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The Adverse Effects of Long-Term Corticosteroid Use

Jennifer Ann. Johnston
University of North Dakota

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THE ADVERSE EFFECTS OF LONG-TERM CORTICOSTEROID USE

By

Jennifer Ann Johnston
Bachelor of Science in Physical Therapy
University of North Dakota, 1995



An Independent Study

Submitted to the Graduate Faculty of the

Department of Physical Therapy

School of Medicine

University of North Dakota

in partial fulfillment of the requirements

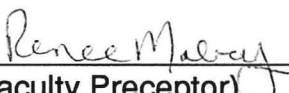
for the degree of

Master of Physical Therapy

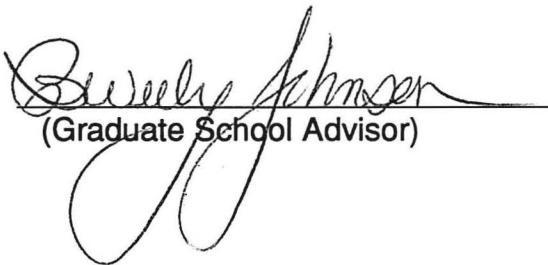
Grand Forks, North Dakota

May
1996


This Independent Study, submitted by Jennifer Ann Johnston in partial fulfillment of the requirements for the Degree of Master of Physical Therapy from the University of North Dakota, has been read by the Faculty Preceptor, Advisor, and Chairperson of Physical Therapy under whom the work has been done and is hereby approved.



(Faculty Preceptor)



(Graduate School Advisor)



(Chairperson, Physical Therapy)

PERMISSION

Title The Adverse Effects of Long-Term Corticosteroid Use

Department Physical Therapy

Degree Master of Physical Therapy

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Signature Jennifer Ann Johnston

Date 3/8/96

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not always easy to say no to spending time with him, but the hard work has paid off.

ABSTRACT

Corticosteroids are an often prescribed anti-inflammatory medication. They are used to treat disease processes of every system of the body. Those disease processes or procedures for which corticosteroids are often prescribed are cancer, bone marrow transplants, collagenous diseases (systemic lupus erythematosus), rheumatoid arthritis, leukemia, and anemia.

However, despite the therapeutic benefits of corticosteroids, many adverse effects are possible. Gastrointestinal difficulties, steroid myopathy, hyperglycemia, osteoporosis, impaired cellular immunity, decreased neuropsychological functioning, and avascular necrosis are just a few of the possible adverse effects.

Patients receiving corticosteroids will often be seen by physical therapists for either their primary or secondary diagnoses. Physical therapists are not often instructed in the possible adverse effects of corticosteroids that may occur. The purpose of this study was to create an increased awareness for health professionals (specifically physical therapists) concerning the possible adverse effects of corticosteroids and how these adverse effects may influence patient evaluation, treatment, and progression. A review of the literature was done. The adverse effects covered were avascular necrosis, osteoporosis, impaired

cellular immunity, GI disturbances, neuropsychological difficulties, and steroid myopathy. For each of the selected adverse effects, the physiologic mechanism, clinical research, and therapeutic intervention were discussed. Finally, precautions or suggestions for the physical therapist relative to working with the patient on corticosteroids was offered.

CHAPTER I

INTRODUCTION

The definition of a physical therapist is someone who is ". . . responsible for evaluating, planning, conducting, and supervising a physical therapy program . . . "1(p1505) Many factors may exist that will alter the evaluation, treatment choices, and progression of a patient's rehabilitation. Medication is one of those factors.

One powerful category of medication is corticosteroids (CS). The most common corticosteroids are cortisone, hydrocortisone, dexamethasone, methylprednisolone, prednisolone, and prednisone.^{2,3,4} These generic names may be marketed under many trade names.

Corticosteroids are prescribed for their strong anti-inflammatory properties and chemotherapeutic qualities. Corticosteroids produce their effects on the body by circulating in the blood, passing through the cell membrane, and attaching to intracellular receptors.⁵ Corticosteroids exhibit anti-inflammatory qualities because they can alter the function of cells involved in the inflammatory process. These cells include macrophages, neutrophils, eosinophils, basophils, endothelial cells, fibroblasts, prostaglandins, and lymphocytes. On the other hand, chemotherapeutic qualities of CS are used to treat hematologic

malignancies and malignant lymphomas as well as malignant tumors.² CS are also used to decrease cerebral edema or cord compression when cancer metastasizes to the CNS or spinal cord injury occurs.² Corticosteroid (CS) receptors exist not only in the cells involved with the inflammatory process but also in most cells of the body; i.e., skeletal muscle. Skeletal muscle is considered a target organ for CS and steroid use often results in CS induced weakness, which is also known as steroid myopathy.

Because of the therapeutic benefits of CS, many patients will receive them for either the primary and/or secondary diagnoses of any system of the body. The major areas for which CS are prescribed are respiratory diseases, allergies, hematologic disorders, collagenous diseases, disorders of the GI system, metabolic and endocrine disorders, hematological disorders, neuromuscular, cardiovascular, renal disorders, and cancer.⁶ The most common disease processes for which CS are used are: 1) asthma, 2) rheumatoid arthritis, 3) ulcerative colitis, 4) Crohn's disease, 5) systemic lupus erythematosus (SLE), and 6) cancer.^{2,7-9} They are also used after any organ, tissue, or bone marrow transplant as one of the many antirejection drugs these patients will have to take for the rest of their lives.²

Despite the therapeutic benefits of CS in these patient populations, a wide range of adverse effects also exist. In addition, just as CS are used to treat disorders/diseases of all systems of the body, the adverse effects may manifest in one or more systems of the body. A review of the literature has produced a

lengthy list of potential adverse effects.^{2,3,5,7} Hypertension, GI complications, avascular necrosis, osteoporosis, electrolyte imbalances, glucose intolerance, myopathy, impaired cellular immunity, atherosclerosis, hyperglycemia, and neuropsychological difficulties are the most commonly agreed upon adverse effects of CS. It is also important to note that not every patient receiving CS will develop any of these adverse effects.

