PULSE THERAPY IN DERMATOLOGY

Rashmi Mittal [a], Sudha R [a], Murugan S [a], Adikrishnan [a], Shobana S [a], Anandan S [a]

ABSTRACT

Pulse therapy means the administration of large (suprapharmacologic) doses of drugs in an intermittent manner to enhance therapeutic effects and reduce adverse effects. Dexamethasone and cyclophosphamide in bolus doses have been widely used in pulse form to treat various dermatological disorders. Pulse corticosteroids have also been tried in other conditions like renal graft rejection, lupus nephritis and other autoimmune disorders. This form of therapy has given excellent treatment response with very few side effects. Corticosteroids, immunosuppressives, antifungals, antivirals are the commonly used drugs administered in pulse doses.

Key words: *Dexamethasone, pulse drug therapy, cyclophosphamide, autoimmune diseases.*

INTRODUCTION

Pulse therapy means the administration of large (suprapharmacologic) doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects [1].

PULSE CORTICOSTEROID THERAPY

The first reported use of pulse administration of corticosteroids is attributed to Kountz and Cohn who used it to successfully prevent renal graft rejection [2]. Thereafter, pulse doses of corticosteroids were used for other diseases such as lupus nephritis, rheumatoid arthritis and pyoderma gangrenosum [3,4]

The introduction of dexamethasone cyclophosphamide pulse (DCP) therapy for a blistering disorder, pemphigus vulgaris, by Pasricha et al has revolutionized the therapy for pemphigus [5]. The therapy has since been used to treat a large number of patients at several centers in India [6] and abroad [7]. The dermatological disorders in which corticosteroid pulse therapy has been advocated are pemphigus vulgaris, an autoimmune blistering disorder, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, pyoderma gangrenosum, toxic epidermal necrolysis, Steven Johnson's syndrome, lichen planus, alopecia areata, sarcoidosis, and systemic vasculitis. Pulse corticosteroid therapy has been proposed as a means of rapidly controlling life-threatening or serious conditions with minimal toxicity, allowing for less aggressive long term maintenance therapy. The selection of drugs and their dosages has been completely arbitary and based upon intuition and convenience. Conventionally, methyl predinsolone was the agent most commonly used. The choice of dexamethasone made the treatment considerably more affordable and accessible to patients. There was concern among some workers about the equivalence of 1000mg of methylprednisolone and 100mg of dexamethasone and some groups have administered pulses of 136mg of dexamethasone. However , a dose of 1000mg of methylprednisolone is as arbitary as a dose of 100mg of dexamethasone and in the absence of evidence that 136mg pulses of dexamethasone are more effective nearly all centres continue to use 100mg boluses.[8] Moreover, the cost of dexamethasone cyclophosphamide pulse therapy works out to be 1/3rd of the total cost of methylprednisolone pulse.

Dexamethasone Cyclophosphamide Pulse (DCP) therapy - divided into 4 phases.

Phase I consists of Dexamethasone 100 mg in 5% Dextrose as a slow IV infusion over 2 hours for three consecutive days along with cyclosphosphamide 500 mg infusion on one of the days. This constitutes one DCP. Such DCPs are repeated every 28 days till no new lesions appear between pulses. Cyclosphosphamide 50 mg / day is given orally. During this phase the patient may continue to develop recurrences of clinical lesions in between the DCPs and can therefore be given conventional doses of oral corticosteroids to achieve quicker clinical recovery. After the skin and mucous membrane lesions have subsided completely and the additional medication withdrawn , the patient is considered to have entered phase II[9].

Phase II consists of the DCP schedule given for a fixed duration of 9 months.

Phase III , only oral Cyclophosphamide 50 mg / day is given for 1 year

Phase IV, all the drugs are with drawn and the patient is followed up.

There was initial alarm and anxiety about the large doses of corticosteroids and cyclophosphamide, but today this therapy is given as a routine infusion, often in a day care or OPD setting, with the patient going home a few hours after completion of the infusion.

There have been modifications of DCP therapy[10]. Cyclophosphamide is known to cause oligo / azoospermia and amenorrhoea. For unmarried patients who have not

CORRESPONDING AUTHOR :

Dr. RASHMI MITTAL
Assistant Professor
Department of Dermatology & STD
Sri Ramachandra Medical College and Research Institute
Porur, Chennai – 600116.
E-mail : saresh15@hotmail.com
[a] Department of Dermatology

completed their family, cyclophosphamide is replaced with azathioprine 50 mg (DAP therapy). Methotrexate, 7.5 mg (DMP) was instituted in patients who were not completing Phase I even after 12 pulses (1 year) of DCP or DAP therapy.

Contraindications of DCP therapy

DCP therapy can be given to patients of all ages but the doses have to be reduced to half for children below the age of 12 years [9]. It can also be administered to patients having other medical problems like diabetes mellitus, hypertension, osteoporosis, tuberculosis. Diabetic patients need to be given 10 units of soluble insulin for every 500 ml bottle of 5% dextrose dissolved in the same drip. In addition they must be given the routine treatment for diabetes mellitus. Similarly patients having concomitant diseases like hypertension and tuberculosis must receive the respective medication. If there is serious infection elsewhere or if the patient has severe bacterial, viral or fungal infections, the pulse may be delayed for a week or two till the infection has been brought under control. Pulse therapy is absolutely contraindicated in pregnant, lactating and unmarried patients.

Laboratory monitoring

As a routine, it is mandatory to admit every patient enrolled for pulse therapy and undertake a complete baseline clinical and laboratory evaluation before starting the first pulse. Haemogram, serum electrolytes, renal and liver function tests, blood sugar (including HbA1C), urine microscopic examination, chest X-ray, electrocardiogram and pregnancy test are some of the preliminary laboratory tests to be done at the first visit of the patient. Blood sugar, serum electrolytes, urine microscopic examination, body weight and blood pressure should be monitored at base line and at each visit of the patient.

