PULSE THERAPY WITH DEXAMETHASONE-CYCLOPHOSPHAMIDE IN PEMPHIGUS

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In order to achieve better therapeutic results, 10 patients having pemphigus vulgaris were treated with repeated pulses of dexamethasone and cyclophosphamide. Each pulse consisted of 100 mg dexamethasone given intravenously in 5% glucose over a period of 1 hour, on three consecutive days. In addition, 500 mg cyclophosphamide was given with the pulse on the first day, followed by 50 mg orally daily even in between the pulses. Such pulses were repeated every 2-4 weeks depending upon the clinical activity of the disease. With this therapy, healing of skin lesions was generally much faster and the patient could as a rule be discharged within 4-5 days. Secondly, the side effects usually associated with prolonged corticosteroid therapy were far milder. In a follow-up varying from $13\frac{1}{2}$ to $26\frac{1}{2}$ months, 6 patients remained free from relapses for 6 to $14\frac{1}{2}$ months, while 4 patients continued to develop relapses at variable intervals after each pulse.

Key words : Pulse therapy, dexamethasone, cyclophosphamide, pemphigus vulgaris.

Pulse therapy consists of giving a very high dose of a drug to bring about a quick result and then withdrawing the drug completely till it is needed again. Pulse therapy with corticosteroids has been used for renal transplant rejection,[1,2] lupus nephritis,[3-5] polyarteritis nodosa,[6] rheumatoid arthritis[7] and pyoderma gangrenosum[8] with the obvious benefit of a quick recovery and relative freedom from side effects. Our first experience with dexamethasone pulse therapy in a patient having Reiter's disease was very promising.[9] To the best of our knowledge, there is no report of pulse therapy having been used for pemphigus except for mention of a single patient having pemphigus foliaceous treated with pulse.[8] We have been using pulse therapy for pemphigus since December 1981; our experience in 10 cases followed up for $13\frac{1}{2}$ to $26\frac{1}{2}$ months is being reported.

Materials and Methods

Two types of pulses were used in these patients. The dexamethasone pulse (DP) consisted of 100 mg dexamethasone dissolved in 500 ml of 5% glucose transfused over one hour. This dose was repeated on 2 more subsequent days. The dexamethasone-cyclophosphamide pulse (DCP) consisted of 500 mg cyclophosphamide combined with 100 mg dexamethasone on the first day and only 100 mg dexamethasone given on the subsequent 2 days. These pulses were repeated at monthly intervals, but in case the lesions reappeared earlier, the pulse was also repeated earlier, but generally not earlier than 2 weeks. In between the DCP, the patient received 50 mg cyclophosphamide a day orally.

All patients were admitted for this study. Before starting the pulse, the following investigations were undertaken; haemoglobin, total and differential leucocyte counts, platelet counts, urine examination especially for red blood cells, blood sugar levels, serum electrolytes, skiagram of the chest, stool examination for occult blood, ophthalmic examination especially for cataract, and weight charting. These investigations were repeated after the last dose of the pulse.

Results

Four patients were initially given only DP but all patients were subsequently shifted to DCP. In all cases, DP or DCP was ablee to

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control the relapses within 3 days. In one patient DP was followed by a remission for 6 months while the remaining 3 patients on DP developed relapses after a variable number of days following each pulse.

Of the 10 patients treated with DCP, 6 patients remained free from pemphigus lesions for 6, 9, 9½, 13½, 14 and 14½ months respectively. So far, these patients have received 22, 7, 7, 10, 19 and 9 DCP. Four patients however, continued to develop relapses after a variable number of days following each pulse. Salient features of these cases are as follows :

Case Reports

Case 1

In February 1980, a 30-year-old male started having pemphigus vulgaris which was controlled with 60 mg prednisolone daily. Subsequent relapses in August 1980, March 1981 and September 1981 were controlled with 40-120 mg prednisolone a day. In between these relapses he had been taking 5-30 mg prednisolone a day. His next relapse in June 1982, was treated with DP, resulting in a complete remission within 3 days. Corticosteroids were completely withdrawn. During the next 3 months, he developed only mild relapses in between each pulse which was repeated every month. Each relapse was controlled with 60 mg prednisolone a day given for 6-12 days. Since December 1982, he is being given 500 mg cyclophosphamide along with each DP and 50 mg cyclophosphamide a day in between the pulses. Since then, he has received 7 DCP and has been almost free from pemphigus lesions for the last 9 months.

