DERMATITIS HERPETIFORMIS TREATED WITH DIAMINO-DIPHENYLSULPHONE (DADPS)

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Dermatitis herpetiformis is a chronic skin disease of unknown aetiology, characterized by intense itching and the presence of grouped erythematous, papulovesicular, vesicular and bullous lesions, which on involution leave pigmented spots and sometimes scars. The disease, which may persist for 10 years or more, has natural remissions and exacerbations.

There is no cure for the disease, but there are several well-tried drugs which control both the rash and the itching. Arsenic was probably the first of these drugs to be used, given either as liquor arsenicalis or as acetarsone. The disadvantage of arsenic is its toxicity, particularly when administered over prolonged periods. Arsenical keratoses with their tendency eventually to develop into squamous epitheliomata are a real hazard to the patient taking arsenic.

Sulphapyridine is also effective in controlling dermatitis herpetiformis, and has probably been the most widely-used drug in this condition. It is, however the most toxic of the sulphonamides, and because of an idiosyncrasy to it, many patients are unable to continue treatment. The treatment of the patient who is unable to take this drug is a difficult problem, and any drugs which are reputed to control the disease are worthy of trial.

SULPHONES

The sulphones, a group of drugs which have been used for some years in the treatment of leprosy and tuberculosis, have also recently been used with good effects in dermatitis herpetiformis.[1, 2] Cornbleet [2] has treated 13 cases of dermatitis herpetiformis with diasone with excellent results; some of these cases were refractory to other treatment, including sulphapyridine. Since it is thought that the more complex sulphones act by liberating diamino-diphenysulphone (DADPS) in the body, it was considered logical to investigate the effect of DADPS on dermatitis herpetiformis, particularly since it has been held by some to be superior to sulphapyridine in controlling the condition.[3] DADPS is better absorbed from the gastro-intestinal track than the more complex sulphones, and blood levels are better maintained with it, since it is the most slowly eliminated of the sulphone compounds.

Toxic effects from its use in leprosy and tuberculosis include dermatitis, lepra reactions, leprous neuritis and iritis. Haemolytic and hypochromic anaemia have also been recorded, as well as jaundice due to hepatitis. The commonest side-effect of sulphone therapy is a

transient normocytic anaemia, which appears during the first few weeks of treatment but clears spontaneously in spite of continued sulphone therapy. Other blood changes include methaemoglobinaemia, which occurred in half of the patients treated by Cornbleet with diasone.

The first cases selected for treatment were those patients unable to tolerate sulphapyridine therapy because of nausea and vomiting or severe leukopenia. Other cases were included in the trial because they did not respond to sulphapyridine therapy and the control of the rash and itching had become a difficult therapeutic problem. The result of this therapy in the first few cases was so impressive that it was decided to treat cases well controlled with sulphapyridine, in order to compare the efficiency of the latter with that of DADPS.

CASE REPORTS

Case 1. H.W., female aged 53 years, suffering from dermatitis herpetiformis since May 1952. She was first seen in August 1952, when she was treated with sulphapyridine, 0·5 g. *t.d.s.* This relieved the irritation, but could not be continued because of nausea, vomiting and weakness. She then underwent various treatments, including liquor arsenicalis, nicotinamide and antihistaminics, with no marked effect. On 5 March 1954 she was started on DADPS, 50 mg. daily, with marked improvement. Two weeks later the dosage was decreased to 50 mg. every second or third day. She has shown no toxic effects and remains completely free of rash and itching. The blood count and haemoglobin level remains normal.

Case 2. E.H., male aged 38 years, suffering from dermatitis herpetiformis since 1947. He was first treated with sulphapyridine in November 1950, with marked subjective and objective improvement, but had to be discontinued after several weeks because the patient developed an acute tonsilitis associated with a leukopenia (white-cell count 3,000 per c.mm., with differential count: polymorphs 54%, lymphocytes 36%, monocytes 8%, band forms 2%). In November 1954 sulphapyridine, 0·5 g. daily, was again given, and in 2 weeks the white cell count fell from 7,000 per c.mm. to 3,000 per c.mm. (normal differential counts). Sulphapyridine was therefore again discontinued. On 15 February 1954 he was put on 50 mg. daily. He was seen again after 2 weeks, when there were no signs of active disease and pruritus had disappeared. Because of a relapse, the dosage was later increased to 100 mg. daily, which completely controls the disease. He shows no toxic effects, and the blood count remains normal.

