Biochemical Tests in Medicine

Urine analysis: current performance and strategies for improvement

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Carefully performed selective biochemical testing of urine may be useful and cost effective.^{1,2} Nevertheless, in addition to ensuring that tests are performed to answer specific clinical questions, it must be ensured that the analysis is carried out correctly. This paper reviews current analytical performance achieved, describes real and potential sources of analytical difficulties, and expands on the details of simple strategies² to overcome these problems.

Performance of urine analysis

Several experimental studies performed over the past quarter century have shown that problems have arisen and are, unfortunately, still apparent.

In 1961 Kirkland and Morgan assessed the urine analysis of glucose and protein in four wards and an antenatal clinic.³ In the major component of the study, 1033 urine specimens were analysed in the ward or clinic and also in the laboratory. It was assumed that the laboratory gave true results. There were 14 false positive results and 132 false negative results for glucose, the laboratory detecting 212 positive results. Proteinuria was stated by the laboratory to be present in 281 urine specimens but the wards and clinic only detected 164 of these, 21 false positives being recorded.

Becker *et al*, in assessing a commercial urinary quality control product, assayed pH level and the concentrations of protein, glucose, ketones, and blood, and at least one error was made in 89% of the assays of the material, these being performed by 12 laboratory staff.⁴ Such errors were apparent even with very loose control limits as follows: pH—5 to 6; protein—trace to 2+; glucose—1+ to 3+; ketones—trace to 2+; blood—trace to 2+. After the staff had been retrained the error rate fell to 38%, but three of the six laboratory staff remaining in post throughout the study did not actually improve their analytical skills.

In 1977 Assa studied urine analysis performed in 35 Israeli laboratories, and, although it was stated that some methods were inaccurate and obsolete, there were few false positive or negative results; in most cases, such apparently erroneous results were in fact due to the nature of the material circulated for analysis.⁵

In order to assess whether the differences between the findings of Kirkland and Morgan³ and Assa⁵ did reflect differences in the experience and training of the staff performing the analyses or whether a genuine improvement in the standard of urine analysis had occurred, Simpson and Thompson provided three specimens of urine to 66 wards and clinics.⁶ An appreciable number of the 1456 analyses were incorrect (table I).

TABLE I—Percentage of false positive and negative results in urine analysis performed by 66 wards and clinics (n=1456)

Analyte	False positive	False negative
Protein	5	5
Glucose	13	10
Ketones	2	11
Bilirubin	<1	13
Blood	<1	18
Urobilinogen	5	1

TABLE II—Percentage of false positive and negative results in urine analysis performed by 81 Australian laboratories and 26 wards and clinics in an Australian hospital

Analyte	Laboratories		Wards and clinics	
	False positive	False negative	False positive	False negative
Protein	3	<1	4	1
Glucose	0	1	<1	<1
Ketones	0	3	2	3
Bilirubin	1	41	2	31
Blood	1	30	2	8
Urobilinogen	3	0	2	0
Nitrite	0	0	<1	6

Comprehensive studies of the performance standards achieved for both quantitative and qualitative urine analyses have been recently performed by a South Australian group. Six contrived urine specimens—that is, normal urine with weighed in amounts of additional analyte—were circulated to 19 South Australian laboratories in 1980, and, although laboratories could generally distinguish between a positive and negative result, the discrimination of degrees of positivity was poor, particularly for glucose and bilirubin.⁷ As a result of this trial, six specimens of urine were circulated to 81 Australasian laboratories in 1981,⁸ and the same six specimens were analysed in 26 wards or clinics of a South Australian teaching hospital.⁹ The specimens were circulated in three batches of two, and educational reports on the performance achieved were issued after each distribution. Table II shows the results obtained by laboratories and in wards and clinics.

Both laboratories and wards and clinics had difficulty in distinguishing degrees of abnormality, particularly for glucose, and had, perhaps not surprisingly, major problems when the analyte concentrations were contrived to give weakly positive results. In view of the poor performance achieved in the hospital a second programme was conducted in 1982,¹⁰ in which four sets of two specimens were distributed to each ward and clinic, educational reports were circulated after each distribution, a tape/slide presentation was made available to all staff after the third distribution, and a demonstration/tutorial was presented to various groups at the same time; the results showed that the analytes that caused problems for Australasian laboratories and in wards and clinics in 1981 continued to cause similar problems and that educational intervention did not appreciably improve performance.