Case 2

Since March 1981, a 30-year-old male had been having pemphigus vulgaris controlled with 120 mg prednisolone a day. For the next two years he continued to take 5 mg prednisolone a day. In March 1983, about 1½ months after stopping the maintenance dose of prednisolone, he developed a mild relapse which could not be controlled with 15 mg prednisolone a day during the next 15 days. On March 12, 1983, DCP was started which led to a complete remission within 3 days. Since then, he has been on 50 mg cyclophosphamide a day in addition to 10 pulses given at monthly intervals without any reactivation of pemphigus. He has not received any pulse since February 1984, and he is still free from lesions when seen last in April 1984.

Case 3

Since October 1980, a 13-year-old boy had several relapses of pemphigus vulgaris at intervals of 15-20 days. The type of treatment taken during the first year is uncertain, but in September 1981, his disease was controlled with 30 mg of prednisolone a day. The subsequent relapses in October 1981, December 1981 (2 relapses), and February 1982, were controlled with either 60 mg prednisolone or DP. In between the relapses he was taking 10-20 mg prednisolone a day. The next relapse in April 1982 was controlled within 3 days with DP which was subsequently repeated every month. During the next 6 months he developed 8 relapses in between the pulses, four relapses required 20-60 mg prednisolone a day for controlling the disease activity till the pulse was given. Since October 1982, cyclophosphamide 500 mg was added with every DP, in addition to 50 mg cyclophosphamide daily in between the pulses. Since then he has received 17 DCP but continues to develop relapses after a variable number of days following the pulse (Fig. 1).

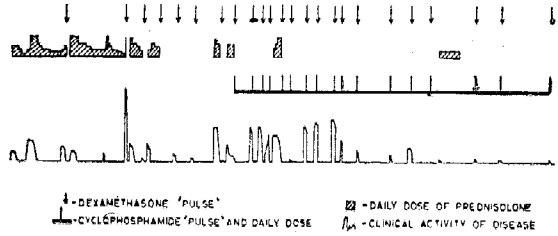

Fig. 1. The clinical course of the disease in case 3.

Case 4

Since May 1974, a 48-year-old male had been having relapses of pemphigus vulgaris at intervals of 1-6 months. The relapses were controlled with 30-120 mg of prednisolone a day and in between the relapses, he was taking 10-20 mg of prednisolone a day. In October 1982, prednisolone was withdrawn completely but he had no relapse for the next 3 months. The next relapse occurred in January 1983, and this was controlled with DCP. In addition, he was given 50 mg cyclophosphamide daily orally. Since then he has received 14 DCP, he recovers quickly from the disease but develops reactivation of the disease after a variable number of days following each pulse.

Case 5

In February 1980, a 30-year-old male started having pemphigus vulgaris. It was controlled with 60 mg prednisolone a day. The next relapse in March 1980, was controlled with 40 mg prednisolone a day. Further relapses occurred in September 1981, December 1981, January 1982, and each of these were controlled with 30 mg prednisolone a day, but in between these relapses he had been taking 10-30 mg prednisolone a day. The next relapse in April 1982 was treated with DP and it led to complete healing within 3 days. Corticosteroids were completely withdrawn after the pulse. However, within 7 days a few lesions appeared which were controlled with 40 mg prednisolone daily. DP were repeated every month to a total of 7 pulses. He did develop a few lesions in between the pulses but by and large no prednisolone was given in between the pulses. Since February 1983, he is being given 500 mg cyclophosphamide with each DP and 50 mg cyclophosphamide daily orally in between the pulses. Ever since he has been free of pemphigus lesions when seen last in November, 1983.

