C J Mieny, U Mennen: Principles of Surgical Patient Care - Volume II

Chapter 12: Endocrine Crises

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Introduction

Under the stress of injury, illness or operation, metabolic reserves are mobilized through collaboration of two reactive systems - nervous and endocrine systems - in attempting to preserve homeostasis under duress. The nervous system activates neurogenic impulses, activates autonomic nervous responses, secretes "releasing hormones" and uses peptidergic neurotransmitters to affect shifts in "fight or flight" physiology to facilitate survival. Some of these neurotransmitters that may usually function as mediators for the nervous system may actually circulate as hormones, and the endocrine system has a feedback influence on the nervous system as well.

The endocrine system is also primarily involved in adaptation to stress and effecting transfer of energy reserves for extraordinary function and repair in critical illness. Some hormones are increased in the stress of crisis, but the endocrine system does not respond with hypersecretion of all hormones; it brings about modulation of some and increased receptivity to others. Some regulatory hormones are suspended or overridden by "counterregulatory hormones" in order to shift to alternate fuels or mobilize energy to support vital functions, even if cannibalization of functional protein is the short-term result. An understanding of which hormones are usually secreted in excess and which are depressed or suspended in crisis helps in an understanding of the physiology of stress, but also in the clinical implications of support treatment to facilitate the function of failing organ systems (see chapter 3.15).

Both neural and humoral reactive responses directly influence each other and act in physiologic collaboration better understood if not separated. The "neuroendocrinology" of stress response in crisis involves feedback loops which typically control excess swings in metabolic processes to preserve against the runaway catabolism of usage of vital body components for fuels to buttress the energy deficit. When either the energy resources of the body or the neuroendocrinologic responses by which compensatory transfer among them is arranged are in deficit, exhaustion of this compensatory response is said to occur in the sequential organ system failure previously described. To protract, delay or prevent this entropic collapse, these neuroendocrine response are important survival mechanisms for stress adaptation in crisis situations. These closely regulated adoptive responses should be observed, understood and supported in the crises of injury or illness management.

Endocrine imbalances, either hormone excess or insufficiency, may of themselves constitute crises and must be managed urgently by the clinician caring for patients exhibiting these deviations from normal. Some endocrine excesses or deficiencies are more critical than others, and we will focus predominantly on those life-threatening crises that must be managed urgently, and defer those that do not constitute immediate threat to life (but may have longer-term consequences) to appropriate consultation and fuller consideration after the crisis has passed. The focus of this chapter, therefore, will be on emergency management of life-threatening endocrine crises.

Table 12.1. Hormones with generally increased secretion during stress

--> Pituirary
- ACTH
- ADH
- Growth hormone
- Prolactin

--> Adrenal
- Aldosterone
- Cortisol
    - Catecholamine

--> Renal
- Renin

--> Gut
- Glucagon

--> Neural
- Endorphins (neuropeptides).

Clinical crises result from either excess or deficiency or both of specific hormones that may cause threat to life, and must be recognized and managed particularly in the surgical patient. Not considered within this chapter are other endocrinological diagnoses that do not constitute clinical crises, such as the hyperfunctions of primary aldosteronism or Cushing's syndrome which, though interesting surgical endocrinological problems, are not comparable to the crises of deficiency in mineralocorticoid and glucocorticoid which must be recognized and managed immediately. Some, but not all, hormones are found in elevated secretion patterns and increased circulating hormonal concentrations during the stress of trauma or illness (table 12.1). These excess hormone level may come from an increased release of the hormone, an increase in secretion, or a decrease in degradation of the hormone, and the increased response may come from an increase in receptor activity, or a decrease in counterregulatory hormone action. Products of pituitary and catecholamine production are nearly immediate, and increases in adrenal corticoids lag somewhat, usually on the basis of the delay built in by the activation of their synthesis and release through peptide releasing or trophic hormones. Some hormones are little changed or are decreased during the stress of illness as seen in table 12.2. Both TSH and the thyroid homrones are little changed, although the form of thyroid hormone may change because of the catecholamine dependency of the iodinase that shifts the position of iodine on thyronine. Insulin secretion is not remarkably changed under conditions of stress even thouhg the insulin effect may differ, particularly under the changes of such illness as sepsis. Sugar metabolism may change dramatically, but changes in glucagon, growth hormone and catecholamine secretions have more to do with this change in sugar metabolism immediately than any difference in insulin secretion. Despite increases in ACTH, different layers of the adrenal cortex respond quite differently according to their receptivity to this trophic hormone, and sex steroids are not appreciably changed or actually decreased.

