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ABSORPTION OF ENTERIC AND NON-ENTERIC COATED PREDNISOLONE TABLETS

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1 Relative rates of absorption of enteric and non-enteric preparations of prednisolone were measured in five renal transplant recipients.

2 The absorption of the enteric coated preparation is delayed and the peak plasma concentration is much lower than that attained using the same dose of the uncoated material.

3 The therapeutic implications of these observations are discussed.

Introduction

The immunosuppressive drug protocol following renal transplantation usually contains corticosteroids, often in the form of prednisone or prednisolone (Hulme, 1972). Many such patients receive the steroid in daily divided doses, although the value of alternative day prednisolone therapy for such patients has been reported by Reed, Lucas & Cohn (1970). It is well known that continued steroid therapy in children produces retardation of growth (Van Metre, Niermann & Rosen, 1960) and this constitutes a major complication for children who have received a renal transplant (Hulme, Kenyon, Owen, Snell, Mowbray, Porter, Starkie, Muras & Peart, 1972). The introduction of alternate day steroid therapy (Soyka, 1972) produces less growth suppression and causes less suppression of pituitary-adrenal function (Carter & James, 1972). To achieve this, it is essential to avoid long-acting corticosteroids and it is probably desirable to administer the drug as a single dose early on the day of treatment. In this hospital, the renal transplant recipients receive enteric coated prednisolone (Pletka, Cohen, Hulme, Kenyon, Owen, Thompson, Snell, Mowbray, Porter, Leigh & Peart, 1969) following the report by West (1959) that patients receiving this preparation had major relief of gastric symptoms while the therapeutic effect was unchanged.

A review of the literature revealed no data on the pharmacokinetics of the gastro-intestinal absorption of prednisolone in the enteric coated preparation, and so we have undertaken an investigation of the absorption of the enteric and non-enteric forms of prednisolone in five renal transplant recipients.

Methods

Studies were undertaken on five renal transplant recipients who had received a graft 1-3 years previously; the clinical details of the patients are given in the Table 1. All patients were receiving azathioprine (3 mg/kg body weight) daily and enteric coated prednisolone (5 mg) three times

Table 1 Clinical details of patients under study

Patient	Sex	Age (years)	Weight (kg)	Time after transplantation (months)	Renal function: Serum creatinine (mg/ml)	Renal function: Creatinine clearance (ml/min)
E	F	15	41	30	0.9	80
H	M	15	36	7	1.0	50
K	F	24	50	18	1.2	40
P	F	20	74	18	0.9	70
R	M	36	70	26	1.6	50

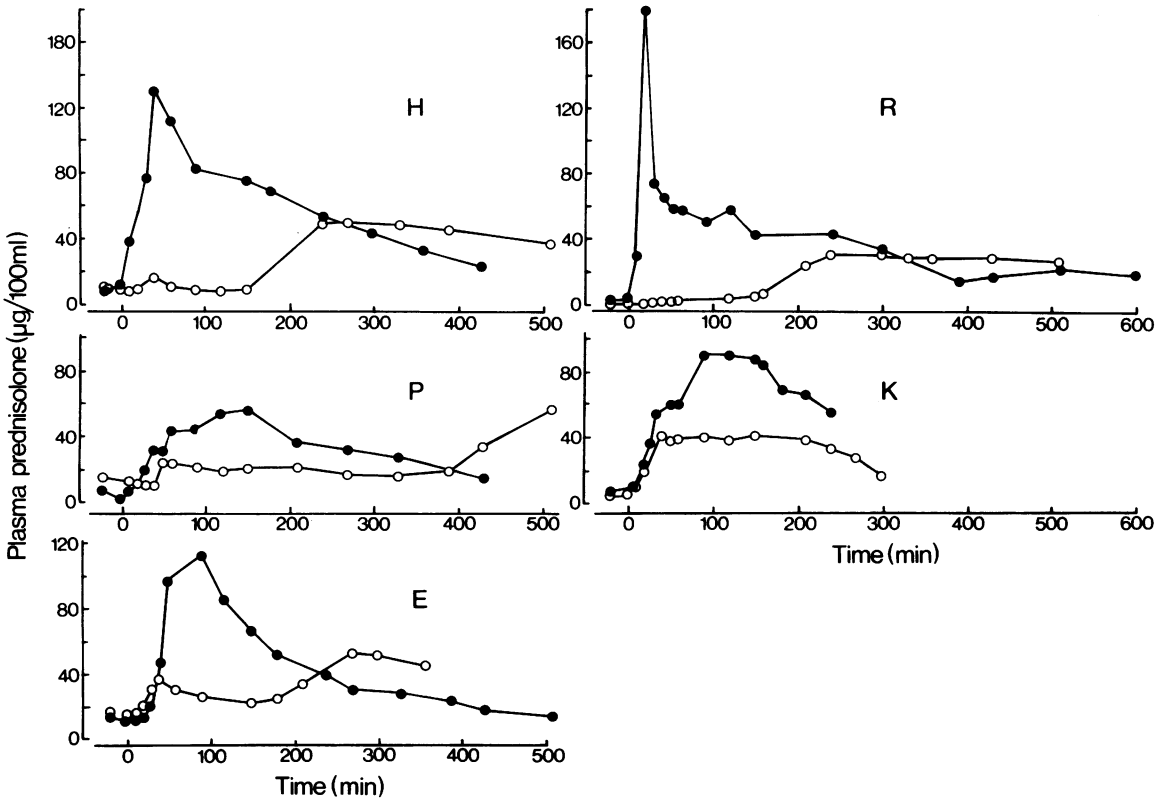

Figure 1 Plasma prednisolone levels in five patients receiving an oral dose of enteric (○) and non-enteric coated (●) prednisolone tablets (30 mg) on two separate occasions.

daily. One patient had undergone sub-total gastrectomy previously, but otherwise all the subjects had apparently normal gastro-intestinal function. On the morning of the test, the patients had fasted for 12 h and after an initial venous blood sample, were given a single oral dose of non-enteric coated prednisolone (30 mg); serial venous blood samples were obtained at 10 min intervals for 60 min and subsequently every 30 min for a total of 8-10 hours. The patients were allowed food and drink 2 h after ingestion of the tablets. The test was repeated 8 days later using enteric coated prednisolone (30 mg). In one patient the test was also repeated with non-enteric coated tablets to check the reproducibility of the test; virtually identical results were obtained.