Case 6

Since November 1981, a 16-year-old girl was having pemphigus lesions in the mouth and genitals and was being treated with 20 mg prednisolone a day. In February 1982, she developed skin lesions for which she was given DP. All the lesions healed within 3 days, corticosteroids were completely withdrawn. During the next 6 months, she continued to develop relapses within 3-15 days after the pulse which was repeated every month. Each relapse was controlled with 40-60 mg of prednisolone a day. Since September 1982, she is being given 500 mg cyclophosphamide with the DP and 50 mg cyclophosphamide a day in between the pulses. During the next 3 months she had 4 relapses. Since December 1982, she has received 14 DCP and is almost free from pemphigus lesions (Fig.2).

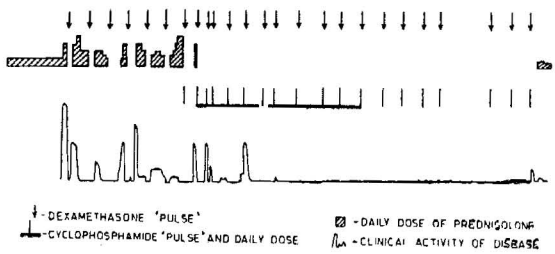

Fig. 2. The clinical course of the disease in case 6.

Case 7

Since January 1982, a 20-year-old male was having lesions of pemphigus vulgaris in the mouth. In April 1982, he developed skin lesions which were treated with 60 mg of prednisolone a day during the next 5 months. The next relapse occurred in October 1982, when he was taking 15 mg prednisolone a day. This was controlled with DCP. During the next 3 months he was given 4 more DCP in addition to 50 mg cyclophosphamide a day. He developed 4 relapses one of which even required 60 mg of prednisolone a day to control its activity. During the next $2\frac{1}{2}$ months he was not given any pulse or cyclophosphamide but he did not develop any relapse. The next relapse occurred in March 1983 when DCP

was again started along with cyclophosphamide 50 mg daily. Subsequently, he received 9 pulses but continued to develop relapses after each pulse at variable intervals. Two of the relapses required 40 mg of prednisolone a day to control the disease activity. Since August 1983, he is almost free from pemphigus lesions and has taken 8 more pulses at one-monthly intervals. He had in addition been taking 1 mg betamethasone whenever required for mild oral ulcerations.

Case 8

In May 1982, a 48-year-old male started having pemphigus vulgaris. It was controlled with 40 mg prednisolone a day. The next relapse occurred in August 1982, while he was on 10 mg prednisolone. Prednisolone even in a dose of 100 mg a day was not able to control the disease activity. In November 1982, DCP was started which led to complete healing of the lesions in 3 days. During the next 3 months he developed 3 mild relapses which were controlled with DCP. Between January 1983 and April 1984, he received 6 DCP in addition to 50 mg cyclophosphamide a day and he had been almost free of the lesions.

Case 9

In July 1982, a 29-year-old male started having pemphigus vulgaris and within one month, the lesions spread all over the body. He was treated with 4 mg dexamethasone daily for 2 months. The next relapse occurred in December 1982. Twenty mg prednisolone a day for 1 month could not control the disease. Thus in January 1983 treatment with DCP was started which led to a complete remission during the next 1 week. Since then he has been taking 50 mg cyclophosphamide a day, and has also received 8 DCP. He had been almost free of lesions except for very mild relapses a few days prior to each pulse. About a week after the 9th pulse he developed a mild relapse, but he stopped cyclophosphamide and shifted to homeopathic treatment. During the next 3 months the lesions spread all over the body. In January 1984, he reported again and was given DCP. This brought the disease under control, and the next pulse given after 2 weeks led to complete healing. He has received 2 more DCP and has been almost free of pemphigus lesions during the last 2 months.

Case 10

In December 1982, a 20-year-old male noticed pemphigus lesions in the mouth. During the next 1½ months he developed skin lesions all over the body. In February 1983, DCP was started with partial healing of the lesions. The next pulse given 2 weeks later led to complete healing. In between the pulses he was given 50 mg cyclophosphamide a day orally. Since then, he has received 20 DCP but continued to develop relapses after a variable number of days after each pulse. During the last 6 relapses he even required 30-60 mg prednisolone a day for controlling the disease activity. For the last 2 months, he is better controlled and did not require any oral prednisolone in between the pulses.

