USE OF DRUGS IN MYOPATHIES

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The most important recent advances in understanding and managing myopathies have occurred in relation to diseases associated with alterations in the immune mechanism: polymyositis and myasthenia gravis. Some progress has also been made in the management of diseases associated with abnormal movement of potassium ions, and in understanding the effects of neuromuscular blocking drugs. Unfortunately, there has been less progress in understanding or managing the muscular dystrophies.

DISEASES OF MUSCLE ASSOCIATED WITH ALTERATIONS IN THE IMMUNE MECHANISM

Polymyositis and Dermatomyositis

DIAGNOSIS *Polymyositis* is an inflammatory myopathy of unknown cause, to which the term *dermatomyositis* is applied when a skin rash is present. These disorders constitute the commonest myopathy of adults, and in children are second in frequency to muscular dystrophy. They are characterized by symmetrical weakness of the limb-girdle muscles and neck flexors, progressing over weeks to months; muscle-biopsy evidence of necrosis of type I and II fibers, diffuse atrophy, and a mononuclear inflammatory exudate, often perivascular; elevation in serum of skeletal muscle enzymes, particularly creatine phosphokinase (CPK); polyphasic motor unit potentials of reduced amplitude and duration; and often heliotrope discoloration and edema of the eyelids and face, and erythematous dermatitis over the dorsum of the hands, knees, elbows, face, neck, and upper trunk (1, 2). Occasionally, the diagnosis may be made in the absence of elevated muscle enzymes in serum or of electromyographic changes, and more than one muscle biopsy may have to be obtained. Some patients have features of one or more of the connective tissue disorders, including scleroderma, systemic lupus erythematosus, rheumatoid arthri-

tis, polyarteritis, and Sjögren's syndrome. Approximately 15% of adult patients have or develop a neoplasm. In these patients, the polymyositis tends to be more resistant to therapy.

PATHOGENESIS There is some evidence that a cellular immune mechanism may be responsible for the muscle injury that characterizes the disease. In guinea pigs repeated injection of heterologous muscle homogenates in Freund's complete adjuvant produces myositis with lymphocytic infiltrates (3). Lymphocytes from patients with active polymyositis produce cytotoxic effects on human fetal muscle-cell cultures by releasing a mediator of delayed hypersensitivity, lymphotoxin (4). Lymphocytes of patients receiving high-dosage prednisone or azathioprine show little cytotoxicity (5). The nature of the hypothetical antigen involved in the postulated cellular immune response is unknown. A role for humoral antibodies has not been established, although deposition of IgG, IgM, and C3 in muscle-vessel walls has been reported (6). In a few patients polymyositis has followed viral infection due to influenza, herpes zoster, rubella, Coxsackie virus, and cytoplasmic inclusion bodies resembling viral particles have been found in some (7). Polymyositis also occurs in trichinosis, which in the acute stage is invariably accompanied by eosinophilia and which can then be treated with corticosteroid and thiabendazole (Mintezol®) (25 mg/kg orally twice daily), and in toxoplasmosis, which can be treated with sulfadiazine (1 g orally four times a day) and pyrimethamine (Daraprine®) (50 mg orally daily for 2 weeks and then 25 mg daily for 2 weeks) (8). Pyrimethamine is a folic acid antagonist that may produce leukopenia and thrombocytopenia, so that blood counts should be obtained twice weekly and folinic acid (leucovorin), 6 mg orally three times a day, administered simultaneously.

TREATMENT *Corticosteroids* are generally considered beneficial in most patients with polymyositis or dermatomyositis, particularly during the acute stage and during exacerbations of the disease (2, 9). In the absence of any controlled study, their long-range effect on the course of the disease is impossible to document. Most (2), but not all (10), studies have indicated a favorable effect. Prolonged administration of relatively high doses of corticosteroid is usually required before muscle strength improves (9). The initial dose should be from 80 to 120 mg of prednisone, or its equivalent, daily by mouth, although occasionally higher doses may be necessary. In patients who are more severely ill, it is preferable to administer this in divided daily doses, but in patients who are only moderately ill a single morning dose or every-other-morning dose may be tried, in an effort to reduce the severity of steroid side effects and suppression of adrenal cortical function. After one to four weeks of corticosteroid administration, the level of serum enzymes derived from muscle, particularly CPK, will begin to fall and will gradually decline over a period of months. The enzymes usually begin to decrease three to four weeks before improvement in muscle strength begins, and the improvement may not be manifest until high doses of corticosteroid have been administered for one to two months. The dose of steroid should not be reduced until there is good evidence of improvement, as indicated by increased muscle strength, decreased muscle tenderness, decreased