The adverse effects of CS may influence a physical therapist's approach to evaluation, treatment, and progression of a patient's rehabilitation program. That is why knowledge of the adverse effects of CS is important for physical therapists and other medical personnel. The adverse effects most pertinent to physical therapy are osteoporosis, gastrointestinal complications, avascular necrosis, reduced cellular immunity, myopathy, and neuropsychological difficulties.

Thus, the purpose of this study is to create an increased awareness for health professionals (specifically physical therapists) concerning the possible adverse effects of CS and how these adverse effects may influence patient evaluation, treatment, and progression. The adverse effects mentioned in the above paragraph are discussed. The physiologic mechanism, clinical research, and therapeutic intervention are presented for each effect as well as precautions or suggestions for the physical therapist relative to working with patients receiving CS.

CHAPTER II

OSTEOPOROSIS

Osteoporosis is probably one of the most recognized adverse effects of long-term corticosteroid (CS) use. A study by Grecu, Weinschelbaum, and Simmons¹⁰ concluded that most bone density is lost within one year after initiating CS therapy. Within that first year bone density may decrease by 4-10%. After the first year, bone loss most likely still occurs but at a much lesser extent.

Mechanism

One mechanism by which CS may induce osteoporosis is fairly well described in today's literature.² Another possible mechanism is briefly mentioned.^{5,11} The mechanism well described in literature begins with corticosteroids inducing hypocalcemia. Because the body becomes hypocalcemic, it will leach calcium from the skeletal system to meet its requirements, leading to a reduction in bone density and eventually leading to osteoporosis. "Steroids cause bone loss by decreasing intestinal calcium absorption and by increasing urinary calcium excretion by the kidney. Decreased blood calcium results in mild hyperparathyroidism, which in turn accelerates bone resorption."^{5(p1206)} Basically there is an imbalance between

bone destruction and bone formation. The other possible physiologic mechanism that may lead to osteoporosis is a reduced level of sex hormones which may increase bone resorption.^{5,11} CS decrease the level of sex hormones in the body by altering gonadal function and the amount of sex hormones produced by the ovaries and testes.¹¹

Clinical Research

Most authors agree that osteoporosis is an adverse effect of CS therapy. The limitation of some studies is that it is difficult to separate the effects of age related osteoporosis versus the effects of corticosteroids; age and corticosteroids most likely have an additive effect relative to osteoporosis.

When bone density decreases, it puts the patient at a higher risk for fractures. Bone density in trabecular bone (such as that of the vertebrae) seems to be affected by CS more than is cortical bone. Boumpas et al⁵ compared trabecular and cortical bone densities in those receiving long-term CS versus those receiving intermittent CS therapy. Neither therapeutic intervention had a significant effect on cortical bone densities and only long-term CS therapy had a negative effect on trabecular bone.

A study by Troiano, Jatkowitz, Cook, Basil, and Zito¹² found that the incidence of fractures was higher while the patient was receiving CS as compared to the incidence for an equal time period before initiation of CS therapy. The medical records of 103 patients with Multiple Sclerosis receiving CS were reviewed. The study reviewed variables such as length of treatment,

cumulative dose of CS, rate of fractures, and the location of fractures. The rate of fractures were as follows: "Overall, 26 (25%) of the patients had had a total of 30 fractures. Twenty (19%) of the patients had 23 fractures after starting steroid therapy and six (6%) of the patients had seven fractures in an equivalent period of time preceding the initiation of steroid therapy."^{12(p1389)} Most fractures were associated with falls, but some were precipitated by less traumatic events, such as turning in bed; in one case a spontaneous fracture was reported.

Although many patients may have no option except to remain on corticosteroids, other medications have been used prophylactically to ward off osteoporosis and the increased risk of fractures.

Therapeutic Intervention

Prophylactic medications which have been used with moderate results are¹¹⁻¹³ calcitrol, calcitonin, and biphosphates. The use of intermittent cyclic therapy (ICT) etidronate is fairly new. A study by Adachi et al¹¹ compared the bone mineral density (BMD) in the lumbar spine of 68 patients being treated with corticosteroids. Thirty-five of those patients were treated prophylactically with ICT etidronate and the control group of 33 received no prophylactic treatment. Bone mineral density was again tested in one year. In the ICT etidronate group, the BMD had increased by 3.82% as compared to a 1.78% decrease in the control group.

Precautions for the Physical Therapist

Because CS are used in many patient populations, physical therapists need to be aware that patients receiving long-term CS may be osteoporotic and special attention must be given while assessing the patient and designing a treatment program. For example, when manual muscle testing (MMT), the shortest lever arm possible should be used to reduce the amount of torque on the skeletal system (especially the long bones of the humerus and femur). Options for strengthening include using pool therapy and closed chain exercises to reduce the shearing forces on the bones.² If the patient is unsteady, the use of an assistive device to help prevent falls is indicated. One of the most important things to do for the patients is to educate them in proper body mechanics during activities of daily living (ADLs).

CHAPTER III

COMPROMISED IMMUNITY

For those receiving CS, a compromised immune system is another adverse effect. Corticosteroids weaken the immune system by decreasing the local inflammatory response which may cause the infection to spread.¹⁴ Many of the disease processes that require treatment with corticosteroids may have already put the body and the immune system in a weakened state. The combination of the disease process at hand and the steroid-induced immunosuppression can be a fatal combination.