Case 3. J.P., female aged 2½ years. First seen on 14 February 1954 with a 2 weeks' history of a rash. There are 5 other children in the family, none with any skin disease. The rash was typical of dermatitis herpetiformis, with blisters and bullae showing an annular arrangement. It affected the vulva, thighs, back, face and limbs. She was first treated with sulphapyridine 0·5 g. daily as an out-patient, but there was no response to treatment and she was therefore admitted to hospital. Here, in spite of continued sulphapyridine therapy and liquor arsenicalis, she did not improve. On 27 March 1954 DADPS 25 mg. daily, was given, with improvement noticeable after 3 days of treatment. She developed a microcytic anaemia while on this dosage, but this has improved and continues to improve though the drug is still taken. The rash is not completely controlled on this dosage, and she still develops new bullae, but whenever the drug is discontinued a very severe relapse occurs. She has shown no serious toxic effects, though on occasions she has had as much as 50 mg. of DADPS a day.

Case 4. J.R., male aged 50 years, suffering from dermatitis herpetiformis for the last 2 years. He had been treated for the past 18 months with sulphapyridine, 3 g. daily. The rash had fluctuated during this period without complete freedom from itching and active signs of disease. He had a past history of a perforated duodenal ulcer in 1943, gastrectomy in 1948, and haematemesis after aspirin in 1951. On 10 February 1954 he still showed active lesions of dermatitis herpetiformis on the elbows, scratched papules, scars and erythema on the sacrum. General examination showed no abnormality. Blood-count normal. He was admitted to hospital and given inert tablets (calcium lactate) for 3 days with no effect on the rash. He was then treated with DADPS, 100 mg. daily, and showed remarkable subjective and objective improvement. He continues to take DADPS daily, with excellent control of the rash.

Case 5. H.C., male aged 36 years, suffering for the last 3 years from dermatitis herpetiformis, which had been fairly well controlled by sulphapyridine, 1 g. 3 times a day, though the patient still had active disease as shown by itching and the presence of vesicles. On 6 April 1954 the sulphapyridine was discontinued and DADPS 50 mg. daily substituted. On this dosage he developed a severe relapse and the dosage was increased 1 week later to 100 mg. daily, but this was insufficient to control the itching and the eruption. On 20 April treatment was then changed back to 3 g. of sulphapyridine a day, which again controlled the rash. On 27 April the sulphapyridine was again stopped and DADPS given, 200 mg. a day. The rash is very well controlled on this dosage, though he still shows vesicles. He states that he much prefers DADPS because of the greater relief of itching. Haemoglobin 80%, and examination of the blood shows methaemoglobinaemia.

Case 6. J.B., male aged 63 years, suffering for 7 years from typical dermatitis herpetiformis affecting the shoulders, elbows and scalp, and with marked pigmentation of the skin over the sacrum. On 29 April 1954 DADPS, 100 mg. daily, was commenced with complete relief from itching and no signs of active disease after 2 weeks of treatment. He continues to take 100 mg. DADPS a day for complete control of the eruption. There is no anaemia and no toxic effects from DADPS have occurred.

Case 7. M.A., female aged 31 years, with dermatitis herpetiformis of 4 years' duration. Since February 1951 she had been treated with sulphapyridine, 2 g. daily, but without complete control of the rash or itching. On 29 March 1954 DADPS, 50 mg. daily was commenced and by 5 April 1954 she was markedly improved; the blood count remained normal. On 13 May 1954, DADPS was increased to 100 mg. a day because of the presence of active lesions. In spite of the presence of new lesions, she states that the itching has completely disappeared and 'I can sleep now'. She has shown no toxic effects.

Case 8. L.W., male aged 36 years, with very severe dermatitis herpetiformis for the last 7 years. Attempts had been made to control the rash with sulphapyridine, but these had been discontinued because of severe relapses. He had also undergone prolonged treatment with liquor arsenicalis, which was discontinued when the patient developed arsenical keratoses of the palms. Thereafter he had had antihistaminics, nicotinamide and suramin. In January 1954 DADPS 50 mg. daily was commenced, which soon relieved the itching. The dose was increased after 3 weeks to 100 mg. a day. The patient stated that this treatment had been more effective in relieving the itching than any of the previous treatments, though he still showed severe active skin lesions. This patient suffered also from bronchiectasis, mitral stenosis with congestive cardiac failure, chronic nephritis and arsenical keratoses. On 13 May 1954 he became jaundiced and showed severe cardiac failure. Though there were signs of active dermatitis herpetiformis, he had very little itching. He died on 18 May 1954.

