Using Protein/Creatinine Ratios in Random Urine

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We assessed the new test paper Multistix PRO IOLS, in which the $\pm$ region of the conventional test for protein was altered so that creatinine correction became possible. Urinary samples from 235 patients with various renal diseases were obtained from the Juntendo University Hospital. We examined 1) the correlation between qualitatively measured values of urinary protein by the new test paper and the conventional test paper, and 2) the correlation between qualitative and quantitative values of protein

(P), creatinine (C), and the P/C ratio measured by the new test paper. There was a good correlation between the P/C ratio observed with the new test paper and that observed by quantitative analysis. There was also a good correlation of the P/C ratio between 24-hr urine and urinary samples obtained at any time of day. Thus, it appears that the results obtained from urinary samples any time of day can predict the amount of protein excreted during the day. *J. Clin. Lab. Anal.* 19:160–166, 2005. © 2005 Wiley-Liss, Inc.

Key words: Multistix PRO IOLS; P/C ratio; various renal diseases

INTRODUCTION

Proteinuria is one of the most important symptoms in patients with renal diseases, and the level of urinary protein excretion is an important index for the clinical evaluation of renal diseases. In general, quantitative evaluations of 24-hr excretion of urinary protein can provide useful, objective information when performed in samples of urine collected for 24 hr. However, such evaluations tend to be ignored for the following reasons: such tests cannot be conducted frequently in outpatients, there may be a lack of accuracy if the urinary samples are not collected perfectly, and the collection procedure is not simple.

In 1983 Ginsberg et al. (1), Sessoms et al. (2), and Shaw et al. (3) stated that as a measurement to replace daily urinary protein excretion, the daily excretion of urinary protein can be estimated by the protein/creatinine (P/C) ratio in any urinary samples. This concept was subsequently examined in Japan (4). In these reports, examinations were made using the results of quantitative measurements. In Japan, no report has appeared regarding the P/C ratio obtained using urinary sample strips.

Urinary protein test paper was developed by Free et al. (5) in 1957. The principle behind the reaction is the error induced by protein in the pH indicator. The sensitivity of measurement is 10–30 mg/dL as albumin; however, several problems, such as low specificity and

low correlation with the total protein method, have been pointed out (6,7). Especially in the region of $\pm$ (trace), the difference in color development is poor and the result is easily influenced by dilution or concentration; therefore, the results must be confirmed by such techniques as the sulfosalicylic acid (SSA) method (8). We recently had the opportunity to examine the new test paper Multistix PRO 10LS (Bayer Medical Ltd., Tokyo, Japan), in which the $\pm$ region of the conventional test for protein was altered to the test portion specific to albumin (9), and a creatinine test portion (10,11) was added to make creatinine correction possible.

MATERIALS AND METHODS

Subjects

We examined 235 patients who were being treated at the Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan.

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General Description of Multistix PRO 10LS

Table 1 gives a general description of the Multistix PRO 10LS. Table 2 shows the quantitative values of P, C, and the P/C ratio corresponding to each color block on the new test paper.

As is done with conventional test papers for urinalysis, various types of test samples are placed on a plastic stick. One of the characteristics of Multistix PRO 10LS is that the protein concentration is measured

in two test regions: 1) the region of high concentration, and 2) the region of low protein concentration (albumin). The measured value is indicated based on results obtained for the two concentrations. The high concentration region is identical to that of the currently used protein test, and covers protein concentrations of 30 mg/dL or higher. The low protein concentration region is identical to the albumin test region used in the Clinitek Microalbumin-Creatinine Test, and covers the 8–30 mg/dL region as albumin. The product includes a

