Published in final edited form as:

Proc Soc Exp Biol Med. 1972 December ; 141(3): 887–889.

Acute Alteration of Plasma Renin Activity by Large Doses of Intravenous Prednisolone (36894)¹

Fred H. Katz, Mordecai M. Popovtzer, Wulf F. Pinggera, Charles G. Halgrimson, and Thomas E. Starzl

Departments of Medicine and Surgery, University of Colorado Medical Center and Veterans Administration Hospital, Denver, Colorado 80220

Large doses of intravenous glucocorticoids given over one to two hours have been utilized for some time now to supplement chronic immunosuppressive drug programs in order to effectively reverse acute or chronic rejection of organ homografts (1-5). Since the renin-angiotensin system has been implicated in chronic and acute renal homograft rejection (6), we have investigated the effects of these rapid infusions of glucosteroids on plasma renin activity (PRA).

Materials and Methods

Fifteen patients and 5 normal subjects were investigated. The patients (7) were receiving oral maintenance doses of prednisone, 20 to 170 mg per day, as listed in our previous publication (7), and azathioprine. All patients and normal individuals were kept supine beginning 1 hr before the study. Each was given 1 g of prednisolone intravenously in 50 to 100 ml of 0.9% saline over one hour. Blood was drawn into sodium-EDTA containing tubes which were kept in ice until they were centri-fuged at 4° and the plasma frozen. Samples were obtained immediately preceding and immediately after the prednisolone infusion in all subjects and in some at the midpoint. PRA was measured by a radioimmunoassay method (8). The normal range for this assay in the supine position is 0.20–3.62 ng angiotensin I/ml/hr on a 113 mEq sodium diet and 2.13–13.8 ng/ml/hr on a 10 mEq sodium diet. None of the patients or normals were being subjected to sodium restriction.

Results

Ten subjects were sampled at all three times (Table I). All four of the normals and 4 of the 6 patients so studied had a reduction of PRA at the infusion midpoint compared to the control level. One out of the 4 normals and 4 of the 6 patients had reductions in PRA at the end point compared to the midpoint of the infusion. Three of the 4 normals and 4 of the 6 patients demonstrated reductions after the infusion compared to before.

In Table II are listed the PRA values for the individuals sampled only before and after the infusion. Six of the 9 patients, as well as the one normal, had reduced their PRA at the end of the infusion.

¹This study was supported by a grant from The Population Council, New York, and by the following grants from the U.S. Public Health Service: AM-06344, AM-0772, FR-00051, AI-04152, FR-00069, AM-12148, and AI-AM-08898.

Copyright © 1972 by the Society for Experimental Biology and Medicine

Judith Anne Smith rendered expert technical assistance.

Thus, in the entire group of subjects studied, all 5 normals and 11 of the 15 patients had a significant ($p < .025$) PRA reduction at either the midpoint or the end of the prednisolone infusion. Two of the 4 patients who did not respond demonstrated chronic rejection (J. M. and H. R.) and the 2 others (S. J. and W. D.) had acute rejection. Several of the responders also had acute rejection. The three subjects receiving the largest maintenance doses of prednisolone (C. E. 170 mg, W. D. 120 mg, S. J. 120 mg) responded slightly or not at all in terms of reduction of PRA.

Discussion

All but two of the homograft patients (J. M. and R. C, Table II) had higher basal PRA levels than the normal subjects. This finding will be described more fully in a later communication.

This study has also shown that rapid infusion of large doses of prednisolone resulted in an acute reduction in PRA in most patients and all normal controls. Previous studies of the effects of glucocorticoids on PRA in man (9,10) were carried out with much smaller doses given over longer periods of time. Those studies showed no consistent change in PRA with glucocorticoid treatment. In the rat, however, moderate doses of glucocorticoid have been found to reduce PRA (11).

The mechanism of prednisolone-induced reduction of PRA is not well understood. Glucocorticoids have been shown to increase acutely extracellular fluid volume in dehydrated dogs, probably by a shift of salt and water from intracellular to extracellular compartments (12). Intravenous administration of glucocorticoids to normal humans induced an acute increase in cardiac output (13). These two phenomena, sudden increases in extracellular fluid volume and cardiac output, might initiate a signal (14) for the reduction of renin secretion which would reduce the vasopressor (15) and salt-retaining (16) effects of both the reduced renal function and of the angiotensin-aldosterone system in a rejection episode. In a previous study from our laboratories (7), however, the latter mechanism was not very effective because sodium clearance was increased only during the first hour of study. This was followed by two hours of relatively positive sodium balance.

