Pulse therapy in dermatology

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Introduction

The efficacy of a drug or a combination of drugs, its dosage schedule, its route of administration, the duration of therapy and other aspects of pharmacokinetics and pharmacodynamics lead to evolution of the therapeutic regimens. Glucocorticosteroids are one group of drugs, which revolutionized the dermatologic therapy. However two major problems are difficult to address even in corticosteroid-responsive dermatoses. First, there are conditions not responding adequately even to a dose considered to be conventionally high; and second, the limitation due to the side effects of long-term corticosteroids. Pulse therapy regimen with corticosteroid alone or in combination with other immunosuppressive drugs addressed these problems to a great extent and made a paradigm shift in the therapeutic approach for some of these corticosteroid-responsive dermatologic conditions. Essentially, pulse therapy means administering a supra-pharmacologic (very high) dose of the drug over a short period of time and then withdrawing the drug completely till it is needed again. The high dose of the drug helps to achieve the therapeutic effects which are not achievable with the conventional daily-dose schedules, and the intermittent administration of the drug helps to reduce the side-effects.

Pulse therapy was initially used to prevent rejection of the renal grafts[1-3] and subsequently applied to serious medical situations such as lupus nephritis[4,5], polyarteritis nodosa[6], rheumatoid arthritis[7], pyoderma gangrenosum[8] and some other diseases, but in most of these conditions the pulses were used only to deal with the emergency situation followed by conventional daily dosage for the maintenance of the therapy. The corticosteroid used was mostly methylprednisolone in a dose of 1 gm infused intravenously over an hour or so. In 1981, Pasricha and Gupta[9] used pulse therapy for the first time in a desperate attempt to salvage a patient having Reiter's disease who was not responding to any of the known conventional therapeutic measures. This patient was bed-ridden with severe joint involvement and bleeding from the gastro-intestinal tract and he was having continuous fever for several weeks and had very extensive crusted lesions all over the body. Dexamethasone 100 mg dissolved in 500 ml of 5% dextrose infused intravenously over an hour and repeated on three consecutive days led to a dramatic improvement. Repeated administration of such pulses at one-month intervals ultimately led to an almost complete recovery and the patient who could have died within a few days lived a fairly useful life for more than a decade. This experience led to use of pulse therapy in other serious skin diseases as well.

In 1982, pulse therapy was used for pemphigus[10] and during the last two decades we have treated more than 1000 pemphigus patients[11-15]. Out of 500 patients whose records were analyzed, 403 patients took this treatment and 367 (91%) patients have already completed the treatment and are completely free of the disease without any maintenance treatment for 5-15 years, the remaining 17 (4.2%) patients are either in remission though yet to complete the treatment or having mild activity of the disease or a relapse[16]. Nineteen patients have died, some of them due to unrelated causes and some of them having very severe disease activity at the time of initiation of therapy and already complications such as septicemia had occurred due to late treatment. It is worth recollecting that pemphigus was known to be a highly fatal disease and in the past, most of the patients treated with the conventional daily-dose regimens of corticosteroids used to either die or had morbidity either because of the disease or the side-effects of therapy. Also, even after the control of the disease, a continuous dose of corticosteroid was required for maintenance and therefore, complete remission or cure without a maintenance dose was usually not achieved. Thus, the pulse therapy regimen has completely changed the poor prognostic outlook in this disease by achieving cure in almost all the patients.

Based on the experience in pemphigus, pulse therapy was used by us and several other workers in other diseases such as systemic sclerosis[17-21], pyoderma gangrenosum[22,23], systemic lupus erythematosus, dermatomyositis, disseminated discoid lupus erythematosus[24], extensive or generalized morphoea, linear morphoea, extensive and rapidly progressive

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vitiligo[25,26], recurrent alopecia universalis[27,28] and leucocytoclastic vasculitis and other vasculitides[29,30]. In addition, there were several other diseases where pulse therapy was used such as extensive lichen planus, prurigo nodularis[31], scleredema, disseminated porokeratosis[32], Hailey-Hailey disease, multicentric reticulohistiocytosis[33], idiopathic thrombocytopenic purpura[34,35], Reiter's disease[36], paraneoplastic pemphigus[37], bullous pemphigoid[38], multiple extensive keloids and even Peyronie's disease. Though the experience in some of these diseases is limited, the results are encouraging.

