South African Medical Journal
Suid-Afrikaanse Tydskrif vir Geneeskunde
P.O. Box 643, Cape Town Posbus 643, Kaapstad

Cape Town, 19 March 1955 Weekly 2s. 6d. | Vol. 29 No. 12 | Kaapstad, 19 Maart 1955 Weekliks 2s. 6d.

SALICYLAMIDE PURPURA

H. B. W. GREIG, M.B., CH.B. (GLASG.)

South African Institute for Medical Research, Johannesburg

The purpose of this article is to draw attention to a thrombocytopenic purpura which has resulted from the taking of salicylamide.

This drug is advertised in the lay press as 'R12' and claims are made for it as a drug which 'not only relieves the pain of rheumatism but actually reduces swelling by dispersing the uric acid accumulation . . . Locked joints become free again.' It is further said to be 'absolutely harmless'. The drug was self-administered in the two cases which came under the author's attention, and the aetiology of cases presenting with a severe haemorrhagic episode may prove baffling, especially as patients are usually loath to admit to taking such self-prescribed remedies.

PHARMACOLOGY

The substance, salicylamide or ortho-hydroxybenzamide, was discovered in 1843, but its use in medicine was first suggested by Baas [1] in 1890. Little was heard of it from that time till 1946, when its use in clinical medicine was revived, principally on the Continent. It was early found by Meyer [2] to have powerful narcotic properties for amphibia—to be more narcotic, indeed, than ethyl alcohol, chloral or acetone. Ichniowski and Hueper [3] also observed narcotic effects after parenteral administration in rats—it was found to be less toxic than aspirin by this route of administration. Perorally, these workers found salicylamide to be of the same order of toxicity as aspirin in acute experiments in rats. In chronic oral experiments in rats, lasting 13 weeks, no anatomical or histological lesions could be found *post mortem* attributable to salicylamide. They did, however, in the salicylamide-treated rats observe leucopenia in 3 out of 20 rats and depressed leucocyte counts (not amounting to leucopenia) in all except 2. No platelet or bone-marrow studies were performed in these experiments, but the prothrombin time was estimated; no hypo-prothrombinaemia was observed.

Kase [4] has reported renal damage with albuminuria and nitrogen retention in dogs, and Holtz and Drebinger[5] in cats; but no information relating to nephrotoxic effects in man has been found in the literature.

The action of salicylamide as an analgesic and antipyretic (if it in fact possesses these pharmacological actions) would not seem to depend on its break-down to the salicyl radicle in the body, since the above w. rkers[3] were unable to detect (by the method of Brodie, Udenfriend and Coburn [7]) the free salicyl radicle in the blood of their rats. Bray,[6] in the course of a comprehensive study of the metabolic pathways of various substituted aromatic compounds, of which salicylamide was one, found that in the rabbit only 4-7% underwent hydrolysis and there was little or no break-down to free salicylic acid (0-1%). Much is excreted conjugated to glucuronic acid as 2 carbamyl-glucuronides, and a fair amount conjugated with sulphuric acid as 'ethereal sulphate'. If, as is asserted,[8] salicylic compounds are dependent for their action on being broken down to free salicyl radicle in the body, then it seems likely that whatever pharmacological properties salicylamide has, its mode of action is entirely different from that of the salicylates.

Considerable work has still to be done to evaluate the place of salicylamide in modern therapeutics; well-documented articles on its clinical use are very scanty and come principally from the Continent of Europe.[5, 9–12] Holtz and Drebinger[5] mention agranulocytosis as a possible complication but state they have not encountered it even using salicylamide in high dosage. They do not mention thrombocytopenia or haemorrhagic phenomena. Only one previous case record of thrombocytopenic complication has been found in the literature (Stettbacher [13]) and its resemblance to the 2 cases to be described is very striking. All 3 occurred in women following self-administration of the drug; all presented with widespread ecchymotic lesions and haemorrhagic lesions in the mouth; perhaps most important, all

showed thrombocytopenia and leucopenia resulting from toxic damage to the marrow.

CASE HISTORIES

Following is a resumé of the salient features of Stettbacher's case. The patient, a 48-year-old woman, took 5 g. of salicylamide daily for 10 days, resulting in the development of tinnitus. She discontinued the drug, to recommence later with 3 g. daily, and after a further 8 days on this dosage she took 1·5 g. daily for 48 days; a total of 144 g. in 3 months. Epistaxis, severe bruising on slight trauma, and mouth lesions then occurred and the patient was admitted to hospital.

Investigations showed a profound thrombocytopenia, a bleeding time of over 20 minutes, and a strongly-positive Hess's test. Examination of the bone marrow showed depression of the myeloid series, and maturation arrest of the megakaryocytes. Recovery was complete in 3 weeks with supportive measures only.

Present Cases

Case 1. Mrs. McN., housewife, aged 57. This patient was admitted to hospital in August 1952 complaining of large bruises all over, a petechial rash for more than 10 days, and haematuria for 2 days. Lesions in the mouth had appeared the day before admission. She had also noticed slight nasal bleeding and that her sputum (from a long-standing chronic bronchitis) had been blood-stained for some days. There was no pain, burning or frequency associated with the haematuria.

The patient gave a history of chronic bronchitis and chronic rheumatism (mainly in the form of fibrositis of the shoulders and lumbar region) for many years, and it was for the latter condition she began taking the salicylamide ('R12') in the prescribed dosage. In this way she consumed approximately 600 tablets or 300 g. in 50 days. (The prescribed minimum dosage on the package is 12 tablets daily, with no maximum daily or total dosage stated.)