Another salutary consequence for the rejecting kidney of the acute reduction in PRA brought about by the prednisolone infusions might be a reduction in the amount of in-trarenal vasospasm as a consequence of intrarenal formation of angiotensin (17).

From the point of view of therapeutic effect, however, it must be noted that the four non-responders in our group had considerable increases in PRA as a result of the infusion, which might be detrimental.

Summary

Large doses of intravenous glucocorticoids have been used in an attempt to reverse homograft rejection. The intravenous administration of 1 g prednisolone over 1 hr resulted in a significant acute reduction of plasma renin activity in 5 normal subjects tested and in 11 out of 15 patients bearing renal homografts. No definite explanation for failure to respond nor the mechanism of this prednisolone effect is readily at hand. An acute decrease in renin activity could be salutary for the chronically or acutely rejecting patient in that it could reduce vasopressor and salt-retaining effects. However, several of the non-responders had an increase in renin activity which could have been detrimental.

References

1. Starzl, TE. Experience in Hepatic Transplantation. W. B. Saunders Co.; Philadelphia: 1969. p. 359

2. Kountz SL, Gohn R. Lancet 1969;1:388.
3. Lucas ZJ, Palmer JM, Payne R, Kountz SL, Cohn RB. Arch. Surg 1970;100:113. [PubMed: 4903964]
4. Coburg AJ, Gray SH, Katz FH, Penn I, Halgrimson C, Starzl TE. Surg. Gynec. Obstet 1970;131:933. [PubMed: 4919384]
5. Bell PRF, Briggs JD, Caiman KC, Paton AM, Wood RFM, Macpherson SG, Kyle K. Lancet 1971;1:876. [PubMed: 4102025]
6. Roguska J, del Greco F, Simon NM. Nephron 1971;8:289. [PubMed: 4949581]
7. Popovtzer MM, Pingerra WF, Robinette J, Holmes JH, Halgrimson CG, Starzl TE. J. Lab. Clin. Med 1971;78:39. [PubMed: 4936366]
8. Katz FH, Smith JA. Clin. Chem 1972;18:528. [PubMed: 4337384]
9. Newton MA, Laragh JH. J. Clin. Endocrinol. Metab 1968;28:1014. [PubMed: 4298943]
10. Spark RF, Gordon SJ, Dale SL, Melby JC. Arch. Intern. Med 1968;122:394. [PubMed: 4301259]
11. Hauger-Klevene JH, Brown H, Fleischer N. Proc. Soc. Exp. Biol. Med 1969;131:539. [PubMed: 5787135]
12. Swingle WW, Parkins WM, Taylor AR, Hays HW. Amer. J. Physiol 1936;116:438.
13. Sambhi MP, Weil MH, Udhoji VN. Circulation 1965;31:523. [PubMed: 14275990]
14. Davis JO. Circ. Res 1971;28:301. [PubMed: 4322898]
15. Porter, KA. Experience in Renal Transplantation. Starzl, TE., editor. W. B. Saunders Co.; Philadelphia: 1964. p. 336
16. Starzl TE. *ibid* :149.
17. Itskovitz HD, Ody C. Science 1971;174:58. [PubMed: 4330571]

TABLE I

Plasma Renin Activity Before, During and at the End of One Hour Infusion of 1 g Prednisolone.

Time of sampling (hr)	Pre	½	1
Subjects	Plasma renin activity (ng Angiotensin I/ml/hr)		
Patients			
L.O.	23.3	15.6	0
C.E.	10.4	8.0	13.5
C.C.	36.2	3.5	11.5
C.B.	29.7	36.5	23.4
M.P.	38.0	23.0	9.7
W.D.	5.1	26.6	15.4
Mean	23.78	18.86	12.25
<i>p</i> value compared to baseline		>.5	<.10
Normal			
P.M.	2.4	1.2	3.1
P.W.	4.9	3.1	2.7
C.A.	2.9	1.3	2.2
G.S.	4.2	0	1.3
Mean	3.6	1.4	2.3
<i>p</i> value compared to baseline		<.05	<.2

TABLE II

Plasma Renin Activity Before and at End of One Hour Infusion of 1 g Prednisolone.

Time of sampling	Pre	Post
Subjects	Plasma renin activity (ng Angiotensin I/ml/hr)	
Patients		
J.M.	2.3	3.0
H.R.	5.2	8.1
P.E.	19.3	17.6
S.J.	21.5	36.1
D.G.	25.2	8.5
T.S.	6.9	2.3
R.C.	1.9	1.3
M.K.	11.0	6.4
S.E.	9.6	5.0
Mean	11.43	9.81
<i>p</i> value compared to baseline		>.5
Normal		
R.J.	1.6	1.1