Independent plasma levels of sodium and glycine during transurethral resection of the prostate

Jonathan R. Zucker MB CHB,
Anthony P. Bull MB CHB

This study was done to evaluate the potential role of plasma glycine levels as an indicator of the biochemical changes occurring during or shortly after transurethral resection of the prostate (TURP). Seventeen patients undergoing TURP were studied to determine the fate of the absorbed glycine and its effects on other amino acids and their relationship to changes in serum sodium and osmolarity. Twelve patients showed more than 100 per cent increase in plasma glycine levels with values ranging to more than 100-fold elevation. Only two patients showed a change in serum sodium of greater than 10 mEq/l with corresponding change in osmolarity. In one such patient there was no accompanying change in plasma glycine. Thus, major changes in plasma glycine and serum sodium may occur independently of one another, and may separately account for manifestations of the reactions following TURP.

Key words
SURGERY: transurethral resection of the prostate, complications, glycine.

The TUR reaction which occurs during or shortly after transurethral resection of the prostate (TURP) has been well described.[1,2] The symptomatology is currently ascribed to acute water intoxication with dilutional hyponatremia as a result of intravascular absorption of a large volume of electrolyte-free bladder irrigating fluid.[3,4] This explanation does not fit with all the facts. There is no correlation between the amount of fluid absorbed and the serum sodium level,[5] or the resultant CNS symptomatology.[6] Grand mal seizures have been reported in the absence of any other symptoms of intravascular absorption of a large volume,[3] and dilutional hyponatremia may not be responsible for the resultant acute cardiovascular collapse.[7]

The most common currently used bladder irrigating fluid is 1.5 per cent glycine in water. It has been suggested that glycine alone or its metabolites may be a cause of visual disturbances and/or encephalopathy following TURP, independently of changes in serum sodium or osmolarity.[8,9] The 1.5 per cent glycine bladder irrigating fluid is 1000 times the normal concentration of glycine in plasma. Thus, absorption and distribution of 15 cc of glycine bladder irrigating fluid into an ECF volume of 15 litres would approximately double the plasma glycine concentration while diluting the serum sodium by only 0.1 per cent. Changes in plasma levels of glycine would therefore be more sensitive than changes in serum sodium as an indicator of biochemical changes accompanying the TURP surgery. We therefore measured the amino acid composition changes along with changes in serum sodium and osmolarity in patients undergoing TURP, to evaluate the potential role of glycine as an indicator of the TUR reaction. We did not try to establish any relationship between these biochemical changes and the symptomatology of the TUR reaction.

Methods

After informed consent was obtained, 17 patients (mean age, 68 years, SD = 7) undergoing TURP were studied according to a protocol approved by our Clinical Investigation Committee. In addition to

From the M.S. Hershey Medical Center, Pennsylvania State University, Hershey, PA 17033.

Address correspondence to: Dr. J.R. Zucker, Department of Anesthesiology, RN-10, The University of Washington School of Medicine, Seattle, WA 98195.

the usual monitoring for surgery, all patients had a central line placed prior to the start of surgery for sampling of mixed venous blood from the right atrium. Anaesthesia was performed with an appropriate dose of subarachnoid tetracaine using a standard technique. Intravenous five per cent dextrose in lactated ringers was administered during surgery according to the patient's requirements. Generally the patients were given 200–500 ml prior to the onset of subarachnoid anaesthesia, and a further 200–500 ml during the procedure. Blood samples were withdrawn from the central line before the start of surgery and at 15–20 minute intervals thereafter for up to 2.5 hours so as to include the postanaesthesia recovery. All monitoring was performed in the routine manner and no attempt was made to evaluate subtle objective psychological or neurological changes.

The blood samples were collected in heparinised tubes and kept on ice until centrifuged within one hour; the plasma was stored frozen until assayed within a month of collection. For each sample, sodium and potassium were measured with an I.L. Flame Photometer model 143, osmolarity with a Precision Systems Osmette A. In an attempt to detect "spurious hyponatremia," glucose and lactate were measured using standard enzymatic methodology (Bergmeyer HU, ed. Methods of Enzymatic Analysis. New York: Academic Press, 1974). Amino acid analysis was performed on a Beckman 119CL Amino Acid Analyser with a lithium citrate buffer system.