serum enzymes derived from muscle, and decreased creatinuria (11). When improvement is manifest, the dose of steroid should be reduced by about 10% every one to two weeks. Too rapid reduction in steroid dose may result in clinical relapse, which usually necessitates an increase in dose. A rise in the level of serum enzymes derived from muscle, or in creatinuria, usually precedes clinical relapse by three to six weeks and may be a helpful sign. Unfortunately, there is not always a good correlation between these laboratory tests and the clinical condition of the patient, which is a more important guide to management (12). Occasionally, the serum enzymes are within normal range despite active myositis, particularly when muscle atrophy is extensive in long-standing disease. If the disease goes into remission, it may be possible to discontinue steroid, but if not, steroid administration is continued at the lowest dose that suppresses active manifestations. Since most patients require long-term administration of steroid, it is necessary that precautions be taken to observe for and attempt to prevent complications of steroid therapy, including steroid myopathy. Decrease in strength accompanied by a rise in serum enzymes derived from muscle is usually due to exacerbation of the disease and warrants an increase in steroid dose. In patients who are receiving high doses of steroid for prolonged periods, decrease in strength without a rise in serum enzymes may be due to steroid myopathy. Unfortunately, there is no laboratory test for steroid myopathy, which can be diagnosed only if reduction in dose of steroid, or gradual discontinuation, is followed by improvement in strength.

The other synthetic analogs of cortisol have no advantage over prednisone in the management of polymyositis, although they differ in potency and duration of action. One mg of cortisol (biologic half-life 8 to 12 hr) has the same anti-inflammatory potency as 0.25 mg prednisolone, methylprednisolone, or triamcinolone (half-life 12 to 36 hr), 0.1 mg paramethasone, or 0.04 mg betamethasone or dexamethasone (half-life 36 to 54 hr) (13). The mechanism of the anti-inflammatory, anti-allergic, and anti-immunologic actions of the corticosteroids is not known. They inhibit the inflammatory reaction to nearly any type of injury by blocking increased permeability of cell membranes, including capillary endothelium, and of lysosomal membranes. They exert a suppressive effect at each stage of the immune response, including phagocytosis of antigens, migration of cells to areas of inflammation, metabolism of lymphocytes, and cell-mediated hypersensitivity reactions. Thymus-derived (T) lymphocytes, which are required for cell-mediated immunity, are more susceptible to the effects of corticosteroids than the bursa-derived (B) lymphocytes that elaborate humoral antibody. Hence humoral antibody production is rarely reduced significantly, except with very large doses of corticosteroids, whereas cell-mediated immunity is modified at lower corticosteroid concentration (13).

The complications of corticosteroid therapy vary with the dose, anti-inflammatory potency, and duration of administration of corticosteroid. The more serious effects include peptic ulceration (often gastric), osteoporosis with vertebral compression fractures and aseptic necrosis of bone, glaucoma and posterior subcapsular cataracts, cerebral edema, and superimposition of bacterial, fungus, and viral infections. Less serious effects include myopathy, psychiatric disorders, edema, elevation of blood pressure, hypokalemic alkalosis, hyperlipidemia, centripetal obesity,

growth retardation, impaired wound healing, acne, and suppression of the hypothalamic-pituitary-adrenal system. Most of these effects appear to be reduced when corticosteroid can be administered on alternate days (13). Steroid myopathy is more likely to occur following fluorinated steroid and prolonged physical inactivity. Cerebral edema (pseudotumor cerebri) is seen mainly in children undergoing withdrawal from corticosteroid treatment, and is manifested by headache, nausea, vomiting, drowsiness, stupor, convulsions, papilledema, and increased intracranial pressure (14). It requires restoring corticosteroid dosage, and then attempting more gradual reduction. Acute adrenocortical insufficiency may occur during or after withdrawal from corticosteroid treatment in the event of physiologic stress, and requires immediate parenteral administration of hydrocortisone and saline.