Pulse therapy regimen

The standard Dexamethasone-Cyclophosphamide Pulse (DCP) regimen as designed by Pasricha et al[16] consists of using two drugs, (1) dexamethasone in a dose of 100 mg dissolved in 500 ml of 5% dextrose given as a slow intravenous infusion over 2 to 3 hours and repeated on 3 consecutive days, and (2) cyclophosphamide in a dose of 500 mg on one of these three days in the same infusion. We usually give cyclophosphamide on the second day. The dexamethasone and cyclophosphamide pulses (DCPs) are repeated at exactly 28-day intervals counted from the first day of each pulse. In between the DCPs the patient receives only 50 mg cyclophosphamide orally per day. For pemphigus, this regimen is now standardized[16].

During the first phase of this treatment the patients are likely to have recurrences of the pemphigus lesions in between the pulses, but with continued treatment most patients can be induced into a complete clinical remission. This is called phase I and the amount of treatment required to induce a complete clinical remission varies widely in different patients. Additional treatments can be used to shorten the duration of this phase. Two additional treatments/ modifications in this phase are:

(a) Use of daily corticosteroids, if the extent of involvement is very high or the patient's oral mucosa is extensively involved and not responding adequately;

(b) Use of additional (or sometimes called interval) dexamethasone pulses (DPs) on 2 consecutive days in between the DCPs, if the disease severity is very high or the initial response is slow.

The most important component of the DCP regimen is that after having achieved complete clinical remission the treatment is continued further. This is called phase II, during which the patient receives at least 6 and preferably 9 DCPs at exactly 28-day intervals along with 50 mg cyclophosphamide orally per day, and if the patient continues to be in clinical remission during this period, no further DCPs are given, but the oral dose of 50 mg cyclophosphamide per day is continued for the next 9-12 months. This is called phase III. Phase II and III are completed in 18 months and this arbitrary fixed period has been evolved after analysis of initial experience of DCP regimen, when either we were not strict about phase II and III or the patient's poor compliance or irregularity in treatment led to more frequent relapses. Next phase is phase IV where the patient continues to be in remission, and even the daily dose of cyclophosphamide is withdrawn. The patient is followed-up further, for as long as possible to look for any tendency for a relapse. This phase is the disease-free phase without any treatment[16].

There are no contraindications for this therapy except that the patients are advised contraception during this period and the pulse therapy is postponed if the patient is pregnant or lactating. Patients having diabetes, hypertension, peptic ulceration, tuberculosis or any other disease can be treated with the pulse therapy regimen, but the treatment for the concomitant disease has to be continued along with. Patients having diabetes mellitus have to be administered 8 units of insulin for every 500 ml of 5% dextrose used for the infusion. Unmarried patients or those who have not yet completed their family and want to have more children should be treated with only dexamethasone pulses (DPs) along with 50 mg per day oral cyclophosphamide. The high dose of cyclophosphamide is to be withheld because this dose is likely to lead to azoospermia / amenorrhoea in some patients. Some workers use azathioprine in place of cyclophosphamide, which is a reasonably good alternative. However, the bolus dose of cyclophosphamide in DCP contributes to a very effective immunosuppressive activity and one should keep in mind that in unmarried individuals and patients who have not completed the family, we are using the alternative regimen (and not the DCP) with a compromise and some of these patients on DPs or DPs plus azathioprine are likely to have relapses. Pemphigus is uncommon in children, but in case the patient is less than 12 years in age the dose of dexamethasone can be halved.