Paired T-testing, Wilcoxon Signed Rank testing and tests on Pearson Correlations were performed using the Statistical Analysis System package of programs (Helwig JT, Council KA. SAS users guide. Raleigh N.C.: SAS Institute, 1979) on an IBM 3033 computer. Normal values used in this study correspond to the laboratory normals for the methods used (sodium = 140 mEq/l; osmolarity = 295 mOsM/l; glucose = 5.5 mMol/l; glycine = 243 μMol/l; alanine = 259 μMol/l; serine = 83 μMol/l).

Results

In the 17 patients studied, the medium peak elevation in plasma glycine concentration was 10.4 times the normal plasma level, serine was 1.9 times the normal, and alanine 1.8 times the normal. The median peak depression in serum osmolarity was a five per cent reduction from the normal level, and for serum sodium it was a two per cent reduction from the normal level. These overall changes as measured by Paired T-testing, and confirmed by Wilcoxon Signed Rank testing on differential data are all significant ($p < 0.01$). The changes in individual patient's glycine, serine, alanine, sodium, osmolarity, and glucose are shown in the Table. These changes are between baseline and peak values and are expressed as a percentage of the normal value. The 17 patients (A to Q) are arranged in the order of the magnitude of change in glycine; the five largest and five smallest changes of each constituent have been flagged. The highest detected glycine concentration in plasma (102 times normal) was 24.8 mMol/l (normal = 0.24 mMol/l).

Changes in glycine, serine and alanine appear to correlate with one another; changes in sodium, osmolarity and glucose are more complex. Changes in osmolarity correlated more closely with changes in glucose than with sodium. In six out of 17 patients, there was a positive correlation ($p < 0.01$) of osmolarity with glucose (r values for A = 0.91; F = 0.97; J = 0.93; K = 0.89; O = 0.81; P = 0.98). Figure 1 (patient F) illustrates this phenomenon; the fall in osmolarity paralleled the change of glucose in the circulation. A positive correlation between osmolarity and sodium was demonstrated in only two patients. A strong correlation ($r = 0.88$, $p < 0.01$) was found in patient E, with imperceptible changes in plasma glycine (Figure 2); a weaker correlation ($r = 0.81$, $p < 0.02$) was found in patient H, who showed the largest change in plasma glycine. In other patients, there was no significant correlation of osmolarity with sodium or glucose. Hyponatremia in patient H correlated better with the change in plasma glycine ($r = -0.94$, $p < 0.001$) than with osmolarity. Similarly for patient F (Figure 1) hyponatremia correlated with elevation of plasma glycine ($r = -0.96$, $p < 0.001$). In contrast, in patient G, hyponatremia correlated with elevation of glucose ($r = -0.86$, $p < 0.01$), illustrating that "spurious" dilutional hyponatremia due to hyperglycaemia does occur.

Whereas the elevated levels of serine noted in our study could only have come from the glycine absorbed, alanine could have been derived from either the glycine via serine, or from intravenous lactate infusion. In this study the only significant ($p < 0.01$) correlation of alanine level was with serine.

TABLE Changes in glycine, serine, alanine, sodium, osmolarity and glucose for 17 patients (A-Q) arranged in decreasing order of glycine change. The changes are expressed in relation to the normal value for each constituent. Refer to the text for details

	Change as per cent of normal					
Patient	*Glycine (↑)*	*Serine (↑)*	*Alanine (↑)*	*Sodium (↓)*	*Osmolarity (↓)*	*Glucose (↑)*
H	10132†	563†	189†	8.0†	8.5†	153
F	7805†	193†	162⁻	5.0†	8.0†	338†
I	1876†	312†	155⁺	2.0	2.0*	273†
L	1802†	156†	90	2.0	2.5	129†
Q	1660†	178†	106⁺	2.0	—	181
A	1310	96	134⁺	1.5	1.5*	143*
C	1158	119	95	1.5	2.0*	172
G	1125	51	43	5.0†	2.5	252†
O	740	41	50	0.5*	4.5	156
N	689	39	20*	3.0†	3.5	156
D	257	41*	50	1.5	3.5	110*
P	129*	22	34*	2.5	13.5†	607†
E	57*	13*	36*	10.0†	10.0†	130†
J	52*	0*	1*	0.0*	5.0	179
B	41*	0*	30*	0.0*	2.0*	124*
K	32*	0*	81	0.5*	5.0†	256†
M	—	—	—	0.5*	2.0*	168

