anticonvulsants and barbiturates is uncertain. Possibly a skeleton damaged by pretransplant uraemia is unusually susceptible to changes in vitamin D metabolism, and changes in liver function produced by immunosuppressive drugs may play a part.

In non-uraemic epileptic patients treated with phenobarbitone and phenytoin there is an increased turnover of 25-hydroxy-cholecalciferol with the production of more polar, biologically inactive metabolites that are excreted in the bile at an accelerated rate.^{13 14} This is attributed to drug-induced enhancement of hepatic microsomal enzyme activity.¹³⁻¹⁵ A similar increased turnover of vitamin D occurs in uraemia.¹⁶ This may well result from an increase in hepatic microsomal activity, which has been found in uraemic patients.¹⁷ Wake and Maddocks¹⁷ have also shown that in uraemic patients hepatic enzymes may be further induced by phenobarbitone by mouth, so that it would not be surprising if anticonvulsants accentuated this abnormality of vitamin D metabolism. In 1974 we suggested a possible aetiological role for enzyme-inducing drugs in the osteomalacia of transplanted patients.⁷ This form of osteomalacia is to some extent resistant to vitamin D. In three of the cases reported here large doses of calciferol (50 000 units daily) were required to effect recovery.

Awareness of the risk of osteomalacia when enzyme-inducing drugs such as phenytoin and phenobarbitone are given in uraemia and after renal transplantation should lead to more cautious use of these drugs and their earlier withdrawal. When their continued use is essential in patients who have had transplants prophylactic treatment with large vitamin D supplements is probably advisable. We have not succeeded in healing osteomalacia in patients on regular dialysis taking enzyme-inducing drugs with calciferol and dihydrotachysterol, and their condition is also relatively resistant to 1- α -hydroxycholecalciferol.

Consequently sedatives and other drugs known to induce hepatic enzymes should be avoided so far as possible during regular haemodialysis.

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Plasma prednisolone levels after administration of prednisolone-21-phosphate as a retention enema in colitis

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Summary

A competitive protein-binding assay was used to measure plasma prednisolone levels after administration of prednisolone-21-phosphate retention enemas to seven patients with colitis. Prednisolone appeared in the plasma of all patients after the enema, and concentrations rose to a peak within three hours. In five of the patients plasma prednisolone levels were also measured after the same dose of prednisolone by mouth. Although in individual patients the plasma levels achieved by enema

were often quite different from those achieved by mouth, overall the levels achieved by each mode of administration were of a similar order. These findings suggest that 20 mg prednisolone given by retention enema may well exert a systemic effect.

Introduction

Prednisolone-21-phosphate administered as a retention enema is valuable in treating colitis¹ but there is doubt about how much prednisolone is absorbed from such enemas. Since it has hitherto been impossible to measure small quantities of prednisolone in blood samples observations on the absorption of prednisolone from the rectum have been indirect. Recent advances in the measurement of prednisolone by competitive protein binding² and by radioimmunoassay³ have allowed nanogram quantities of the steroid to be measured directly in plasma. We describe here the use of a competitive protein-binding method to measure the amount of prednisolone absorbed from the rectum. We compared the levels observed after an oral dose of prednisolone with those after an equivalent dose given by retention enema in the same patient.

Patients and methods

Prednisolone was measured in 2-ml plasma samples using a competitive protein-binding assay² modified as described by Wilson

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*et al.*⁴ Plasma samples were extracted after addition of 6,7 (*n*)-³H-prednisolone (2 nCi). Prednisolone and cortisol were separated by thin-layer chromatography on silica gel plates and the prednisolone was located using a radiochromatograph spark chamber (Birchover Instruments, Letchworth, Herts). The recovery of the prednisolone from the plasma samples after chromatography was calculated from the loss of ³H-prednisolone marker. The purified prednisolone was then measured by the competitive protein binding method of Pegg and Keane⁵ by equilibration with ³H-prednisolone bound to transcortin. The unbound steroid was then adsorbed on to dextran T₇₀-coated charcoal, the samples centrifuged, and the ³H in the supernatant phase measured by liquid scintillation counting. A standard curve of % total bound ³H prednisolone was constructed and the prednisolone concentration of the sample read off.

