Discussion

These findings show that in patients with hypopituitarism both CSF and plasma β -MSH concentrations are maintained within the normal range, the CSF:plasma ratio remaining normal at about 3:1. Gonadotrophin and growth hormone secretion decline early in hypopituitarism; ACTH secretion declines later on⁴ and would be expected to be well below normal in our patients with severe hypopituitarism.⁵ Thus there seems to be a dissociation between the secretion of β -MSH and the secretion ACTH in hypopituitarism.

The source of the β -MSH is unlikely to have been the pituitary because some of the patients had severe panhypopituitarism while others had had a surgical hypophysectomy. Residual pituitary tissue would in any case be an unlikely explanation of the findings because there seems to be no direct route for pituitary hormones into CSF other than through the blood. Thus the CSF concentration of most pituitary hormones increases above their plasma concentration only when there is suprasellar extension of a pituitary tumour,² and preliminary studies (unpublished) have shown that even when plasma β -MSH concentrations are grossly raised the CSF concentration remains normal. Thus it is unlikely that CSF β -MSH concentrations are maintained by pituitary secretion into the blood.

An attractive explanation of our findings is that β -MSH is produced by and secreted from nervous tissue. To test this we have looked for and found considerable amounts of immunoreactive β -MSH in various regions of the brain; we also found comparable amounts of biologically active MSH,⁶ which suggests that the immunoreactive β -MSH found was not due to non-specific activity. It therefore seems likely that the high concentrations of β -MSH in CSF arise from direct secretion by neural tissue and it will be interesting to see whether high concentrations of other neuropeptides⁷ are also found in the CSF. Further studies are required to confirm that the brain can indeed maintain normal plasma β -MSH levels after complete surgical hypophysectomy because this suggests that the turnover of brain β -MSH is much faster than in the normal

pituitary, since total brain β -MSH is only about 5% of that of the pituitary.⁶

The chemical nature of immunoreactive β -MSH in CSF is unknown, but it is believed that in the pituitary and plasma β -MSH occurs only as part of the larger lipotrophin (LPH) molecule⁸ which cross-reacts in our assay.⁹ The C terminus (61-91) of β -LPH has been shown to have a high affinity for brain opiate receptors and thus an important physiological role in the nervous system^{10 11}; in addition, the portion of the molecule common to the MSHs (51-58) also influences central nervous activity.¹²⁻¹⁶ Our study suggests that MSH peptides are produced by the central nervous system as well as acting on it.

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SIDE EFFECTS OF DRUGS

Proximal myopathy after perhexiline maleate treatment

Perhexiline maleate (Pexid) has proved effective in treating angina pectoris, and adverse reactions to the drug have been minor.^{1 2} We report here a case of proximal myopathy that occurred after perhexiline treatment.

Case report

A 67-year-old woman presented in October 1976 with an 18-month history of ischaemic chest pain provoked by exertion. Two weeks before presentation the pain had become more frequent and more prolonged and associated with shortness of breath. There were no other relevant features or medical history. Physical and electrocardiographic examination showed nothing abnormal. Angina pectoris was diagnosed, and treatment with perhexiline maleate 200 mg twice daily was started.

Two weeks after starting treatment the patient developed unsteadiness and weakness in her legs. After three weeks' treatment she developed an itching, burning, generalised rash, so the drug was stopped. On admission to hospital 10 days later she had a fading generalised scarlatiniform rash with erythema and desquamation, particularly of the palms and back but also of the buccal mucosa, scalp, and body. The muscles of both shoulders and hips were very weak, and she could not rise unaided from a squatting position. There was no muscle wasting; cranial nerves, tendon reflexes, and sensation were normal; and plantar reflexes were flexor. No other abnormality was found. It was considered that her skin lesions and proximal myopathy were due to perhexiline.

Further investigations included a full blood count; urine analysis; chest radiograph; electrocardiogram; and blood urea, blood sugar, and electrolyte estimation—all of which were normal. Serum calcium, serum creatinine phosphokinase, liver function, plasma cortisol, and serum thyroxine were also normal. The erythrocyte sedimentation rate was 37 mm in the first hour. Antinuclear factor was positive to a titre of 1/64, but LE cells were absent.

Nerve conduction velocity was normal at 48 m/s (lateral popliteal nerve). Electromyography of quadriceps femoris showed no insertional activity and no fasciculation at rest. Maximal contraction produced a moderately full interference pattern of low amplitude motor potentials of high frequency, which was compatible with a diagnosis of myopathy.

The rash settled within three weeks of stopping the perhexiline and the myopathy resolved within two months.

Comment

Perhexiline maleate is an effective treatment for angina pectoris, but unwanted side effects are common though not usually serious.^{1 2} Adverse reactions occur mainly within the first month of treatment and are readily reversed by stopping the drug.² Abnormalities of liver function tests and peripheral neuropathy tend to occur later in the course of treatment but are still reversible.^{3 4}

Proximal myopathy is a well-recognised feature of several endocrine and metabolic disorders and occurs as a side effect of many drugs. In our patient there can be no doubt of the diagnosis, since she had both the clinical and electromyographic features of proximal myopathy. Because she had no evidence of any metabolic or endocrine disorder and had taken no drug other than perhexiline, it seems probable that perhexiline was the cause of her myopathy.