*= lowest 5.
†= highest 5.

This occurred in five out of 17 patients (r values for F = 0.87; H = 0.90; J = 0.96; O = 0.97; Q = 0.94). No correlation between alanine and glucose values could be found, suggesting that the majority of alanine was not derived from infused five per cent dextrose in lactated ringers, but rather derived from absorbed glycine.

Discussion

The symptomatology of the TUR reaction is currently ascribed to intravascular absorption of bladder irrigation fluid, resulting in acute water intoxication with hypo-osmolarity and dilutional hyponatremia.[3,4] This may, however, not be the sole mechanism. Many authors[1,7,10–13] have shown that absorption occurs not only directly through open prostatic venous sinuses, but also into extravascular sites through small perforations of the bladder (which may be far more common than expected), or through defects in the prostatic capsule.[11] Oester and Madsen, using a double radioisotope technique, found that more than two thirds of absorption occurred extravascularly, into the perivesical and retroperitoneal spaces.[10] The initial effect of this electrolyte-free bladder irrigating fluid in the extravascular space would be for sodium to diffuse out of the intravascular compartment. At the same time the water from the moderately hypo-osmolar bladder irrigating fluid would tend to diffuse into the intravascular compartment. If either or both of these rates of diffusion exceeded the rate of diffusion of the osmotically active glycine molecules from the

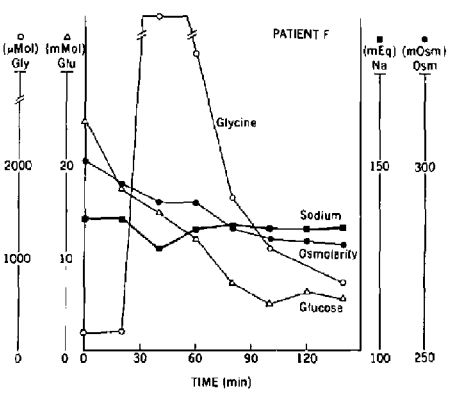

FIGURE 1 Changes in patient F of glycine (μMol), glucose (mMol), sodium (mEq) and osmolarity (mOsm) with time (mins). The transient drop in sodium correlates with a massive elevation in glycine; while the fall-off in osmolarity correlates with the removal of glucose from the circulation.

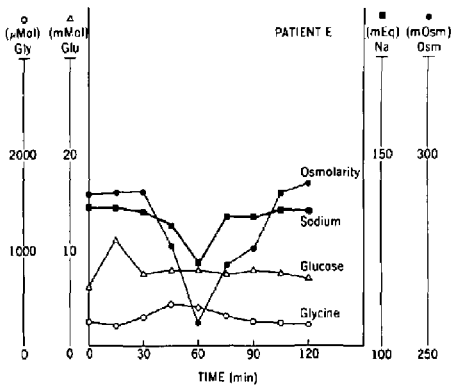

FIGURE 2 Changes in patient E of glycine (μMol), glucose (mMol), sodium (mEq) and osmolarity (mOsm) with time (mins). The noticeable drop in osmolarity correlates with the significant drop in sodium, which occurs in the absence of any major change in glycine.