Table 12.2. Hormone with decreased or unaltered secretion during stress

--> TSH
    T4
    - T3
--> Insulin
--> Sex steroids
    - FSH-LH and ovarian hormones
    - FSH-LH and testicular hormones
    - Adrenal androgens.

The immediate metabolic effect of rapid endocrine change in stress is tissue wasting and weight loss as a consequence of energy mobilization to meet the challenge of survival. Acute semi-starvation is one cause of this breakdwon, but the postinjury catabolism shows a much greater loss in protein than in more expendable body fuel reserves (table 12.3).

Table 12.3. Metabolic effects of hormone changes

--> Tissue wasting and weight loss
    - Postinjury catabolism
    - Mimics semi-starvation
--> Disproportionate protein loss in
    - Sepsis
    - Shock and anoxia
    - Failure of adaptation mechanisms
    - Withholding of calories and amino acids
    - Healthy youing men rathern than elderly.

The salutory effects of these endocrine stress adaptations are an increased delivery rate of nutrients in the circulation with volume expansion and increase in utilizable cellular fuel by increasing the concentration of the energy sources and shifting aerobic mechanisms of energy utilization (table 12.4).

Table 12.4. Homeostasis effects of endocrine stress adaptation

--> Circulation
    - Salt and water conservation
    - Blood pressure maintenance
    - Delivery of substrate and oxygen
--> Fuel
    - Gluconeogenesis
    - Glycolysis
    - Lipolysis
    - Mobility of calories
--> Aerobic energy utilization
    - Heart
    - Skeletal muscle
    - CNS.

A classic clinical pattern seen in the patient following injury, illness or operation involves four generally recognized phases of response and recovery (table 12.5). As originally described by Moore, there is an acute early phase of catabolism which lasts, depending on the degree of injury, some 48 hours or more with a "crisis" marking a turning point in the second phase when nitrogen loss shows a sharp decrease. In the third phase muscular strength is gained and positive nitrogen balance is seen in the anabolism of this period followed later by positive energy and calorie balance.

Table 12.5. Phases of response to injury as described by Moore

--> First: injury and acute response catabolism
--> Second: turning point corticoid withdrawal
--> Third: muscular stranegth anabolism
--> Fourth: fat gain, nitrogen balance, but positive energy and calorie balance.

These clinical phases are seen regularly after injury or illness, particularly in elective operation for a disease that is corrected without complication ensuing. However, this normal pattern can be intercepted whether by complications such as sepsis, failure to correct the underlying surgical disease, or hormonal failure. Special conditions such as pregnancy, the growth requirements of infancy, the degenerative processes of ageing, and the enormous caloric requirement for repair and rehabilitation seen in such circumstances as burn victims or septic shock place further requirements on the neuroendocrinologic response patterns and should be considered as special circumstances of the exaggerated phases of predictable response to injury.

The further considerations in this chapter deal with abnormalities in which the endocrine response itself is the source of the clinical crisis. These endocrine syndromes may be first unmasked during or complicate the course of stress response normally seen in compensatory reaction to illness or injury.

Chapter 12.1: Thyroid

Hypothyroidism

Hypofunction of the thyroid is not uncommon as a clinical problem, but rarely as a crisis requiring urgent management. Certainly hypothyroidism in the newborn should be recognized to avoid the developmental consequences of cretinism, and relative hypothyroidism in the adult or elderly population may be an infrequently recognized source of heart failure. However, in the acutely stressed individual, TSH is not increased and thyroid hormone measurements show either no change or a decrease in circulating thyroid hormone species. Only one hormone in the thyroid shows an actual increase in circulation levels, and that is the biologically inactive "reverse T3". Protein binding and hormone degradation are both decreased, but free thyroxine measurements are unchanged or unreliably measured without clinical correlation. Hypermetabolism in some states of septic shock does not appear to be mediated by thyroid hormone and the "sick-euthyroid syndrome" appears to be a quenching mechanism for breaking the catabolism of other hormone excess states, such as catecholamines and corticosteroids. The sick-euthyroid state can be differentiated from those patients who are truly hypothyroid by a TRH test (thyrotropine-releasing hormone). TRH belongs to the neuropeptide class generally seen to

be elevated in stress. The majority of patients in intensive care units, however, are indifferently treated by thyroid supplementation or may actually be injured by it. A much more serious threat to life is the runaway catabolism of thyrotoxicosis.

