

The “Big Shot” Revisited: 25 Years of Methylprednisolone Pulses.

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Introduction

The title of this review comes from that of an editorial in *Lancet* in 1977 [1] which discussed with some surprise the relatively benign nature of the then new but increasing use of large intravenous boluses of corticosteroids in transplants, nephritis and systemic lupus erythematosus in adults. It is an extension of a talk at the Park City IV meeting of Pediatric Rheumatology [2], and, while meant as a review, it includes editorial opinion and personal unpublished experience. The reason for writing the review is that, despite 25 years of use, there are still great differences in the way boluses are given and in what is expected of them in respect to both beneficial results and complications in different centers. While pediatric rheumatologists and nephrologists are in general comfortable and experienced with the use of “pulse” steroid boluses, the general pediatric and medical community is not always so. This review will try to cover what is known about “mega-dose” corticosteroid therapy, and to point out areas about which we are still ignorant. As with many of our drugs, not all effects of pulses can be explained by what we know. The situation is complicated by the fact that the term “pulse” has been used to describe single boluses, boluses given for 3 days in a row, or in a variety of alternate day programs for periods of up to 12 days.

History

Very large intravenous doses of glucocorticosteroids, large by comparison with the usual daily oral doses, had been used in desperate situations such as acute transplant rejection [3] or severe renal involvement in systemic lupus erythematosus since the late 1960's [4, 5]. Pediatric nephrologists started to use methylprednisolone boluses on alternate days for 2 weeks followed by gradually less frequent boluses to treat children with resistant nephrotic syndrome in the early 1970's [6]. The doses used in adults, 1 to 2 g, were based on a study of young normal adult male volunteers to determine a safe dose to use in treating traumatic shock [7], and this was translated into doses of about 30 mg/kg in children. Initially the times of infusion were also based on the study done in young normal adults, 10 to 20 minutes.

The pharmacokinetics of intravenous methylprednisolone are complex [8]. There is a rapid peak with a subsequent serum half life of 3 hr. A very large proportion of the intravenous bolus rapidly enters the gut, manifest in part by the appearance of a metallic taste in the mouth, and this reenters the venous space via the splanchnic circulation causing a secondary peak in the serum level. Studies specifically in children have shown similar kinetics, but up to 5 fold variations in serum half-lives between individual children [9]. The drug must be demethylated in the liver to become pharmacologically active as prednisolone, a fact which led to a comparative study with similar doses of oral prednisolone [8]. The kinetics of equivalent doses of oral prednisolone were essentially the same as intravenous methylprednisolone [8]. Prednisolone is not available in an oral form which would allow very large doses in the United States, but parenteral prednisolone powder can be put into gelatin capsules and be given orally. However, an attempt to use prednisolone in this manner in a few children at

Stanford resulted in complaints of nausea and malaise for several hours, and the children definitely preferred the intravenous infusion. This should be looked at again with the use of ondansitron.

At the time that we started using mega-dose pulses of corticosteroids at Stanford in the mid 1970's, there was anticipation that there would be significant and limiting metabolic side effects. When these problems were not seen in our first desperately ill patients, we started to use pulses children who were less severely ill, but had resistant disease or were unacceptably toxic on their more standard medication [10]. We compared two regimens: single boluses of methylprednisolone at 30 mg/kg up to 1 g, or 4 repeated doses of 500 mg of hydrocortisone at 6 hour intervals. We measured urinary excretion of sodium, potassium and uric acid for 24 hr before and for 2 days after the one or first bolus. As expected there was reduced excretion of sodium and increased excretion of potassium and uric acid, but only for the first 24 hr, and the differences were so slight that only the reduction in excretion of sodium after infusion of hydrocortisone reached statistical significance. No differences were noted in total blood cell counts cells. Although the use of hydrocortisone in this manner has disappeared, two of our early patients expressed a clear preference for it because they suffered less malaise than after methylprednisolone, and it might be considered a viable alternative in some patients.