Case 9. A.B., male aged 34 years, with 3 years' history of dermatitis herpetiformis. He had undergone various treatments including liquor arsenicalis, suramin, nicotinic acid and sulphapyridine. The rash was comparatively well controlled by sulphapyridine, 2 g. daily. On 10 March 1954 treatment was changed to DADPS, 100 mg. daily, later increased to 150 mg. a day. The patient states that he feels much better on these tablets and sleeps better because of the absence of itching. He continues to take 150 mg. daily as a maintenance dose and has shown no toxic effects.

Case 10. S.E., male aged 42 years, with dermatitis herpetiformis of 2 years' duration controlled only moderately well by 2·5 g. of sulphapyridine daily. On 9 April 1954 DADPS, 50 mg. daily, was substituted and he relapsed within a few days, so that the sulphapyridine was again given in the same dosage. On 7 May 1954 he still had active vesicles, and 200 mg. of DADPS daily was commenced. This produced complete control of the rash and itching. He shows no active disease after 3 months on 200 mg. daily as a maintenance dose. He much prefers these tablets to sulphapyridine, as the latter made him feel 'off colour'. His blood-count remains normal. He has shown no toxic effects.

Case 11. A.B., male aged 37 years, seen on 9 April 1954 with a 4 months' history of typical dermatitis herpetiformis affecting the beard, axillae, elbows and sacral area. He was given sulphapyridine 2 g. daily with marked relief, both objective and subjective. On 21 May 1954, in spite of the sulphapyridine he had relapsed, and DADPS, 100 mg. daily, was substituted. His rash has virtually cleared, with complete disappearance of itching.

Case 12. E.S., male aged 67 years, with 8 years' duration of rash very well controlled by sulphapyridine, 0·5 g. every alternate day, though occasional itching and vesicles were present. On 7 May 1954 treatment was changed to DADPS 100 mg. daily. By 21 May the rash was still well controlled. The patient states that as far as he is concerned there is no difference between these tablets and the previous ones. He continues to take DADPS 50 mg. daily as a maintenance dose. His blood-count and haemoglobin remain normal.

Case 13. C.W., male aged 51 years, with dermatitis herpetiformis for the last 15 years. He had undergone occasional arsenical therapy and since 1951 had taken 0·5 g. of sulphapyridine daily. On 30 April 1954 he still showed active signs of disease. The sulphapyridine was stopped and DADPS, 100 mg. daily, given. The relief of itching is more complete than with sulphapyridine. He continues to take this dose to control the rash. He has shown no toxic effects.

Case 14. E.G., female aged 63 years, first seen in August 1952 with typical dermatitis herpetiformis. From that time she had been on sulphapyridine, 1·5 g. daily, with comparative comfort and control of the rash. On 6 May 1954 sulphapyridine was stopped, and 3 days afterwards she developed a severe relapse. DADPS 100 mg. daily was started on 20 May 1954 with good control of the rash and itching. She continues on this dosage. The rash is well controlled and no toxic effects have occurred.

Case 15. D.S., male aged 37 years, with rash since 1949. He had been on liquor arsenicalis, 2 m. *t.d.s.*, for one year. In 1950 treatment was changed to sulphapyridine 3 g. daily with no marked response. In April 1954 he was seen with active vesicles, papules, and itching. DADPS was given, 100 mg. a day, and 2 weeks later there was no itching and no signs of any activity. He was last seen on 15 July 1954, when he was taking 25 mg. daily for complete control of the rash. He has shown no toxic effects.

Case 16. W.S., male aged 45 years, with dermatitis herpetiformis since 1947. Treated for 2 years with liquor arsenicalis, 3 m. *t.d.s.* He developed severe relapses when arsenic was stopped. Since January 1949 he has been treated with sulphapyridine 0·5 g. daily. On 14 June 1954 his haemoglobin was 80%, colour index 1·0, and white-cell count 5,000 c.mm., with a normal differential count. DADPS, 200 mg. daily, was then substituted for sulphapyridine, and 6 weeks later there was no itching and complete control of the rash. The patient prefers this treatment to any previous one. There was no change in the blood-counts after 6 weeks of treatment; no abnormal pigments were found on spectroscopic examination of the blood.