Hyperthyroidism

Hyperthyroidism is a serious clinical condition which may become critical in thyrotoxicosis or very often lethal in thyroid storm. Since thyroid hormones are not generally increased in the stress of injury, an increase in circulating thyroid hormone is diagnostic of hyperthyroidism and an inappropriate response in the stressed patient. Some forms of hyperthyroidism are easily recognized because of concomitant features, such as the eye signs and infiltrative dermopathy of Graves' disease. These clinical features are not properly the result of excess thyroid hormone, but are features of increased circulating thyroid-stimulating immunoglobins (TSI).

But Graves' disease is only one form of hyperthyroidism which may also include other syndromes with excess thyroid hormone and its response absent the clinical findings of TSI unique to Graves' disease.

The thyrotoxic patient may enter a hypermetabolic state in which the body temperature rises, excessive protein catabolism occurs, high energy requirements follow with high output failure and cardiac arrhythmias may result from thyrotoxicosis sensitizing the myocardium to catecholamines. The ultimate in runaway hypermetabolism is described as "thyroid storm" distinguished by remarkable hyperpyrexia with temperatures rising so high as to inactivate important enzyem systems such as cytochromes. Leucocytosis also is part of this storm and excess metabolic demand exhausts all convertible fuel sources and rapid degradation of functional protein results. Treatment requires a decrease in metabolism and energy requirements, often by hypothermia units, which if used all by themselves would actually increase fuel and oxygen demands by causing shivering. As a consequence, hypothermia is used with paralysis and controlled mechanical ventilation set for the high oxygen requirements, also relieving the patient of the work of breathing. These ancillary supportive methods are used with employment of a vigorous antithyroid regimen that consists of at least three classes of drugs used in sequence for control of hyperthyroidism (table 12.6).

Table 12.6.

--> Decrease thyroid hormone *release:*
- Iodides (Lugol's solution)
- Lithium

--> Decrease thyroid hormone *production*
- Thiocyanates
- Perchlorates
- Thionamides (PTU)
- Methimazole (MTZ)

--> Decrease thyroid hormone *response,* by adrenergic interference
- Catecholamine depletion (reserpine, guanethidine)
- Beta-adrenergic blockade (propanolol).

The mechanism by which hyperthyroidism can be controlled include first, the decrease of thyroid hormone release. This can be done with iodides or lithium. Frequently employed is a saturated solution of "cold iodine" in Lugol's iodide. Second is use of drugs that decrease thyroid hormone production, and thionamides are the most popular agents including PTU (propylthiouracil) or MTZ (methimazole). A third drug treatment strategy is todecrease the thyroid hormone response by adrenergic blockade. The most successful use of these agents has been the liberal use of Propranolol.

These agents constitute the drug therapy of hyper-thyroidism. Urgent thyrotoxicosis may need small intravenous doses of Propranolol to block acute hyperactivity, such as during operations. Definitive management of thyrotoxicosis often eludes drug therapy alone, and some form of ablation is called for either employing radioiodine or surgical therapy. Radioiodine is slower in bringing hyperthyroidism under control and, if successful, almost invariably results in late hypothyroidism, insidious in onset. Surgical therapy not only controls hyperthyroidism immediately through subtotal thyroidectomy (albeit with surgical risks to airway, voice, and parathyroid glands), but has the advantage of restoring the patient to normal pituitary-thyroid autoregulation.

Chapter 12.2: Parathyroid

Both parathyroid hyperfunction and hypofunction are critical in their effect on calcium homeostasis, upon which nerve excitation and muscle contraction and relaxation depend. Tetany is a clinical manifestation on either end of parathyroid hormone's normal range of activity. That which is due to hypocalcaemia may affect cardiovascular function exhibited in hypotension and cardiac failure, increased intracranial pressure, hyperreflexia and hyperirritability that may give rise to muscle spasms and even seizures.

The biologic activity of circulating calcium is limited to that ionized form not bound or chelated, and that fraction depends on the serum protein concentration and also on blood pH. Hyperventilation and the respiratory alkalosis that follows, make initial symptoms of hypocalcaemia worse. Although the total level of calcium does not change, the shift from ionized calcium to the biologically inactive bound calcium occurs with a rise in pH. Low serum protein can decrease the amount of bone calcium even though the biologically active ionized form is less affected in this total serum calcium decrease.