There are relatively few reports of the metabolic effects of large boluses of methylprednisolone. Cortisol levels do drop initially but return to normal levels within 24-48 hr after infusions [11]. The 5 patients studied at Stanford after long courses [10] had normal morning and evening cortisol variation and ACTH responses after 3 months to 5 years of weekly boluses. Bijlsma et al. [12, 13] studied bone metabolism in adults with rheumatoid

arthritis, finding decreased calcium gut absorption and renal excretion, increased parathyroid hormone and 1,25 dihydroxycholecalciferol, and decreased bone resorption and formation immediately after single boluses [12], but no net change except for a slight decrease in hydroxyproline excretion after 3 boluses given on alternate days [13]. This was confirmed by a study of deoxypyridinoline excretion as a measure of bone collagen degradation [14].

There are reasons to believe that the very high levels of steroid obtained by pulse methylprednisolone therapy have qualitatively different pharmacologic effects which are not just a result of more drug molecules exaggerating the same mechanisms. Boumpas [15] found that high doses of glucocorticoids increased NF-*kappa*B binding proteins in the cytosol thus reducing the amount of the pro-inflammatory transcription factors that could reach the nucleus and activate the genes for IL-1, IL-6, and TNF-*alpha*, but this only occurred at concentrations within the cell obtainable by the highest oral or intravenous doses. Buttgereit et al. [16] have postulated 3 “modules” of glucocorticoid effect on cells resulting from different concentrations: 1) low concentrations bind to cytosol receptors which move to the nucleus to become direct transcription factors for genomic events; 2) medium concentrations bind as well to cell surface receptors which activate cross membrane signal transmission for genomic and non-genomic intracellular events; and 3) at very large concentrations steroids dissolve in the cell membrane resulting in greater membrane stability and reduced non-genomic cell function generally. Both groups propose that the effects they describe or postulate may be related to increased immunosuppression, although this is an effect which has not in fact been demonstrated (*vide infra*).

Immunology and Anti-inflammatory Activity

Silverman and Myones [17] showed that there was an acute drop in circulating T and B cells 5 hr after infusion of methylprednisolone, but that pre-infusion levels had returned within 24 hr, except for the population stained by Leu-3a monoclonal antibodies, presumed helper T cells, which reached normal levels by 48 hr. This data, using different labeling methods for CD 4 and CD 8 cells has been confirmed by others [18]. These findings, along with the lack of significant rise in uric acid excretion, indicate that these doses do not, as expected, kill a measurable number of cells, but probably caused transient redistribution between the circulation and lymphoid organs.

Normal immune responses do not appear to be affected by large pulses of methylprednisolone. Fan et al. [19] found no change in circulating immunoglobulins, primary or secondary antibody responses, or delayed hypersensitivity skin reactions after single boluses of 1 g or pulses of 1 g per day for three consecutive days in adults. We studied 5 children who had received single boluses once per week for periods of from 3 months to 3 years but no oral steroid or immunosuppressant drugs, and found normal immunoglobulin levels in 4 of 6, abnormally low levels in one, and abnormally high levels in one [10]. Primary responses to pneumococcal vaccine were normal as were delayed hypersensitivity reactions to antigens to which the children had been exposed before the treatment. However, Smith et al. [20] found that in adults with rheumatoid arthritis a three day pulse resulted in lowered immunoglobulins and a drop in the titer of rheumatoid factor and levels of circulating immune complexes, but, again, delayed hypersensitivity remained intact. Other presumed auto-antibodies have been reported to decrease after pulse steroid therapy alone [4,21]. However, immunological effects of pulse steroids have been studied in the

absence of immunosuppressive drugs in only a few instances, and do not allow us to be sure that the change in autoantibody levels are not just secondary to the anti-inflammatory effect.

Most of the work on the mechanisms of anti-inflammatory action of steroid pulses has been done by Smith's group in Australia in adults with rheumatoid arthritis [22-26]. They labeled peripheral blood and synovial fluid neutrophils from patients with radioactive technetium, and re-injected them intravenously or back into the synovial cavity before and after single steroid boluses [22]. Before pulsing, the neutrophils injected intravenously localized in the inflamed joints while the synovial fluid cells appeared to migrate to draining lymph nodes, although it is not clear whether they were following intact cells or cell debris draining from the joints. After the pulse, circulating neutrophils no longer entered the joints while the synovial cells still migrated to lymph nodes as before. They subsequently demonstrated a decrease in the cell surface adhesion molecules CD 11b, CD 18 and L-selectin on neutrophils in peripheral blood after a 1g intravenous bolus of methylprednisolone [23]. Synovial fluid neutrophils had decreased cell surface CD 11b and CD 18, but increased L-selectin. Histological studies of synovial biopsies after similar boluses showed reduction of expression of the adhesion molecules E-selectin and ICAM 1 in endothelial cells, and of ICAM 1 in synovial lining cells [24]. These adhesion molecules are up-regulated by proinflammatory cytokines, particularly *TNF-alpha* [27], and Youssef et al. [25] have shown that expression of *TNF-alpha* is decreased in peripheral blood, synovial fluid, and synovial tissue after single boluses of methylprednisolone. In addition, macrophages in the synovial lining layer, but not deeper in synovial tissue, had reduced cell surface marker proteins associated with activation and cytokine production after pulses [26]. Thus it