Immunosuppressant therapy is employed in patients whose strength does not improve following the administration of at least 60 mg prednisone daily for at least two to four months, and in patients who are unable to tolerate the large doses of steroid that may be required to suppress the disease (15). In the latter, it is usually possible to reduce the dose of steroid if supplemented by immunosuppressive medication. Methotrexate (Amethopterin®), a folic acid antagonist, has been used most (15, 16). In a group of patients who failed to respond to prednisone, intravenous weekly injections of methotrexate normalized serum CPK in 77% of the group in a mean of 10 weeks, and improved strength in a mean of 13 weeks (16). The initial dose was 10 to 15 mg, which was increased if well tolerated to 0.5 to 0.8 mg/kg (30–50 mg) at weekly intervals. After several weeks, methotrexate administration was decreased to biweekly, triweekly, or monthly intervals. It is necessary to perform preinjection blood counts and serum alkaline phosphatase activity, and to check for the occurrence of stomatitis, sore throat, skin rash, purpura, fever, or gastrointestinal complaints. Although the reported beneficial effects of methotrexate in polymyositis have been with weekly intravenous administration, weekly, or semiweekly intramuscular or oral administration may also prove to be effective (15). Other immunosuppressive drugs that have been employed with variable success include azathioprine (17), cyclophosphamide, 6-mercaptopurine, and chlorambucil (15, 16). Thoracic duct drainage of lymph to remove lymphocytes has also been employed, but without benefit (16).

Azathioprine (Imuran®) is inactive until it is converted, primarily in the liver, into its active metabolite, 6-mercaptopurine, a purine analog that inhibits purine synthesis and disrupts both RNA and DNA function. It is administered orally in dosages of 2 to 3 mg per kg daily. Toxic effects requiring decrease in dose or discontinuation include leukopenia, granulocytopenia, pancytopenia, gastrointestinal distress, and superimposed infection. Patients should have weekly blood counts for the first four weeks and at least every two or three weeks thereafter. Since azathioprine and 6-mercaptopurine are metabolized by xanthine oxidase, the dosage of azathioprine, and perhaps of other cytotoxic drugs as well, should be decreased by one half to two thirds in patients receiving the xanthine oxidase inhibitor, allopurinol (18).

Cyclophosphamide (Cytoxan®) is converted by the liver into several alkylating agents that bind guanine nucleotides on the DNA helix and have cytotoxic effects, including on T and B lymphocytes. The initial oral dose is 50 mg daily. If after four

weeks there have been no therapeutic or toxic effects, the dose is increased to 100 mg daily, and if no effects after another four weeks, to 150 mg daily. Complete blood counts are obtained weekly, and the drug is withheld when the white blood count falls below 2500 per mm^3. Other toxic effects include nausea, vomiting, diarrhea, reversible hair loss, thrombocytopenia, hemorrhagic cystitis, and amenorrhea or azoospermia (19).

Antilymphocyte and antithymocyte globulins have been used as immunosuppressive agents on an experimental basis, but their clinical application is not yet clear (20, 21).

Levamisole, an antihelminth that has been found to stimulate the immune response and to restore impaired cutaneous hypersensitivity, is receiving clinical trial in some diseases associated with abnormal immune response, including rheumatoid arthritis (22).

Drug-Induced Polymyositis

Weakness, elevation of serum enzymes derived from muscle, including CPK, and histologic changes in muscle, resembling those of polymyositis, have been reported following the administration of clofibrate (Atromid-S®) (23) or penicillamine (Cuprамine®) (24), and in severe alcoholism (25). Administration of penicillamine has also been reported to be followed by a lupus-like syndrome (26), glomerulonephritis, and myasthenia gravis (27). Penicillamine has been reported either to accelerate or suppress the antibody response to serum albumin, depending on the timing of the doses (28), and it has been suggested that the drug may affect the immune mechanism by acting as, or forming a haptene.

Myasthenia Gravis

DIAGNOSIS Myasthenia gravis is a chronic disease characterized by weakness and abnormal fatigability of skeletal muscle. The muscles innervated by the cranial nerves are particularly affected, and usually those of the neck, trunk, and extremities. In severe cases, weakness of the muscles of respiration occurs. Smooth and cardiac muscles are not involved. The disease usually becomes generalized, but in a minority of cases it remains localized to the extraocular muscles. The weakness is due to deficient action of the transmitter (acetylcholine) on the motor end-plates of involved muscles, probably owing to a competitive (acetylcholine-inhibitory) block, similar to that produced by *d*-tubocurarine in normal subjects (29). The weakness is usually ameliorated, although to a variable degree, by anticholinesterase compounds, which enhance the action of transmitter by inhibiting muscle cholinesterase. This response serves as the basis for diagnosis and management of the disease (30).