Several factors have contributed to the success and widespread acceptance of this regimen. One important factor was the choice of corticosteroid. Conventionally, methylprednisolone was the agent most commonly used in corticosteroid pulse therapy. On reviewing the studies where these two corticosteroids were used, some workers found that dexamethasone

pulse and methylprednisolone pulse are similar in efficacy and side effects[39]. However, the choice of dexamethasone makes the treatment affordable due to its low cost. There was also initial concern about the equivalence of 1000 mg of methylprednisolone and 100 mg of dexamethasone and some dermatologists have administered pulses of 136 mg of dexamethasone[40]. However, a dose of 1000 mg of methylprednisolone is as arbitrary as a dose of 100 mg of dexamethasone and in the absence of evidence that 136 mg pulses are more effective we continue to use 100 mg pulses. There was initial anxiety about such large doses of corticosteroids being administered and some centres would administer the therapy in the ICU under continuous cardiac monitoring. However, with such vast experience with pulse therapy, now it is given as a routine infusion, often in a day-care setting, with the patient going home a few hours after completion of the infusion. In early phase I, some of the patients should be hospitalized, because monitoring of the disease activity and supportive measures for bacterial infections, candidal infection and other concomitant diseases can be supervised better. Patients with milder disease in phase I and all the patients in phase II now receive pulse therapy in day-care setting. Another factor responsible for the effectiveness of this regimen is that it has evolved in response to observations of the results of treatment in earlier patients where only dexamethasone pulses were used and cyclophosphamide was added because relapses were frequent with dexamethasone alone.

The pre-pulse evaluation[16] should consist of a detailed history and a thorough physical examination to look for any concomitant disease and this should be supplemented with relevant laboratory investigations, so that appropriate measures can be such evaluations should be repeated at appropriate intervals to record the side-effects or the development of concomitant diseases during the treatment though there is no need to undertake to frequent investigations. Our experience suggests that one should go by the complaints/clinical examination of the patient and laboratory investigations are required only periodically and not before each pulse. We have also evolved a simple method of charting the course and clinical monitoring of concomitant diseases and its management[16].

Mechanism of action[41]

There is some evidence that the pulse therapy may be acting in more than one way and it is not only the effect of high doses of corticosteroids in simplistic term. However, the exact mode of action is still not clear. It is known that corticosteroids act by binding to the intracellular receptors, forming dimers and subsequent binding to specific DNA regulatory sequences. This interaction leads to up-regulation or down-regulation of specific genes that encode proteins responsible for the action of corticosteroids eg. cytokines and adhesion molecules. Some of these relate to immune cell function and production of inflammatory mediators. There are also post-transcriptional effects of corticosteroids which include effects on RNA translation, protein synthesis, and secretion. The end result of these effects is that corticosteroids inhibit the access of inflammatory cells to tissue, interfere with function of fibroblasts and endothelial cells, and suppress production and effects of humoral factors.

In addition, corticosteroids may also exert their effects by non-genomic mechanisms, such as membrane bound receptors or physico-chemical interactions with cellular membranes. Some of these effects are too rapid to be mediated by genomic action. This mechanism might explain additive benefits of pulse therapy with corticosteroids. In addition, apoptosis of inflammatory cells, especially peripheral blood CD4+ T lymphocytes, may occur only at pulse doses.

With prolonged use of daily corticosteroid the receptors are down-regulated, making corticosteroids less effective. This receptor down-regulation may be one factor that explains why aggressive treatment (pulse therapy) is effective, as compared to a gradual increase in the daily dose, which results in more toxicity and less beneficial clinical effects.

Safety / toxicity of pulse therapy

It has been widely accepted now that corticosteroids given in the form of pulse therapy produces relatively few side-effects in spite of the fact that the doses used for the pulse therapy are extremely large[16]. Intensive investigations undertaken during the earlier part of our study revealed that pulse therapy does not produce significant changes in the levels of serum electrolytes, total and differential leucocyte counts, platelet counts, blood pressure, blood sugar level etc. Long-term follow-up of the patients on pulse therapy further revealed that the incidence of diabetes mellitus, hypertension, peptic ulceration/osteoporosis, psychiatric disturbances, acne, striae distensae, hirsutism, cataract, glaucoma etc was far low compared to the patients given corticosteroids on a daily basis even when the doses were much smaller[16].

