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PULSE THERAPY: A Decisive Treatment Modality in Dermatological Disorders

KEYWORDS

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ABSTRACT *Pulse therapy is the process of administering suprapharmacologic doses of drugs especially corticosteroids in an alternating manner to enhance the therapeutic effect and reduce the side effects of the drug. Various drugs have been employed in this therapeutic procedure either as a single drug or in combination with other drugs.This paper intends to throw light on the various available pulse therapy regimens with dosages, indications and contraindications in detail.*

INTRODUCTION

Human beings have been suffering from various inflammatory and autoimmune diseases since the beginning of time. Corticosteroids, being an important class of naturally occurring and synthetic hormones, have well known uses in such conditions.[1]

The concept of pulse therapy was first introduced in 1969 by Kountz and Cohn to achieve graft survival immediately after renal transplant where a high dose of steroid was transfused directly through the renal artery into the renal graft.[1]

In India, pulse therapy was first used by Dr. JS Pasricha in 1981, in an attempt to give relief to a patient of severe Reiter's diseases. Pulse therapy was followed by marked improvement and the patient was relieved of the symptoms.[2]

In the recent years, pulse therapy (PT) has been widely used in the treatment of various immunological related disorders. The theoretical aims of pulsing are to achieve more rapid and effective disease control compared with conventional oral dosing, thus allowing a reduction in long-term maintenance corticosteroid doses and their side effects.

DEFINITION

Pulse therapy has been defined as discontinuous or intermittent intravenous infusion of very high doses of drugs over a short time.[3]

DRUGS USED IN PULSE THERAPY:

a) Corticosteroids

b) Immunosuppressives

c) Antifungals

e) Antibiotics

PULSE CORTICOSTEROID THERAPY:

Pulse therapy refers to discontinuous infusion of high-dose glucocorticoids in short bursts.In context of corticosteroids, pulse therapy refers to discontinuous IV infusion of high doses of the medication.There are no guidelines of administration; which therefore includes single boluses, daily boluses given for 3 days in a row, or on alternate days for up to 12 days.[4]

Pulse therapy with corticosteroids has two distinct advantages. Firstly, the very high doses used for pulse therapy often produce therapeutic responses. Secondly, the intermittent therapy does not produce any of the well-known side effects of prolonged therapy.[5], [6]

DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE (DCP) THERAPY:

This refers to the intermittent administration of high doses of intravenous corticosteroids and cyclophosphamide, usually three daily doses of dexamethasone (100 mg) or methylprednisolone (500–1000 mg) and a single dose of cyclophosphamide (500 mg) given monthly.[7]

Cyclophosphamide is a unique immunosuppressant. These drugs are most destructive to rapidly proliferating tissues and appear to cause cell death when they tend to divide.[8]

Dexamethasone Cyclophosphamide Pulse therapy is divided into 4 phases[6,9]

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. 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 withdrawn and the patients are followed up.

ADVERSE EFFECTS:

The adverse effects of DCP therapy precipitate infections, diabetes mellitus, hypertension, hyperacidity and osteonecrosis.[6,10]

Table 1: Immediate and delayed adverse effects following DCP[11]

In a study conducted by Pasricha et al., 255 Indian patients with pemphigus were treated with dexamethasone plus cyclophosphamide pulse (DCP) at 4-weekly intervals. Low-dose oral cyclophosphamide (50 mg daily) was administered between pulses. Oral cyclophosphamide was then continued alone.In this study, overall rate of complete re-

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mission was 72%.In addition, 62% of Indian patients experienced amenorrhea occurred in 0.6% (2 patients).[12-14]

Dhabhai et al. used intravenous dexamethasone cyclophosphamide pulse therapy to treat SLE. Fourteen patients with definite clinical criteria were treated by DCP therapy. The side effects commonly observed with conventional daily dose regimen of corticosteroids were not present or were mild. Fever,rash and oral ulceration responded early but photosensitivity, discoid rash, alopecia and joint pains took some more time.[15]

DEXAMETHASONE AZATHIOPRENE PULSE (DAP) THERAPY:
There have been modifications of DCP therapy. Cyclophosphamide is replaced with azathioprine 50 mg (DAP therapy).[16]

Side effects from azathioprine are bone marrow suppression including leukopenia (common), thrombocytopenia (less common), and/or anemia (uncommon), increased susceptibility to infections (especially varicella and herpes simplex viruses), hepatotoxicity, alopecia, GI toxicity, pancreatitis.[17]