Mechanism

The mechanism by which CS suppress the immune system is fairly well understood but also complex. One explanation begins with the depression of lymphocytes and monocytes¹⁵ which occurs four to six hours following the administration of CS. Boumpas et al⁵ summarize what occurs at the cellular level: "glucocorticoids inhibit the access of leukocytes in inflammatory sites; interfere with the functions of leukocytes, endothelial cells, and fibroblasts; and suppress the production and effects of humoral factors involved in the inflammatory response."^(p1198) In a sense, corticosteroids bind well to sites of inflammation and do not allow the leukocytes, fibroblasts, etc. to invade the site

and fight off the infection. Several studies exist that conclude that CS put the patient at a higher risk for acquiring infections.^{2,5,15}

Clinical Research

A meta analysis of 71 trials involving 2000 CS treated patients concluded that the relative risk for infection was approximately two times that of controls.⁵ Dowell and Bresee¹⁵ came to a similar conclusion. In their 1993 study, they concluded that the use of CS multiplies the risk (incidence) of severe varicella or “chicken pox.” They studied 35 children who were suffering from severe varicella and 10,000 control subjects. The purpose of their study was to determine if there is a correlation between CS use and severe varicella. Sixteen of the 35 children in the experimental group had been exposed to some form of CS, whereas in the control group, only 20 out of the 10,000 subjects had been exposed to CS. The dosages of corticosteroids in the experimental group ranged from .5-2.5 mg/kg/d. Among the experimental group, four of the 16 exposed to CS succumbed to the severe varicella. Dowell and Bresee¹⁵ concluded “the odds of steroid use in otherwise immunocompetent children who contracted severe varicella was 178 times higher than in the general population.”^(p225)

Dowell and Bresee¹⁵ identified three limitations in their study. One limitation was the small number of subjects. Secondly, they may have overestimated the odds ratio. Finally, a third factor may exist that ties together the risk of severe varicella and the use of steroids. Regardless of the limitations

of the study, the authors still feel that steroid immunosuppression should be a concern among doctors and those receiving CS.

Therapeutic Intervention

In the review of the literature, no information was found on any substance that could be used to decrease the likelihood of steroid induced immunosuppression.

Precautions for the Physical Therapist

Physical therapists will often treat patients who are immunosuppressed by CS. There are many ways to protect the patient. The single most effective way to prevent the spread of infections is proper hand-washing techniques for the physical therapist and the patient.² Jennifer Grant² of John Hopkins Hospital states, "it is encouraged that patients with a white blood cell (WBC) count of less than 1000 mm³ or a neutrophil count of less than 5000 mm³ should wear a protective mask."^(p58) Physical therapists should be responsible for using universal precautions and gowning and gloving when appropriate. The patient should be educated to avoid public areas where many people congregate as the possibilities of contracting an unwanted infection abound.

CHAPTER IV

GI COMPLICATIONS

Gastrointestinal complications often occur in those taking CS. The most common complications are perforation of peptic ulcers and perforation of colonic diverticula.

Mechanism

For perforation of both peptic ulcer and colonic diverticula, there are separate possible mechanisms of injury. Three primary explanations of how CS may cause peptic ulcer perforation exist. Alexander, Schuman, and Vetto's¹⁶ stated mechanism of peptic ulcer perforation is by "lymphoid depletion in the colonic lymphoid patches, resulting in bacterial invasion and subsequent perforation." As discussed previously, CS leave the patient in an immunosuppressed condition, which decreases the leukocyte counts and leave the patient less able to fight off the bacteria that enter the GI tract. Finally, corticosteroids are also thought to decrease the turnover of the mucosal cells lining the GI tract leaving the lining of the GI tract susceptible to infection and subsequent perforation.

A second complication is perforation of colonic diverticula. Arsur¹⁷ believes areas of the colon are repetitively traumatized by fecal material. If

mucosal regeneration is slowed by CS, bacteria have a chance to invade the lining of the colon and eventually cause perforation.¹⁷⁻¹⁸ Because of CS induced immunosuppression, the patient is in a more vulnerable state for bacterial invasion.^{17,18}

Clinical Research

There are many studies identifying a statistically significant correlation between CS use and perforation of ulcers and colonic diverticula of the GI tract. One study used 71 controlled trials. Subjects were randomly assigned to Group 1 or 2. Group 1 received CS, Group 2 received non-steroidal treatment. Subjects were treated for four days. The incidence of peptic ulcers was 1.8% in Group 1 and 0.8% in Group 2.⁴

Warshaw, Welch, and Ottinger¹⁸ strongly suggested that CS may cause perforation of the colon. Their quasi experimental study included 13 subjects whose average duration on steroids was 3.4 years. All subjects were receiving CS for diseases other than that of the bowel. Surgery to repair a perforated colon was needed in 10 of the 13 cases. In five cases, the areas of perforation were close to areas of diverticula, but in the other eight cases, the perforations were in unusual areas. Of the eight cases that were unusual, five had punched out perforations, which are not normally seen. One subject had perforations at the rectosigmoid colon. Other unusual findings were perforations of the transverse and descending colon and areas of gangrene. The authors felt that because of the uniqueness of the perforations and the fact that the patients were

being treated for diseases other than that of the GI tract, the CS therapy most likely contributed to the perforation in these patients.