Hypocalcaemia

If the hypocalcaemic patient has experienced a cardiovascular emergency such as cardiac arrest or electromechanical dissociation of myocardial action, or neurologic emergency such as tetany or convulsions, parenteral calcium should be administered in the form of two grams calcium chloride solution that will yield over 100 mg of calcium. For the average adult size patient, serum calcium levels should rise by 0.12 mmol/L, half of which would be protein bound. Slow infusion of this calcium solution should be monitored by cardiography or until tetanic symptoms abate.

Longer-term calcium supplementation is more safely administered by enteral route and appropriate vitamin D supplementation is selected for longer-term facilitation of gut calcium absorption.

Most hypocalcaemia in surgical patients is seen following parathyroid, thyroid or radical neck operation, and much of this is transient until the hypocalcaemia itself is a stimulus for return to function of parathyroid remnants.

Hypercalcaemia

Hypercalcaemia is an ominous finding in the biochemical screening determination done routinely, since it denotes either phosphate retention from failing kidneys, excess bone resorption such as seen with osteolytic metastatic neoplasm or excess absorption of calcium as can be seen with vitamin D intoxication. However, hypercalcaemia is often seen today in asymptomatic individuals in whom hyperparathyroidism is a reasonable consideration for differentiation.

The subject of concern for this chapter, however, is the symptomatic patient who comes to medical attention because of "parathyroid poisoning", acute parathyroid toxicosis requiring urgent treatment. Along with others forms of acute hypercalcaemia, clinical management methods should be reflexive to obtain urgen hypercalcaemia control.

Table 12.7 outlines seven steps to be employed in the urgent management of hypercalcaemic crisis. Specifically excluded from this list is the use of chelating agents such as EDTA which may reduce serum calcium, but do so with much more danger to the patient than those alternative methods employed in sequence. Saline infusion is a first step in treatment to replace some of the sodium deficit often seen with calcium diuresis. If furosemide natriuresis is added to the saline infusion, this form of parenteral therapy often can bring hypercalcaemia under early control. Neutral phosphates such as sodium brushite or binding resins prevent the absorption of calcium while calcium excretion with saline and furosemide diuresis is ongoing. Nearly one gram of calcium is lost in 24 hours which may reduce by approximately 0.24 mmol/L the elevated serum calcium level. A synthetic calcitonin modelled after salmon calcitonin may be administered in doses up to 50 units three times daily, and this treatment is often combined with corticosteroids. A cancer chemotherapy agent, mithramycin, is a highly effective agent for reducing hypercalcaemia of metastatic malignancy, but also has considerable marrow toxicity. Urgent haemodialysis against a low calcium bath or zero calcium dialysate is a further step in reducing dangerously elevated serum calcium levels.

Table 12.7. Hypercalcaemia control

--> Oral neutral phosphates
--> Saline infusions
--> Furosemide diuresis
--> Mithramycin
--> Calcitonin
--> Dialysis
--> Urgent parathyroidectomy.

Progressive steps may be taken to reduce symptomatic hypercalcaemia to levels safer for anaesthesia induction. However, on some occasions, urgent parathyroidectomy is indicated for "parathyroid poisoning".

Acute hypercalcaemia from "parathyroid poisoning" may come from either very large parathyroid adenomas or those large adenomas that have undergone infarction and haemorrhagic cystic degeneration. It may also be seen with parathyroid carcinoma. If the patient with dangerously elevated serum calcium levels has a low phosphate and elevated chloride blood level and X-ray determination of radial absorption of the distal subperiosteal phalanges can be obtained, such a patient is a candidate for urgent parathyroidectomy as an ultimate step in hypercalcaemic control and definitive management of "parathyroid poisoning".

Chapter 12.3: Adrenocortical Crisis

Excessive corticosteroid hormones may come from all three layers of the adrenal cortex with different clinical syndromes resulting from predominant hypersecretion of aldosterone, cortisol or sex steroid. The prominant feature of primary aldosteronism is hypertension which is not malignant and is relatively easily managed. The hypokalaemia of aldosteronism is rarely critical, though it does require replacement of potassium. Glucocorticoid excess in Cushing's syndrome has blood sugar and blood pressure abnormalities and metabolic disturbances which, fascinating as they are in giving clues to stress response, are not critical in the excess of cortisol, and emergency treatment for Cushing's syndrome is not generally necessary. Excesses of sex steroids are not in themselves important, but in such critical circumstances as adrenogenital syndrome the deficiency in glucocorticoid and not the excess of sex steroid is the critical component.