TABLE 1. Comparison between new and conventional test paper

Test paper		New test paper (Multistix PRO 10 LS)	Conventional test paper (N-Multistix SG-L)	
Measurement items		Nine items: protein (low concentration range, high concentration range), creatine, occult blood, leukocytes, nitrite, glucose, ketone bodies, pH, specific gravity, bilirubin	Ten items: protein, occult blood, leukocytes, nitrite, glucose, ketone bodies, pH, specific gravity, bilirubin, urobilinogen	
Sensitivity of protein		Low concentration region: 8–15 mg/dL albumin, High concentration region: 30–65 mg/dL protein	15–30 mg/dL albumin ^a	
Reaction stage of protein		Negative, 15 mg/dL (2 steps)		
Low concentration		(–), (±), 30(1+), 100(2+), 300(3+), 1,000(4+) ^a (6 steps)		
High concentration		0 (–), 30 (1+), 100 (2+), 300 (3+), 1,000 (4+) mg/dL ^a (5 steps)		
Time for reaction		Test item	Reaction time (seconds)	Test item
		Protein (low concentration)	50	Protein
		Protein (high concentration)	50	Occult blood
		Creatinine	60	Leukocytes
		Occult blood	60	Nitrite
		Leukocytes	120	Glucose
		Nitrite	60	Ketone bodies
		Glucose	30	pH
		Ketone bodies	50	Specific gravity
		pH	60	Bilirubin
		Specific gravity	50	Urobilinogen
		Bilirubin	30	
Calculation of protein/ creatinine ratio		Visual reading		
		Obtain from conversion Table, evaluation in 3 steps of re-test, normal range and abnormal range ^b		N/A
		Instrumental reading	Results automatically calculated, evaluation in 5 steps: re-test, normal range, abnormal range of 150, 300, and 500 mg/gCr ^b	
Operational method		Dip and read method		
Instrumental evaluation		Measurement is possible with Clinitek STATUS, 50, 100, 500		Measurement is possible with Clinitek STATUS, 50, 100, 200, 200+, 500

^aIn the instrumental reading, there is no 1,000 mg/dL(4+) response.

^bWhen protein is normal and creatinine is too low, it is recommended to conduct a re-test using urine excrete at another time.

TABLE 2. Quantitative values correspond to the color blocks for protein, creatinine, and P/C ratio in new test paper

	Color block (mg/dL)	Quantitative value (mg/dL)	
	—	<8	Albumin
	15	8–29.9	
Protein	30	30–64.9	Protein
	100	65–199.9	
	300	200–399.9	
	1,000	≥ 400	
Creatinine	10	<25	
	50	25–74.9	
	100	75–149.9	
	200	150–249.9	
	≥ 300	≥ 250	
	Results of P/C ratio (mg/gCr)	Quantitative value (mg/gCr)	
P/C ratio		Protein <8 mg/dL	
Normal dilution		Albumin <8 mg/dL	
		Creatinine <25 mg/dL	
Normal		<80	
150		80–299.9	
300		300–499.9	
≥ 500		≥ 500	

new creatinine test portion added for determination of the urinary creatinine concentration, and the P/C ratio is calculated qualitatively using the result for urinary protein.

The results of this product can be obtained visually and by instrument reading. In the visual analysis, the test paper is dipped into a urinary sample, the excess urine is removed, and the test paper is evaluated by means of the color chart at the time set for evaluation. To separate the evaluation times for different items, some alterations were made in the times for evaluation compared to those used for the conventional test paper. A table is used for calculation of the P/C ratio in the visual evaluation method, while such data are automatically calculated, followed by display and printout, for the instrumental evaluation method. The Clinitek (CT) 50/100/500 can be used for such measurements. A cartridge type of PRO reagent for the CT Atlas XL is also available. To enable the use of conventional test paper, the ID code is pasted on this product for analysis of the test paper, and the test paper is automatically recognized by the CT 50/100. The test results from the instrumental evaluation are displayed and printed out for each test, similarly to the previous method, and the P/C ratio from the reexamination is also displayed and printed out in five steps from the normal to abnormal regions.

MATERIALS AND METHODS

The following measurements were performed for each urinary sample: total protein concentration in urine by

the pyrogallol red (PR) method (microTP-AR; Wako Junyaku Kogyo K.K., Tokyo, Japan), urinary micro-concentration of albumin by the latex agglutination immunity method (LX reagent Eiken ALB-II; Eiken Kagaku K.K., Tokyo, Japan), and urinary creatinine concentration by Jaffe's method (creatinine HR; Wako Junkayu Kogyo K.K., Tokyo, Japan). At the same time, measurements were performed using the CT 500 with Multistix PRO10LS and N-Multistix SG-L.

We evaluated 1) the correlation between qualitatively measured values of protein by the new test paper and the conventional test paper, and 2) the correlation between the qualitative and quantitative values of P, C, and the P/C ratio measured by the new test paper.

RESULTS

Correlation Between Qualitative Values of Protein

Table 3 shows the correlation between the values obtained from 235 patients with the conventional and new test papers. The rate of complete coincidence (i.e., the rate at which the same values were observed at each step for the two products) was 83.8%. Rates of 98.5%, 92.1%, and 95.7% were observed for sensitivity, specificity, and coincidence from the 2 × 2 table with the standards of the conventional test paper. However, we observed a tendency for the new test paper to give slightly higher values compared to the conventional test paper.