Dayton, Kleckner, Dennistoun, and Brown's³ study evaluated (1) the incidence of steroid-related ulcer perforation and (2) the clinical problems and prognosis of patients with this complication. They did retrospective chart reviews of 151 patients with peptic ulcer perforation. Twenty-five (17%) of the subjects had received CS within one week of perforation. The authors agree that this incidence is similar to the findings of other studies and is slightly higher than the 5% to 10% incidence of peptic ulcer perforation found in the general population. Therefore, if the patient is receiving CS, he/she has a greater chance of peptic ulcer perforation than if he/she was not taking CS. The prognosis for patients was poor. There was an 85% mortality rate for those over 50 years of age and 17% for those under 50 years of age. The authors concluded that CS therapy causes a significant number of all perforations and there is a high mortality for these patients.

Diethelm¹⁴ also concluded that "steroid ulceration" is a complication that may occur in 10% to 30% of those on CS for more than one month. He also reported that the dosage levels of cortisone and prednisone may be associated with an increased incidence of ulceration. Daily dosage levels greater than 50 mg/d of cortisone and 20 mg/d of prednisone appear to be associated with an increased risk of ulceration.

Carson et al¹⁹ disagreed with these conclusions. The authors found the overall risk of GI complications in users of CS to be 2.8 per 10,000 person-months. They concluded that the rate of GI complications did not warrant the use of prophylactic medication.

Therapeutic Intervention

Perforation of the GI tract often ends in surgical intervention. Prior to perforation, however, prophylactic medications may ward off steroid-induced complications.

Antacids and H₂ blockers have been used with moderate success to guard against ulcer formation¹⁴ and the use of ranitidine has also been suggested.²⁰ Seale and Compton⁴ disagree with the prophylactic use of medications, such as antacids and H₂ blockers, as their use is not warranted.⁴

Precautions for the Physical Therapist

As physical therapists, recognizing the signs and symptoms of ulceration and/or perforation would facilitate immediate referral to a physician. Signs and symptoms may include 1) pain which is burning, gnawing, or aching, 2) soreness, 3) an empty feeling, or 4) hunger.²¹ Pain is usually unrelenting and may range from mild to severe. Pain may be lessened by the use of dairy products, antacids, or H₂ blockers.

CHAPTER V

AVASCULAR NECROSIS

Avascular necrosis (AVN) is a recognized adverse effect of CS therapy.²²⁻²⁶ Four common features of corticosteroid-induced AVN exist.²⁷ First, no known trauma is implicated. Second, no other underlying cause of nontraumatic avascular necrosis is found. Third, the patient has been receiving corticosteroids for an extended period of time and in excess of physiological requirements. Last of all, the disease process for which the patient is receiving CS does not cause AVN.

AVN most commonly occurs in the hip joint.²⁴ The knee, ankle, shoulder, elbow, and wrist have also been implicated.¹⁴ When avascular necrosis affects the femoral head, total hip arthroplasty is the most common surgical intervention. The specific cause of steroid-induced avascular necrosis is not known, but a few causes have been hypothesized.

Mechanism

Wang, Sweet, Reger, and Thompson²⁸ proposed three possible mechanisms of steroid-induced AVN. The first theory is that the blood hypercoagulates and there is subsequent vascular insufficiency to the femoral head. The second possible cause of AVN is osteoporosis which may eventually lead to

fracture and collapse of the femoral head. The last mechanism of AVN may be a result of hyperlipidemia. The alteration of fat metabolism by CS may cause the liver to become excessively fatty and cause the liver to release small fat emboli. These small fat emboli may impair the circulation of the femoral head, causing bone death and resultant AVN. This latter theory appears to be the most popular school of thought.^{3,22,24,25,27,28}

A study by Fisher et al²² supports this theory. Fisher studied 66 New Zealand rabbits. The 66 rabbits were split into two experimental groups and one control group. Two experimental groups of 30 subjects each were formed. The only difference between the groups was that they received slightly different corticosteroids. The six remaining rabbits made up the control group. The rabbits in the experimental group received dosages of CS in excess of physiological requirements. Five rabbits in each experimental groups and one from the control group were killed each month for six months. Histological and general autopsies were done. The results indicated that high doses of CS cause hyperlipidemia and an excessively fatty liver. The reason for hyperlipidemia is not well understood. One theory states that CS cause lipid mobilization in the adipose tissue. The increased lipid mobilization causes the liver to become so full of fat that the cells eventually burst. Fat emboli enter the bloodstream via the hepatic circulation. Through the hepatic circulation, the emboli enter the circulatory system of the heart and lungs and are transported to the periphery of

the circulatory system. Fisher and associates found fat emboli in subchondral bone of the rabbits and areas of osteocytic death after three to five months.

Clinical Research

Alarcón and associates²⁶ describe an atypical case of a 48-year-old woman who developed AVN of the femoral head after long-term corticosteroid use. She was receiving corticosteroids for "feigned" bronchial asthma. "Feigned" bronchial asthma is considered a factitious disorder. "Factitious disorders are characterized by physical and/or psychological symptoms that are intentionally produced or feigned."^{26(p139)} In 1990, the woman was evaluated for refractory asthma. She stated she had had asthma since she was 13 years old but her asthma did not become severe enough to elicit the use of CS until she was 37 years old. She used parenteral, oral and inhaled corticosteroids. Her history and physical revealed that she had undergone 11 knee surgeries, two of which were total knee arthroplasties. At the time of the evaluation, she relied on a wheelchair for locomotion secondary to the condition of her knees. She had a host of other problems and was receiving nine different medications. At the time of her evaluation, chest X-rays were unremarkable as were the results of her pulmonary function tests. In 1990 and again in June 1991, she was advised to decrease the use of her CS. She was lost to follow up until March 1992 when she presented with left hip pain. The diagnosis of AVN was made. Conservative treatment with core decompression was done, but in June 1992, she required a total hip arthroplasty (THA). During this hospitalization time, she

did agree to taper her CS dosage. At discharge she was taking only 8 mg of prednisone every other day and eventually was able to taper it to 5 mg every other day. Alarcón and associates stated that no cause of AVN, other than CS could be shown.