Seven patients, six with ulcerative colitis and one with Crohn's disease affecting the rectosigmoid, were studied. Each patient gave his informed consent to the study. Patients received no prednisolone other than the experimental doses during the study and 12 hours before. The extent of the colitis was assessed radiologically and the severity of the mucosal inflammation was judged by sigmoidoscopy.^{6,7} The distance travelled by a therapeutic enema of 100 ml was assessed radiologically before or after the study.⁷

On one day blood samples were taken at intervals during the eight hours after administration of 20 mg prednisolone (as prednisolone-21-phosphate) in tap water (100 ml) as a retention enema. On another day blood samples were taken over the same period after oral administration of 20 mg of prednisolone in one dose to the fasting subjects. The time of blood sampling after the administration of the prednisolone was noted, and the plasma was immediately separated and stored at -30°C until assayed.

Results

Table I shows the clinical details of the patients, and the results after oral and rectal administration are shown in table II. No prednisolone was detected in blood samples taken immediately before administration of the enema or tablets. After administration of the retention enema prednisolone appeared in the blood in all patients and the plasma prednisolone level rose to a peak within three hours. In cases 4 and 7

Plasma prednisolone concentrations in four patients after oral and rectal administration of 20 mg.

Conversion: SI to traditional units—Prednisolone:

TABLE I—Clinical details of patients in plasma prednisolone study

Case No	Age and sex	Extent of disease	Distance travelled by enema	Sigmoidoscopic appearances	Time enema retained (hours)
1	56 M	Proctosigmoiditis	Splenic flexure	Normal	>6
2	34 F	Proctosigmoiditis	Mid-sigmoid	Moderately active	3
3	71 F	Substantial*	Mid-transverse	Inactive	>3
4	68 M	Proctosigmoiditis	Mid-sigmoid	Active	1.6
5	27 M	Extensive†	?	Inactive	>2.5
6	77 F	Proctosigmoiditis	Sigmoid	Moderately active	>3
7	61 M	Left-sided‡	Splenic flexure	Active	0.6

*Substantial = Distal to hepatic flexure.

†Extensive = Involving colon proximal to hepatic flexure.

‡Left-sided = Distal to splenic flexure.

TABLE II—Plasma prednisolone levels after administration of 20 mg orally and rectally in seven patients

Case No	Mode of administration	Plasma prednisolone levels (nmol/l) hours after administration*										
		0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	7.0	8.0
1	Rectal		178	186	250	264	203	175	225	72	28	0
	Oral	452	932	971	843	547	755	807	591	447	438	380
2	Rectal		269	241	322	289	366	336	241	244	208	158
	Oral		363	657	696		594	716	682	632	530	
3	Rectal	461	302	341	469	447	394	302	216	144	0	0
	Oral	555	391	377	322	252	230	166	155	122	111	
4	Rectal	233	191	361	203	158	119	105	86			
	Oral	730	1207			1151	932	1135	816	882	599	571
5	Rectal	427	560	860	810	638	613	538	383	272	166	
	Oral	275	239	228	219	252	186	258	136	83	83	
6	Rectal			39		333	130	19	11	89		83
	Oral											
7	Rectal	344	275	0	42		0	0	0	0	0	
	Oral											

*Prednisolone was estimated at slightly different times in each patient, but all results have been grouped under intervals corrected to the nearest half hour.

Conversion: SI to traditional units—Prednisolone: 1 nmol/l ≈ 0.36 ng/ml.

the enema was retained for only 0.6 and 1.6 hours respectively and the peak tended to occur earlier and the levels fell after evacuation. Concentrations in the remaining patients varied widely and there was no obvious correlation with the activity of the disease or the distance travelled by the enema. The comparisons between the plasma prednisolone levels after oral and rectal administration for the four patients who retained the enema (see fig) show that in two patients the levels were higher after oral administration, in one the levels were higher after the enema, and in one they were similar.