In drawing attention to this uncommon side effect of perhexiline

we suggest that patients on this drug should be carefully assessed regularly so that lesser degrees of muscle weakness are not overlooked.

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Severe thrombophlebitis with Praxilene

Intravenous or intra-arterial naftidrofuryl oxalate (Praxilene) infusions are used in patients with vascular insufficiency for rest pain and pre-gangrene or trophic ulceration. For intravenous use it is recommended that 200 mg (25 ml) of naftidrofuryl should be infused over one and a half to two hours diluted with 200 ml of dextrose, dextrose-saline, or low-molecular-weight dextran. In our early experience with this regimen we found that patients rapidly developed severe thrombophlebitis in the infused veins. This led us to perform a prospective survey of patients who had naftidrofuryl infusions. In most cases the thrombophlebitis necessitated one or more changes of drip site so that 13 infusions in seven patients were ultimately available for analysis.

Patients, methods, and results

Seven consecutive patients who were given naftidrofuryl infusions were studied. In each case the indication was severe lower limb ischaemia with rest pain in an elderly patient (five men and two women). A standard dose of the drug was given twice daily (200 mg in about 200 ml of dextrose or saline). The infusion site was inspected after each dose by one of us: the area of any erythema or thrombosis was measured and the patient asked about pain. The investigator did not influence the treatment or selection of drip sites, and in some cases the infusion was continued after the first signs of inflammation had appeared (see table).

Ten cases of thrombophlebitis occurred in 13 infusions (see table). The affliction was far more severe and developed far more rapidly than infusion thrombophlebitis seen with dextrose 5% or saline alone. All but one patient (case 7) had at least one episode. The two women were less severely affected, though the numbers were too small to show a significant difference. In six cases the first sign occurred after only one dose of the drug—that is, after about two hours of infusion. Fortunately the condition resolved after the

cannula was removed. The pain was severe in some cases and was relieved with kaolin poultice and mild oral analgesics. The inflammation settled over about 48 hours but all patients were left with the "cord" of thrombosed vein. No cases of suppurative thrombophlebitis occurred.

Comment

Mild thrombophlebitis is a common complication of intravenous infusions: the reported incidence is between 12% and 39%, but it may approach 100% if the infusions are continued for long enough. In the cases reported here the thrombophlebitis began after only short periods of infusion and was particularly severe. We believe that this is an effect of naftidrofuryl.

The aetiology of thrombophlebitis is multifactorial. The low pH of naftidrofuryl (2.75) and the diluting fluid may be relevant. Commercial dextrose 5%, for example, has a pH around 4.2, but if the pH is raised to a physiological level the incidence of thrombophlebitis is dramatically reduced.¹ Naftidrofuryl 200 mg in 200 ml of dextrose-saline has a pH of 3.4.

With naftidrofuryl, however, the inflammation began very early (often during the first two hours), and this is not a characteristic of infusions with dextrose or saline alone. It has long been recognised that the thrombophlebitis rate increases with the duration of the infusion, but Elfring, in a large series, recorded a very low complication rate in infusions lasting less than two hours, and the few cases of thrombophlebitis were mild.²

Some patient factors predispose to infusion thrombophlebitis, but these were not found consistently in our cases: they include severe illness,³ middle age,^{1,2} the female sex,² adjacent infection,³ and burns.⁴ Our patients were in an advanced stage of peripheral vascular disease but were otherwise well. Their advanced age might have been protective.¹ Immune deficiency states have been associated with this condition,⁴ but, although the immune status of our patients was not investigated, we have no reason to suppose that any abnormality existed.

The frequency and severity of the reactions that we observed were probably due to some factor in naftidrofuryl other than the pH. Several studies have shown the damaging effects of drugs added to infusions and different factors are entailed with each drug.⁵ To clarify the effects of naftidrofuryl we are undertaking animal studies. In the meantime it would seem wise when infusing naftidrofuryl to change the drip site often, if possible after each dose. It is not yet clear whether naftidrofuryl has any effect on the central veins, and infusion into these should be undertaken with caution.

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Local thrombophlebitis after administering naftidrofuryl 200 mg by infusion over one and a half to two hours

Case No	Sex	Cannula (gauge and type)	Diluent	Drip site*	Pain	Area of erythema (mm)	Length of thrombosis (mm)	No of doses given	No of doses before first sign	Severity†
1	M	18, Medicut Butterfly	5% Dextrose	R forearm	++	300 × 40	300	3	1	S+
			Dextrose	L forearm	+++	175 × 60	175	3	1	S+
2	M	18, Medicut	Saline	L hand	++	170 × 50	170	2	1	S+
3	M	18, Medicut	5% Dextrose	R forearm	++	140 × 50	140	2	1	S+
4	F	18, Medicut	Isotonic saline	L forearm	+	Minimal	115	8	8	S
			Dextrose-saline	R forearm	+	130 × 30	130	6	2	S
5	M	18, Medicut	Isotonic saline	L forearm	+	85 × 40	140	5	1	S
				R forearm	+	210 × 50	100	4	2	S
6	M	18, Medicut	5% Dextrose	LACF	++		220	2	2	S+
				RACF	++	210 × 50	210	4	1	S+
7	F	18, Medicut	Dextrose-saline	L hand	—	Minimal		2	2	O

*L(R)ACF = Left (right) antecubital fossa.

†S+ = Very severe. S = Severe. O = None.