Plasma prednisolone was measured by a competitive protein binding method using pregnancy plasma as a source of binding protein and [H^3]-corticosterone as tracer. This is essentially the technique described by Murphy (1967) for the measurement of plasma cortisol, but takes advantage of the fact that prednisolone also competes effectively for the binding protein. Provided plasma cortisol is completely suppressed, the method can be used directly to measure plasma prednisolone. Patients receiving daily continuous steroid therapy as in the patients under study have plasma cortisol levels which are sufficiently low so as not to interfere with the method. In other subjects supression of plasma cortisol is readily achieved by administration of dexamethasone (2 mg) on the night prior to the test. For all patients the plasma cortisol was monitored throughout the study using a fluorometric technique (Townsend & James, 1968) and prednisolone does not interfere with this method. In none of the five patients studied did the plasma cortisol alter through the test from the low basal level.

Results

The results of the five studies are shown in Figure 1. Although each patients received the same dosage of prednisolone under the same conditions, there was a surprisingly wide pattern of response. With the non-enteric coated tablets, the plasma prednisolone levels had risen by 40 min after ingestion in all subjects and the peak plasma concentrations was attained at 30-160 min; the peak level varied between 50 and 180 μg%. At 8-10 h, when sampling was discontinued, plasma prednisolone levels were approaching zero but were still slightly elevated.

In contrast, the pattern seen was entirely different when the same five subjects were given the same dose of the enteric coated tablets. In most subjects the plasma levels were very low for the first 3 h after ingestion and the peak concentration attained was considerably lower; furthermore, the peak was delayed several hours compared with the non-coated tablet and a significant plasma concentration was still present up to 10 h after ingestion.

Discussion

Although prednisolone is a very widely used steroid preparation, there appears to be very little information available on the plasma concentrations attained following oral administration. The limited study reported here, together with other unpublished data has shown how variable the absorption pattern may be from one subject to another. The site of prednisolone absorption is probably in the upper jejunum and the rapid absorption observed in one patient (R in Figure 1) who had a peak of prednisolone level of 180 μg% only 30 min after ingestion may be explicable by the fact that this subject had had a subtotal gastrectomy several years prior to transplantation. The variable time to achieve peak plasma levels in the other subjects is probably related to variable gastric emptying times and the different disintegration times for the tablets. The variable peak plasma concentrations from subject to subject is probably related to differences in body weight as no attempt was made to administer the same dosage on a body weight protocol.

The addition of an enteric coating to the prednisolone tablet appears to prolong the absorption time of the prednisolone, presumably due to delayed disintegration of the tablets. In the patient (R) who had previously undergone a subtotal gastrectomy, no prednisolone was detected in the plasma until 3.5 h after ingestion and this may be due to rapid transit through the stomach remnant with little or no gastric acid secretion. However, a similar delay was seen in another patient (H) who had no known abnormality of gastrointestinal function. The enteric coated preparation produced a sustained plasma concentration, extending at least for 10 h after ingestion. Such a preparation is theoretically unsuitable for the single dosage alternate early morning drug protocol as it may not allow a return of the normal responsiveness of the hypothalamic-pituitary-adrenal axis. Nevertheless, it must be admitted that we do not know for certain if a brief increase of plasma corticosteroid levels is more or less advantageous for this purpose than a prolonged increase which reaches a lower maximum level.

At the end of the period of study, plasma prednisolone levels had not returned to zero and so it is impossible to make accurate comparisons of the bioavailability of the drug using the two preparations. It appears though, that the bioavailability from the non-enteric coated tablet was greater and so this preparation might be more effective therapeutically than the same dose given in an enteric coated form. More extensive clinical and biochemical studies are needed to establish this.

It is not possible to draw any straightforward conclusions from the findings with regard to the therapeutic effects of the two preparations, since the pattern of plasma steroid levels for optimum clinical effectiveness remains to be established. Nevertheless, the markedly higher plasma levels produced by the non-enteric coated tablet is likely to produce different effects to those due to the same dosage of enteric coated prednisolone.

An attempt was made to transfer three children (patients E, H and a 14 year-old male subject) from daily to alternate day prednisolone therapy as all had shown complete suppression of growth since renal transplantation. The non-enteric preparation was used. All children showed a growth spurt within 3 months of the change of therapy, suggesting less suppression of pituitary function. Four adult patients were transferred to alternate day therapy on account of very severe side effects. Of these, one patient had diabetes, requiring hypoglycaemic drugs (patient K), two had severe hypertension (patient P, and one other adult male subject), and one had recurrent infections (patient R). In all four there was a marked reduction or improvement of their symptoms.

The advantage of alternate day therapy using non-enteric coated prednisolone would appear to outweigh the possible risk of an increased incidence of gastro-intestinal problems. Whether daily enteric coated prednisolone is more or less

effective immuno-suppressive therapy for renal cadaveric transplant recipients remains to be established.

Our results do not answer the question of the optimum therapeutic pattern of plasma steroid levels, but they reveal the considerable variation which exists between patients and between preparations and the need for an awareness of this variation in comparing different therapeutic regimes.

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