salicyl" amounting to 10 or 15 per cent., which is considerably more than estimation errors. The possibility of acetyl salicylic acid disappearing from the plasma in a short time after absorption, as suggested by Lester et al. (1946), seems to be remote if treatment with the drug is continuous, although incubation in vitro of plasma with aspirin shows that hydrolysis does take place in a short time. Our results are not in accordance with those of Smith et al. (1946).
The increase of blood level with general routine therapy, that is, intake every four hours of sodium salicylate or of calcium aspirin, is shown in fig. 4. This appears to be steady during the first two or three days, and then the daily individual variation ranges between 10 and 15 mg. per 100 ml., even many weeks after the start of the treatment. These variations are mostly related, in our experience, to the time of the ingestion of the drug. This correlation is not mentioned by other authors.

These results are in agreement with those of Coburn (1943), Butt et al. (1945), and Lester et al. (1946), and in contrast with those of Stevens and Kaplan (1946) and of Erganian (1947).

In fig. 5 are shown the plasma levels of several patients treated with large doses of sodium salicylate or calcium aspirin for periods up to two months or more. The danger of any cumulative effect and the occurrence of toxic symptoms is small. On administration being stopped after many weeks' treatment, the drug completely disappeared from the blood and urine in from forty-eight to seventy-two hours (see figs. 6 and 7).

The quantity of salicylate that can be recovered from the urine of normal subjects taking single doses is about two-thirds of that ingested. Variation in percentage of the excretion showed no correlation to dosage or to urinary volume; but forcing fluid intake seems to produce a quicker excretion.

In rheumatic patients treated continuously, the salicylate recovered in the urine amounts to 50 or 60 per cent. or less of the intake, especially during acute periods. These observations are in accordance with those of Hanzlik (1926), and Coburn (1943), in adults. The low level of excretion seems to be due, in Coburn's opinion, to a more extensive modification of salicylate rather than to storage, as the time of disappearance after stopping the
medication is not increased. It has been suggested that the rheumatic disease contributes to this increased destruction of salicylate, but it was observed that other patients, with fever not reduced by this drug, also showed a low salicylate output, Kapp and Coburn (1942).

The relation between intake of salicylate and body weight in our cases produce plasma values slightly lower in children than in the adults, even considering individual variations amounting to more than 10 mg. per 100 ml.

To obtain a steady blood level of at least 25 mg. per 100 ml., it is necessary to give a daily dosage of 0.12 to 0.18 g. per kilo of body weight (1 to 1.5 gr. per pound of body weight), which is approximately the dose that has been used for a long time in this hospital.

With due regard to individual differences in absorption and excretion, an insufficient salicylate level in the blood corresponds to an inadequate intake or inaccurate administration.

Concerning absorption of sodium salicylate administered per rectum, there is no accord of opinion (Mackenzie, 1943; Huntington et al., 1946). The argument was recently reviewed by Mackenzie, who obtained in children, with other methods, high individual variation in absorption. In our cases salicylate could be detected in the urine thirty minutes after rectal administration of a 1 per cent. solution without sodium bicarbonate in tepid water; the quantity increasing considerably between six and eight hours (fig. 8).

It is possible to obtain with continuous treatment (four enemata daily) a serum level up to 15 or 20 mg. per 100 ml. after administering 0.16 to 0.20 g. per kilo of body weight. The quantity of salicylate recovered after a single dose in normal subjects was between 50 and 60 per cent. of the intake, which is only slightly less than when administered by mouth, and it takes approximately twenty-four hours for a dose of 1 g. to disappear. The rate of absorption of sodium salicylate given by enema is not materially different from the rate when given by mouth, so this method of administration may have a place in the treatment of patients with severe vomiting.