Side effects : Ten patients received a total of 185 pulses—24 dexamethasone pulses and 161 dexamethasone-cyclophosphamide pulses. Of these, 9 patients experienced increased susceptibility to skin infections, and most of them had to be given antibacterial drugs concomittently. Two patients developed reactivation of tuberculosis which was controlled with antitubercular drugs. Occult blood in the stools was seen on 22 occasions in 10 patients, for 2-4 days after the pulse. On six occasions, it followed DP and on 16 occasions the DCP. Two patients developed leucopenia and one patient developed thrombocytopenia on one occasion each after the DCP. The counts however returned to normal within 3 days without any specific therapy, and further pulses could be continued without recurrence of leucopenia or thrombocytopenia. Posterior subcapsular cataract observed in one patient,

and in another, the cataract present earlier continued to progress. Rise of blood sugar was observed only in one patient. Cushingoid obesity, osteoporosis, electrolyte imbalance and urinary tract infections often seen with prolonged corticosteroid therapy were not seen in any patient. In fact, most of the patients lost their excessive weight which they had gained during the earlier treatment.

Comments

The chief problems in the management of pemphigus patients consist of delayed healing of lesions, need for large doses of corticosteroids for long periods, and frequent relapses. The outcome of all these is that, (1) the patient has to stay in the hospital for prolonged periods resulting in disruption of the personal as well as the family life, and (2) serious side effects of prolonged corticosteroid therapy often adding to the morbidity and the fatalities of the disease. Immuno-suppressive agents in combination with corticosteroids do reduce the side effects of corticosteroids but immuno-suppressive agents themselves have their own serious side effects. Gold therapy, as well as plasmapheresis also are no better.

The chief advantage of pulse therapy has been to induce a quick remission. It is remarkably assuring to see all the lesions dry up within 3 days of the pulse therapy. As a routine therefore, we admit the patient only for 5 days—3 days for the pulse and 1 day before and after the pulse for investigations. The patient is then sent home to resume his duty and the hospital bed is available for the next patient.

The second advantage of the pulse therapy is freedom from side effects. Weight gain, electrolyte imbalance, diabetes mellitus, osteoporosis, hypertension, acne etc were remarkably not encountered. Leucopenia and thrombocytopenia are also infrequent when a patient is using only 50 mg cyclophosphamide a day. The chief side effect with the pulse was increased susceptibility to infections or reactivation of tuberculosis and there is need to remain alert about these.

The current limitation of pulse therapy is the cost of the drugs, but when this cost is compared to the loss due to prolonged admission of the patient for conventional therapy, the high cost seems to be largely compensated.

References

1. Bell PRF, Calman KC, Wood RFM et al : Reversal of acute clinical and experimental organ rejection using large doses of intravenous prednisolone, Lancet, 1971; 1:876-880.
2. Feduska NJ, Turcotte JG, Gikas PW et al : Reversal of renal allograft rejection with intravenous methylprednisolone 'pulse' therapy, J Surg Res, 1972; 12: 208-215.
3. Cathcart ES, Scheinberg MA, Idelson BA et al : Beneficial effects of methylprednisolone 'pulse' therapy in diffuse proliferative lupus nephritis, Lancet, 1976; 1:163-166.
4. Levinsky RJ, Cameron JS and Soothill JF : Serum immune complexes and disease activity in lupus nephritis, Lancet, 1977; 1:564-567.
5. Ponticelli C, Tarantino A, Pioltelli P et al : High-dose methylprednisolone pulses in active lupus nephritis, Lancet, 1977; 1:1063.
6. Neild GH and Lee HA : Methylprednisolone pulse therapy in the treatment of polyarteritis nodosa, Postgrad Med J, 1977; 53:382-387.
7. Liebling MR, Leib E, Mclaughlin K et al : Pulse methyl-prednisolone in rheumatoid arthritis, Ann Int Med, 1981; 94:21-26.
8. Johnson RB and Lazarus GS : Pulse therapy, Arch Dermatol, 1982; 118:76-84.
9. Pasricha JS and Gupta Ramji : Pulse therapy with dexamethasone in Reiter's disease, Ind J Dermatol Venereol Leprol, 1982; 48:358-361.