Adrenal Insufficiency

For the purpose of this chapter, the adrenal cortical crisis that requires urgent management is hypofunction - the specific clinical entity referred to as Addisonian crisis.

The original adrenal insufficiency described by Addison came from tuberculous ablation of the adrenal gland, and unexpected encounters today with such similar problems can often bee seen with adrenal replacement by metastatic disease such as lung cancer metastases. Some forms of sepsis may give adrenal haemorrhagic destruction (Waterhouse-Fridrichsen syndrome) or autoimmune primary adrenocortical atrophy may be the source of some primary adrenal insufficiencies. Bilateral adrenalectomy is carried out for fewer adrenal diseases, but many nonadrenal diseases such as malignant breast or prostate conditions can leave a patient without adrenal glands, which are necessary for life. However, the most prevalent adrenal insufficiency seen today is the relative hypocorticolism seen after withdrawal of exogenous corticosteroid treatment or stress encountered without an increase in steroid replacement. Exogenous administration of steroids suppresses ACTH and "adrenal exhaustion" is a natural consequence when a stressed patient has inadequate secretion from the atrophic adrenal glands.

Clinical features of acute adrenal insufficiency include nausea, vomiting, weakness, hypotension, hypothermia, and hypoglycaemia. The normal reaction to stress of illness or injury can increase secretion of corticosteroids to double or fourfold the resting state. Inability to adapt stress level steroid secretion can cause the collapse of the patient in Addisonian crisis. However, even under severe stress, the patient requires only stress level steroid treatment and not the pharmacologic doses often used for other actions quite apart from their replacement value.

Steroid Therapy

The figure illustrates a stress level steroid schedule that can be tapered to replacement therapy for the patient who has had bilateral adrenalectomy or has drug or disease induced pituitary or adrenal failure. Adrenal cortical replacement should be given as long as there is insufficient production of cortisol from the patient's own adrenal glands, which means in perpetuity for the patient with adrenalectomy. A special "stress kit" for parenteral steroid administration in the event that the patient is unable to take or retain oral steroid replacement or has developed special needs for stress levels, is appropriate. Also, the patient should carry upon his or her person some form of identification that can communicate the fact that the adrenal glands are absent or corticosteroid drugs are required in the event that the patient is unable to express during an Addisonian collapse.

Chapter 12.4: Pheochromocytoma Crisis

There is no clinically significant deficiency state of circulating catecholamines that constitutes a crisis. However, there is a devastating catecholamine excess that may originate in an adrenal or chromaffin tumor that can produce sustained or episodic catecholamine excess. Unexpected encounter with pheochromocytoma which is not recognized in circumstances of stress, such as general anaesthesia during operation for some other cause or labour and delivery is a lethal surprise, even in the improved intensive care circumstances of the later 1980s. Epinephrine and norepinephrine have inotropic and chronotropic cardiac action in potency that is well known to most clinicians who use these agents therapeutically. However, intolerable quantities of these hormones can be injected from endogenous sources, and certain anaesthetic agents sensitize the myocardium to the arrhythmic potential of catecholamine excess.

The figure illustrates the successful removal from a patient of a large pheochromocytoma first encountered in the delivery room. The crisis that attended labour was difficult to manage and the diagnosis was only made after premature delivery but then satisfactory preparation, monitoring and blockade allowed the patient to undergo major operation safely when the pheochromocytoma was known and the circulation protected from potentially lethal infusions of catecholamine concentrations.

Blockade

Once phaeochromocytoma was suspected in this patient and during the course of proving and localizing it, alpha adrenergic blockade was instituted and later beta adrenergic blockade was added. Indications for these adrenergic blockades are listed in tables 12.8 and 12.9. Alpha adrenergic blockade employing phenoxybenzamine at gradually increasing doses began with 10 mg every eight hours and worked up to a 24 hour total of 80 mg incrementally over several days with gradual volume expansion and blood volume reconstitution. For the cardiac arrhythmias beta blockade was added. If beta blockade is used first, pulmonary edema may result from the unopposed alpha stimulation of the catecholamines and beta blockade.

