SHORT REPORTS

Increase in serum cholesterol during phenytoin treatment

Long-term treatment with phenytoin is often accompanied by various metabolic and endocrine abnormalities. Particular attention has been paid to effects on pancreatic β-cells, where it inhibits the release of insulin and suppresses the response of plasma insulin to various stimuli.[1] Phenytoin also influences thyroid function, reducing serum levels of thyroid hormones and increasing thyroid-stimulating hormone.[2]

Since serum lipid levels are increased in both insulin deficiency and thyroid hypofunction a prospective study of serum lipids, glucose tolerance, and insulin response in patients on phenytoin has been carried out.

Patients, methods, and results

Eleven formerly untreated patients with epilepsy aged 15-58 years were studied before the institution of phenytoin treatment and 3, 6, 9, and 12 months afterwards. Their weights ranged from 89% to 116% of normal, and their serum cholesterol and triglyceride levels ranged from 4·7 to 9·4 mmol/l (181 to 363 mg/100 ml) and 0·43 to 2·0 mmol/l (38 to 177 mg/100 ml), respectively. No patient had clinical or latent diabetes. The dose of phenytoin varied from 300 to 450 mg/day. At each examination body weight, fasting serum cholesterol and triglyceride levels, blood glucose, plasma insulin, and serum levels of phenytoin were measured, and a standard 50-g oral glucose tolerance test was performed.

Two patients were lost from the study after three months. In the nine who completed the 12-month schedule the serum phenytoin levels ranged from 10 to 63 μmol/l (2·5 to 15·9 μg/ml). The patients maintained stable body weights throughout the study, the greatest individual change being an increase of 2 kg. The serum cholesterol levels increased by 6 to 48% (mean 19%; $P<0·05$) in 9 of the 11 patients during the first three months on phenytoin, the higher level being maintained up to the end of the 12-month period. No consistent change was found in the fasting serum triglyceride levels during treatment (table). Phenytoin caused no significant changes in oral glucose tolerance but there was a clear trend of a diminishing response of plasma insulin to oral glucose during phenytoin administration (table).

Serum Cholesterol and Triglyceride Levels, Oral Glucose Tolerance, and Plasma IRI Response to Oral Glucose in Nine Epileptic Patients before and during Treatment with Phenytoin. Figures are Means ± S.E. of Means*

	Before Phenytoin	After being on phenytoin for:		
		3 Months	6 Months	9-12 Months
Serum cholesterol (mmol/l) ..	5·5 ± 0·6	6·5 ± 0·8	6·4 ± 0·7	6·8 ± 0·9
Serum triglyceride (mmol/l) ..	0·93 ± 0·2	1·01 ± 0·2	1·33 ± 0·3	0·95 ± 0·2
Sum of baseline glucose value plus values ½ an hour and 1, 2, and 3 hours after oral glucose loading (mmol/l)	23·5 ± 1·2	22·2 ± 1·5	23·2 ± 0·8	23·2 ± 1·2
Sum of IRI values ½ an hour and 1, 2, and 3 hours after oral glucose loading (mU/l) ..	163 ± 50	107 ± 13	118 ± 22	97 ± 12

*IRI = Immunoreactive insulin.
Conversion: SI to Traditional Units
Cholesterol: 1 mmol/l ≈ 38·5 mg/100 ml.
Triglyceride: 1 mmol/l ≈ 88·5 mg/100 ml.
Glucose: 1 mmol/l ≈ 18·0 mg/100 ml.

Discussion

The mechanism by which phenytoin increases the serum cholesterol level is obscure but the known pharmacological effects of the drug offer at least two possible explanations. Phenytoin decreases the level of circulating thyroid hormones including free thyroxine and triiodothyronine,[2] and the increase in serum cholesterol could be due to subclinical hypothyroidism. Another explanation is based on the phenobarbitone-like effect of phenytoin on hepatic microsomal enzymes. Phenobarbitone stimulates the hepatic synthesis of cholesterol[3] and increases the formation and pool size of bile acids,[4] which in turn may increase the intestinal absorption of cholesterol by facilitating micelle formation.

An increase in serum cholesterol may be regarded as an untoward effect of long-term phenytoin treatment because it increases the risk of coronary heart disease. We therefore suggest that serum cholesterol should be regularly checked in patients undergoing such treatment.

The lack of deterioration in glucose tolerance may have been due to the relatively small doses of phenytoin used. The mean plasma insulin response to oral glucose also remained unchanged during treatment, though a clear tendency of a diminishing insulin secretion occurred, particularly in patients with high pretreatment levels. This observation agreed with the experience of Stambaugh and Tucker.[5]

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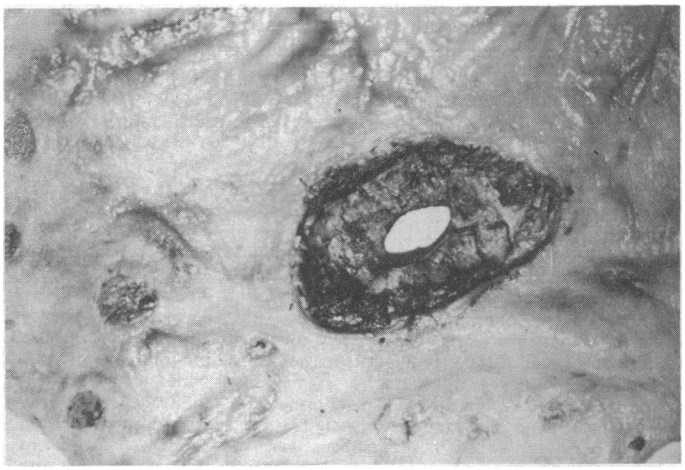
Enteric-coated aspirin overdose and gastric perforation

Enteric-coated aspirin is claimed not to irritate gastric mucosa. We report a case of fatal gastric perforation due to Safapryn. Safapryn consists of a sugar-coated tablet containing 250 mg of paracetamol outside an enteric-coated core of 300 mg of aspirin. The enteric coat is cellulose acetate phthallate, which disintegrates when the pH rises to 6·8.



Mucosa of greater curvature of stomach showing perforation and erosions at sites of contact with enteric-coated aspirin cores.