appears that the methylprednisolone pulses down regulate macrophage activation and proinflammatory cytokine production leading to reduced expression of adhesion molecules and reduced movement of neutrophils into inflamed joints. Interestingly, these effects are qualitatively similar to those seen with anti-TNF-alpha therapy [28].

While there is no reason to doubt that these anti-inflammatory effects also occur in children, they do not explain all of the clinical phenomenon seen after pulses. Down regulation of the state of activation of, and cytokine production by, phagocytes in systemic-onset juvenile idiopathic arthritis would explain the sometimes dramatic, transient effect on fever spikes. However, it is hard to relate these findings to the more reliably obtained dramatic drops in muscle-derived enzymes after boluses of methylprednisolone seen in juvenile dermatomyositis, in which acute inflammation with macrophages or neutrophils is not ordinarily seen. It is tempting to speculate that methylprednisolone also depresses TNF-*alpha* expression by muscle fibers directly since TNF-*alpha* is over expressed in muscle fibers in some untreated children with dermatomyositis [29]. Alternatively one could postulate a direct effect on endothelial cells, where the primary pathology occurs in this disease, or perhaps an effect on myocyte membrane stability as proposed by Buttgereit et al. [16].

There is an extensive cardiovascular surgery literature on the use of large methylprednisolone boluses which has recently been reviewed by Chaney [30]. Thirty m/kg boluses are routinely given before or before and during cardiac bypass surgery to ameliorate the “systemic inflammatory response syndrome” which is thought to be the result of mechanical activation of the complement system by bubble oxygenating pumps. Chaney [30] has a strong bias that this use of bolus methylprednisolone has not been

shown in fact to have clinical efficacy, but he quotes extensive literature that shows that patients with this syndrome who receive bolus steroids have lower circulating levels of complement activation fragments and the pro-inflammatory cytokines IL-1, IL-6, IL-8 and TNF-*alpha* and have higher levels of anti-inflammatory IL-4 and IL-10.

Toxicity

Adverse side effects of high dose methylprednisolone boluses in adults are quite diverse in adults [31,32] and in children [33]. In spite of the early expectations, serious side effects in children are rare, although mild ones are common. In my experience most patients complained of a metallic taste in the mouth, malaise for several hours after the infusion, and a manic or euphoric state on the day after. Mild hypotension occurred in otherwise normotensive children during the relatively rapid infusions that were used early in our experience. Klein-Gitelman's detailed study of adverse effects in children [33] noted more and varied significant behavioral complaints, but only in 10% [33]. The most significant serious effects in children are increased blood pressure in already hypertensive children during and in the hours after the infusion, seizures particularly in systemic lupus erythematosus [32], which may be related to the flux in electrolytes in patients with clinical or sub-clinical central nervous system disease, and anaphylactic shock after even only one prior infusion. This last is due to the methylprednisolone itself [34, 35]. Other forms of corticosteroids may also cause anaphylaxis [35], but it is not clear whether all are contraindicated after a reaction to one, since skin test reactivity varies from one to another steroid in individual patients [34] but never seem very reliable from patient to patient [35]. As with oral steroids, prolonged use of pulses may be

associated with cataract formation, but most other effects, such as Cushingoid facial appearance are not as severe as with daily steroid therapy. Bradycardia and cardiovascular collapse have been reported in the pediatric oncology literature [36]

