Short report

The effect of diphenylhydantoin on metabolic and growth hormone changes during and after exercise

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SUMMARY Metabolic and human growth hormone responses to exercise were investigated in six normal healthy subjects on two occasions with and without an oral dose of diphenylhydantoin (500 mg). Serum diphenylhydantoin concentrations were similar in all subjects and were just below the accepted therapeutic range for epileptic patients. There was no significant difference in blood lactate, pyruvate or glucose concentrations with diphenylhydantoin. Plasma free fatty acids, and blood glycerol and total ketone concentrations were greater after exercise following diphenylhydantoin. Significantly greater concentrations of human growth hormone occurred during exercise with diphenylhydantoin. Further investigation of the mechanisms by which diphenylhydantoin alters lipolysis and human growth hormone release would be of value as these metabolic and hormonal effects could influence exercise tolerance in athletics and other pursuits.

Diphenylhydantoin is known to impair insulin release in response to glucose loading^{1,2} and there is evidence that it inhibits insulin release from isolated pancreas³. Such hormonal effects may have important implications for treatment with diphenylhydantoin and it was therefore decided to investigate the effect of the drug on carbohydrate and fat metabolism in response to exercise. In addition, the effect of diphenylhydantoin on the release of growth hormone was also examined.

Methods

Subjects and procedure

Six normal healthy subjects aged 22-40 years (mean 29) were investigated on two separate occasions. The subjects were asked to fast overnight before each investigation. On the first occasion the subjects received diphenylhydantoin (500 mg) by mouth overnight and the following morning exercised on a bicycle ergometer at 100 watts for 30 minutes. On the second occasion the same subjects per-

formed an identical exercise test at least seven days later but received no medication.

Blood samples were taken from a cannula in an antecubital vein before, at 10 minute intervals during exercise and at 5, 15, 30, 60, 90 and 120 minutes after exercise. Blood samples were analysed for lactate and pyruvate,⁴ acetoacetate and 3-hydroxybutyrate,⁵ glucose⁶ and glycerol.⁷ Plasma samples were analysed for free fatty acids,⁸ growth hormone,⁹ and resting serum samples for diphenylhydantoin.¹⁰ The significance of differences were examined using the Mann-Whitney non-parametric U test for small samples.¹¹

Results

SERUM DIPHENYLHYDANTOIN

Serum concentrations of diphenylhydantoin were similar (mean 30.7 $\mu\text{mol/l}$; range 23.2-44.4 $\mu\text{mol/l}$) and were just below the accepted therapeutic range (40-80 $\mu\text{mol/l}$) for epileptic patients.¹²

BLOOD LACTATE AND PYRUVATE

Basal blood lactate and pyruvate concentrations were similar on both occasions. During exercise, blood lactate reached maximum levels after 10 minutes of 3.4 $\mu\text{mol/ml}$ and 3.1 $\mu\text{mol/ml}$ (mean concentrations with and without diphenylhydantoin

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respectively). Blood lactate concentrations returned to normal resting levels 60 minutes after the end of exercise. The changes in pyruvate concentrations are similar. There was no significant difference between concentrations of lactate or pyruvate at any time during the investigation on the two occasions.

PLASMA FREE FATTY ACIDS (fig 1)

Basal plasma free fatty acids concentrations were not significantly different on the two occasions. There was a rise in free fatty acids concentrations towards the end of exercise on the two occasions and the mean concentrations after diphenylhydantoin were higher than the corresponding control values after exercise and were significantly greater 15 minutes after exercise ($p < 0.05$).

Fig 1 Plasma FFA, blood glycerol and total blood ketone (acetoacetate + 3-hydroxybutyrate) concentrations ($\mu\text{mol/ml}$, mean $\pm$ SEM) during and after exercise in six normal subjects with (●—●) and without (○---○) administration of DPH (500 mg).

BLOOD GLYCEROL (fig 1)

Basal blood glycerol concentrations were similar on both occasions. Exercise was associated with a rise in blood glycerol concentrations and the glycerol concentrations after diphenylhydantoin were significantly greater than the corresponding control values at 5, 15, 30 and 60 minutes after exercise ($p < 0.01$, 0.01, 0.05 and 0.05 respectively).

TOTAL BLOOD KETONES (fig 1)

Basal concentrations of total ketones (acetoacetate + 3-hydroxybutyrate) were similar on both occasions. After exercise ketone concentrations rose on both occasions and the concentrations after diphenylhydantoin were significantly greater than the corresponding control values at 15, 30, 60, 90 and 120 minutes after exercise ($p < 0.05$, 0.01, 0.001, and 0.001 respectively).