TABLE 3. Correlation between portions for protein test between the new test paper and conventional test paper*

	Conventional test paper, protein test portion (mg/dL)					
	–	±	30 (1+)	100 (2+)	300 (3+)	Total
New test paper, protein test portion (mg/dL)						
–	93	2				95
15	8	4				12
30		12	30	1		43
100			6	42	2	50
≥ 300				7	28	35
Total	101	18	36	50	30	235
Conventional test paper, protein test portion ^a						
Negative Positive Total						
(–) (≥ ±)						
New test paper, protein test portion						
Negative (–)	93	2	95			
Positive (≥ 15)	8	132	140			
Total	101	134	235			

^aSensitivity = 98.5%; specificity = 92.1%; rate of coincidence = 95.7%; rate of complete coincidence = 83.8%.

Correlation Between the New Test Paper and the Quantitative Method

Protein

Table 4 shows the correlation between the quantitative analysis and qualitative values of the test paper. The protein test results of the new test paper show the urinary albumin concentration in the low-concentration region, and the urinary total protein concentration in the high-concentration region. Therefore, in the high-concentration range (> 30 mg/dL), a comparison was made between the qualitative values of the new test paper and the quantitative value of total urinary protein. In the low-concentration range (< 29.9 mg/dL), a comparison was made between the qualitative values and the urinary albumin concentration. In the high-concentration range, an excellent correlation was shown between the qualitative value and the total urinary protein concentration. In the low-concentration range, variation in the qualitative values was observed. However, the rate of complete coincidence of the qualitative and quantitative values was good (77.0%).

Creatinine

Table 5 shows the correlation between the results of quantitative analysis and qualitative values with the new test paper. There was a tendency for slightly higher values with the new test paper compared to those for

TABLE 4. Correlation between quantitative method and protein test portion of the new test paper*

	Urinary albumin concentration (mg/dL)		Urinary total protein concentration (mg/dL)				Total
	< 8	8–29.9	30–64.9	65–199.9	≥ 200		
New test paper, protein test portion (mg/dL)							
–	82	13					95
15		12					12
30		18	25				43
100			11	35	4		50
≥ 300				8	27		35
Total	82	43	36	43	31		235
Quantification method (8 mg/dL based on negative and positive results)							
Negative Positive Total							
(< 8) (≥ 8)							
New test paper, protein test portion							
Negative (–)	82	13	95				
Positive (≥ ±)	0	140	140				
Total	82	153	235				

^aSensitivity = 91.5%; specificity = 100%; rate of coincidence = 94.5%; rate of complete coincidence = 77.0%.

TABLE 5. Correlation between quantification method and creatinine test portion of the new test paper*

	Urinary creatinine concentration (mg/dL)					Total
	< 25	25–74.9	75–149.9	150–249.9	≥ 250	
New test paper, protein test for creatinine (mg/dL)						
10	14	8		1		23
50	2	68	14		1	85
100		8	64	12		84
200			6	25	7	38
300		1	3		1	5
Total	16	85	87	38	9	235

*Rate of complete coincidence = 73.2%.

quantitative analysis. In two cases the qualitative values were markedly lower than the quantitative values (164 and 561 mg/dL, respectively). The rate of complete coincidence was 73.2%.

P/C ratio

Table 6 shows the correlation between the P/C values obtained from the quantitative and qualitative values. Twelve cases judged as normal by the new test method

TABLE 6. Correlation of P/C ratio between quantitative analysis and the new test paper

TABLE 3. Correlation of P/C ratio between quantitative analysis and the new test paper						
P/C (quantification) (mg/gCr)						
	Normal dilution	< 80	80–299.9	300–499.9	≥ 500	Total
New test paper, P/C ratio (mg/gCr)						
Normal dilution	3	4	2	2	1	12
Normal		72	4			76
150		3	7			10
300			12	2	6	20
> 500		1	3	16	97	117
Total	3	80	28	20	104	235
Quantification method (80 mg/gCr was the basis of negative and positive results) ^a						
	Negative (< 80)	Positive (≥ 80)	Total			
New test paper, P/C ratio						
Negative (Normal)	72	4	76			
Positive (≥ 150)	4	143	147			
Total	76	147	223			
Quantification method (300 mg/gCr was the basis of negative and positive results) ^b						
	Negative (< 300)	Positive (≥ 300)	Total			
New test paper, P/C ratio						
Negative (normal)	86	0	86			
Positive (≥ 300)	16	121	137			
Total	102	121	223			

^aWhen qualitative data with a P/C ratio of 150 mg/gCr or higher is taken as positive; sensitivity=97.3%; specificity=94.7%; rate of coincidence=96.4%; rate of complete coincidence=77.0%.

