Effect of Nitroprusside on Peritoneal Dialysis Clearances

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We have studied the effect of intraperitoneal nitroprusside on small (urea) and middle (vitamin B₁₂) molecule dialysis clearances in patients maintained on chronic peritoneal dialysis. Clearances were measured in six patients during the addition of 6 mg of nitroprusside to three and seven consecutive, hourly two-liter exchanges during the course of a routine dialysis treatment. Results indicate that clearances of urea and B₁₂ both increased about 35 percent with the addition of the vasodilator for three exchanges. Clearances immediately returned to baseline values when administration of the vasodilator was discontinued. Addition of the drug to seven consecutive exchanges resulted in a sustained 35 percent increment in clearances.

We conclude that addition of 6 mg of nitroprusside to peritoneal dialysis solution can result in a significant increment in both small and middle molecule clearances. Maintenance of the higher clearances requires sustained administration of the drug, which can be tolerated for at least six exchanges with no adverse side effects.

INTRODUCTION

During the past few years, maintenance peritoneal dialysis has been utilized increasingly as a therapeutic modality for patients with end-stage renal disease. A major limitation of this therapy is the long duration of treatment required to achieve satisfactory clinical results [1]. Attention has been focused, therefore, on finding ways to increase the rates of solute removal and thus perhaps decrease the time required for maintenance dialysis therapy [2–6]. For example, the intraperitoneal instillation of vasodilators during peritoneal dialysis has been clearly shown to result in significant increments in small molecular clearances in patients [2] and both small and middle molecule clearances in laboratory animals [4].

The present study was undertaken to obtain data on the effect of intraperitoneal nitroprusside on small and middle molecule clearances in patients maintained on chronic peritoneal dialysis. Previous studies in the rat [4] demonstrate a proportional increase of small and middle size molecules. While Nolph has reported an increase in small molecule clearances in patients treated with intraperitoneal nitroprusside [14], a systematic evaluation of middle size molecules has not been performed. Since molecules in the 300–5000 dalton range may be important mediators of uremia, this study was undertaken to measure the effect of intraperitoneal nitroprusside on middle molecule clearances. While other vasodilators have been used in experimental dialysis including isoproterenol [3], hydralazine [2], phentolamine [2], dopamine [3], histamine [4], and bradykinin [4], nitroprusside has been demonstrated to be safe in humans and was chosen for study. Specifically, dialysis clearances of urea (MW 60) and vitamin B₁₂ (MW 1350) were measured during the addition of nitroprusside to
three and seven consecutive two-liter exchanges during the course of a routine maintenance dialysis treatment.

METHODS

Six medically stable patients with end-stage renal failure, who were maintained on chronic peritoneal dialysis via an indwelling two-cuff Tenckhoff catheter for a mean ± SE duration of 17 ± 4 months, were studied. No patients had positive peritoneal dialysis fluid cultures at the time of or in the four months prior to the study. Each patient was dialyzed for 24- or 36-hour periods and received 36 to 48 hours of peritoneal dialysis each week.

Commercially available bottled 1.5 percent dextrose dialysate (Travenol) was used throughout the study and maintained at 37°C by a constant temperature bath. One-hour exchanges of 2 liters each were used. Each peritoneal clearance determination was made with an exchange consisting of 10 minutes' inflow time, 30 minutes' dwell time, and 20 minutes' drain time, as described previously [7-9]. Exchanges were considered to be technically acceptable for clearance calculations if the 2000 ml inflow was achieved in ten minutes, there was no significant leakage of fluid about the catheter exit site, and dialysate return measured 1900-2300 ml.

At the start of each dialysis a blood sample was collected and analyzed for B₁₂ binding protein [10,11]. Previous studies [7] indicated that the level of B₁₂ binding protein did not change during the course of an individual peritoneal dialysis. 0.5 mg of vitamin B₁₂ was then given intramuscularly; this amount was found to give plasma B₁₂ levels that exceeded the level of plasma B₁₂ binding protein by a factor of four to ten for the duration of dialysis.