PATHOGENESIS There is increasing evidence that myasthenia gravis is associated with alterations in the immune mechanism. The IgG fraction of the serum of 19 to 68% of patients binds with complement, cross striations of skeletal muscle, saline extract and ribonucleoprotein of skeletal muscle, cytoplasm of thymic epithelial cells, thyroglobulin, and nuclei of various cells (31). In 50% of myasthenic patients

the thymus is hyperplastic, in 75% it contains numerous germinal centers, and in 15% there is a thymoma. The number of binding sites for acetylcholine in biopsied nerve-muscle junctions is reported to be decreased (32). Serum globulins from one third of patients competed with α-bungarotoxin for the acetylcholine binding sites on rat muscle acetylcholine receptor protein (33). The sera of 72 of 74 patients were found to contain antibody to human acetylcholine receptor protein (34). Immunization of guinea pigs with subcellular fractions of calf thymus and skeletal muscle homogenates produced thymitis and a partial neuromuscular block (35). Immunization of rats, guinea pigs, or rabbits with acetylcholine receptor protein from the electric organs of *Electrophorus electricus* and *Torpedo californica* resulted in weakness and neuromuscular block which improved following the administration of anticholinesterase compounds (34).

TREATMENT *Anticholinesterase compounds* are administered for the amelioration of weakness in day-to-day management. The most useful of these are pyridostigmine (Mestinon®, 60–180 mg orally every 4 hr), neostigmine (Prostigmin®, 15–30 mg orally every 3 hr or 0.5–1 mg intramuscularly every 2–3 hr), and ambenonium (Mytelase®, 5–10 mg orally every 4 hr). Another and shorter acting anticholinesterase compound, edrophonium (Tensilon®) is useful in diagnosis (10 mg intravenously) and in evaluation of adequacy of dose of the longer-acting compounds (2 mg intravenously). The maximum strength obtained after optimal doses of any of these compounds is approximately the same. The compounds differ mainly in their duration of action (ambenomium > pyridostigmine > neostigmine > edrophonium), and in the severity of their parasympathomimetic side effects (neostigmine > ambenomium > pyridostigmine > edrophonium). The administration of graded doses of any of these compounds results in an increase in strength in muscles affected by the disease, but the maximal strength obtained is usually below normal, and may be far below normal (30).

Corticosteroids and corticotropin are administered to patients who are responding poorly to anticholinesterase medication. If the patient is severely ill, treatment should be initiated in an intensive care unit with methylprednisolone (60 mg intramuscularly) or prednisone (100 mg) or dexamethasone (12 mg) orally, in divided doses, or corticotropin (100 units) intramuscularly, daily for 10 days (36–39). Exacerbation of weakness occurs in about half the patients during the first week, and may require intubation or assisted respiration. Improvement occurs in most patients, to a marked degree in about half, usually beginning during the second week. If improvement does not occur, repeated courses of hormones should be reinstituted within one or two weeks until improvement begins, following which smaller doses of oral prednisone (35 mg) or dexamethasone (4 mg) should be administered every other day. On this regimen improvement persists for three to six months in about one half the patients, and over a year in one fourth. If exacerbation of the disease recurs, higher doses of steroid should be reinstituted. In patients who are less severely ill, prednisone can be administered orally in smaller doses [100 mg on alternate days (40), or 25 mg daily and gradually increased (41)]. This results in

slower improvement, but also in a lower incidence of initial exacerbation, which may nevertheless be severe (42).

It has been suggested that the initial exacerbation may be due to adverse interaction between corticosteroid and anticholinesterase medication (43), and that withholding anticholinesterase medication during prednisone administration may be advantageous (40). Evidence has been presented in experimental animals that prolonged administration of anticholinesterase compounds produces impairment of neuromuscular structure and function (44) and myopathy (45). While excessive doses of anticholinesterase medication should be avoided, as this may not only precipitate cholinergic crisis but may also accelerate the development of drug resistance (acetylcholine refractoriness) (46), there is no good evidence that withholding anticholinesterase medication improves the response to steroid or the rate of remission (36, 37, 47). In the severely ill patient, withholding such medication may be hazardous, and it is preferable to administer the smallest dose needed to improve respiration, cough, and deglutition.