^bWhen qualitative data with a P/C ratio of 300 mg/gCr or higher is taken as positive; sensitivity=100.0%; specificity=84.3%; rate of coincidence=92.8%; rate of complete coincidence=77.0%.

and the quantitative method were excluded from the calculations for sensitivity, specificity, and coincidence rate.

The rates of sensitivity, specificity, and coincidence were 97.3%, 94.7%, and 96.4%, respectively, for cases judged as positive with the data of 150 mg/gCr by the new test paper method, and 80 mg/gCr by the quantification method. When cases with 300 mg/gCr or more in both the new test paper method and the quantification method were taken as positive, the rates of sensitivity, specificity, and coincidence were 100.0%, 84.3%, and 92.8%. The rate of complete coincidence was 77.0%.

DISCUSSION

Currently in Japan, about 30,000 patients with renal failure undergo initial renal dialysis every year. The total number of patients who require renal dialysis exceeds 200,000, with medical expenditures of more than one trillion yen per year. The first step in treating renal diseases is to perform urinalysis for the early detection of hematuria and/or proteinuria. The use of

urinalysis has been established for patients of all ages, from newborns to the elderly, and urinary protein test paper, as well as urinary occult blood test paper, is widely used.

The reaction principle of urinary protein test paper, which was developed in 1957, depends on an error in the pH indicator, based on the protein content. The detection sensitivity is 10–30 mg/dL; however, several problems have been cited, including the different reactivities of the test paper depending on the albumin content in the total urinary protein, and the marked influence exerted by the urinary volume (concentration or dilution). Particular disadvantages include a small color variation in the region of $\pm$ (trace) and errors in the positive direction for samples with a high specific gravity. The reliability is somewhat low with respect to the accuracy of measurement, and therefore it is necessary to confirm the results by such techniques as the sulfosalicylic acid (SSA) method (8).

Because individual variations are small in the urinary excretion of creatinine, the P/C ratio calculated on the basis of 1 g of creatinine is an excellent clinical index by which to observe the clinical progress of a patient (12).

This value is widely used as the index for estimating the daily urinary protein excretion. Even though there are limitations, such as individual variations or sex differences in creatinine excretion, and the rate of urinary excretion of protein is not constant (being dependent on the body position, body movement, diet, and blood pressure), the P/C ratio has been used clinically as a simple method for evaluating urinary protein with no influence from the dilution or concentration of urine collected in the outpatient clinic. Therefore, it is important to be able to clinically screen the P/C ratio using test strips.

We examined a new test paper strip (the Multistix PRO 10LS) in which the $\pm$ region of the protein test was changed into the test portion specific to albumin, and a creatinine test part was added. With this test paper, it is possible to obtain a P/C ratio as the protein content adjusted to the creatinine excretion. When we studied the correlation between the new test paper and the conventional paper, the sensitivity, specificity, and rate of coincidence were 90% or more, and there was a tendency for slightly higher values to be obtained with the new test paper. Therefore, we did not encounter any problems in changing the test paper. In the protein testing portion of the new product, the low-protein region shows the urinary albumin concentration, and the high-protein region shows the total urinary protein concentration. In the high-protein-concentration region, the quantitative results for total urinary protein showed a good correlation with the results of the qualitative analysis; however, in the low-concentration region, the data were scattered in the qualitative analysis as compared to the urinary concentration of albumin. In a comparison between the quantitative measurement of creatinine and the qualitative values obtained with the new test paper, the rate of complete coincidence was slightly low (73.2%), with the qualitative value being slightly higher. In a few cases the value obtained by the qualitative measurement was smaller than that obtained by the quantitative measurement. The reaction principle of the creatinine reagent is based on the peroxidase reaction between creatinine and the copper complex, with possible interference by highly concentrated ascorbic acid as a reducing agent. However, in the conventional test, the qualitative value of creatinine was reduced by one rank in the presence of ascorbic acid at a concentration of 1,000 mg/dL. The mechanism behind this difference is unknown and must be clarified in future studies.