Discussion

The method used for measuring prednisolone is time consuming but has the advantage of measuring prednisolone specifically in the presence of cortisol or other steroids. It can measure levels above 56 nmol/l (20 ng/ml), and when reproducibility is checked there is a variation in duplicate samples of less than 10%.⁴ The plasma prednisolone levels observed after an enema were much the same as those observed after an equivalent dose of prednisolone taken by mouth, both in these patients and in 26 others without gastrointestinal disease studied after an oral dose.⁸ The individual levels observed in any patient may vary considerably, however: in two of our patients the levels after enema were less than those after oral administration; in one the levels were greater than after oral administration; and in one the levels were similar.

There has been some controversy about the absorption of prednisolone from retention enemas. At least two studies have shown evidence of some adrenal suppression^{9,10} but another showed none.¹¹ Wood *et al.*¹² measured urinary prednisolone

metabolites and suggested that 0.1-4% of the dose was excreted but they were unable to distinguish between prednisolone and its metabolites. Investigation⁹⁻¹³ of the excretion of ¹⁴C-labelled prednisolone or prednisone administered per rectum showed that much of the radioactivity appeared⁹⁻¹³ in the urine.

There has been no published comparison of the therapeutic efficacy in colitis of prednisolone administered in equal doses by mouth and by enema. A controlled therapeutic trial¹⁴ showed only that 40 mg of prednisolone given per rectum was more effective in acute colitis than 20 mg given by mouth.¹⁴

Prednisolone probably does exert a local effect because patients are seen in whom an enema of inadequate volume successfully treats the distal colon, but proximal inflammation persists.⁷ Our results suggest that prednisolone in a dose of 20 mg by retention enema may also exert a systemic effect.

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Do placebos alter sleep?

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Summary

Deliberate suggestion that an inert capsule was a sleeping pill was found not to influence subjective ratings of sleep quality or anxiety or the electrophysiologically recorded features of sleep in 10 volunteers aged 41-62 years.

Introduction

Efforts are being made to persuade doctors to prescribe fewer sleeping pills. It is often asked whether an inert substitute might be effective through suggestion alone. Kales *et al*¹ compared the effect of placebo with that of no treatment in eight young men with complaints about their sleep and found no difference in objective measurements—delay to falling asleep, duration of sleep, or distribution of sleep stages—or in subjective ratings of sleep. Hartmann *et al*,²⁻³ in two studies, also found no clear effects. Their proposed relationship between placebo administration and an increased amount of rapid-eye-movement (REM) sleep may have been an artefact of unbalanced design.

We here report the results of a further study in which 10 volunteers were given a placebo disguised as a sleeping pill.

Patients and methods

The 10 volunteers, six women and four men, were aged 41-62 (mean 57) years. This age and sex distribution is representative of patients who most often complain of inadequate sleep. They were asked to keep to a regular daily routine and to take no drugs or alcohol.

The volunteers were given the following written statement: "You will be given a mild sleeping pill; it will help to make your sleep more restful without causing any hangover." An inert pink pill was given 30 minutes before lights-out on half of the recorded nights. The volunteers attended the laboratory in pairs, only one of them receiving the pill on any one night. The experiment was divided into two periods of two weeks separated by 21 weeks. During each period the volunteers attended for electrophysiological recording on eight nights, the first two serving for adaptation. Thus each person received the pill on six nights and nothing on another six nights, the order being balanced.

The electroencephalogram (EEG), eye movements, and submental muscle tone were recorded from 22.30 until 07.15. The recordings were categorised⁴ by a scorer who was unaware of the experimental condition, and the sleep and wakefulness data then analysed for their mean accumulation in minutes after one hour, two hours, and so on up to seven hours of sleep.

Each evening the volunteers rated their average anxiety for the day, and each morning rated their sleep, using 10 cm visual analogue scales. The scales ranged from "terrible agitation" to "imperturbable tranquillity," and from "the worst" to "the best night imaginable." Correlated *t* tests were used to compare the 60 placebo nights and 60

FIG 1—Mean cumulative minutes of wakefulness during night's sleep of 10 volunteers on pill nights and no-treatment nights (*t* = 0.90; DF = 9; NS).

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