Leading Article

Drug and non-thyroid induced changes in thyroid function tests

Ian Ramsay

Department of Endocrinology, North Middlesex Hospital, London N18 1QX, UK.

The basis of good medicine is a careful history and a thorough examination, supplemented by a minimum of tests to confirm the diagnosis. There is, however, an increasing tendency to perform screening tests just in case (Bahemuka & Hodkinson, 1975; Hodkinson & Denham, 1977). Screening tests for thyroid disease are particularly fraught with difficulty, since there are at least 11 different tests available, each of them capable of being carried out by several different techniques and the results of each of them can be subject to alteration in one direction or another by non-thyroidal disease or by drug therapy, as illustrated by an article in this issue (Wilkins et al., 1985).

Thyroxine (T₄) is the main hormone secreted by the thyroid gland. Once in the circulation most of it is bound to thyroxine-binding globulin (TBG), a lesser amount of thyroxine-binding pre-albumin (TBPA) and albumin and a small fraction (0.05%) remains in the free form. Peripherally 25% of the T₄ is mono-deiodinated to form the more active hormone triiodothyronine (T₃), though a small amount of T₃ is also secreted directly by the thyroid gland. T₃, like T₄, is bound to the above mentioned proteins, though less so than T₄. The main effects of non-thyroid illness and of drugs are on the binding proteins, the degree of binding and on the conversion of T₄ to T₃. Changes in any of these may alter thyroid function tests and lead to misleading diagnoses of either hyper- or hypothyroidism.

The most commonly seen abnormality in clinical practice is the rise in total T₄ and T₃ in women who are pregnant or who are on oral contraceptives; this is caused by an oestrogen-dependent rise in TBG and thus in total hormone bound to it. A measurement of the free thyroxine index (FT₄,I) or of free thyroxine (fT₄) measured by equilibrium dialysis will be normal in euthyroid patients on oral contraceptives, but it should be noted that in pregnant patients, particularly in the third trimester, the FT₄,I may be slightly elevated (Ramsay, 1984) and the fT₄ and fT₃ may be below the normal non-pregnant range (Ramsay, 1984). Drugs other than oestrogens which may cause rises in T₄ and T₃ due to increased binding include clofibrate, 5-fluorouracil, heroin and methadone (Wenzel, 1981). A small number of patients may have an increased amount of TBG due to porphyria (Kaplan, 1984) or as an inherited familial disorder (Jones & Seal, 1967).

Reduced amounts of T₄ and T₃ in the blood may be due to a low level of TBG. This may be either familial or due to diseases such as Cushing's syndrome, acromegaly and nephrotic syndrome (Kaplan, 1984). A drug-induced reduction in the binding proteins may also occur; the drugs responsible are androgens, anabolic steroids and danazol (Graham & Gambrell, 1980; Wenzel, 1981), but the commonest cause is a drug-induced inhibition of binding, most often due to fenclofenac (Ratcliffe et al., 1980), though this drug has now been withdrawn from the UK market. Other drugs which can produce the same phenomenon are diazepam, heparin, phenylbutazone, salicylates, sulphonylureas (Wenzel, 1981), halofenate and o-p' DDD (Kaplan, 1984).

Another mechanism by which levels of T₄ and T₃ may be reduced by drugs is by enzyme induction in the liver. The drugs involved are those used in the treatment of epilepsy and include carbamazepine, phenobarbitone, phenytoin and primidone (Larsen et al., 1970; Heyma et al., 1977; Wenzel, 1981).

Both iodide and lithium inhibit the release of thyroid hormones from the thyroid and may lead to low levels of T₄ and actual clinical hypothyroidism, particularly in those who are genetically susceptible to thyroid autoimmune disease (Braverman et al., 1971; Spaulding et al., 1977). Amiodarone, which contains large amounts of iodine, can do the same thing or conversely may cause an iodide-induced thyrotoxicosis in a patient who is predisposed to Graves' disease or who has an autonomously functioning multinodular goitre (McKenna et al., 1983). Other effects of amiodarone are discussed below. Sodium nitroprusside and co-trimoxazole have a slight thyroid inhibiting effect and may cause lowered T₄ levels (Wenzel, 1981). Somatostatin has a similar effect.
though via inhibition of TSH release by the pituitary (Wenzel, 1981).

