Today's Treatment

Drug-induced diseases

Drug-induced metabolic disease

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All drug-induced disease is metabolic; this paper is confined to drug-induced disturbances of water and electrolyte, urate, and carbohydrate metabolism. To avoid pitfalls in common conditions is its prime purpose. No attempt is made to present a comprehensive review of drug-induced metabolic disease, or to explore the mechanisms of such disease in any detail. The points touched on here are mostly common knowledge, but failure to apply this knowledge is, unfortunately, equally common.

Water and electrolyte metabolism

SALT AND WATER RETENTION

Patients with incipient heart failure or oedema from any cause are at risk from the following common drugs: anti-inflammatory drugs such as phenylbutazone and indomethacin; carbenoxolone; tricyclic antidepressants; oestrogens; and hypotensive drugs. All these promote salt and water retention. Hypotensive drugs have a non-specific homoeostatic salt and water retaining effect proportional to the fall in blood pressure and some also have additional mechanisms—for example, potent vasodilators such as diazoxide and minoxidil are intensely salt-retaining out of proportion to the fall in blood pressure; beta-adrenergic blockers predispose to oedema partly on account of a negative inotropic effect on the heart.

Excessive intravenous infusion of sodium is a commonly overlooked cause of saline overload on both medical and surgical wards, largely from failure to consider intake in relation to the variable ability to excrete salt and water during illness or after surgical operation. Problems should be few if the patient is carefully examined daily (especially for oedema); is weighed daily; and if only a few simple intravenous solutions are used so that intake can readily be calculated. Intravenous fluids must be prescribed with deliberation and care, and only one day at a time—sometimes less. It is important not to give intravenous nutrition without considering the fluid and electrolyte consequences: some amino-acid solutions, for example, contain 120-150 mmol (mEq) of sodium per litre, enough by itself for most patients and too much for those whose renal function is still under the shadow of operation.

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SALT AND WATER DEPLETION

Even with great care it is difficult to avoid sometimes making patients ill with diuretics. The usual cause is failure to reduce the dose of diuretic soon after the onset of a satisfactory diuresis; normally a diuresis is more difficult to induce than to maintain; and it is usually both possible and desirable to reduce the dose during treatment.

Diuretic treatment should always be reviewed periodically to ensure that the dose is appropriate (especially when other strongly protein-bound drugs are given that increase the plasma concentration of free diuretic by displacement) and indeed that the treatment is still necessary at all. An excessively large or rapid diuresis may profoundly reduce cardiac output, especially in the elderly, causing weakness, confusion, and deteriorating renal function.

HYPONATRAEMIA AND HYPERNATRAEMIA

The plasma sodium concentration indicates the balance between salt and water—by itself, it gives no certain information about overall saline deficiency or excess. If thirst and antidiuretic hormone (ADH) release are normal they together ensure that saline retention or loss is isotonic and that the plasma sodium concentration therefore is in the normal range. Drug-induced hyponatraemia has two causes: replacement of salt loss (commonly diuretic-induced) with water; and an ADH-like action of drugs (such as chlorpropamide and carbamazepine). Further complexity occurs in serious disease because of the associated inappropriate secretion of ADH. The implicated drug must be stopped and water restricted (sometimes to as little as 500 ml daily at first); in emergency, slow intravenous infusion of up to 250 ml of five-times physiological saline (4·5 g/l) is indicated but it carries a risk of acute heart failure in predisposed patients; it is neither necessary nor wise to attempt rapidly to correct the plasma sodium fully to normal.

Hypernatraemia almost invariably indicates water depletion, combined sometimes with excessive sodium intake as, for example, when unconscious patients are tube-fed with hypertonic solutions containing a large amount of both sodium and protein. More salt is supplied than water, and urea derived from the protein induces an osmotic urea diuresis, adding an absolute water deficiency to the previous relative deficiency; hypertonic feeds also cause diarrhoea with further loss of water. Similar risks, without the diarrhoea, exist with intravenous feeding: rapid hypertonic glucose infusion may exceed glucose tolerance causing glycosuria with osmotic diuresis; amino-acids are converted to urea causing urea diuresis; and many solutions add sodium to the insult of osmotic water loss. Over-diuresis of patients unable to respond to thirst because of impaired consciousness is another iatrogenic cause of hypernatraemia.

HYPOKALAEMIA AND HYPERKALAEMIA

Drug-induced hypokalaemia is usually attributable to diuretics, adrenal corticosteroids, or carbenoxolone (which has a mineralocorticoid-like action on the distal tubule). Small potassium supplements do not reliably prevent hypokalaemia in patients taking thiazides or loop diuretics nor are they routinely necessary, but the elderly and patients taking digoxin should receive a supplement sufficient to maintain a normal plasma potassium concentration. The blood concentration must be checked at least once at about three months because requirements vary considerably and no standard dose (whether in a combined tablet of diuretic and potassium or not) can be relied on to be sufficient. Hypokalaemia is best prevented in patients with chronic heart failure or hypoproteinaemic oedema who are taking thiazides or loop diuretics by simultaneous treatment with spironolactone, which competitively inhibits secondary hyperaldosteronism. Most other patients taking thiazides (the most appropriate diuretics for treating hypertension) do not need a routine potassium supplement; measuring the plasma potassium concentration at about three months will normally pick out those who do.