Adverse effects of DCP therapy

The adverse effects of pulse therapy are those of its constituent drugs. Corticosteroids precipitate infections, diabetes mellitus, hypertension, hyperacidity and osteonecrosis. Side effects attributed to cyclophosphamide are leucopenia, hematuria, gonadal failure, hyper pigmentation and hair loss. These side effects are infrequent compared to daily corticosteroid therapy. Side effects peculiar to pulse therapy include hiccups [11], facial flushing [12], diarrhea, weakness, generalized swelling and weight gain, joint and muscle pains, [13] arrhythmias and shock. Arrhythmia is attributable to rapid efflux of potassium and influx of sodium in the myocardium.

MINI PULSE CORTICOSTEROID THERAPY

Oral betamethasone has been given at a dose of 10 mg once weekly in dermatoses like vitiligo, lichen planus, alopecia areata with variable success. 10 mg of betamethasone is split in 2 equal doses on 2 consecutive days a week.

OTHER FORMS OF PULSE THERAPY

1. Cyclophosphamide pulse therapy

Gokhale et al [14] evaluated the response to pulse intravenous cyclophosphamide therapy in patients of pemphigus vulgaris. Cyclophosphamide 500 mg pulses are given in 500 ml of 5% dextrose solution slowly intravenously. These pulses are given monthly for 12 months and 2 monthly for further 6 pulses. Close monitoring of kidney and bladder function was done. The response to therapy was good to excellent in more than 60% of patients. This form of pulse therapy has been tried in other conditions like lupus nephritis, serious central nervous involvement in lupus erythematosus and Wegener's granulomatosis.

2. Pulse therapy with antifungals

Itraconazole, fluconazole are used to treat superficial and deep fungal infections. These drugs are administered in weekly doses every month.

Itraconazole - 400 mg / day for 1 week every month for 3 months, for treatment of Tinea unguium.

Fluconazole - 400 mg once a week for 1 month, for treatment of Pityriasis versicolor

Each pulse is given for 7 days every month.

3. Isotretinoin therapy for acne vulgaris

1 mg / kg / day of isotretinoin is administered for 7-10days every month.

4. Pulse therapy in Psoriasis

Weinstein Frost regimen - Methotrexate 7.5 mg – 25mg ,administered every week. It is used for the treatment of psoriasis

CONCLUSION:

Pulse therapy appears to be novel path breaking therapy for pemphigus vulgaris, a host of autoimmune dermatoses and systemic diseases. In India, maximum work has been done on pulse therapy in pemphigus vulgaris. However, the steroid molecule used is dexamethasone, not methyl predinolone. Pharmacokinetic and immunologic studies are grossly lacking in Indian perspectives which would help us to understand the mechanism of action and refine this path breaking therapy further. For practical purposes, every evaluation of pulse therapy should address few clinical outcomes: the time to clinical remission, the duration of remission while on treatment and duration of remission after withdrawal of treatment.

REFERENCES:

1) Bell PR, Breggs JD, Calman KC, Patron AM, Wood RF, Macpherson SG et al. Reversal of acute clinical and experimental organ rejection using large doses of intravenous prednisolone. Lancet 1971; i: 876-80.

2) Kountz SL, Cohn R. Initial treatment of renal allografts with large intrarenal doses of immunosuppressive drugs. Lancet 1969; i : 338-40.

3) Liebling MR Leib E, Mc Laughlin K Blocka K, Furst DE, Nyman K, et al. Pulse methylprednisolone in rheumatoid arthritis. Ann Int Med 1981; 94:21-6.

4) Cathcart ES, Idelson BA, Scheinberg MA, Couser WG. Beneficial effects of methylprednisolone "pulse" therapy in diffuse proliferative lupus nephritis. Lancet 1976; 1: 163-66.

5) Pasricha JS, Srivastava G. Cure in Pemphigus a possibility. Indian J Dermatol Venereol Leprol 1986; 52: 185-6.

6) Kaur S, Kanwar AJ. Dexamethasone cyclophosphamide pulse therapy in pemphigus. Int. J Dermatol 1990; 29: 371-74.

7) Becker LR, Bastian BC, Wesselmann U, Karl S, Hamm H, Brocker EB. Paraneoplastic pemphigus treated with dexamethasone / cyclophosphamide pulse therapy. Eur J Dermatol 1998; 8: 551-3.

8) M Ramam. Dexamethasone pulse therapy in dermatology. Ind J Dermatol, Venereol, Leprol 2003 ; 69(5):319-22.

9) Pasricha JS. Pulse therapy as a cure for autoimmune diseases. Ind J Dermatol, Venereol, Leprol 2003 ; 69(5): 323 - 28

10) Rao P.N, Lakshmi TSS. Pulse therapy and its modifications in pemphigus: A six year study. Indian J Dermatol Venereol Leprol 2003; 69(5): 329-33.

11) Kanwar AJ, Kaur S, Dhar S, Ghosh S. Hiccup – a side effect of pulse therapy. Dermatology 1993; 187: 279.

12) Dhar S, Kanwar AJ, Facial flushing – a side effect of pulse therapy. Dermatology 1994; 188: 332.

13) Appelhans M, Monsmann G, Orge c, Brocker EB, Dexamethasone – cyclophosphamide pulse therapy in bullous autoimmune dermatoses. Hautarzt 1993; 44: 143-47.

14) Gokhale Neeta R et al. Treatment of pemphigus with intravenous pulse cyclophosphamide. Indian J Dermatol Venereol Leprol 2003; 69 (5):334-37.