Case 17. F.H., male aged 47 years. Since 1950 this patient suffered from typical dermatitis herpetiformis not fully controlled by sulphapyridine, 1·5 g. daily. He was seen on 31 May 1954 with active lesions on the back and scalp, when treatment was changed to DADPS, 100 mg. daily. On 10 June 1954 his haemoglobin was 73%, colour index 0·87, and white cell count 7,000 c.mm., with a normal differential count. DADPS therapy was continued. On 28 June 1954 haemoglobin was 95%, faecal urobilinogen was normal, and examination of the blood showed methaemoglobin present; fragility of the red cells normal. Both the patient and his relatives were alarmed at his appearance, which was due to methaemoglobinaemia, but they were reassured and he agreed to continue treatment. On 5 July 1954 he still had a peculiar colour due to methaemoglobinaemia, but his relatives were no longer concerned about his appearance. His rash remains well controlled on 100 mg. of DADPS a day.

Case 18. E.I., male aged 57 years, with dermatitis herpetiformis of 5 years' duration, only partially controlled by sulphapyridine and later by liquor arsenicalis. When seen on 12 May 1954 he showed active lesions on the scalp, and DADPS, 100 mg. daily, was prescribed. On 29 July 1954 he had no itching, no signs of any activity, and no toxic effects. He continues to take 100 mg. a day as a maintenance dose.

Case 19. F.C., male aged 69 years, with 3 years' history of rash well controlled with sulphapyridine, 1 g. daily. On 10 June 1954 his blood count showed an eosinophilia, and the haemoglobin was 102%. DADPS, 200 mg. daily, was given. On 21 June 1954 he complained of a constant headache, he was very cyanosed and blood examination showed sulphaemoglobinaemia. All treatment was stopped. By 10 July 1954 his cyanosis had disappeared, but the rash had relapsed. DADPS 100 mg. daily was given, and on 26 July 1954 the patient again complained of severe headaches. He was again cyanosed, and sulphaemoglobin was again present on spectroscopic examination of the blood. The DADPS was continued and ascorbic acid, 900 mg. daily, was given. As the cyanosis persisted on this treatment, the DADPS was discontinued.

RESULTS OF TREATMENT

The 19 cases of dermatitis herpetiformis treated with DADPS include one case of the infantile type of the disease. All these cases responded to treatment. The relief of itching and the disappearance of the rash was quite dramatic in most cases. The dosage of DADPS appears to be directly proportional to the dosage of sulphapyridine necessary to control the eruption. No case required more than 200 mg. of DADPS a day to control the rash, the average maintenance dose being 100 mg. a day. As with sulphapyridine, relapses generally occur on the 3rd day after the patient discontinues treatment. Since the disease is characterized by spontaneous remissions and exacerbations, patients were told to modify their dosage as they found necessary. Only one patient (case 12) noted no difference between DADPS therapy and sulphypyridine. All the other patients preferred DADPS therapy because of the greater relief from itching and the absence of side effects.

TOXIC EFFECTS

Kruizinga and Hamminga [3] noted no severe toxic effects in their 12 cases, nor were there any present in our 19 cases.

One patient (case 19) was obliged to discontinue treatment because of sulphaemaglobinaemia associated with severe headaches. This did not respond to big doses of ascorbic acid, so DADPS was discontinued.

Two cases showed methaemoglobinaemia. These continued with their DADPS therapy and had no other toxic effect from this drug.

One patient (case 8) when first seen, was very ill, suffering from bronchiectisis, mitral stenosis and chronic nephritis. Though he obtained substantial relief of itching from DADPS, he continued to show large numbers of vesicles and blisters. This may have been due to insufficient dosage of the drug, and the continued absorption of iodine from the lipiodol in his bronchiectatic cavities. Though he was jaundiced for 2 weeks before his death, the jaundice could not be attributed definitely to the DADPS.

DISCUSSION

The mode of action of DADPS in dermatitis herpetiformis is unknown. The more complex sulphones, e.g. diasone and sulphatrone [1, 2] have been used in the treatment of dermatitis herpetiformis with favourable results, though their action is generally inferior to that of sulphapyridine. As these more complex sulphones are thought to be broken down in the body to DADPS,

it is understandable that DADPS should also have a favourable action in dermatitis herpetiformis.

SUMMARY

Nineteen cases of dermatitis herpetiformis were treated with DADPS for an average period of 3½ months. All cases responded to treatment provided dosage was sufficient. The relief of itching and the control of the rash is more pronounced with DADPS than with sulphapyridine.

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