During operation, short-acting blood pressure control pharmacology can be used such as nitroprusside. The newer addition of labetolol also has facilitated intraoperative management of phaeochromocytoma.

Table 12.8. Alpha-blockade in pheochromocytoma

Alphalytic agents (phentolamine, phenoxybensamine)

--> Severe diastolic hypertension (> 200/130 mm Hg)
--> Frequent, severe paroxysmal attacks
--> Contracted plasma volume (hematocrit > 50%)
--> Use of betalytic agents.

Table 12.9. Beta-blockade in pheochromocytoma

Betalytic agent (propranolol)

--> Tachycardia (pulse > 140/min)
--> Arrhythmia
--> Ventricular extrasystole
--> Pure epinephrine-secreting tumor.

Localization

The methods by which the tumor is localized require careful thought, since a patient undergoing physical, pharmacological or psychologic stimulation or invasion may experience disastrous consequences. CT scanning has been thought to be non-invasive, but with the addition of contrast material and glucagon administration to dilate the viscera, a very serios pharmacologic stimulus is added. Glucagon is among the most potent of the catecholamine releasing agents known, and its addition can make a non-invasive study pharmacologically very invasive. Any patient undergoing localization studies by such a hazardous method as an arteriographic injection - now largely supplanted by better methods of resolution with far less hazard - should be monitored, pharmacologically prepared and attended. These studies are usually employed immediately preoperatively, and should never be used as random screening tests. Before the diagnosis is confirmed, the patient who undergoes localization studies can have insignificant adrenal non-disease imaged, and the connection between the patient's symptoms and the alleged morphology is not made stronger by the addition of one radiographic image after another if none prove the incidental finding is the source of the catecholamine excess.

Treatment by Resection

Surgical technique is also important in facilitating the safe resection of a phaeochromocytoma. Excess stimulation to the patient during anaesthesia induction is avoided. Abdominal massage during some form of preoperative skin preparation is also foregone. The surgical technique is described as "dissecting the patient away from the tumor". An early step in control of the potentially harmful catecholamines within the tumor is identification of venous effluent and early occlusion to protect the circulation from influx of the catecholamines during adrenal manipulation. As seen in the figure, the adrenal vein has remained intact while adrenal dissection occurred, but the first step was occlusion of this vein and isolation of the adrenal gland from circulation.

After the adrenal gland has been removed, successful use can be made of that

glucagon stimulation effect; with all blocking agents discontinued, 1 mg of glucagon may be slowly infused to see if there is any undetected excess chromaffine tissue in other sites, including the opposite adrenal gland, before closure.

Chapter 12.5: Insulin Crisis

Diabetes

Hypofunction of the beta pancreatic islets or resistance to the insulin may produce least of all the complications of diabetes. Diabetic patients may have crises, particularly when sepsis is part of the illness. There is not really a relative deficiency of insulin in stressful illness, but rather an excess of "counterregulatory hormones" that assure hyperglycaemia for abundant energy fuel to the central nervous system and skeletal muscle. Catecholamines, glucagon, and the glucocorticoids are counterregulatory hormones that all affect an increase in blood sugar. As discussed earlier, insulin is one of the hormones whose secretion is unaltered or decreased during stress, and therefore, insulin hypofunction is not generally an urgent crisis.

Hyperglycaemia in the stressed patient is a normal physiologic response to the stress adaptive excess of counterregulatory hormones, but if it persists, rehydration and insulin therapy are appropriate while monitoring blood sugar, osmolality and potassium. For the management of diabetic patients with critical illness or for the newly diagnosed glucose intolerant patient, regular insulin is the only form practically needed for crisis intervention. It is often given with sugar, frequently by continuous infusion of insulin at low dosage. The urgent requirement of the central nervous system is a supply of glucose and oxygen with the insulin that will facilitate their use. The complications of diabetes are important but not clinically urgent crises and are therefore considered no further.

Hypoglycaemia is much more dangerous than hyperglycaemia because of the dependence of the central nervous system on adequate sugar and oxygen delivery. In the stressed patient there may be deficient glucose production because of a failure of reserves of carbohydrate stores (as an example, alcoholic cirrhosis of the liver gives deficient glycogen deposition) or a deficiency of enzymes and hormones to convert from protein or lipid metabolism to glucose production (glucocorticoid deficiency, or glucagon or thyroid hormone disturbance). Failure of gluconeogenesis is one of the reasons that adrenal insufficiency constitutes a clinical crisis.