BLOOD GLUCOSE

Exercise was associated with a similar small fall in glucose concentrations on both occasions but after exercise levels returned quickly towards basal concentrations. There was no significant difference in blood glucose concentrations on the two occasions at any time during the investigation.

PLASMA GROWTH HORMONE (fig 2)

There was no significant difference in basal growth hormone concentrations on the two occasions. Exercise produced a marked rise in human growth hormone concentrations reaching a peak at the end of exercise on both occasions. Growth hormone

Fig 2 Plasma human growth hormone concentrations (mU/l, mean $\pm$ SEM) during and after exercise in six normal subjects with (●—●) and without (○---○) administration of DPH (500 mg).

concentration during exercise with diphenylhydantoin were significantly greater than the corresponding control concentrations at 10, 20 and 30 minutes ($p < 0.05$, 0.001 and 0.01 respectively).

Discussion

The present observations demonstrate that a single dose of diphenylhydantoin administered to normal subjects alters metabolic and human growth hormone responses to exercise. The subjects had serum diphenylhydantoin levels just below the accepted therapeutic range but it should be noted that diphenylhydantoin was administered on the evening preceding the investigation and that the metabolic and hormonal effects relate to falling diphenylhydantoin concentrations. Administration of diphenylhydantoin for fourteen days in normal subjects has been reported to reduce the insulin response to oral glucose² whereas other investigators did not find evidence of altered carbohydrate tolerance or insulin levels in patients receiving long term treatment with non-toxic levels of diphenylhydantoin.¹³ The effects of acute and chronic administration of diphenylhydantoin may vary and further studies will be required to establish if there is any evidence of similar changes in metabolic and hormonal responses in patients receiving long term treatment.

The metabolic effects associated with diphenylhydantoin in the present investigation consisted of a greater rise in free fatty acids and blood glycerol after exercise and this suggests that diphenylhydantoin produces greater lipolysis after exercise. The development of marked post exercise ketosis was also noted following diphenylhydantoin treatment. The factors responsible for the increased lipolysis associated with diphenylhydantoin treatment are unknown.

Moderate exercise has been shown to cause a rise in plasma cortisol as exercise continues,¹⁴ and diphenylhydantoin stimulates hydroxycorticoid excretion.¹⁵⁻¹⁷ Cortisol inhibits free fatty acids reesterification and potentiates fatty acid release by adrenaline.¹⁸ Plasma catecholamine concentrations are reported to increase with exercise¹⁹ and catecholamines promote lipolysis.²⁰ It is not known if changes in circulating levels of cortisol or catecholamines after exercise were important factors leading to increased lipolysis after diphenylhydantoin treatment in the present study and this requires further investigation.

Ketone concentrations did not alter greatly during exercise on both occasions suggesting that ketone production and utilisation were closely matched during exercise. Treatment with diphenylhydantoin was

associated with a marked rise in ketones after exercise. The greater rise in ketone concentrations is probably related to the greater lipolysis after exercise combined with a decreased aerobic oxidation through the citric acid cycle. This effect may have been produced by a reduced rate of reesterification of free fatty acids after exercise. Insulin levels are known to fall during exercise and to rise immediately after exercise, paralleling changes in adrenergic activity.²¹ A failure of release of insulin after exercise in the subjects treated with diphenylhydantoin would be consistent with the known effects of diphenylhydantoin in inhibiting insulin release¹⁻³ and such an effect could delay reesterification of free fatty acids as insulin is known to limit fat mobilisation.²²

The present observations indicate that diphenylhydantoin produces a greater human growth hormone response to exercise. Growth hormone is known to have lipolytic properties^{23,24} but the absence of an increase in human growth hormone during exercise in patients with hypopituitarism did not prevent fat mobilisation during exercise.²⁵ It therefore seems unlikely that the greater elevation of human growth hormone produced the greater level of lipolysis after exercise in the present investigation. Hypoglycaemia²⁶ and a fall in free fatty acids²⁷ have been reported to stimulate human growth hormone release. These metabolic changes are unlikely to have been important stimuli in the present study as blood glucose concentrations were similar on both occasions during and after exercise and free fatty acids concentrations increased in a similar manner during exercise on both occasions. Further studies of the mechanisms by which diphenylhydantoin alters lipolysis and human growth hormone release are indicated as the increased susceptibility to ketosis after the ingestion of diphenylhydantoin could influence exercise tolerance in athletics and other pursuits.

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