Hyperkalaemia is usually the consequence of giving potassium with a diuretic to a patient with poor renal function; giving a potassium supplement together with a distal tubular diuretic; or giving a distal tubular diuretic to a patient with renal failure. As a general rule neither distal tubular diuretics nor potassium supplements should be given to patients with renal failure. Combined diuretic and potassium tablets increase the risk that potassium will unthinkingly be prescribed for patients with poor renal function. Today's good renal function may be tomorrow's renal failure, and the appropriateness of a potassium supplement or the use of a distal tubular diuretic may change with time and intercurrent illness.

HYPERCALCAEMIA AND HYPOCALCAEMIA

Excessive dosage of vitamin D (or newer analogues) or of soluble calcium salts used as antacids (fortunately rarely used in Britain but common abroad) are the only likely causes of iatrogenic hypercalcaemia. The plasma calcium concentration must be watched at intervals of a month or two for as long as pharmacological doses of vitamin D are given—and the indications for such treatment are few. A very large dose of vitamin D may be necessary in post-thyroidectomy hypoparathyroidism, for example, but the initially effective dose will almost invariably eventually cause hypercalcaemia (with nephrocalcinosis and renal failure) if not reduced at the right moment.

Osteomalacia sometimes develops in association with prolonged anticonvulsant treatment, especially in the elderly. Induction of increased hepatic hydroxylation of vitamin D is largely responsible, but the intestinal effects of vitamin D on calcium absorption may also be impaired. The symptoms are insidious and may be most disabling—weakness, bone pain, and pathological fractures—and they respond well to treatment with vitamin D; the symptoms must, however, be correctly diagnosed to be cured.

Urate metabolism

Diuretics increase plasma urate: thiazides by interfering with tubular secretion of urate, and all by reducing plasma volume. Plasma urate concentration should be measured before giving diuretics; it will be high in patients with chronic renal failure and in a few hypertensive patients. Gout is the obvious risk and is surprisingly rare in association with the hyperuricaemia of chronic renal failure, probably because rapid changes in concentration are more important than the absolute concentration itself; gouty interstitial nephritis is a less obvious danger, whose incidence is uncertain.

Acute attacks of gout may also be precipitated by allopurinol and other drugs that rapidly lower the plasma urate concentration. Cytotoxic drugs are apt to release sufficient nucleoprotein to produce a dramatic and dangerous rise in the plasma urate concentration (acute renal failure being the major hazard) and for that reason allopurinol is given as a prelude to chemotherapy.

Carbohydrate metabolism

Drugs cause diabetes mellitus either, like thiazides, by interfering with release of insulin or, like adrenal corticosteroids, by opposing the actions of insulin. (Other mechanisms, such as the cytotoxic effects of the alkylating agent streptotozine on the pancreas, are outside the scope of this article.) Symptomatic hyperglycaemia may take years to develop, depending on initial glucose tolerance and perhaps age, or may appear within weeks as with diazoxide. So insidious may be the onset of symptoms and so chronic the treatment that has eventually caused them that diagnosis may be long delayed, and the cause of the maturity-onset diabetes may even escape detection altogether. Many oral contraceptives impair glucose tolerance but it has yet to be shown that the impairment is of practical consequence.

Although it is perhaps obvious that overdose of drugs designed to control metabolic disease—that is, antithyroid drugs or thyroxine—will produce the opposite disease, the danger of overactivity of long-acting hypoglycaemic agents, such as chlorpropamide, must be emphasised, especially in elderly patients and in those taking beta-adrenergic drugs, which impair the hepatic mobilisation of glucose in response to hypoglycaemia. Hypoglycaemic coma caused by chlorpropamide may be rare, but confusion and dementia are probably more prevalent than is realised. Long-acting insulins are likewise best avoided in the elderly.

Lactic acidosis, the result of lactate production exceeding its utilisation, is usually a byproduct of serious acute disease but it can be caused by intravenous fructose, sorbitol, and ethanol, and by drugs such as phenformin and metformin, especially in patients with renal, respiratory, or cardiac failure. These compounds should be avoided in such patients and used with caution in others.

Conclusion

Drug-induced metabolic disease is usually predictable and arises not out of ignorance but from failure to assess correctly the risks of a changing picture of disease, age, diet, or interactions with other treatment. Each move on the chessboard of treatment carries consequences that must be foreseen to be avoided.

WORDS CARBUNCLE, ANTHRAX, and BOILS. The cardinal signs of inflammation according to Celsus (AD 30) are calor, rubor, tumor, dolor—heat, redness, swelling, and pain. CARBUNCLE, manifests the heat; L *carbunculus*, a small glowing coal, diminutive of L *carbo*, coal, burning, or burnt wood; whence also the element CARBON. ANTHRAX by a similar analogy is Greek for coal; whence also ANTHRACOSIS, an accumulation of coal-dust in the lungs. More pitfalls for foreigners! In French it is the reverse. *Le charbon* means coal or anthrax, while *l'anthrax* means boils. BOIL, on the other hand, does not denote the *calor* of inflammation but the *tumor* or swelling in the sense of ebullition—that is, bubbling from the application of heat, cf BULLA, a bubble. While we are on the subject of acute purulent skin lesions, FURUNCLE and FURUNCULOSIS also denote swelling, from the alleged similarity to a disease of vines in which there are knobs on the plant which "steal the sap." L *furunculus* is a petty thief, diminutive of *fur*, a thief.