Not only is AVN implicated in long-term corticosteroid use, such as in the above case, but is also infrequently noted in short-term CS use. Anderton, Orth, and Helm²⁵ reported the case study of a 27-year-old male whom after a seven-day course of dexamethasone for increased intracranial pressure presented with avascular necrosis of both humeral heads and femoral heads. The man was first seen for complaints of shoulder pain that had persisted for one year. No history of trauma to the shoulders was present. Two years prior to the onset of symptoms the patient had been treated with oral dexamethasone for increased intracranial pressure. No definitive diagnosis was given for the increased intracranial pressure. He received 4 mg of dexamethasone every six hours for seven days. Complete recovery was achieved. At the time of evaluation, three years after receiving the dexamethasone, range of motion (ROM) in both shoulders was compromised. X-rays showed marked AVN of bilateral shoulders and moderate involvement at both hips. Other possible causes of AVN from disease processes or systemic involvement were ruled out. Anderton et al concluded that even a short duration of CS does not rule out the possibility of AVN.

Fisher and Bickel²⁷ along with help of Patterson and company reviewed 77 cases of non-traumatic avascular necrosis at the Mayo Clinic. Patient histories were reviewed and prescriptions for CS were noted. Prednisone was the most common drug prescribed. Every case except one was receiving dosages in physiological excess. Of the 77 subjects, 23 were receiving CS for collagen-vascular difficulties, 16 for dermatological problems, 5 for hematologic problems, 7 for gout, 5 for pulmonary disease, and 21 for miscellaneous diseases. The time period between the onset of symptoms and diagnosis of AVN, via X-rays, was determined. The average time between initiation of CS treatment and onset of symptoms was nine months. All cases had the classic signs of corticosteroid-induced AVN.

Therapeutic Intervention

In the review of the literature, no reference was made to any prophylactic medications that offset the chance of AVN in patients receiving corticosteroids. Intervention normally occurs only after the diagnosis of AVN has been made. By the time AVN is diagnosed, it has usually progressed so far that surgical intervention is needed.^{2,18,26,27} With avascular necrosis of the femoral head, total hip arthroplasty (THA) is the intervention of choice.¹⁴ Total hip arthroplasty allows the patient to be free of pain and improve his/her ambulatory skills.

A fairly new conservative treatment of AVN of the femoral head is showing promise as an option to THAs. The new procedure involves using a vascularized fibular graft.²³ Malizos and associates salvaged 10 hips of eight

patients using a vascularized fibular graft. All patients experienced relief of pain following surgery. Patients utilized a pair of crutches for six months and advanced to one crutch for three more months. Not one of the patients needed any additional hip surgeries in the two-year follow-up of this study.

Precautions for the Physical Therapist

Once a patient is diagnosed with AVN, little to nothing can be done to prevent the progression of AVN. A conservative way to alleviate pain is the use of a cane. Another way to alleviate pain and prevent further collapse of the bone is to exercise the surrounding joint musculature in a non-weight bearing position.² However, this conservative treatment will most likely not provide enough relief for the patient and surgical intervention will be needed.

As a physical therapist, knowing the signs and symptoms of AVN will allow for differential diagnosis and referral to a physician.²⁹ Pain is the major patient complaint. The pain is localized to the joint and the patient will usually complain of stiffness. Upon palpation, the patient may complain of tenderness and the joint may be swollen. Restricted range of motion will be noted.

CHAPTER VI

NEUROPSYCHOLOGICAL DIFFICULTIES

Many neuropsychological symptoms have presented in patients receiving corticosteroids. The most common neuropsychological side effects of CS in adults are euphoria, depression, and psychotic reactions characterized by delusion, hallucination, stupor, and catatonia.³⁰ The most common neuropsychological side effects in children are affective changes, insomnia, restlessness, depression, reduced verbal memory, increased irritability, and fatigue.³¹ The effects of CS on neuropsychological functioning are variable. In the systemic lupus erythematosus (SLE) patient population, CS have been found to improve cognition, mood, and symptom rating.³² The intensity of psychological changes may depend on dosage, sensitivity of the patient, and the patient's underlying personality.²

Mechanism

In the review of the literature, no explanation for the alteration in an adult's neuropsychological functioning was offered. For children, one hypothesis has been stated.³³ Corticosteroids suppress the formation of adrenocorticotrophic hormone (ACTH), a naturally occurring hormone in the body. Naturally occurring glucocorticosteroids are said to facilitate brain maturation.

With the use of oral, parenteral, or inhaled corticosteroids, ACTH production is suppressed, therefore possibly delaying full formation of the central nervous system.³³

Clinical Research

The first case study relative to neuropsychological functioning is that of a 17-year-old adult male who received many different CS for a bout of ulcerative colitis and who eventually developed steroid induced stupor (depression).³⁴ He was given hydrocortisone (HC) for two days at 100 mg q.i.d. While on the HC, he experienced an anxiety attack. He was next given oral prednisone for six days at 20 mg t.i.d. His ulcerative colitis symptoms exacerbated and he was again put on HC at 100 mg q.i.d. This time while on HC, he became extremely agitated and made a suicide attempt. The ulcerative colitis improved and his medication was switched to ACTH at 40 units i.m. daily. This dosage was decreased gradually over 10 days. After these 10 days, his bowel problems were markedly improved but his psychological state had deteriorated and he went into a catatonic stupor.