The most important characteristic of this new test paper is that with it one can calculate the P/C ratio using the qualitative values of creatinine and protein. The value of the P/C ratio can be obtained using the table with a visual reading. With instrumental reading, the

calculation is made automatically and the value is displayed and printed by the device. When the creatinine concentration is 10 mg/dL and the protein concentration is negative, the urine samples might be diluted, and "re-test" is displayed.

The normal range of the P/C ratio is <80 mg/g Cr for the new test paper. The abnormal range is divided into three parts: 80–299.9 mg/gCr, 300–499.9 mg/gCr, and >500 mg/gCr. It has been reported that in Japan the normal value of the urinary excretion rate (mg/gCr: albumin/creatinine (A/C) ratio) of albumin is less than 24.6 mg/gCr (13). In the Diabetes Treatment Guide of the Japanese Diabetes Society, the presence of early renal lesions is indicated by microalbuminuria of 30–300 mg/gCr. If the level is more than 300 mg/gCr, the presence of kidney lesions is clearly indicated. This situation corresponds to continued positive (+) results of the qualitative test for urinary protein. Therefore, there is no problem in designating 300 mg/gCr as abnormal; however, values of less than 80 mg/gCr require further discussion.

Warram et al. (14) reported that in type 1 diabetes mellitus with microalbuminuria with an A/C ratio of 70 mg/gCr, apparent albuminuria does not occur, but at 132 mg/gCr there is a possibility of apparent proteinuria. In the low range of protein concentration, it is reasonable to designate 80 mg/g Cr as abnormal, since the region of low protein concentration in the new test paper is relatively high with respect to albumin specificity. For screening of diabetic nephropathy, an A/C ratio of 30 mg/gCr or more should be considered abnormal.

In a previous study (4) the daily urinary excretion was estimated from the P/C ratio in random urinary samples collected at a clinic, and the P/C ratio in random urine samples was substituted, with certain restrictions, as the daily protein excretion. In that study, quantitative measurements were compared between 24-hr urine and random urinary samples. In our study, we did not compare 24-hr urine and random urine using the new test paper. However, we compared P/C ratio values obtained by the quantitative method and the test paper method. As a result, we observed a good correlation and excellent sensitivity, specificity, and rate of coincidence if ≥ 80 mg/gCr was considered as positive in the quantitative method. Based on these results, we believe it is possible to estimate daily protein excretion from the P/C ratio by the test paper method.

The following procedure for evaluating proteinuria is recommended in the "Clinical Diagnosis and Guidelines for Clinical Treatment" by the National Kidney Foundation (15): Using urinary samples, obtained early in the morning or at any other time, albumin is determined with a specific test paper, or the A/C ratio

or P/C ratio is obtained. The Japanese Society of Nephrology undertakes educational activities all over the country using "Recommendations for Urinalysis," and the Society is also considering the preparation of guidelines. Because A/C or P/C ratios are useful for correction of data with respect to the dilution or concentration of urinary samples, we hope that the test paper examined in this study will be used for that purpose. The clinical usefulness of this new test paper should be examined in many types of disease, including IgA nephropathy, diabetic nephropathy, nephrotic syndrome, and nephrosclerosis.

CONCLUSIONS

We examined a new test paper, the Multistix PRO 10LS, in which the $\pm$ (trace) region of the conventional test portion for protein was made specific with respect to albumin, and a portion for creatinine was added so that a correction could be made on the basis of creatinine. We reached the following conclusions: 1) With this new test paper, results for urinary protein can be obtained from two types of information displayed in regions of low protein concentration (albumin) and high protein concentration. 2) Roughly similar results were obtained with the conventional test paper and the new test paper. The new test paper was slightly more sensitive, and the new test paper tended to give slightly higher values compared to the conventional test paper. 3) With the new test paper, we observed a good correlation between the low-concentration region and the quantified value of albumin, and between the high-concentration region and the quantified value of total protein. 4) There was a good correlation between the qualitative value of creatinine measured by the new test paper and that measured by the conventional quantification method. Cases with a much lower qualitative value than quantitative value were observed; however, the reason for this is unclear and awaits further study. 5) There was a good correlation between the P/C ratio obtained with the new test paper and that observed with quantitative analysis. Also there was a good correlation in the P/C ratio between 24-hr urine and urinary samples obtained at any time of day. Therefore, it is possible to predict the amount of protein excreted during the day from results obtained using urinary samples any time of day.

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