The major side-effects of the DCP therapy were increased susceptibility to pyogenic infections of the skin and candidiasis in the mouth if the patient had skin/mucosal ulcers. This tendency however was seen

in phase I, which is explainable and was not observed after the skin/mucosal ulcers had healed. Some patients developed reactivation of tuberculosis for which anti-tuberculous treatment (ATT) was instituted concomitantly without interrupting the pulse therapy or if required, the pulses are deferred by 3-4 weeks after initiation of ATT so that infection is well-controlled. Amenorrhoea/azoospermia was the other major side-effect, it was however ignored if the patient had completed his/her family as there was no effect on the libido[16]. It is also important to mention that all patients do not develop azoospermia/amenorrhoea and a conscious decision may be taken in severe cases if the patient wishes to undergo DCP therapy to achieve the best results.

Adrenocortical suppression manifesting as weakness for a few days after the pulse was observed in some patients. This however, disappeared as the treatment progressed. In a study of pituitary-adrenal function in patients on pulse therapy, it was found to be suppressed in about half the patients one month after the last pulse of phase II. However, these patients were asymptomatic and did not require any supplementation. Therefore, the clinical application of the abnormal tests is not clear[42].

The other side-effects included generalized pigmentation, hiccups, facial flushing, diarrhoea, transient weakness and lethargy. Only 5 out of 403 patients developed haemorrhagic cystitis. Normally, we do not use Mesna for our patients on DCP and adequate hydration alone is sufficient. Diffuse hair loss observed in some of the patients was found to be transitory and reversible in almost all the patients, but malignancies were not detected in any patient in spite of the long-term follow up. An interesting observation in all these patients was that the weight gain and cushingoid obesity so commonly seen in patients given daily doses of corticosteroids were not observed in the patients treated with the pulse therapy regimen. Patients who had already developed weight gain/cushingoid features due to the corticosteroids administered previously were observed to lose their excess weight and revert back to their normal appearance as the pulse therapy progressed[16].

Relapse/failure of pulse therapy

The major aim of the DCP regimen has been that the patient achieves a complete clinical remission and does not develop a relapse in future. In the earlier part of the study, most patients did not follow the instructions and defaulted at some time or the other and had relapses. In patients who did not take the 6 or 9 mandatory DCPs during phase II of the regimen, the relapse rate was 55%. Another group of patients who did take the 6 DCPs during phase II but did not follow the 28-day cycle regularly, showed the relapse rate to be nearly 20%. In the latter part of our study, we started giving 9 DCPs during phase II followed by 9 months of phase III and instituted strict compliance of the 28-day cycle for the DCPs. Some workers use pulse therapy reluctantly and if a patient has a prolonged phase I, there is a tendency to give up pulse therapy and label it as failure. This was also our experience in the initial period, but with time we learnt to deal with such situations and continued with pulse therapy and had excellent results[16,43].

At present, the relapse rate in the patients treated regularly and properly as per DCP regimen has been less than 10%. For obtaining optimum results, we feel that it is absolutely necessary to administer a fixed amount of treatment after achieving complete clinical remission, and this should consist of 6-9 DCPs during phase II given at exactly 28-day intervals followed by 12 or 9 months of phase III. This is irrespective of the amount of treatment given during phase I. The patients who developed a relapse due to the incomplete/irregular treatment during the first course or a genuine relapse, respond usually to the administration of another course of the DCP therapy[16].

Conclusions

Pulse therapy has made a major change in the outcome of pemphigus[16,44-46], other bullous diseases[47], systemic sclerosis, SLE, dermatomyositis and several other diseases[43]. It is safe and effective with minimal side effects. However, there are areas which need to be studied further such as its exact mechanism of action, its pharmocodynamics and pharmacokinetics, its long-term effect on bone density etc. The choice of adjuvant immunosuppressive agent may differ in some situations and it also depends upon the condition for which pulse therapy is used. In our experience cyclophosphamide is the best option for pemphigus. The modifications or improvement in the present regimen are welcome, but only in certain situations with a definite purpose and not just for the sake of looking different.

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