DEXAMETHASONE-METHOTREXATE PULSE (DMP) THERAPY:
Cyclophosphamide is replaced by 7.5 mg of methotrexate (three doses of 2.5 mg at 12 hourly intervals) weekly given orally, during the first three phases of pulse therapy along with Dexamethasone pulses in first two phases. Methotrexate (DMP) is instituted in patients who are not able complete Phase I even after 12 pulses (1 year) of DCP or DAP therapy.[16]

Patients should be started on a low dose and cautiously increased every week to the target dose.[17]

The most common adverse effect of methotrexate is hepatotoxicity. [17, 18]

METHYL PREDNISOLONE PULSE THERAPY (MPPT)
Methylprednisolone(MP) is an intermediate acting, anti-inflammatory agent with a low tendency to induce sodium and water retention compared to hydrocortisone.[19]

DOSAGE
Methylprednisolone is administered at a dose of 20-30 mg/kg (500-1000 mg/m2) per pulse; up to a maximum dose of 1 g.[19]

INDICATIONS
MPPT has been used in the treatment of lupus nephritis, nonrenal lupus, rapidly progressive glomerulonephritis, rheumatoid arthritis, multiple sclerosis and polyarteritis nodosa.[20]

A European study reported complete remission in 12 patients with severe oral pemphigus vulgaris treated with three courses of 3 – 5 days of methylprednisolone pulse therapy plus oral azathioprine.[21]

Lee et al. studied the immediate effects of high-dose intravenous methylprednisolone pulse therapy. They treated ten patients with active systemic lupus erythematosus, six with renal and three with central nervous system involvement with three daily 1gm intravenous doses of methylprednisolone and measured the immune response before and just after discontinuation of the drugs. After the treatment, the mean serum IgG, IgA and IgM levels were essentially unchanged. Likewise, serum C3 and C4 levels were not changed significantly. In nine of ten patients, methylprednisolone pulse therapy reduced the levels of circulating immune complexes. Thus the immediate clinical improvements with methylprednisolone pulse therapy are suggested to be the result of depression of the circulating immune complex levels.[22]

CYCLOPHOSPHAMIDE PULSE THERAPY
Cyclophosphamide is an alkylating agent that has been used as a carcinotoxic drug in the treatment of malignancies and as an immunosuppressant in the treatment of various autoimmune disorders.[23]

DOSAGE
Pulse intravenous cyclophosphamide therapy is given at a dose of 500 to 1000 mg/m2 over 1 hour. Because only a small portion of the absorbed drug is metabolized during the first pass through the liver, bioavailability approaches 100%.[24]

Gokhale et al. 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[24]

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.[24,25]

USES
Cyclophosphamide has been used in the treatment of a variety of cutaneous diseases.

One of the first reports of use of intravenous pulse cyclophosphamide for the treatment of pemphigus vulgaris appeared in 1988, when Pasricha et al. reported remission in 60 of 79 patients treated with an arbitrary regimen of intermittent intravenous high-dose dexamethasone and cyclophosphamide coupled with 50 mg/d of oral cyclophosphamide. Of the 67 patients available for follow-up at the end of the study, 25 were in remission off treatment, 25 were in remission on oral cyclophosphamide only, 10 were disease-free but still receiving intravenous pulse therapy, and 7 had active disease.[23]

Appelhans et al. treated 20 patients (7 with bullous pemphigoid, 6 with pemphigus vulgaris, 5 with pemphigus foliaceus,2 with cicatricial pemphigoid) with a similar regimen reported by Pasricha. After 6 months of therapy, 13 patients were free of symptoms and 4 patients experienced improvement in control of their disease.[26]

ORAL MINI PULSE CORTICOSTEROID THERAPY:
The patients on PT have to be continuously monitored in a hospital set-up because high doses of drugs are given intravenously, its unnecessary in patients with only oral lesions. To deal with this, 20 years ago a new therapeutic regimen called oral mini pulse therapy (OMP) was formulated. It ensures better compliance and decreases the risk of short- and long-term side effects associated with corticosteroid therapy.[2]

Oral betamethasone has been given at a dose of 10 mg once weekly in dermatoses like vitiligo, lichen planus with

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variable success. 10 mg of betamethasone is split in 2 equal doses on 2 consecutive days a week.[2]