Therapeutic Use

Rational use of single or of three repeated methylprednisolone boluses should be based on the premise outlined above: i.e. that profound but transient anti-inflammatory effects are to be expected, but not immunosuppression. In theory pulse methylprednisolone should be adequate and less toxic than daily oral steroids in inflammatory diseases in which natural remissions are expected, as in systemic-onset juvenile idiopathic arthritis, a disease known to be associated with over-expression of pro-inflammatory cytokines [37]. Indeed, Adebajo and Hall [38] have reported treating 18 patients with this disease by using single pulses of methylprednisolone and non-steroidal drugs without oral steroids or to decrease oral steroids, using return of fever or systemic features as an indication to repeat the bolus, but never more frequently than every 4 days. This usually resulted in frequent boluses at the initiation of therapy but gradual reduction in frequency. All parameters of inflammation showed improvement in greater than 50% of the patients. In my experience at Stanford using exactly the same method, most children treated in this manner reached remission of systemic features in several months without becoming Cushingoid or hypertensive. Relapses occurred in some but not all children. The course of the arthritis *per se* in these children, as opposed to the systemic manifestations, is not clear, particularly in respect to the longer term outcome. Three day pulses followed by a bolus of

cyclophosphamide and weekly methotrexate have been reported to be effective for months in this disease [39].

Empirically steroid boluses are known to be useful in juvenile dermatomyositis, but, as pointed out above, the reason for the effectiveness is not clear. When pulse therapy first came into vogue, attempts were made to treat juvenile dermatomyositis by pulses alone because the effect on muscle enzyme concentration in blood is so rapid and usually dramatic, but this is potentially a devastating disease, and this treatment should not be primary but as an adjunct to aggressive oral therapy. In the leucocytoclastic vasculitides characterized by polymorphonuclear cell infiltration of the vessel wall, pulse methylprednisolone pulses should reduce acute inflammation but not remove the immune complexes presumably triggering the inflammatory cascade, nor affect the causative agent. In my experience pulmonary hemorrhage and hemolytic anemia in systemic lupus erythematosus rapidly and reliably respond to steroid pulses, but boluses in lupus carry a risk of hypertension and seizures, must be used cautiously, and mainly are indicated as an adjunct to cyclophosphamide pulse therapy for lupus nephritis [40]. I do not consider as “pulses” the high doses of methylprednisolone given at 6 hour intervals for several days in lupus crises or in CNS lupus. There is, of course, a large body of experience reported in the pediatric nephrology literature regarding use of intravenous pulse steroid therapy, particularly in the nephrotic syndrome [6]. Newer uses have been reported in Kawasaki’s Disease [41] and in Henoch Schonlein Purpura [42]. Huppertz and colleagues have reported successful pulse therapy in such diverse diseases as cold-hemagglutinin disease [43] and sympathetic ophthalmia [44].

Although less used by internist rheumatologists than by pediatricians, pulse methylprednisolone therapy is being used in rheumatoid arthritis [11-14,18,20-26,31,32]. Particular interest has been its role as “bridge” therapy while waiting the effects of slower-acting disease modifying drugs [45,46]. It has been compared equivalently for efficacy and toxicity with the effects of infliximab in theory [28] and in practice [47]. As with children, there are many individual case reports of successful use in a variety of inflammatory diseases.

Although pulse methylprednisolone may provide symptomatic relief in inflammatory diseases, it may not change the long term course of any specific disease. The girl with ankylosing spondylitis described in detail previously [10] had had to drop out of high school due to pain uncontrolled by any modality then available, but was able to finish a Master’s degree while receiving weekly pulses. However, her spine fused completely during that period in spite of her relative comfort. Similarly, eye disease progressed to blindness in a child with early onset sarcoidosis whose anterior chamber cell count, arthritis, and skin disease were controlled by boluses every other week.

Summary and Conclusions

Pulses of high doses of methylprednisolone, either singly or repeated over a period of three days, have a significant but transient anti-inflammatory effect, probably due to down regulation of phagocyte activation. They must also have other effects not yet understood, and probably have unique pharmacologic properties not just related to exaggerating mechanisms obtained with lower doses. In the absence of other therapy, they have not by themselves been shown to suppress normal

immune responses. When used in appropriate diseases and circumstances, large intravenous pulses of corticosteroid are cumulatively less toxic than sustained steroid treatment at lower quantitative dosage, but no evidence exists that by themselves they can cure or alter long term outcomes in diseases which are not by themselves self-limited.

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