The complications of steroid treatment have included, in addition to initial exacerbation of the disease, those described under the treatment of polymyositis. Because of these complications, steroid should be reduced in dose as improvement occurs, and discontinued whenever possible. Most physicians have limited the prolonged use of steroid to patients with generalized myasthenia gravis, but administration of corticotropin or prednisone may also be helpful in refractory ocular myasthenia gravis (48).

Thymectomy is followed by improvement in most myasthenic patients, sometimes over a period of months, but more often over many years (49–51). While the natural history of the disease is that of gradual improvement after the first one to three years, patients who have had thymectomy early in the disease do appear to have a more benign course. Therefore, thymectomy is recommended in patients with generalized myasthenia gravis who are not able to carry out normal activity on anticholinesterase medication. If there is no radiologic evidence of thyoma, thymectomy can be performed through a transverse neck incision, with the aid of a mediastinoscope (49).

Immunosuppressant drugs (azathioprine, methotrexate, and 6-mercaptopurine) have been administered to patients with severe generalized myasthenia gravis who have become unresponsive to anticholinesterase medication and corticosteroids (52). The doses, precautions, and complications are the same as described for the treatment of polymyositis. Improvement is reported to have occurred in a majority of patients after periods ranging from weeks to months. Removal of lymphocytes by drainage of thoracic duct lymph has been reported to produce improvement within 48 hr (53).

Other drugs that may produce slight improvement in strength in a minority of patients include potassium chloride (2 g orally in dilute solution three times a day), ephedrine sulfate (25 mg orally three times a day), calcium gluconate (1 g orally four times a day), aldosterone antagonists [spironolactone, 50–100 mg orally, or triamterin 100–200 mg orally (54)], oxtriphylline [Choledyl®, a choline salt of theophyl-

line, 0.3–2.4 g orally daily in divided doses (55)], and germine diacetate. Certain drugs may increase neuromuscular block and should be avoided. These include certain antibiotics [streptomycin, neomycin, kanamycin, vancomycin, novobiacin, polymixin, rolitetracycline, colistin, and colistimethate (56)], *d*-tubocurarine, succinylcholine, quinine, quinidine, magnesium sulfate, sodium lactate (57), and drugs that may produce a lupus-like syndrome, including procainamide, penicillamine (24), and trimethadione (58).

Myasthenic Syndrome

The Eaton-Lambert syndrome is manifested by weakness and fatigue, usually most marked in the extremities and sometimes accompanied by aching (59). It is usually, but not always, associated with neoplasm, particularly small-cell bronchogenic carcinoma, and may have an immunologic basis (60). The syndrome resembles myasthenia gravis in symptomatology, and usually in increased reactivity to *d*-tubocurarine and abnormal reactivity to decamethonium and succinylcholine. It differs from myasthenia gravis in that the muscle action potentials evoked by nerve stimulation are much smaller than normal, and increase markedly in amplitude following repetitive stimulation or voluntary contraction. Only a minority of patients with the Eaton-Lambert syndrome improve following administration of anticholinesterase compounds, but most improve following administration of guanidine sulfate (125–250 mg orally four times a day). The syndrome is due to deficient release of transmitter from the nerve endings (59). Guanidine increases release of transmitter. The drug is seldom helpful in myasthenia gravis and may aggravate weakness in some patients with lower motor neuron disease (61). The defect in the Eaton-Lambert syndrome is also partially corrected by epinephrine, methylxanthines, calcium, and caffeine, which has led to the suggestion that it may be due to impairment of cAMP and calcium-activated acetylcholine release (60).

DISEASES ASSOCIATED WITH ELECTROLYTE DISTURBANCE

Potassium

HYPOKALEMIA Reduction in body and serum potassium may develop when there is deficient intake or absorption of potassium, or excessive loss in vomitus, stool, or urine. Approximately half of patients who receive 50 mg hydrochlorothiazide twice daily, as in the control of hypertension, develop a decrease in serum potassium concentration of at least 0.5 meq/liter for more than two months. Hypokalemia may also occur as a result of excessive movement of potassium into cells of the liver following the administration of large amounts of glucose and insulin in the treatment of diabetic acidosis, into cells throughout the body in alkalosis, or into muscle in hypokalemic periodic paralysis. There is sufficient reduction in whole-body potassium in most diabetic patients, particularly in those who are poorly controlled, to require daily replacement even in the presence of normal serum potassium (62).