On examination the patient was found to be covered in a purpuric rash and showed massive ecchymotic areas all over, but particularly on the legs and abdomen. The buccal mucosa and tongue showed several blood-filled bullae, some of which were broken and presented raw bleeding ulcers. No lymphadenopathy was present, nor were the liver or spleen enlarged. Hess's test was strongly positive, and the bleeding time greater than 12 minutes. An estimation of the prothrombin index at this time gave a value of 101%, and a blood count showed the following results: Haemoglobin 8·7 g.%, erythrocyte count 2·74 millions per c.mm., haematocrit 26%, MCV 94·0 c.μ., MCHC 33·5%. The total leucocyte count was 2,600 per c.mm., with the following differential count: neutrophils 60%; monocytes 2%; lymphocytes 37%; eosinophils 1%. Platelets numbered less than 10,000 per c.mm.

A bone-marrow examination done on two occasions at two different sites, showed marked hypocellularity (6,000 and 11,000 nucleated cells per c.mm. respectively) and hypoplasia of all elements, the majority of the cells present being lymphocytes. Treatment was by blood transfusion and the exhibition of ACTH. Recovery was rapid, and 48 hours after the commencement of the ACTH the Hess's test became negative and the platelets rose to 90,000 per c.mm. Red cells disappeared from the urine, and no fresh bruising or haemorrhage occurred. The mouth lesions healed rapidly and had practically disappeared in 6 days. After 11 days of ACTH therapy the peripheral blood count was as follows: Haemoglobin 12·3 g.%, erythrocytes 4·03 millions per c.mm., haematocrit 39%, platelets 500,000 per c.mm. After 13 days the ACTH was stopped. A further bone-marrow examination now showed an almost complete return to normal. The patient has since remained clinically well.

Case 2. Mrs. O., housewife, aged 61 years. This patient gave a history of painful joints since 18 months ago, the joints principally affected being the knees, fingers, and toes. At this time she had a course of injections (the precise nature of the drug given is not known). Four months before admission she began taking salicylamide as 'R12' in the prescribed dosage.

On admission in November 1952 the patient complained of epistaxis for 2 months and a petechial rash for 1 month. These symptoms had become progressively worse, and on admission large ecchymotic lesions were present all over, with lesions in the mouth and on the conjunctivae. Hess's test was positive; the bleeding time was greater than 8 minutes. A blood count at this time showed the following: Haemoglobin 12·6 g.%; erythrocytes 3·33 millions per c.mm.; total leucocyte count 1,600 per c.mm.; differential count: neutrophils 53%, monocytes 6%, lymphocytes 33%, eosinophils 6%, and basophils 2%. Less than 10,000 platelets per c.mm. were present. Examination of the bone-marrow revealed a hypocellular marrow with hypoplasia of all elements. With supportive measures (blood transfusions) and anti-histamine therapy an uneventful recovery took place. The possibility that the previous course of injections (possibly gold) might have an aetiological connection with the purpura in this case cannot be excluded, but it does not seem likely in view of the time-lapse of 18 months and the prompt recovery on cessation of salicylamide medication.

CONCLUSIONS

Another drug must be added to the ever-increasing list of those compounds which are capable of inducing blood dyscrasias.

The mechanism in the case of salicylamide appears to be direct marrow depression, affecting principally the megakaryocytes and myeloid cells. Stettbacher [13] attempted to show sensitivity in his patient by administration of a test dose and following the platelet level at 4-hourly intervals thereafter. No fall was observed in the course of 24 hours. We attempted skin tests with the substance in our first case, but no sensitivity could be demonstrated. We also repeated Ackroyd's experiments [14] relating to the *in vitro* instability of platelets from cases of sedormid purpura, when suspended in plasma containing the offending drug. Platelets from our first patient were suspended in various concentrations of salicylamide in both saline and plasma. Controls were set up in normal plasma and saline. No difference in the degree of agglutination or lysis of platelets was observed between the tests and controls. Finally, the marrow studies suggest a direct action on haemopoietic tissue, rather than a peripheral sensitivity reaction.

SUMMARY

Two cases are presented which showed a thrombocytopenic haemorrhagic syndrome following prolonged self-administration of salicylamide ('R12'). The pharmacology of salicylamide is reviewed, and a note added in conclusion on the probable mechanism of the thrombocytopenia in these cases.

REFERENCES

1. Baas (1890): Hoppe-Seyl. Z. physiol. Chem., **14,** 416 (quoted by Holtz and Drebinger [5]).
2. Meyer (1899): Arch. exp. Path. Pharmak., **42,** 109.
3. Ichniowski, C. T. and Heuper, W. C. (1946): J. Amer. Pharm. Assoc., Sci. ed., **35,** 225.
4. Kase, K. (1929): Biochem. Z., **205,** 21.
5. Holtz, F. and Drebinger, I. (1950): Schweiz. Med. Wschr., **80,** 1175.
6. Bray, H. G., Ryman, B. E. and Thorpe, W. V. (1948): Biochem. J., **43,** 561.
7. Brodie, B. B., Udenfriend, S. and Coburn, A. F. (1944): J. Pharmacol., **80,** 114.
8. Goodman, L. and Gilman, A. (1941): *The Pharmacological Basis of Therapeutics*, 1st. ed., p. 225. New York: Macmillan.
9. Wieland, O. (1949): Med. Klinik, **44,** 1530.
10. Wegmann, T. (1950): Schweiz. med. Wschr., **80,** 62.
11. Litter, M., Moreno, A. R. and Donin, L. (1951): J. Pharmacol., **101,** 119.
12. Euler, E. and Remy, R. (1950): Med. Klinik, **45,** 1178.
13. Stettbacher, H. R. (1950): Schweiz. med. Wschr., **80,** 1177.
14. Ackroyd, J. F. (1949): Clin. Sci., **8,** 269.