Blood samples were obtained at the midpoint of each clearance period. At the end of each exchange, the drainage bag was vigorously shaken and an aliquot of dialysate was obtained. Blood and dialysate samples were analyzed for urea [12], and B₁₂ concentrations [13].

Urea and vitamin B₁₂ clearances were calculated using the standard formula [5]

\[ C = \frac{\text{clearance (ml/min)}}{t \times C_b} \]

\[ = \frac{Cd \times V_d}{t \times C_b} \]

where \( Cd \) = concentration of solute in dialysis drainage fluid, \( V_d \) = volume of dialysis drainage fluid, \( t \) = time of one exchange, \( C_b \) = concentration of solute in serum during the exchange. In the clearance calculation the level of B₁₂ binding protein, and hence bound B₁₂, was subtracted from the total level of serum B₁₂. B₁₂ binding protein in dialysate was found to be unmeasurable and hence all of the B₁₂ in the dialysate was considered unbound. As previously reported [7], recovery rates of vitamin B₁₂ from 1.5 percent dextrose dialysate were between 95 percent and 105 percent over the range of dialysate B₁₂ concentrations observed in the study.

Since previous studies by our group have shown that from the seventh to the thirty-sixth exchange clearances with hourly 1.5 percent dextrose dialysate exchanges remain constant [7], the effect of instillation of intraperitoneal nitroprusside on clearances was studied during eight consecutive exchanges after the sixth exchange using two protocols. Each of the six patients was studied with both protocols within a two-week period of time. In Protocol A, 6 mg nitroprusside was added to exchanges 3-5 and no drug was added to exchanges 1-2 and 6-8 (Table 1). In Protocol B, 6 mg nitroprusside was added to exchanges 3 to 8 and no drug was added to exchanges 1-2 (Table 1). Period II is defined as exchanges 3 to 5. The sixth exchange is regarded as a
PERITONEAL DIALYSIS CLEARANCE

TABLE 1

| Methods | Hour | Dialysate | Protocol A | Protocol B | Clearance Period |
|---------|------|-----------|------------|------------|------------------|
|         | 1    | 1.5% dextrose | no drug    | no drug    | I                |
|         | 2    | 1.5% dextrose | no drug    | no drug    |                  |
|         | 3    | 1.5% dextrose | 6 mg nitroprusside | 6 mg nitroprusside | II              |
|         | 4    | 1.5% dextrose | 6 mg nitroprusside | 6 mg nitroprusside |                  |
|         | 5    | 1.5% dextrose | 6 mg nitroprusside | 6 mg nitroprusside |                  |
|         | 6    | 1.5% dextrose | no drug    | 6 mg nitroprusside | washout          |
|         | 7    | 1.5% dextrose | no drug    | 6 mg nitroprusside |                  |
|         | 8    | 1.5% dextrose | no drug    | 6 mg nitroprusside |                  |

washout exchange. Period III is defined as exchanges 7 and 8. Mean clearances were calculated for periods II and III.

Blood pressure and pulse were monitored every 20 minutes through the eight-hour study protocols. No significant change in these parameters occurred in any patient.

Statistical analysis was performed by paired "t" testing.

RESULTS

Protocol A (Table 2)

Addition of intraperitoneal nitroprusside in exchanges 3–5 (period II) resulted in significant ($p < 0.001$) increments in urea and $B_{12}$ clearances and dialysate to plasma solute ratios. Urea clearance increased 36 percent, and $B_{12}$ clearance increased 37

TABLE 2

| Patients | Mean ± SEM |
|----------|------------|
| Urea clearance |           |
| Period I | 16.9 ± 1.4 |
| Period II | 22.9 ± 2.2 |
| Period III | 18.1 ± 1.7 |
| D/P* urea ratio |        |
| Period I | .41 ± .08  |
| Period II | .63 ± .06  |
| Period III | .49 ± .04  |
| $B_{12}$ clearance |      |
| Period I | 6.2 ± 1.3  |
| Period II | 8.5 ± 1.8  |
| Period III | 6.3 ± 1.1  |
| D/P $B_{12}$ ratios |    |
| Period I | .18 ± .04  |
| Period II | .24 ± .05  |
| Period III | .17 ± .03  |

*D/P is dialysate to plasma ratio
percent. After withdrawal of the nitroprusside (period III), urea and B₁₂ clearances and dialysate to plasma solute ratios were no longer significantly different from baseline values (period I).