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In South Australia an annual screening programme, using urine analysis for protein, glucose, blood, and nitrite, is made available to the general public by the rotary clubs. In 1983 a specimen of urine was circulated to all centres performing the urine analysis; the specimen, a commercial quality control urine, had values said by the manufacturer to be: protein—1+ to 2+; glucose—trace; blood—2+ to 3+; and nitrite—positive. The results from 32 centres showed that the incorrect results were obtained for protein, glucose, blood, and nitrite at rates of 19%, 72%, 19%, and 50%, respectively, 9%, 9%, 6%, and 50% of the results being false negative results (Fraser CG, unpublished results). The analysts included nurses, general practitioners, and individuals in a range of occupations not allied to medicine.

Current problems

The studies of the performance standards attained for urine analysis suggest that laboratories generally have somewhat better performance than that attained in wards and clinics. There are several main analytical problems associated with urine analysis. Analyses of pH, ketones, and urobilinogen have no particular problems. For urinary protein, the major problem is the differentiation of negative and trace positive results. Glucose analyses do differentiate between negative and positive results, but there is poor discrimination between degrees of positivity. Bilirubin assays pose the problem that many false negatives are found. For blood, false negative and positive results are found, and there is poor differentiation between degrees of positivity. The major problem with nitrite analyses is false negative results.

Many false negative results are found, particularly when the analyte concentrations are just above the detection limit. Many urine analysis tests are performed for screening purposes²—that is, to detect disease in the apparently healthy or in particular groups at risk. For such clinical purposes it is highly desirable not to miss cases, and therefore false negative results should not occur.

Sources of the problems

There are many factors which can affect analyses of urine using reagent pad dipsticks. In urine analysis, the analyst has a major effect on the results obtained, and the differences obtained by individuals testing the same urine specimens have been highlighted in certain evaluations of the performance characteristics of dipsticks. Individuals do have different perceptions of identically coloured reagent pads. Moreover, certain of the colour changes on some dipsticks are subtle, especially when the urine specimens are dark in colour or contain blood or bilirubin. Undoubtedly, experience plays a large part in gaining the correct results; unfortunately, urine analysis is often considered a task to be performed by junior members of staff. In addition, results are usually transcribed into notes, and transcription errors can and do occur. Furthermore, the analytical technique used can affect results; for example, the finding of false trace protein results can be in part explained by the fact that if a dipstick where pH and protein reagent pads are adjacent is soaked with alkaline urine and held vertically rather than the excess urine being shaken off and the dipstick held horizontally the reagent runs over from the pH pad to the protein pad.

The environment in which urine analysis is performed can also affect results, particularly the illumination in the workplace and the colour of the walls of the room. Furthermore, reagent pad dipsticks do have a finite shelf life, and their performance does deteriorate with time. Many of the false negative results seen in the surveys discussed earlier may have been due to the use of outdated materials. Moreover, certain reagent pads, notably for glucose and blood, do give a speckled appearance; the correct interpretation of such findings is that the colour of the darkest speckles should be compared with the colour comparison chart.

The common survey finding that degrees of positivity for glucose were not consistent show an important source of error—namely, the reading of the colours at inappropriate times. Certain reagent pad

dipstick reactions are very kinetic in nature, and strict adherence to timing is essential. If this cannot be achieved, it has been recommended that urine analysis is performed strictly as a qualitative procedure (negative/positive) rather than as a semiquantitative test.¹¹

Strategies for improving performance

In clinical biochemistry laboratories all tests are subject to quality control procedures; such procedures are essential not only to monitor progressive performance but also to try to prevent errors occurring and to improve laboratory performance.¹² Guidelines on the performance of tests outside laboratories stress the great importance of quality control.^{13,14}