Although T₄ levels are sometimes reduced in euthyroid hospital in-patients (Gooch et al., 1982), because of low levels of binding proteins, it is more common to find increased T₄ in this population (Mankikar and Clark, 1981; Gooch et al., 1982). The cause is either a high TBG which is familial or due to pregnancy, oestrogens, chronic active hepatitis (Schussler et al., 1978), primary biliary cirrhosis (Schussler et al., 1978) and acute intermittent porphyria or to collagen disease and myeloma (Kaplan, 1984).

In many acutely or chronically ill euthyroid patients a slight rise in T₄ is due to inhibition of the peripheral conversion of T₃ to T₄. There are reduced T₃ levels (Bermudez et al., 1975; Gooch et al., 1982) and an increase in the inactive hormone reverse T₃ (rT₃). These changes are seen in febrile states, renal failure, anorexia nervosa, cirrhosis, disseminated malignancy and following surgery (Cavaliere & Rapoport, 1977). However, it is important to note that T₃ levels are normally lower in old age than in the young (Cavaliere & Rapoport, 1977). Similar slight rises in T₄ with reduction in T₃ and an increase in rT₃ may be found with amiodarone (Burger et al., 1976), sodium iopodate for oral cholecystography (Bürgi et al., 1976; Wu et al., 1978; Beng et al., 1980), propranolol and certain other β-adrenergic receptor blockers (Kristensen & Weeke, 1977; Cooper et al., 1982; Perrild et al., 1983), high dose glucocorticoids, iobenzamide and tyropanoic acid (Wenzel, 1981). Propylthiouracil (Geffner et al., 1975) and iodide will tend to reduce the T₄ also because of a direct inhibiting effect on the thyroid gland.

How then is one to sort out whether a patient with an abnormal T₄ or T₃ has or has not got thyroid disease? Direct measurement of fT₄ or fT₃ by radioimmunoassay after equilibrium dialysis will be normal in most circumstances but note that fT₄ can be elevated by sodium iopanate (Bürgi et al., 1976), propranolol (Kristensen & Weeke, 1977; Cooper et al., 1982; Wilkinson et al., 1985 this issue) and acetylsalicylic acid (Langer et al., 1978) and decreased by phenytoin (Larsen et al., 1970), phenylbutazone (Abiodun et al., 1973) and fenofenac (Humphrey et al., 1980). Likewise the fT₃ can be reduced by sodium iopanate (Beng et al., 1980), amiodarone (Burger et al., 1976), propranolol (Wilkins et al., 1985), in pregnancy (Ramsay, 1984), fever, renal failure, following surgery, cirrhosis and disseminated malignancy (Cavaliere & Rapoport, 1977).

In most cases where hypothyroidism is suspected because of low thyroid hormone results, but the patient is really euthyroid, the basal thyroid stimulating hormone (TSH) levels will be within the normal range. Borderline high TSH results can be sorted out by means of the thyrotrophin releasing hormone (TRH) test (Hall et al., 1973) when an exaggerated response will suggest hypothyroidism, particularly if thyroid antibodies are also present. The TRH testing is also useful in the converse situation, that of suspected hyperthyroidism. A flat response of TSH to TRH (Hall et al., 1973) is compatible with the diagnosis. There is only situation in which one might get a drug-induced flat response is if a patient is on high dose (e.g. 8 mg per day) dexamethasone (Cavaliere & Rapoport, 1978). Even here the response in a euthyroid patient is not completely flat (Wenzel, 1981) and a normal response can be achieved by increasing the dose of TRH (Otsuki et al., 1973).

References