Kumar et al. treated a resistant case of oral lichen planus with 5 mg betamethasone as a single dose in the morning after breakfast for two consecutive days followed by five days off, every week for a period of three weeks.Dose of betamethasone was tapered by 0.5 mg every week. At the sixth week, the patient developed a new ulcerative lesion. Hence, from the sixth to the ninth week the patient was maintained on a dose of 3.5 mg betamethasone. During this period the ulcerative lesion disappeared and the erythema present on the other areas healed, with the pigmentation and burning sensation completely reduced. From the tenth week the dose was further tapered down by 0.5 mg every week. At the fifteenth week the patient was taking 0.5 mg and this dose was maintained for three weeks. The therapy was stopped after complete remission of the lesions was achieved.[2]

Al-Mutairi et al. treated acute generalised lichen planus with weekly betamethasone 5 mg oral mini pulse therapy. Systemic treatment with oral corticosteroids in the form of ten tablets of betamethasone 0.5 mg in a single dose was given after breakfast on two consecutive days every week. Complete arrest of progression, control of itching and flattening of lesions was achieved within three weeks.[27]

TOPICAL CORTICOSTEROID PULSE THERAPY

Topical corticosteroid pulse therapy comprises of intermittent use of superpotent corticosteroids. Prolonged continuous therapy with such agents in patients with psoriasis results in certain side-effects whereas intermittent therapy may achieve beneficial effects for maintenance of remissions with an advantage of diminishing the side effects.[28] Clobetasol propionate (0.05%), weekly topical treatment with three consecutive applications at 12 hour intervals is used mainly in psoriasis.[28]

PULSE THERAPY WITH ANTIFUNGALS

Itraconazole, fluconazole are used to treat superficial and deep fungal infections.[6]

Itraconazole - 400 mg / day for 1 week every month for 3 months, for treatment of Tineaunguium.[6]

A randomized single-blind clinical comparative study was undertaken on 120 patients of onychomycosis to compare the clinical efficacy of oral itraconazole pulse therapy and oral terbinafine pulse therapy in onychomycosis. Sixty patients were randomly assigned to receive oral itraconazole 100 mg, two capsules twice daily for seven days a month and the other group of sixty patients received oral terbinafine 250 mg, one tablet twice daily for seven days every month. Four such monthly pulses were administered for each drug.

The patients were evaluated at 4-weekly intervals till sixteen weeks and then at 24, 36 and 48 weeks. A clinical cure rate of 82% and mycological cure rate of 90% in the group of patients treated with itraconazole was observed while the group with terbinafine showed clinical and mycological cure rates of 79% and 87% respectively. [29]

PULSE DOSING OF ANTIBIOTICS

Pulse dosing is a novel approach to antibiotic delivery that produces escalating antibiotic levels early in the dosing interval.This pulse dosing technology is presently in development for drugs like metronidazole. Fractionating the antibiotic dose and administering the drug in a pulsatile fashion may expose the target bacteria to high concentrations of antibiotic at various phases of the bacterial growth cycle, attacking the most vulnerable bacteria.[29]

CONCLUSION

Since its advent in 1986, pulse therapy has revolutionized the management of various life threatening conditions. Various studies have shown pulse therapy to have high rate efficiency. However further research and review of treated cases in a longer duration is necessary to assess the adverse effects of the drugs used in this therapy.

Side Effect (%)	Time of Appearance	Time of Disappearance
Immediate side effects		
Flushing (53.4)	2-4 hrs	Subsides with Pigmentation
Palpitations (7.5)	During the administration	2-6 hrs after Pulse
Hiccups (6.1)	During the administration	3-7 hrs after Pulse
Numbness of feet (3.6)	During the administration	5-7 hrs after Pulse
Psychosis (3.6)	4-6 hrs	6-24 hrs after Pulse
Polyurea (9.5)	All days of Pulse	1-2 days after Pulse
Delayed side effects		
Weakness (55.4)	2.8 pulses (1-5)	3-6 months. Phase II
FBS rise (18)	5.3 pulses (4-7)	6-8 months. Phase II
Headache (14)	1.8 pulses (1-3)	7-10 days of Pulse
Sleep disorder (24.6)	4.5 pulses (3-8)	4-5 months. Phase II
Arthralgia (13)	4.8 pulses (3-8)	4-5 months. Phase II
Blurring of vision (9.5)	7.8 pulses (5-12)	4-6 months. Phase II
Menstrual disorder (46)	4.9 pulses (5-8)	3-5 months. Phase II
Hair loss (8.9)	3.6 pulses (2-7)	Spontaneous regrowth
Taste loss (13)	4.8 pulses (2-9)	3-4 months. Phase II
Nail discolouration (16)	8.2 pulses (6-11)	6-8 months. Phase II

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