He was given neuroleptic medication, and over the next four weeks, his stupor mildly improved while his psychomotor functioning only moderately improved. He again became suicidal. Because of the ineffectiveness of the neuroleptic medications, electroconvulsive therapy (ECT) was used. He responded very well to a course of ECT comprised of five treatments. The intensity of the symptoms in this patient was most likely precipitated by the high

dose of CS that he was receiving and the fact that he was receiving them intravenously. Medications injected intravenously are rapidly absorbed in the bloodstream and remain more concentrated. His personal sensitivity to the CS may also have been a factor. It was noted that family and personal history of psychological problems was unremarkable.

Neuropsychological changes occur not only in adults but also in children. Bender, Lerner, and Poland³¹ studied the psychological functioning of 32 children, ages 8-16 years old (mean=14 years), who were currently hospitalized for exacerbations of severe asthma. The children received burst therapy of oral prednisone, a common CS, as well as inhaled CS and oral theophylline. Burst CS therapy uses alternating high/low dosage days, with high dosages averaging 61.4 mg and low dosages averaging 6.97 mg. All subjects were evaluated at high steroid and low steroid dose.

Psychological functions that were tested included hyperactivity, fine motor control, mood, attention, impulsivity, and memory. Other areas assessed were asthma severity, intelligence, socioeconomic status, and family functioning. All testing was done while the child's asthma symptoms were stable. Three areas of psychological functioning were found to significantly fluctuate between high and low steroid dosage days, while the other areas were relatively unchanged. All children reported higher anxiety levels during high versus low dose days. Verbal memory scores were decreased and the children also scored higher on the test for depression. Bender and associates³¹ found no factors that would

indicate the above changes were from anything other than the steroids. In addition, age, intelligence, socioeconomic status, and asthma severity did not predict a child's susceptibility to neuropsychological difficulties. However, impaired psychosocial functioning and family dysfunction were moderately associated with mood and memory deterioration. This study showed how dosage, patient susceptibility, and underlying personality may affect sensitivity to CS.

Most studies dealing with neuropsychological functioning in patients receiving corticosteroids report a decrease in CNS functioning.^{30,31,33,34} However, Denburg, Denburg, and Carbotte³² reported improvement in cognition, mood, and/or systemic lupus erythematosus (SLE) symptom rating in ten women after low doses of CS. The 10 women participating in the study had not received CS for at least six months prior to this study. They completed three randomly assigned drug/placebo pairings. Those receiving CS had 0.5 mg/kg of prednisone daily. Analysis of variance (ANOVA) yielded "positive drug effects for cognition, mood, and SLE symptom ratings."^{32(p1311)} Despite the short time this study was run, the authors feel that more research should be carried out in this area because of positive CS effects on the patient living with SLE.

Therapeutic Intervention

In the review of the literature, one prophylactic medication was noted.³⁰ Lithium has been used prophylactically to decrease the neuropsychological side

effects of CS in people with multiple sclerosis and retrobulbar neuritis. Mild to moderate results have been achieved.

Precautions for the Physical Therapist

As physical therapists, you cannot alter the moods of your patient. But being sensitive to changes in your patient's personality or mood is very important if he/she is receiving CS. If intense personality and mood changes are observed, the physician should be notified so possible adjustments in dose and form of CS may be made.

CHAPTER VII

STEROID MYOPATHY

Steroid myopathy is a common adverse effect of corticosteroids. In the literature, there are two forms of steroid myopathy.^{2,3,7,8,35-39} The two forms are chronic steroid myopathy and acute necrotizing myopathy.

Chronic steroid myopathy presents with distinguishing characteristics.^{2,7,8,35,38} The onset of muscle weakness is insidious, chronic, and painless. Weakness is symmetrical and begins in the pelvic girdle, moving to the shoulder girdle and then to the distal extremities. Type IIB (fast twitch) muscle fibers are the most often affected. Tests will reveal an elevated creatine excretion in the urine which is an indicator of protein wasting of the muscles. Although pain is not the main complaint, patients may complain of mild myalgia and arthralgia.

Acute necrotizing steroid myopathy is associated with the use of corticosteroids and neuromuscular blockades (NMBs). It most often occurs when NMBs are used to paralyze the respiratory muscles of patients who are suffering from status asthmaticus. NMBs allow easy intubation by paralyzing the respiratory muscles that are in spasm. Intubation is necessary so the patient can receive the proper ventilation he/she needs, by way of a respirator or

mechanical ventilation. The severe nature of status asthmaticus often requires that patients be maintained on both CS and NMBs for an extended period of time. Acute necrotizing steroid myopathy is discovered when the use of NMBs are discontinued. Acute necrotizing steroid myopathy has also been associated with the use of steroids alone.

Both etiologies of acute steroid myopathy are characterized by the following signs and symptoms.^{35,37,39} They both have an acute onset. Moderate to severe flaccid weakness will develop and atrophy of the muscles will be evident. In acute steroid myopathy, the distal extremities are the most severely affected. High creatine excretion will also be noted. Electromyographic (EMG) readings will give mixed results.

Both chronic and acute steroid myopathy are reversible with exercise and dose reduction of both NMBs and CS.² Complete recovery may take from one to four months or up to two years.²

Mechanism

The mechanisms leading to chronic or acute steroid myopathy can only be hypothesized^{2,7,35,36,38,40} One theory is that corticosteroids cause an accelerated breakdown of muscle protein.³⁵ Skeletal muscle has many CS receptors and is considered a "target" organ of CS.² The breakdown of muscle protein may be induced by corticosteroids by "decreased uptake of amino acids by skeletal muscle and inhibition of amino acid incorporation into proteins."^{2(p59)} It has also been theorized that when muscle is immobilized, either naturally or

induced by NMBs, the number of corticosteroid receptors increase.^{35,36,40} The increased number of receptors causes the patient to become hypersensitive to the deleterious effects of CS and accelerate muscle wasting.