**Effect of Bicarbonate**

Smull et al. reported in 1944 that the administration of sodium bicarbonate with sodium salicylate to both rheumatic and non-rheumatic subjects resulted in a lower concentration of salicylate in plasma than when salicylate was given without bicarbonate. They did not estimate the output of salicylate in the urine. From a more detailed review of the literature we find that in 1875 Fleischer reported a shortening of the period of excretion from thirty-six to fourteen hours when the patient was given bicarbonate. Also Ehrmann in 1907, and Morris and Graham in 1931 made the same observations. Recently other authors (Smith et al., 1946; Lester et al., 1946, etc.) have confirmed there is an increase of salicylate excretion in the urine of rheumatic patients who were given bicarbonate; and Lester et al. (1946) showed that in normal subjects taking acetyl salicylic acid with sodium bicarbonate (1:2), there is an increase of more than 50 per cent. in the rate of elimination.

In our cases the intake of a double proportion of sodium bicarbonate seemed to increase the rapidity of the absorption, and the blood salicylate reached the same level as it did without sodium bicarbonate, but these blood levels decreased with greater rapidity (fig. 9), diminishing even to half the other levels after from four to six hours. We have also found an increased rate of excretion in the urine in the first twelve hours. (These excretions are in
excess of any individual variations found in any of the subjects studied.)

From fig. 10 there appears to be a certain relation between the proportion of the added sodium bicarbonate and the rapidity of the excretion, which is considerably slower when the salicylate and bicarbonate are present in equal quantities (1:1) and almost nil with half doses. From our experiments, giving single doses of sodium salicylate together with different quantities of sodium bicarbonate, we observed that the salicylate recovered from the urine was increased relatively to the increase of the sodium bicarbonate. It is difficult to say whether that was due to a better absorption from the intestinal tract or to an impaired destruction after giving sodium bicarbonate, particularly in view of the increased rapidity of evacuation from the stomach (Lotti and Smith, 1946) following the intake of alkaline substances. Using magnesium oxide as anti-acid in double proportion, the rate of excretion and the quantity recovered were the same as with a small quantity of sodium bicarbonate (fig. 11).

The more rapid excretion of the salicylate in the first twelve hours after giving a double dose of sodium bicarbonate (fig. 7) is often accompanied by a larger output of urine (see table). We must conclude, therefore, that in children the sodium bicarbonate not only relieves the gastric disturbance but also exerts some influence on the rate of excretion, and to a less extent on the absorption. These two results are apparently contradictory in view of the aim to attain maximum efficiency with minimum doses of the drug. We consider that a mixture of equal parts of sodium salicylate and sodium bicarbonate (1:1) given every four hours is sufficient to relieve the gastric trouble without exerting any appreciable influence on the excretion; the proportion may be 1:2 if the interval is reduced to two hours.
If we consider as a detoxifying action the increased rate of excretion by the urine of sodium salicylate given with double proportion of sodium bicarbonate, we should be in agreement with Peters (1947), who attributes a detoxifying property to the sodium bicarbonate. But we are of the opinion that there is rather an indirect action increasing the pH of the urine, and hence the excretion, especially considering that, following the concurrent administration of ammonium chloride, there is a reduction of the rate of output and an increase of the salicylate in the blood (Smith et al., 1946). Gubner and Szucs (1945) have reached the conclusion that sodium bicarbonate is ineffective in decreasing the toxicity of salicylate.

From the hypothesis that sodium bicarbonate in great amount increases the extracellular fluid, thus producing a decrease of the salicylate level in the circulating blood (Smull et al., 1944; Peters, 1947), and the demonstration of a quicker output through the kidney, as shown by our observations and those of other authors, producing a rapid increase of the renal clearance with increase of the pH of the urine, we believe that the effect of the sodium bicarbonate is more concerned with the mechanism of the secretion than with the disturbance of the water balance of the body.

Finally, the action of some other drugs (papaverine, spartein, glucose, etc.) on the fixation of sodium salicylate by the heart has been shown by the experimental work of Mercier et al. (1941). The possible influence also of bicarbonate needs further study.