extravascular space into the intravascular compartment, then the net flux of water and osmotically active molecules would produce a transiently hypo-osmolar intravascular compartment. One of the patients in our study did in fact demonstrate this type of phenomenon with acute water intoxication due to non-intravascular absorption of bladder irrigating fluid with a relatively imperceptible change in plasma glycine, but with significant hyponatremia and hypo-osmolarity (patient E, Figure 2). The extent of perivesical or periprostatic absorption of irrigating fluid in other patients in this study could not be determined, but reports suggest the retropubic and perivesical spaces are often filled with irrigation fluid.[10] The diffusing of electrolytes from the ECF into an accumulation of extravasated non-electrolyte fluid has been postulated to contribute to the reported increase in exchangeable sodium with hyponatremia.[1,7] Attendant fluid shifts could conceivably lead to initial hypovolemic and later hypervolemic cardiovascular collapse.[7,10,14]

Desmond[2] noted that even though marked falls in plasma sodium occurred in 19 per cent of his cases, osmolarity changed in only two out of 72 cases studied. The mechanism for this apparent paradox may not depend on the quality of left ventricular function as was proposed.[2] Assuming that intravascularly absorbed glycine is immediately distributed in 15 litres of ECF volume, absorption of 1.5 litres of sodium free fluid with 200 mMol/l (200 mOsm/l) glycine will result in a drop in sodium concentration from 140 mEq/l to 127 mEq/l (9.6 per cent change), while osmolarity will drop from 290 mOsm/l to 282 mOsm/l only (2.3 per cent change). This dilutional hyponatremia resulting from intravascular absorption of a large volume of osmotically active glycine bladder irrigating fluid would produce very high levels of plasma glycine. Thus, dilutional hyponatremia should be viewed as separate from acute water intoxication resulting from perivesical absorption of bladder irrigating fluid which may produce imperceptible changes in plasma glycine. Other changes in blood chemistry may depend not only on the route of absorption of bladder irrigating fluid but also on the relative amount and the composition of the infused intravenous hydration fluid. For example an apparent change in osmolarity occurred in six out of 17 patients due to uptake and metabolism of infused glucose. Thus it is not surprising that changes in sodium and osmolarity very seldom correlated.

High plasma levels of glycine can also be produced by a very small volume of absorbed bladder irrigating fluid which will not significantly alter plasma sodium or osmolarity. These high plasma glycine levels may increase the net flux of glycine across the blood brain barrier, temporarily overwhelming the active extrusion of glycine from the CSF and allow glycine to function as an inhibitory transmitter throughout the CNS.[15] It is therefore possible that cerebral symptomatology, reported in the absence of the classical symptomatology of the TUR reaction, may be the result of a direct neurotoxic effect of glycine, in the absence of significant changes in either serum sodium or osmolarity.

Handler[16] infused glycine solutions intravascularly in dogs and found that glycine, infused at 5.3 $mg \cdot kg^{-1}$/min, caused death in eight out of 12 dogs. When infused at rates in excess of 5.3 $mg \cdot kg^{-1}$/min it was invariably lethal. The fluid intake accompanying glycine infusion, bore no quantitative relationship to toxicity.[16] In humans, toxic manifestations described as the result of infusion of 2.5 per cent glycine at a rate of 3.5 $mg \cdot kg^{-1}$/min included malaise, marked weakness, intense nausea, vomiting and headache.[17] A rate of 5.3 $mg \cdot kg^{-1}$/min translates to 25 cc of 1.5 per cent glycine bladder irrigation fluid absorbed by a 70 kg body per minute. This rate of absorption is