**Protocol B**

Addition of nitroprusside to six consecutive exchanges resulted in a sustained increased clearance level. Thus, as in protocol A, urea and inulin clearance and dialysate to plasma solute ratios increased significantly \((p < .001)\) in period II. Continued addition of nitroprusside through exchange 6–8 (period III) did not result in a further increase in clearances. Urea clearance remained about 25 ml/min and B₁₂ clearance about 9 ml/min.

**DISCUSSION**

The present data demonstrate that addition of 6 mgm of nitroprusside to 2000 cc of peritoneal dialysis solution can improve the efficiency of small and middle molecule solute removal during a routine peritoneal dialysis. Continued use of nitroprusside is apparently necessary to sustain the increased rate of solute removal, since in protocol A clearances during the exchanges following discontinuation of intraperitoneal nitroprusside returned to baseline level. Administration of intraperitoneal nitroprusside for six consecutive exchanges did not result in a further increment in clearances. Treatment with intraperitoneal nitroprusside for six exchanges was well tolerated by all six patients, with no significant changes in blood pressure or pulse occurring. Whether more prolonged administration of intraperitoneal nitroprusside can be safely achieved remains to be determined.

The mechanism by which intraperitoneal nitroprusside results in enhanced clearances is not clear. Recent studies in which the micro circulation of rat cremaster muscle bathed in peritoneal dialysis solution was studied demonstrated that addition of nitroprusside to the dialysis fluid established continuous perfusion of arterioles

### TABLE 3

**Protocol B**

| Patients | Urea clearance | D/P Urea ratio | B₁₂ clearance | D/P B₁₂ ratios |
|----------|----------------|----------------|---------------|----------------|
|          | Period I | Period II | Period III | Period I | Period II | Period III | Period I | Period II | Period III |
| AB       | 15.1     | 20.7     | 22.4       | .50     | .59     | .60       | 5.6      | 7.6      | 8.8      |
| PC       | 19.4     | 29.7     | 26.2       | .43     | .59     | .60       | 6.9      | 11.6     | 9.4      |
| VG       | 14.9     | 20.0     | 19.3       | .42     | .54     | .53       | 3.7      | 5.7      | 7.6      |
| LS       | 17.3     | 21.4     | 21.1       | .49     | .58     | .57       | 4.6      | 5.2      | 5.0      |
| QP       | 29.7     | 34.2     | 35.1       | .85     | .99     | .98       | 14.5     | 16.0     | 16.3     |
| RC       | 19.1     | 25.4     | 24.1       | .59     | .67     | .67       | 5.3      | 7.8      | 7.6      |
| Mean ± SEM |         |          |            | .56 ± .06 | .68 ± .07 | .67 ± .07 | 6.8 ± 1.6 | 9.0 ± 1.7 | 9.1 ± 1.6 |
that had been perfused either intermittently or not at all [14]. Thus, nitroprusside may increase the endothelial area available for peritoneal transfer by increasing the total area of arterioles and capillaries perfused. The proportional increment in small and middle molecule clearances in response to intraperitoneal nitroprusside noted in a rat model of peritoneal dialysis supports this hypothesis [4]. Similarly, in the present study the increments in urea and B\textsubscript{12} clearances were both about 35 percent. However, the interpretation of this proportional increase is complicated by the possible limitations imposed in the urea clearance by the dialysate flow rate of 33 ml/min.