**Salicylate Intoxication**

Many disturbances following salicylate therapy have been described since the introduction of these drugs to medicine, related either to high variation of individual susceptibility or to excessive doses. Tinnitus, nausea, anorexia, headache, vomiting, hyperventilation, nervous disorder, oedema, albuminuria, the presence of reducing substances in the urine, etc., are the most frequently described symptoms. In paediatric practice, anorexia, nausea, and vomiting are the commonest disorders, the latter sometimes of such a degree as to interfere with the administration of the drug by mouth. There is a difference of opinion, even after the most recent gastroscopic studies (Douthwaite and Lintott, 1938; Paul, 1943; Caravati and Cosgrove, 1946) as to whether salicylates affect the gastric mucosa, but the fact of gastric upheaval is established without doubt by clinical observation. It is also known that vomiting appears with the same, or even greater frequency after intravenous administration (Taran and Jacobs, 1945; Caravati and Cosgrove, 1946) without any salicylate being present in the gastric contents. Thus, it is fairly generally accepted that vomiting is more related to the action on the cerebral centres than to a local effect on the alimentary tract. From our observations it would seem that there is no constant relationship in the same subject between the height of the salicylate blood level and the beginning of vomiting, but that the severity of the toxic symptoms in the same subject is greater when the plasma salicylate level is high. In our experience, the vomiting appears more often at the beginning of treatment, and later disappears even with higher levels of salicyl in the blood, even in patients taking double proportion of sodium bicarbonate from the beginning of treatment.

The whole question of salicylate intoxication was recently reviewed by Rapoport et al. (1943) and Guest et al. (1945) who have brought new experimental support to the idea of a respiratory alkalosis developed by hyperpnoea with a lowering of the carbon dioxide tension, which may or may not be accompanied by a decrease of bicarbonate. In our patients who developed toxic symptoms, alkalinity of the urine was a common finding.

A few words must be added about other relatively recent information on the effect of salicylate therapy.

**Prothrombinopenic action of the salicylate drugs.** Since the first experimental observation of Link (1943) many authors have confirmed that in patients treated with salicylate drugs there is a decrease of prothrombin in plasma (Shapiro et al., 1943; Meyer and Howard, 1943; Jager and Alway, 1946; and others). Severe cases of haemorrhagic damage during salicylate treatment and considered to be due to prothrombin deficiency have been reported only rarely, while haemorrhagic manifestations have been observed in many instances. These were sometimes considered as caused by the disease, rather than by the therapy or by other mechanism (thrombocytopenia). The correctness of attributing the haemorrhagic manifestations to prothrombin deficiency is debatable (Shapiro et al., 1943; Coombs et al., 1945; Butt et al., 1946; Peters, 1947; and others). The mechanism of the action of the salicylate on the prothrombin is not clear. Shapiro et al. (1943) stated that patients with hepatic damage, and according to Link et al. (1943) animals with vitamin K deficiency, are more sensitive to salicylate prothrombinopenic action. The rapid elevation of prothrombin after stopping salicylate therapy is rather against an effect through hepatic damage (Clausen and Jager, 1946). Advice to administer vitamin K during salicylate therapy as given by Shapiro 1944 and Zimmerman and Shapiro (1946), is not generally accepted (Higley, 1945).

In the experience of physicians of this hospital (Wilkinson and Smelle) and those of the Clinica Pediatrica, Rome (Frontali), there is very little danger of haemorrhagic manifestation.

**Ascorbic acid and salicylate drugs.** Since the first communication of Daniels and Everson (1936) on the influence of aspirin on the urinary excretion of ascorbic acid, other authors have confirmed that salicylate drugs increase the urine output of vitamin C (Keith and Hickmans in this laboratory 1938; Samuels et al., 1940; and Nofert, 1944-45). We
can confirm that in patients treated by salicylate there is also a decrease of the vitamin C in the blood even after adding vitamin C to the diet (25 to 50 mg.) (unpublished data), thus pointing to the advisability of administering vitamin C to these subjects in larger quantity. According to Gubner and Szucs (1945) ascorbic acid has a detoxifying action on salicylates.