Hypokalemia due to any cause, if severe, may impair the function of skeletal, cardiac, and smooth muscle. Weakness may involve the muscles of one or all extremities, and the neck, trunk, and respiration, but seldom the muscles innervated by the cranial nerves. Severe loss of potassium, whether in the gastrointestinal tract as a result of steatorrhea, malabsorption, or cathartics (63), or in the urine as a result of diuretics or renal tubular injury from disease or drugs such as amphotericin B (64), may result in profound weakness, elevation of serum enzymes derived from muscle, and muscle degeneration, necrosis, and infiltration by macrophages (hypokalemic myopathy) (65). Hypokalemia may also produce broadening and lowering of the T wave of the electrocardiogram, depression of the ST segment, extrasystoles and other arrhythmias, and increased sensitivity to the arrhythmic effects of digitalis.

Treatment of potassium deficiency is accomplished by supplying potassium, either orally or parenterally if necessary. For mild deficiency, at least 60 meq of potassium chloride is required daily. Potassium-containing foods, such as orange juice (5 meq per 100 ml) or bananas (10 meq per 100 g), are seldom ingested in sufficient amount to provide adequate replacement. For severe deficiency, several times this amount may be required. In the presence of normal renal function, the only practical limit to the amount of potassium given orally is the development of abdominal cramps or diarrhea, which usually occur at doses greater than 150 meq of potassium per day. Potassium salts in tablet form may cause stenosis of the esophagus (66) and small bowel (67), with or without ulceration, even when enteric-coated, and should never be used. A wax-coated, slow-release tablet (Slow-K) has been introduced (68), but has been reported to produce esophageal ulceration and stricture (69). The organic anion compounds of potassium are more palatable than the chloride, but are somewhat less suitable, since most of the organic anions, such as gluconate or citrate, are converted to bicarbonate, and may aggravate the metabolic alkalosis accompanying hypokalemia. For intravenous treatment, potassium chloride (40 meq/L) is administered at a rate of 20 meq per hour, or more rapidly if necessary, with electrocardiographic monitoring.

Hypokalemic periodic paralysis is managed by the daily oral administration of potassium (40 to 80 meq), spironolactone (100 mg), or acetazolamide (500 mg), in an attempt to prevent attacks of weakness (70), which usually occur during sleep, and administration of two or three times these amounts to treat attacks (71). Spironolactone probably acts by reducing kaliuresis, and acetazolamide by producing metabolic acidosis, which retards the entry of potassium into muscle (71). The vacuoles that occur in the muscles of some patients are not visibly altered during attacks or by treatment (72), nor does treatment affect the chronic myopathy that may ensue. In the hypokalemic periodic paralysis that occurs in a few patients with thyrotoxicosis, and which may occur in previously euthyroid patients following the ingestion of thyroid extract (73), attacks of weakness have been prevented and treated with propanolol (40 mg orally four times a day) (74, 75).

HYPERKALEMIA Hyperkalemia results mainly from renal insufficiency, usually with oliguria or anuria, from muscle necrosis due to paroxysmal myoglobinuria or

trauma, or from excessively rapid administration of potassium. Hyperkalemia, if severe, results in impairment of skeletal, cardiac, and smooth muscle, with weakness, peaked T waves in the electrocardiogram, heart block, and asystole. Emergency treatment consists of infusion of glucose (100 g), insulin (25 units), and sodium bicarbonate (50 meq every 20 min), to produce an intracellular shift of potassium, and of calcium gluconate (1 g) to antagonize the cardiac toxicity of hyperkalemia. If the patient was previously digitalized, calcium should be omitted, since it increases digitalis toxicity. For longer-lasting treatment the patient can be hemodialyzed and given Kayexalate® cation exchange resin (20–40 g four times a day) orally or by enema.

In *hyperkalemic periodic paralysis,* potassium moves out of the muscle during attacks of weakness, which usually occur after exercise or exposure to cold and which may be accompanied by myotonic contractions. Attacks of weakness can sometimes be prevented by the prior administration of diuretics such as acetazolamide or chlorothiazide, which increase excretion of potassium, or by the intravenous administration of calcium, glucagon, or epinephrine (76).