Insulinoma

A special case could be made for excess beta islet cell function as in insulinoma. In this instance hypoglycaemia may be profound, and the low blood sugar does not turn off insulin production from an autonomous source. "Insulin shock" may occur from such a beta islet cell adenoma as well as from factitious insulin shots or oral hypoglycaemic agents.

The symptoms of hypoglycaemia result from activity in two nervous systems. The central nervous system depends upon this sugar for its function, and hypoglycaemia itself is a powerful stimulus to the autonomic nervous system and catecholamine release. The catecholamine release would function as a counterregulatory hormone to the insulin, but

the surge of insulin is often manifested mainly by the catecholamine surge which follows it. In the anaesthetized patient who has lost central nervous system function, one of the few methods that hypoglycaemia can be detected is through its catecholamine response. The patient may have tachycardia, cold clammy skin, and dilated pupils, even in the absence of the central nervous system response that can be monitored.

It is necessary to infuse sugar to maintain an adequate substrate to the central nervous system in the patient who has insulin excess. Pharmacologic agents can be employed to blunt or block the insulin effect. Diazoxide therapy is sometimes useful both acutely and over the long term to control hyperinsulinaemia. A newer form of therapy which has had success in not only controlling peptide excess such as hyperinsulinaemia, but has even been suggested as an agent for a negative trophic effect on tumours, is somatostatin therapy. An analog of somatostatin is now available that can be injected and would constitute a very potent "counterregulatory hormone" while the source of the excess insulin is identified by non-invasive imaging such as CT scan, arteriographic localization or portal venous sampling, and ultimately surgical exploration with or without such techniques as operative ultrasonographic imaging. The pathologist can confirm what the blood sugar response suggests when the source of excess insulin is removed and blood sugar values return to normal.

Summary

Endocrine crises stem from exhaustion of normal responses to stress of illness or injury or from primary endocrine excess or deficiency that threatens life when no compensatory system furnishes fuel or alternate energy sources to maintain aerobic metabolism. For those crises that require urgent intervention, patterns of recognition and methods of management are suggested. The goal of physiologic stress response and therapy is to restore volume delivery of energy substrates and facilitate their utilization in efficient aerobic energy metabolism. Often this involves the appropriate excess function of "counterregulatory hormones". However, if these hormones are autonomously or excessively secreted, a primary endocrine crisis results. When autoregulation fails, "decompensation" may lead to an entropic collapse in whcih one organ system after another fails in sequence (Chapter 3.15) leading to the collapse of the organism. Recognition and intervention in these endocrine crises can restore homeostasis to the point of survival and recovery of normal unstressed physiology and reaccumulation of energy reserves.

Comment

Endocrine Crises

R J van Rooyen

Thyroid Storm

The symptomatology of a thyroid storm may involve the cardiovascular or central nervous system, or both. With the cerebrobulbar form the patient becomes agitated, confused, or sometimes even comatose, or bulbar palsy - particularly of the IXth cranial nerve - may develop. In the cardiovascular form tachycardia, auricular fibrillation, heart

failure, pulmonary oedema and shock predominate. Gastrointestinal signs with diarrhoea are often present as an isolated feature. Rarely the picture may be more subtle, with apathy, prostration and coma, but with only slight elevation of temperature. Treatment consists of two concurrent phases:

--> Supportive therapy that inlcudes glucose, saline, vitamin B complex and glucocorticoids. Patients should then be placed in a humidified oxygen tent, and if hyperpyrexic, a cooling blanket is used. In those patients with atrial fibrillation digitalization is required to control the atrial fibrillation. Pressure amines should be used if shock is present.

--> Measures to alleviate thyrotoxicosis consist of suppression of hormone synthesis by the immediate and continued administration of antithyroid agent (ie, carbimazole) orally or by nasogastric tube.