The catabolic effects of CS are most pronounced in the muscles that are the least active in protein synthesis.² When muscle is exercised on a regular basis, it becomes more active in protein synthesis than when it is immobilized or not exercised on a regular basis. This also supports the theory that immobilized muscle will be more susceptible to myopathy. Therefore, if a person is on CS and does not exercise regularly, he/she may be more at risk for steroid myopathy. Because their muscles are not active in protein synthesis and because they may contain more CS receptors, people who do not exercise regularly are most affected by the catabolic effects of CS. Horber, Scheidegger, Grünig, and Frey⁴⁰ concluded that exercise may reduce the effects of steroid myopathy. Their study will be discussed in further detail later in this chapter.

Clinical Research

Askari, Vignos, and Moskowitz⁸ presented a case study of eight women who developed chronic steroid myopathy while receiving high doses of prednisone. They were receiving prednisone for various disease processes of connective tissue: 1) polymyositis, 2) systemic lupus erythematosus (SLE), 3) rheumatoid arthritis (RA), and 4) shoulder hand syndrome (SHS). All of the women experienced an insidious onset of weakness. In almost all of the women muscle weakness was symmetrical and most pronounced in the pelvic girdle with

less involvement at the shoulder girdle and distal musculature. Five of the women reported diffuse myalgia. Creatine excretion was elevated in all the women. The authors concluded that no correlation existed between the extent of the myopathy and the cumulative dose of CS that the patient had received. All the women recovered from this bout of steroid myopathy through dose reduction of CS and an active exercise program. None of the women showed a relapse of myopathy during the follow-up time of 120 to 360 days. As a point of interest, all of the women had developed at least two or more of the other adverse effects of CS, with osteoporosis being the most common.

Jennifer Grant² adapted a functional classification system from this case study (Table 1).³⁸ This classification uses difficulty in functional activities to determine the level of weakness. During Class I, or advanced level of functioning, the patient only has difficulty in climbing stairs. In Class 2, or high level of functioning, the patient cannot rise from a chair without assistance of some kind. If patients cannot walk without assistance, they are classified as Class 3, or intermediate level of functioning. In the final class, Class 4, or low level of functioning, patients cannot elevate their extremities or move in bed.

Pangyres, Squier, Mills, and Newsom-Davis³⁸ reported the case study of a 13-year-old Greek girl who developed acute steroid myopathy from steroids alone. NMBs were not used in this case. The child was receiving CS for myasthenia gravis. She had received a total dose of 5.48 grams of methylprednisolone. Weakness was most evident distally. She was unable to

Table 1.—Functional Classification of Muscle Weakness^a

Class	Level	Functional Capacity
1	Advanced	Has difficulty in climbing stairs
2	High	Cannot rise from chair
3	Intermediate	Cannot walk without assistance
4	Low	Cannot elevate extremities or move in bed

^aFunctional classification categories are adapted from Askari A, Vingnos PJ, Moskowitz RW. Steroid myopathy in connective tissue disease. *Am J Med.* 1976;61:485-492 and Grant J. Corticosteroid side effects: implications for PT. *PT Mag Phys Ther.* 1994;2:56-60.

lift her legs from the bed. Her facial muscles were also affected and she had difficulty swallowing and talking. Tendon reflexes were absent with the exception of bilateral tricep jerks. EMG studies showed normal motor and sensory conduction. The clinical features of this case did not appear to be from the myasthenia gravis. Signs and symptoms of myasthenia gravis are²¹ ptosis, diplopia, and muscle fatigability. Ocular muscles are affected in 85% of the cases. Deep tendon reflexes are normal. Because the signs and symptoms did not fully correlate with myasthenia gravis, the authors felt that a large dose of CS was the possible cause of the weakness. Myasthenia gravis at times blocks transmission at the neuromuscular junction such as a neuromuscular blockade works to immobilize the muscles. Therefore, the muscles are less active in protein synthesis and become hypersensitive to the myopathic effects of CS, as stated previously in this chapter.³⁸

A third form of steroid myopathy is that induced by a combination of CS and NMBs. Steroids and NMBs may be used together when a patient goes into status asthmaticus as described earlier.^{9,35,36,39,41}

A case study by Griffin and colleagues⁴¹ was carried out on a 29-year-old man. He came to the emergency room with wheezes and signs of an upper respiratory tract infection (URI). His past medical history was positive for steroid dependent asthma. Because of his abnormal arterial blood gas (ABG) readings, he was intubated immediately. Before intubation, NMBs were used to facilitate the process. He remained on CS and NMBs for many days to aid with

ventilation and proper air exchange. On day 16 of his hospitalization, all NMBs and sedatives were discontinued but he remained on a ventilator. On examination, after discontinuation of NMBs, flaccid quadriplegia existed. Deep tendon reflexes were severely decreased but sensation was intact. Myoglobin was detected in the urine, indicating muscle breakdown. He was weaned from the respirator on day 31, and with the help of physical therapy, he was able to ambulate independently after one month. The authors felt that this patient's flaccid quadriplegia was due to the combination of steroids and NMBs as the patient had full nutritional support all through his hospitalization, his electrolytes were kept in balance, and he had no past medical history of a neuromuscular disorder.