Calcium

HYPOCALCEMIA Hypocalcemia may occur in rickets, osteomalacia, hypoparathyroidism, steatorrhea, and uremic phosphate retention. Hypocalcemia, or reduced ionization of calcium without change in concentration, which occurs in alkalosis due to hyperventilation or sodium bicarbonate ingestion, results in increased irritability and spontaneous discharge of sensory and motor nerves and muscle, producing paresthesias, twitching, and muscular spasms (tetany). Most patients are not weak, but some with osteomalacia (77–79) or hypoparathyroidism (80) develop proximal muscle weakness and histologic changes compatible with myopathy, and one patient (79) developed increased serum enzymes derived from muscle. Improvement occurred following treatment with calcium and vitamin D, or, in one patient (77), phosphate.

HYPERCALCEMIA Hypercalcemia may occur in primary or secondary hyperparathyroidism, sarcoidosis, administration of calcium and alkali or of vitamin D, and in malignant disease with or without bony metastasis. Hypercalcemia results in a moderate decrease in muscle strength and tone, decreased intestinal motility, drowsiness and nephrocalcinosis. Some patients with primary (81) or secondary (79) hyperparathyroidism had more pronounced proximal weakness and wasting, myopathic potentials, and atrophy of type I and type II muscle fibers. Improvement occurred following removal of a parathyroid adenoma or alleviation of the cause of parathormone stimulation.

Sodium

Hyponatremia results from loss of sodium in the urine, gastrointestinal glands, or sweat, or from inappropriate secretion of antidiuretic hormone. *Hypernatremia* may result from restriction of water intake, dehydration, hyperaldosteronism, or certain lesions of the brain. Either hyponatremia or hypernatremia may result in lassitude or weakness, which, in severe hypernatremia, may progress to paralysis (82).

DISORDERS ASSOCIATED WITH ABNORMAL RESPONSE TO DRUGS

Malignant hyperthermia is a potentially lethal, autosomal-dominant syndrome characterized by an abnormal response of muscle to certain inhalational anesthetic agents such as halothane, and skeletal-muscle relaxants such as succinylcholine or *d*-tubocurarine (83–85). Some members of many, but not all susceptible families have increased muscle bulk, cramps, local or general weakness, ptosis, myopathic potentials, elevated serum enzymes derived from muscle, and histologic changes in muscle. Susceptible patients develop during anesthesia fulminant hypermetabolism of muscle, which may be induced by a sudden rise in myoplasmic calcium released from the sarcoplasmic reticulum. This results in a vast rise in heat production, fever, release of potassium, enzymes, and myoglobin from muscle, muscle rigidity, flushing, cyanosis, tachycardia, hypotension, hypoxia, tachypnea, and respiratory and metabolic (lactic) acidosis. Late complications include muscle and pulmonary edema, consumption coagulopathy, decerebration, and acute renal shutdown. Management relies on prompt cessation of all anesthetics and muscle relaxants, hyperventilation with oxygen, cooling, and the intravenous administration of sodium bicarbonate to correct the lactic acidosis; procaine or procainamide (0.5–1 mg/kg per min) under electrocardiographic control to correct arrhythmias and restore calcium to the sarcoplasmic reticulum; glucose and insulin to correct hyperkalemia; and mannitol and furosemide to flush myoglobin out of the renal tubules. If renal failure persists, dialysis may be necessary. The mortality of recognized cases has been over 50%. Members of affected families should avoid inhalational anesthetic agents (except nitrous oxide), all muscle relaxants, lidocaine, mepivacaine and cardiac glycosides, but they may receive barbituates, tranquilizers, narcotics, and procaine or tetracaine.

Plasma cholinesterase deficiency may occur as a genetic disorder, or as a result of liver disease, acute febrile illness, or the administration of anticholinesterase compounds. The only resulting abnormality is delay in the breakdown of esters such as succinylcholine, which are hydrolyzed by this enzyme. Persistence of succinylcholine results in prolonged and increased neuromuscular block, with persistence of paralysis and apnea. Respiration must be sustained mechanically until the effect of the drug wears off, which may take hours. Patients with the deficiency should be identified so that anesthetists may be duly warned, and, if no cause is found, family members should be examined (86).

Burns, trauma, upper and lower motor neuron lesions, and tetanus increase the sensitivity of muscle to depolarizing agents, including succinylcholine, which cause efflux of potassium from muscle during depolarization. Following the administration of succinylcholine to patients with these disorders, the serum potassium may rise to toxic levels and may cause cardiac arrest (87).