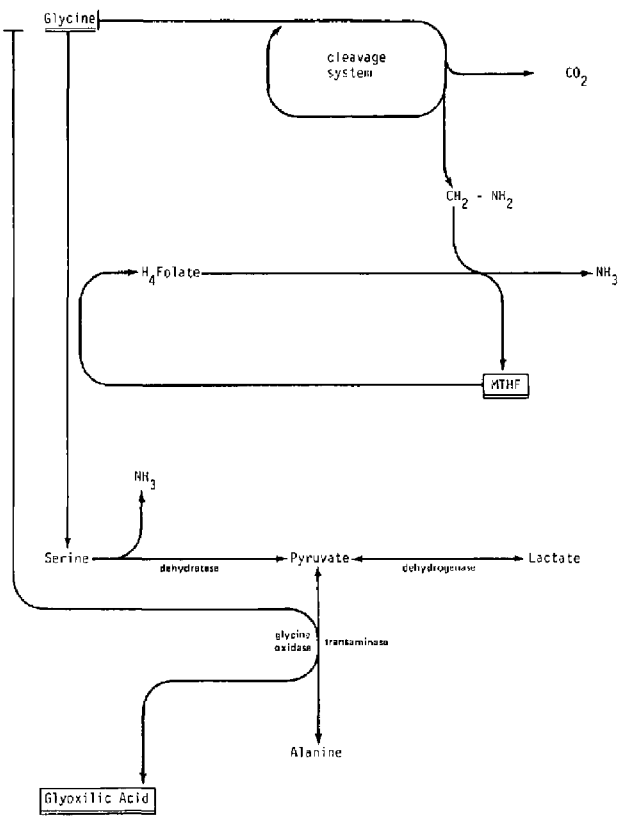

FIGURE 3 Metabolic pathway illustrating putative neurotoxic metabolic products of glycine. See text for details.

probably exceeded several-fold in clinical practise; it is likely that such toxic levels of glycine would go undetected by simply measuring serum sodium or osmolarity.

Some authors believe it is the total dose of glycine (>400 mg·kg^{-1}) that causes toxic manifestations.[16] This level was documented in one of our patients (25 mMol/l). Others believe that the rate of infusion is more important.[17] Rapid loading of glycine may exceed the ability to detoxify either glycine or products of its metabolism. Previous attempts to evaluate the potential toxicity of glycine have related its toxicity to ammonia production,[9,15,16,18] and its possible conversion to glyoxilic acid,[16] an inhibitor of oxygen consumption and oxidative phosphorylation which can cause death preceded by brief convulsive seizures.[19] Other toxic metabolites may be implicated. The major product of glycine metabolism is serine.[20,21] This is borne out by our findings of elevated levels of serine and alanine in the patients in our study. An intermediate in that pathway of metabolism is methylene tetrahydrofolate (MTHF)[21] (see Figure 3), which has been implicated in the neurotoxic inhibition of presynaptic uptake of glutamate or other similar endogenous excitant in the CNS.[22–24]

On the basis of the documented biochemical changes, the TUR reaction may consist of a

composite of one or more of three distinct entities. (1) Dilutional hyponatremia with only moderate hypo-osmolarity caused by intravascular absorption of osmotically active glycine. (2) Acute water intoxication caused by perivesical absorption of electrolyte-free irrigating fluid into the abdominal cavity as may occur with a small perforation of the bladder setting up sodium and osmotic shifts. (3) Direct neurotoxic effects of glycine or its metabolites. The latter could occur independently and possibly in the absence of any gross change in measured serum sodium or osmolarity. Further studies on glycine toxicity to clarify the nature of the toxicity as well as its clinical relevance are urgently needed.

Acknowledgements

We thank Dr. Janet Pavlin for assistance in reviewing the manuscript.

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Résumé

Cette étude a été entreprise pour évaluer le rôle possible des concentrations plasmatiques de glycine comme indicateur des changements biochimiques survenant durant ou immédiatement après la résection de la prostate par voie trans-urétrale. Dix-sept patients soumis à cette chirurgie ont été étudiés; on a suivi la destinée de la glycine absorbée et observé ses effets sur les autres amino-acides de même que sa corrélation avec les changements de la natrémie et l'osmolarité. Chez 12 malades on a observé une augmentation de 100 pour cent des niveaux plasmatiques de glycine avec certaines valeurs extrêmes allant jusqu'au centuple de la concentration de départ. Chez deux patients seulement a-t-on observé un changement de la natrémie plus grand que 10 mEq accompagné d'une modification d'osmolarité dans le même sens. Chez un de ces malades il n'y a eu aucune modification de la glycine plasmatique. Ainsi, on peut voir que des modifications importantes des niveaux plasmatiques de glycine et de la natrémie peuvent survenir indépendamment l'une de l'autre et peuvent, chacune pour son propre compte, expliquer les réactions qu'on observe à la suite de prostatectomie trans-urétrale.