Previous studies of Nolph et al. [14], in which the effects of intraperitoneal nitroprusside on peritoneal dialysis clearances in patients were examined, reported an increment of about 20 percent in small molecule clearances with the addition of the vasodilator. However, clearances of inulin, which were determined in only one patient, increased over 200 percent during the addition of 9 mg of nitroprusside to nine consecutive two-liter exchanges. This large increase in the clearance of inulin was associated with a 63 percent increment in the calculated mass transfer coefficient for inulin. In the present study the percent increment in clearances of larger sized molecules was not as marked as observed by Nolph. Differences between the present study and Nolph's report include the measurement of vitamin B\textsubscript{12} (MW = 1350) clearances versus inulin (MW = 5200) clearances, and the dose of nitroprusside used (6 mg versus 9 mg per two liters of dialysate).

The effect of intraperitoneal nitroprusside on urea and inulin peritoneal dialysis clearances in the rat [4] is similar to that observed in the present study. The only difference is that, in the rat model, the increased clearances persist during the three exchanges following the discontinuation of nitroprusside administration. A major difference between the rat and patient studies is the duration of each exchange: 15 minutes in the rat and 60 minutes in the patients. Perhaps the effect of nitroprusside on dilating capillaries and arterioles is of sufficient duration to cause persistently increased clearances in the protocol used in the rat studies but not of sufficient duration to result in increased clearances in period III of protocol A in the present study.

In summary, the addition of 6 mg of nitroprusside to peritoneal dialysis solution can result in a significant increment in small and middle molecule clearances. Maintenance of the higher clearances requires sustained administration of the drug, which can be tolerated for at least six exchanges with no adverse side effects.

REFERENCES

1. Tenckhoff H, Curtis FK: Experience with maintenance peritoneal dialysis in the home. Trans Am Soc Artif Intern Organs 16:90, 1970
2. Nolph KD, Ghods AJ, VanStone J, et al: The effect of intraperitoneal vasodilators on peritoneal clearances. Trans Am Soc Artif Intern Organs 22:586, 1976
3. Gutman RA, Nixon WP, McRae RL, et al: Effect of intraperitoneal and intravenous vasoactive amines on peritoneal dialysis. Study in anephric dogs. Trans Am Soc Artif Intern Organs 22:570, 1976
4. Brown EA, Kliger AS, Goffinet J, et al: Effect of hypertonic dialysate and vasodilators on peritoneal dialysis clearances in the rat. Kidney Internat 13:271, 1978
5. Henderson LW, Nolph KD: Altered permeability of the peritoneal membrane after using hypertonic peritoneal dialysis fluid. J Clin Invest 48:992, 1969
6. Zelman A, Gisser D, Whittam P: Augmentation of peritoneal dialysis efficiency with programmed hyper-hypooosmotic dialysate. Trans Am Soc Artif Intern Organs 23:203, 1977
7. Brown EA, Kliger AS, Finkelstein FO: Peritoneal dialysis clearances. A practical approach to the measurement of small- and middle-molecule clearances. Nephron 21:310, 1978
8. Finkelstein FO, Kliger AS, Bastl C, et al: Chronic peritoneal dialysis in diabetic patients with end-stage renal failure. Proc Dialysis Transplant Forum 5:142, 1975
9. Finkelstein FO, Kliger AS, Bastl C, et al: Sequential clearance and dialysance measurements in chronic peritoneal dialysis patients. Nephron 18:342, 1977
10. Silverstein E, Herbert V: Rapid determination of vitamin B₁₂ binding α- and β-globulins in serum. Blood 31:518, 1968
11. Baglay JA, Hall CA: Measurement of vitamin B₁₂-binding proteins of plasma. I. Technique. Blood 45:281, 1975
12. Henry RJ: Clinical chemistry. New York, Harper & Row, 1964, p 293
13. Tibbling G: A method for determination of vitamin B₁₂ in serum by radioassay. Clinica Chim Acta 23:209, 1969
14. Nolph K, Ghods A, Brown P, et al: Effects of nitroprusside on peritoneal mass transfer coefficients and microvascular physiology. Trans Am Soc Artif Intern Organs 23:210, 1977