OTHER METABOLIC MYOPATHIES

Hyperthyroidism results in mild to moderate weakness and wasting in 70% of patients, and marked weakness and wasting, termed *chronic thyrotoxic myopathy,* in a small number. Rarely, patients with severe hyperthyroidism may develop acute

myopathy or encephalomyopathy, characterized by the acute development of severe weakness, marked tremor, delerium, and sometimes dysphagia, dysarthria, and coma. Concomitant myasthenia gravis should be excluded by the edrophonium test. Management of thyroid "storm," with or without encephalomyopathy, relies on rapid institution of antithyroid treatment with potassium iodide and propylthiouracil, supplemented by propanolol, reserpine, and corticosteroid (88).

Hypothyroidism results in mild weakness of proximal muscles, increased muscle bulk, slowness of movement and of muscle contraction and relaxation in response to percussion of the muscle or its tendon, and sometimes muscle stiffness, aching, and cramps. The serum enzymes derived from muscle, including CPK, are elevated. Treatment with thyroid hormone reverses all these changes (88).

Mitochondrial myopathy is characterized by proximal limb-girdle weakness and wasting, a hypermetabolic state despite normal thyroid function, and muscle mitochondria that are structurally abnormal and are associated with partial uncoupling of oxidative phosphorylation. The heart may also be affected. Elevated plasma levels of lactic and pyruvic acids and of alanine may occur, especially after exercise. No definitive therapy is available, but heavy exercise should be avoided, and sodium bicarbonate may be administered for the acidosis (89).

McArdle's syndrome is characterized by muscle stiffness and cramps after exercise. Glycogen accumulates in the muscle because of deficiency of amylophosphorylase. Ingestion of 100 to 200 g of glucose or fructose prior to exertion is reported to be helpful (90).

Paroxysmal myoglobinuria is characterized by muscle pain, cramps, and weakness, and myoglobinuria after exercise. Limitation of exercise is essential. If hyperkalemia and renal failure occur, these must be treated.

Type-IV hyperlipoproteinemia may result in muscle stiffness and aching, as well as arthralgias (91). It is treated by diet and clofibrate administration.

Vitamin E ingestion, 800 IU daily for 3 weeks, was reported to result in fatigue, weakness, creatinuria, and elevated serum CPK (92).

Allopurinol administration to patients with gout resulted in deposition of crystals of hypoxanthine, xanthine, and oxipurinol in skeletal muscle, but no clinical manifestations of muscle disease (93).

Chronic renal failure may produce not only neuropathy, but also proximal weakness and wasting attributable to myopathy. Maintenance dialysis or renal transplantation resulted in dramatic improvement (94).

MUSCULAR DYSTROPHIES

DUCHENNE MUSCULAR DYSTROPHY Prednisone administration was reported to produce in 13 of 14 patients improvement in motor power, which was maintained for up to 28 months in 8 patients (95). Serum CPK fell in 9 patients by more than 45%, but subsequently returned to pretreatment levels. However, other studies have indicated no significant clinical effect of prednisone, despite reduction in serum CPK (96). α-Tocopherol, Vitamin E, anabolic steroids, amino acids, and mixtures of nucleotides were at one time proposed for management, but have been found to be

ineffective (90). Management is limited to physical therapy, avoidance of obesity, and careful attention to respiratory complications.

MYOTONIC DYSTROPHY There is no treatment for the weakness, which is the main problem in this disease. However, the myotonia can be improved by administration of quinine (0.6 g), procainamide (250–500 mg), or diphenylhydantoin (100–200 mg) orally four times a day (90).

CONGENITAL MYOTONIA These patients have myotonia, but little or no weakness or wasting, so that management with the above drugs is satisfactory.

CENTRAL CORE DISEASE, NEMALINE MYOPATHY, MYOTUBULAR MYOPATHY There is no drug treatment for these diseases. Management is limited to physical therapy.

SUMMARY

Some progress has been made in understanding the pathogenesis of muscle diseases that are associated with alterations in the immune mechanism, and in treating them with corticosteroids and immunosuppressant drugs. The diseases associated with electrolyte disturbances, abnormal response to drugs, and endocrine and metabolic changes are also usually amenable to management. The challenge for the future lies in learning the pathogenesis and treatment of the muscular dystrophies.

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