Hirano et al³⁵ presented a similar case study. An 18-year-old male was admitted to the hospital because of a severe asthma attack. He was treated with intravenous (IV) methylprednisone and paralyzed with vecuronium (a NMB) before intubation and for the next 12 days. Following discontinuation of NMBs, he had flaccid quadriplegia and had lost 10 kg of body weight. He remained on the methylprednisone. He was mentally alert and cranial nerves were intact. Sensation was normal and deep tendon reflexes were present. Nerve conduction studies were unremarkable. On day 42 he was extubated, his methylprednisone was decreased and he began to improve. On day 68 he was able to walk short distances in the parallel bars. Because of the lack of

neurogenic changes, the authors believed that the flaccid quadriplegia was due to a combination of CS and NMBs.

Therapeutic Intervention

Three options exist to lessen the effects of steroid myopathy. The first option is either discontinuing the CS or decreasing the dosage.^{7,8} The second option is changing the medication to another steroid derivative.⁸ The last option is to institute an active exercise program for those who receive corticosteroids.

Horber, Scheidegger, Grünig, and Frey⁴⁰ concluded that myopathy can be reversed by active exercise. "The purpose of their research was 1) to quantify the decreases in thigh muscle strength in patients with prednisone and 2) to establish whether the thigh muscle area can be increased and its function improved by training."^(p83) The study included 24 subjects (12 experimental and 12 control subjects). The 12 in the experimental group were all at least six months status post renal transplantation and were receiving 12.6 ± 3.3 mg/day of prednisone. The 12 control subjects were not currently participating in any physical training or receiving CS. A Cybex II was used to assess muscle strength and power. Isokinetic tests were done on five occasions; specifically, on two different days before training, on day 35 of training, and on two days post training. The 12 experimental subjects trained isokinetically on the Cybex II three times per week for 50 days. To determine thigh muscle area and density, computerized tomography (CT) of the thigh was done. As compared to the control group, before instituting training, the experimental group had 1) a higher

fat to muscle ratio, 2) a lower mean torque, and 3) a decreased total work output. At the end of training, the two groups were equal in the three tested areas. This suggests that active exercise may offset the adverse effects of prednisone.

Precautions for the Physical Therapist

It is important for the physical therapist to differentiate between chronic and acute steroid myopathy. The signs and symptoms of each of the myopathies were presented in the introduction to this chapter. One red flag for the physical therapist is to note any increase in creatine excretion (above the normal) in the urine, which indicates protein catabolism. This seems to be an accurate indicator of even mild myopathy.²

With an active exercise program the patient will improve. However, return of strength may be fast or slow. Complete recovery may be as quick as one to four months or it may take up to one or two years.

Treatment of the patient should include active exercise and functional activities.^{2,40} Sample exercises to correlate with Askari's functional classifications were given by Jennifer Grant,² MS, PT. They have been reprinted in Table 2. Goals of treatment should be to increase strength, regain endurance, and teach energy conservation techniques. Assistive devices may be needed for some patients. Proper home instructions and referral to a physician should be made.

Table 2.—Sample Exercise Prescription Based on Functional Status^a

Low Level	Intermediate Level	High Level	Advanced Level
Active range of motion (AROM)	Light resistive exercise against gravity	Toe raises in standing position	Bench step
Gravity eliminated	Assisted bridging	Bridging	One-leg bridging
Against gravity	Semi-squats with upper extremity support	Squats with extremity support	Lunges
	Chair pushups	Half kneel to standing position	

^aReprinted with permission. Grant J. Corticosteroid side effects: implications for PT. PT Mag Phys Ther. 1994;2:56-60.

CHAPTER VIII

CONCLUSION

This project discussed a few of the possible adverse effects of CS use and their implications for the physical therapist. A physical therapist cannot decide whether or not a patient should be on CS. However, he/she should be aware of the signs and symptoms of the possible adverse effects from the use of these medications which may be apparent during evaluation and/or assessment.

Being aware of the medication complications will allow the therapist to make the appropriate clinical decision and provide quality care to that patient. The therapist may have to alter how he/she conducts the evaluation. When planning the treatment and progression of a patient, the therapist must also take into consideration the secondary effects of CS, whether it be osteoporosis, a compromised immune system, GI complications, avascular necrosis, neuropsychological difficulties, or steroid myopathy.

It is also the duty of the physical therapist to inform the physician of any observed changes in the patient's functioning, such as a decrease in the proximal strength of the lower extremities and a decrease in general endurance. A therapist will know how to treat steroid myopathy, but the physician may also be able to decrease the dosage of CS or switch the patient to another form of

CS. The therapist and physician together can help the patient maintain his/her highest level of function.

The adverse effects discussed may or may not affect a patient receiving CS. Throughout the literature it seems apparent that the adverse effects are very patient specific. Patient susceptibility to CS may play a significant role in whether or not he/she will develop any of the adverse effects and to what extent they will affect the patient.

Although CS are therapeutic agents, one question remains. Do the benefits of CS in treating the primary diagnosis outweigh the risks and consequences of the adverse effects? It is a Catch 22. On one hand, the primary diagnosis may be exacerbated without the use of corticosteroids, but on the other hand, the adverse effects of CS may be debilitating. But in most cases, the benefits of CS outweigh the potential adverse effects.

APPENDIX A

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Jennifer Grant, MS, PT
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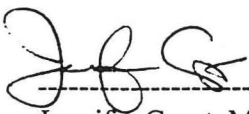
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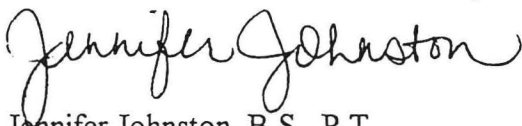
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