Medical Memorandum

Granulocytopenia Occurring During Sodium Gentisate Therapy

Sodium gentisate, an oxidation product of salicylic acid, was introduced to clinical medicine by Meyer and Ragan (1948), who found that, like salicylates, it inhibited the spreading power of hyaluronidase. They used it in a small series of cases of acute rheumatism and found that it had an antirheumatic effect. Camelin *et al.* (1949, 1950), who studied its clinical use in more detail, believe it to be as effective as sodium salicylate without the latter's toxic side-effects. They gave sodium gentisate in doses of up to 20 g. a day by mouth without noting any constitutional reaction or change in the blood picture.

Both the following cases were given 10 g. of sodium gentisate daily by mouth during the treatment of attacks of acute rheumatism, and both developed neutrophil leucopenia with an absolute lymphocytosis. In one case these blood changes were detected during the administration of the drug, in the other during the weeks following its withdrawal.

CASE 1

A girl aged 13 developed a sore throat three weeks before admission to hospital. Two weeks later she became feverish and complained of headache, backache, and pain and swelling of the right knee and the right first metatarsophalangeal joint.

On admission five days later she was ill and febrile and the knee-joint was still swollen and tender, though physically she was otherwise normal. Salicylates were not started at once, but within 48 hours the arthritis had shifted to involve the left knee-joint and both ankle-joints. At this stage she was given sodium salicylate, 120 gr. (8 g.) daily, with an equal quantity of sodium bicarbonate. Her temperature dropped during the next two days and the pain in her joints disappeared. On the eighth day after admission her E.S.R. was 40 mm. in one hour (Wintrobe), and her white blood cells numbered 7,650 (neutrophil polymorphs 30%, lymphocytes 61%, eosinophils 7%, monocytes 2%). Her haemoglobin was 70%.

The salicylate course was continued for another 18 days, but, as she was having a slight evening fever, her appetite was poor, and she was complaining of some tinnitus, it was decided to stop the salicylate and to change to sodium gentisate, 10 g. daily. This treatment was continued for three weeks, the dose being then reduced to 5 g. daily. One month after the start of gentisate therapy a further blood count showed a total of 11,650 cells, with 5% polymorphs and 95% lymphocytes. Her haemoglobin was 92%. One week later her polymorph count was unaltered, so it was decided to abandon the sodium gentisate, which it was thought might be a leucotoxic agent. The possibility that the blood changes might be due to a virus infection was considered, but there was nothing on clinical examination to support this view. Her Paul-Bunnell reaction was negative to a dilution of 1/640.

Serial blood counts showed a polymorph leucopenia persisting for a further three weeks and then only gradually returning to normal figures. Her lymphocyte count remained somewhat high. Clinically she had completely recovered by the end of the second month and her E.S.R. was down to normal limits, yet at this time her polymorphs numbered only 630 cells per c.mm. A sternal puncture was later performed, though not until the eighteenth week, when the blood picture was starting to recover. The marrow was richly cellular and entirely normal. A chest x-ray film at this time had shown a normal heart and lungs, and shortly afterwards she was discharged to convalescence. Three months later her total white count was 6,200 cells, with 55% neutrophil polymorphs and 32% lymphocytes.

CASE 2

A girl aged 14 developed a swinging fever with pain and swelling of both wrist-joints and elbow-joints 10 days before admission to hospital. She had been treated with sodium salicylate by her own practitioner. The joint pain and swelling had subsided in a couple of days and her fever had lessened, but she had remained ill and toxic and was sent to hospital.

On admission she had a low fever, her joints were normal, and her heart was not enlarged, though a harsh systolic murmur was heard at the pulmonary area. Her E.S.R. was 24 mm. in one hour (Wintrobe), and an electrocardiogram showed a corrected Q-T interval (Q-Tc) of 0.423 second. Her rheumatism still seemed to be active, so she was put on to 10 g. of sodium gentisate daily by mouth. No white blood cell count was done until one week later, when it was 8,400 (47% polymorphs, 52% lymphocytes). Her E.S.R. had fallen to 8 mm. in one hour and she was clinically improved. Sodium gentisate was stopped after four and a half weeks, when her white-cell count was within normal limits. The count then started to drop, the polymorphs reaching a minimal figure of 750 per c.mm. five weeks after stopping treatment but thereafter tending to recover. She never became anaemic, and at no time was there any clinical indication that she might have suffered any superadded infection capable of affecting her blood count. A chest x-ray film taken late in her stay in hospital showed no abnormality, and after 17 weeks under observation she was discharged to convalescence. Three months later her total white-cell count was 8,750 (55% polymorphs, 37% lymphocytes).

COMMENT

Fairly full descriptions of these two cases have been given to show that both were typical of rheumatic fever. No other drug was given to either case during or after the course of sodium gentisate, so that this cause of granulocytopenia can be dismissed. The maintenance of normal haemoglobin levels throughout the time when the polymorph count was depressed excludes the possibility of a generalized effect on haemopoiesis from the acute rheumatism itself. Acute rheumatism in its active stages is a well-known cause of polymorph leucocytosis (Hubbard and McKee, 1939), and I can find no record of a leucopenia being attributed to it at any stage in the disease. It must, however, be noted that in Case 1 there was some depression of the polymorph count in the early stages, when salicylates were still being given. Nevertheless it seems probable that the granulocytopenia with its associated lymphocytosis was due to the effect of sodium gentisate. This may have resulted from an idiosyncrasy to the drug reminiscent of the effect of amidopyrine. Camelin *et al.* did not find any alteration in the blood picture in their series of cases treated with sodium gentisate, while Schaefer *et al.* (1950), who gave their cases 18 g. of sodium gentisate daily, found a polymorph leucocytosis in two patients who developed septic complications while on this treatment. It therefore seems unlikely that granulocytopenia will prove to be a common complication of gentisate therapy, but whenever the drug is used it would be advisable to keep a watch on the total and differential white counts both during and for a few weeks after its administration.

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REFERENCES

- Camelin, A., Accoyer, P., Pellerat, J., Lafuma, J., and Coirault, R. (1949). *Bull. Soc. méd. Hôp. Paris*, 65, 826.
— Stieger, R., Morel, M., and Tary, A. (1950). *Presse méd.*, 58, 889.
Hubbard, J. P., and McKee, M. H. (1939). *J. Fediat.*, 14, 66.
Meyer, K., and Ragan, C. (1948). *Science*, 108, 281.
Schaefer, L. E., Rashkoff, I. A., and Megibow, R. S. (1950). *Circulation*, 2, 265.