Inhibition of hormone release is sought through the administration of iodine by mouth or IV. The iodinated X-ray contrast agent, sodium ipodate, can be administered instead of iodine and has the added action of also inhibiting the peripheral conversion of T4 to T3. Administration of adrenergic antagonists are perhaps the most critical part of the therapeutic regimen in the absence of cardiac failure. If given intravenously careful electrocardiographic monitoring is mandatory. Dexamethazone is given IV at a rate of 2 mg every six hours since this inhibits hormone release, impairs peripheral generation of T3 from T4 and provides adrenal support. Infection should be looked for as the possible triggering mechanism and the appropriate antibiotic administered as is deemed necessary.

Hypercalcaemic Crisis

The choice of therapy for hypercalcaemia depends on the underlying disease, the severity of the hypercalcaemia, the serum organic phosphate level and the patient's renal, hepatic and bone marrow dysfunction. Mild hypercalcaemia (3 mmol/L) can usually be managed by hydration, sodium chloride and furosemide alone. Severe hypercalcaemia (3.75 mmol/L) requires aggressive sodium-calcium diuresis with furosemide and is only undertaken if appropriate monitoring is available and cardiac function is adequate. Mithramycin is often the drug of choice because of effectiveness and simplicity of use, although renal, hepatic and bone marrow disease may preclude its use. If diuresis or mithramycin is contraindicated, infusion of neutral phosphate is given at a slow rate in order to prevent calcium phosphate precipitation in soft tissues. Monitoring of the serum creatininium concentration is mandatory. The treatment should be used with caution because dosage is difficult and critical.

Addison Crisis

The primary treatment consists of an intravenous infusion of 5% glucose in normal saline solution, combined with a bolus intravenous infusion of 100 mg cortisol, thereafter followed by a continuous infusion of cortisol at a rate of 10 mg/hour. It is also prudent to administer 50 mg cortisone acetate intramuscularly in case the infusion becomes infiltrated or inadvertently stopped. Aggressive repletion of sodium and water usually constitutes adequate treatment for hypotension and dehydration. Vasoconstrictive agents like dopamine may be indicated only in extreme conditions as adjuncts to volume replacement.

Supplementary mineral corticoids under these conditions are usually superfluous in view of the large doses of steroids.

Hypoglycaemia

Because the prognosis of hypoglycaemic coma worsens from minute to minute, it is imperative to administer sufficient quantities of glucose for sufficient duration. Sometimes a bolus injection of 20 g of glucose is sufficient; other patients may need a primary dose of 25-50 g glucose as a 50% solution, followed by a constant glucose infusion over many hours, sometimes in combination with repeated intramuscular or intravenous injection of 1 mg glucagon. The most important therapeutic goal is to maintain a blood sugar value in excess of 8.5 mmol/L. This is possible if 5-10% glucose is administered intravenously at a rate of 1-2 mL/min. Under these conditions 100 mg soluble cortisol is also given intravenously or in the infusion every six hours. The constant infusion of glucose is persisted with until the patient is able to eat a meal. Since patients with adrenal or pituitary insufficiency do not handle water adequately, they should receive a physiological solution rather than glucose in water, which causes severe water intoxication and hyponatraemia.

Phaeochromocytoma

To abolish the physiologic and metabolic consequences of the excess catecholamine production, two entirely different mechanisms of drug action are employed: the blockade of alpha-adrenoreceptors and the inhibition of catecholamine synthesis. Both have the ultimate aim of preventing excess catecholamine effects.

Alpha-receptor blocking agents antagonize the activity of catecholamines on the alpha-adrenoreceptors causing a fall in blood pressure owing to the reduction of peripheral vascular resistance. Because of the long duration of action the therapeutic effects are cumulative, and the optimal dose must be achieved gradually with careful monitoring of supine and upright blood pressures.

Phenoxybenzamine should be administered for at least 10 to 14 days prior to surgery. The same therapeutic effect may be achieved through the inhibition of tyrosine hydroxylase, thereby reducing endogenous catecholamines, and thus suppressing the formation of DOPA. Prazosin, the selective alpha1-antagonist, has been employed in the preoperative management of a small number of patients. The relatively short duration of action may be a disadvantage compared with phenoxybenzamine. Nitroprusside is the only other hypotensive agent that reliably reduces blood pressure in patients with pheochromocytoma and may be useful on occasion.

Beta-adrenergic drugs are particularly helpful in the treatment of tachycardia and tachyarrhythmias, particularly those potentiated by anaesthetic agents. However, their use should not preclude the establishment of alpha-blockade, since administration may cause a paradoxic increase in blood pressure by antagonizing beta-mediated vasodilatation in skeletal muscle.