**Thiamine and salicylate drugs.** Another question still requiring study is the relation between the salicylates and thiamine. Cleland (1943, 1946), in clinical and experimental research, observed that over short periods of time salicylates increased the excretion of thiamine in urine but over long periods of therapy they caused a reduced output, presumably due, according to her, to a loss of body stores during the preliminary period of increased excretion.

Lutwak-Mann (1942) injected rats with acetyl salicylate and found that after four and seven hours blood pyruvate values were lower than the control, but after twenty-four hours these were equal to the control.

We have had the opportunity of estimating the pyruvic acid in the blood (unpublished data) of subjects taking salicylate for long periods and have found values within the normal range.

**Enzymes.** The proof that other changes in metabolism are produced by salicylate was provided by the results obtained of numerous experiments by Lutwak-Mann (1942), and Euler and Ahlstroem (1943), of the influence of salicylate on enzymes. Recently Guerra (1946), and Dorfman et al. (1947) have proved that sodium salicylate inhibits in vivo the diffuse effect of hyaluronidase, this proof opening up a new possibility for the interpretation of the mechanism of the action of salicylate in rheumatic fever.

The disappearance within four to seven hours after the injection of salicylate in rats of nearly all the liver glycogen, and its full restoration within twenty-four hours, indicates an effect on several as yet unidentified enzymic processes. We can confirm the above results of Lutwak-Mann after giving a massive dose of salicylate by lavage to rats (Hickmans, 1947, unpublished data).

**Conclusion**

An appropriate scheme of salicylate therapy in children with rheumatic fever should include:

1. The oral use of freshly prepared solutions of sodium salicylate in flavoured water with sodium bicarbonate added in the proportion 1:1 when given every four hours, or 1:2 when given every two hours. The last dose in the evening and the first in the morning may be double to permit a longer interval during the night. The administration by enema seems to be indicated in patients with severe vomiting. Aspirin or calcium aspirin in tablets can also be used.

2. The quantity of sodium salicylate which in children raises the level up to 25 or 35 mg. per 100 ml. is in the range of 0.12, 0.18 gr. per kilo of body weight. The estimation of salicylate plasma level seems advisable, to control the accuracy of the administration and to avoid over-dosage.

3. The patients should have plenty of fluid, with addition of sugar or fruit juice.

4. There should be a supplementary administration of vitamin C in order to avoid the depletion of ascorbic acid reserves.

In the experience of some authors, the giving of vitamin A in addition seems to be useful. The administration of vitamin K to prevent prothrombin diminution is necessary only after control of the prothrombin time.

5. In case of any sign of intoxication—the frequency of the respiratory movement should be observed—the administration of high doses of sodium bicarbonate together with fluid, given if necessary parenterally, can accelerate the excretion of the salicylate from the body.

**Summary**

The absorption and excretion of sodium salicylate and aspirin, given orally and per rectum, to rheumatic and non-rheumatic children, either in single doses or continuously, was investigated.

To attain a level of 25 to 35 mg. per 100 ml. of plasma, it is necessary to give 0.12 to 0.18 gr. per kilo of body weight (that is 1 to 1.5 gr. per pound body weight). When bicarbonate (1:2) is added, the blood level decreases more quickly than without bicarbonate, owing to the increased rate of excretion in the urine, especially in the first twelve hours.

The advisability of adding vitamins B, C, and K is discussed.

The author wishes to thank the Honorary Staff of the Children's Hospital for allowing him to use their cases and Professor J. M. Smellie for his helpful advice. He is also much indebted to Dr. E. M. Hickmans, Biochemist to the Children's Hospital, for her criticism and help throughout the work.

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