PREDNISONE-INDUCED INCREASE OF PROTEINURIA IN PATIENTS WITH A NEPHROTIC SYNDROME

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Summary

Administration of prednisone to patients with nephrotic syndromes of different aetiologies caused an abrupt increase of proteinuria. The proteinuric effect started four hours after oral or intravenous administration and reached its maximum effect after eight to sixteen hours. In nine patients with epimembranous glomerulopathy mean proteinuria on non-prednisone (NP) days was 43.7 per cent lower than on prednisone (P) days. Variations were significantly greater at higher creatinine clearances. However, in individual patients there were neither differences in creatinine excretion nor in creatinine clearance between P and NP days.

Introduction

In some types of nephrotic syndrome glucocorticosteroids can induce a complete or partial remission. However, it has also been reported that these drugs can cause a marked increase in proteinuria [1]. We found that in most patients with a nephrotic syndrome treated with prednisone on alternate days, proteinuria was greater on prednisone (P) days than on non-prednisone (NP) days. We have studied this phenomenon systematically in nine patients with epimembranous glomerulopathy.

Patients and methods

A group of nine patients between 15 and 65 years with epimembranous glomerulopathy was treated with 125 or 150mg prednisone orally on alternate days while on a fixed salt intake of 20mmol/day. Urine was collected in 24 hour periods and creatinine, protein content and volume were determined. Serum creatinine and albumin were measured serially. Observation periods ranged from 10 to 22 days. Percentual decreases of proteinuria on NP days were calculated.
per mmol of creatinine as follows:

$$100 - \left( \frac{\text{proteinuria NP}}{\text{proteinuria P}} \times \frac{\text{creatinine excretion P}}{\text{creatinine excretion NP}} \times 100 \right)$$

To study the time course of the proteinuria after drug administration urine was collected in four hour periods in one patient.

**Results**

The proteinuric effect of prednisone started four hours after its oral administration, reached a maximum after eight to sixteen hours, and had disappeared after 20 hours (Figure 1). After intravenous administration the time course was exactly the same. On NP days, changes in proteinuria were only slight, minimal values being reached during the night. Figure 1 also shows that the effect was not accompanied by an increased creatinine excretion. Serum creatinine values remained unchanged.

![Figure 1. Protein and creatinine excretions in four hour urine collections on P days (hatched bars) and NP days (open bars) in one of the patients](image)

Table I shows the effect on 24 hour protein and creatinine excretion rates in all nine patients. The mean percent decrease of proteinuria on NP days was 43.6 per cent with a wide range between individual patients (0–78.4%). Changes
TABLE I. Effect of prednisone on urinary protein and creatinine excretion rates in nine patients

| Age (yr) | GFR (ml/min) | Proteinuria¹ (g/24 hr) | Urine creatinine (mmol/24 hr) | No. of paired observations | Decrease of proteinuria on NP-days² (%)
|----------|--------------|------------------------|-----------------------------|--------------------------|--------------------------
| 62       | 35           | 14.4                   | 12.4                        | 13.7                     | 11.8                     | 7                        | 0                        |
| 41       | 46           | 9.6                    | 8.5                         | 8.6                      | 9.4                      | 8                        | 19                       |
| 45       | 73           | 9.2                    | 8.6                         | 11.9                     | 14.0                     | 10                       | 20.6                     |
| 28       | 102          | 14.5                   | 5.9                         | 15.6                     | 15.9                     | 7                        | 60.1                     |
| 46       | 123          | 9.3                    | 2.3                         | 11.0                     | 12.6                     | 5                        | 78.5                     |
| 65       | 133          | 10.7                   | 4.0                         | 13.5                     | 14.6                     | 6                        | 65.4                     |
| 33       | 140          | 14.3                   | 7.1                         | 13.0                     | 13.2                     | 5                        | 51.1                     |
| 38       | 148          | 10.4                   | 7.8                         | 22.5                     | 21.1                     | 8                        | 20.0                     |
| 15       | 233          | 6.7                    | 1.5                         | 16.4                     | 17.0                     | 11                       | 78.4                     |

¹ Mean values
² P = prednisone (125 or 150mg)
³ NP = no prednisone
⁴ See methods for calculations

in proteinuria were greater at higher creatinine clearances (r=0.73, p<0.05). However, in the individual patients we found no differences in creatinine excretion rates nor in creatinine clearances between P and NP days.

Increases in proteinuria were also seen at lower prednisone dosages. In one patient a slight but definite proteinuric effect was still present after administration of 7.5mg. Figure 2 depicts the observation in a patient with minimal change glomerulopathy who showed the proteinuric effect while reaching a remission.

Discussion

The results show that prednisone can induce a substantial and abrupt increase of proteinuria in patients with nephrotic syndrome. The occurrence of this effect was independent of the cause of the nephrotic syndrome and was more pronounced at higher creatinine clearances. This suggests a relationship with renal function. Glucocorticoids are known to increase glomerular filtration rate (GFR) in man, dogs and rats by an increase in renal blood flow (RBF) [2]. We could not demonstrate changes in GFR in individual patients as measured by creatinine excretion rates or clearances, even when we looked more closely during four hour collecting periods. More accurate measurements of GFR and RBF will, however, be necessary before definite conclusions can be drawn. Although there is a rapid increase in GFR after intravenous injection of dexamethasone in the rat, this is accompanied initially by only a slight increase in albuminuria. Only 14 to 32 hours later increased albuminuria appears at a time when GFR has already returned to normal [3]. This suggests that factors other than a rise in GFR are responsible for the proteinuric effect. Reduction of tubular reabsorption of protein by glucocorticoids has to be excluded. In the
Figure 2. Prednisone-induced increase of proteinuria in a patient during induction of a remission of his nephrotic syndrome

rat, this factor seems unimportant since a rise in lysozyme excretion rate ran parallel to the rise in GFR and had disappeared at the time of maximal albuminuria [3].

Thus, the cause of the proteinuric effect remains unexplained for the time being. It is of practical importance to be familiar with this paradoxical phenomenon: an initial increase of proteinuria during prednisone treatment does not necessarily point to resistance to treatment as is illustrated by our observation in a patient with minimal change glomerulopathy.

References
3 Zager R. Renal Physiol 1981; Basel 4: 37

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