Traditionally, quality control procedures are considered simply to encompass the analysis of materials with known values for each analyte each time an analysis is performed.¹² This technique is simple, and control materials are available from the commercial suppliers of reagent pad dipsticks or can be made up by a laboratory. The use of commercial materials does, however, add expense, the analyte concentrations are always the same for a particular batch of control material, the material is not exactly the same as human urine, and such material is usually freeze dried and requires careful reconstitution with an exact amount of distilled water being pipetted into the container. It is probably of most value for hospitals to enlist the aid of the clinical biochemistry laboratory staff, as recommended in published guidelines on the performance of analytical tests outside laboratories,^{13,14} and for the laboratory to distribute a wide range of specimens containing different concentrations of analyte to all areas where urine analysis is performed in sufficient volume for all who do such tests to assess their own performance. As with all quality control programmes, this should be done on a continuous basis.

A simple, cheap method of quality control is replicate analyses. For urine analysis, it could be policy that some specimens, preferably with results covering a range of analyte values, are retained by each analyst for the subsequent analyst to assay. Differences between the sets of results would undoubtedly highlight errors in technique and interanalyst variability.

Further quality control procedures can be easily instituted in all situations where urine analysis is performed. These include the quality control of reagents, making sure that none has expired and that they are adequately stored, and of the environment where urine analysis is performed, ensuring that the surroundings are well lit and of a neutral colour.

Although objective studies have suggested that education does not improve existing standards, increased emphasis on the theory and practice of urine analysis in early medical and nursing training could be advantageous, particularly if such instruction was provided by clinical biochemists using a tutorial/demonstration/practical class approach rather than formal, more didactic teaching.

The clinician also has a most important part to play in quality control. When a result does not fit in with either clinical impressions or previous results for the same patient a questioning attitude should be adopted and the possibility of analytical error raised with the staff members performing the urine analysis. Quality control should also be extended to specimens, and only fresh uncontaminated urine should be passed as suitable for analysis.

Conclusions

Urine analysis, as currently performed in wards, clinics, and general practitioners' surgeries, does have deficiencies. It is by no means unique in this respect.¹⁵ The few objective studies that have been performed have shown that laboratory performance of glucose, bilirubin, and blood gas analyses is superior to that achieved nearer the patient. In part, this is likely to be due to the degree of complexity of current laboratory instruments, and the centralisation of urine analysis using the automatic analytical equipment now available—for example, Ames Clinitek, Ames

Clinitek Auto 2000, and Boehringer Mannheim Urotron—may eliminate many of the avoidable errors commonly encountered.

Nevertheless, I believe that this would be impracticable, expensive, and undesirable. Urine analysis fulfils many of the criteria of the ideal laboratory test, being simple to perform, inexpensive, easy to interpret, quick, applicable in many clinical settings, and able to be carried out in a wide variety of situations. The problems that arise with urine analysis generally occur for explicable reasons. These difficulties are common enough to make current standards unsatisfactory. I urge the adoption of the quality control strategies outlined here with a view to generally improving analytical performance. This can only result in better clinical care.

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(Accepted 2 May 1985)

Is unselective biochemical urine testing cost effective?

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Forty years ago clinical laboratories could analyse very few biochemical constituents in plasma or serum, and urine testing was widely used as an aid to diagnosis. This testing was usually left to nurses and medical students, who often used out of date or even wrongly prepared reagents and dirty test tubes, with misleading results. Indeed, the validity of the results was so doubtful that in 1962 their diagnostic value was compared to that of palmistry.¹

The development of sensitive plasma or serum assays, which can often detect changes associated with mild or very early disease, should have reduced the need for urine testing. At about the same time, however, it became possible to manufacture reagent strips and tablets; single strips were impregnated with several bands of different reagents and it was soon possible to test for several substances simultaneously, making unselective urine testing deceptively easy but not cheap. Single test strips cost between £1.65 and £6.34/100 (table), whereas the price of the popular multireagent strips varies from £3.20 to £12.00/100 (table); in 1984 this hospital spent about £18 000 on reagent strips and tablets. Collection containers and staff time probably cost at least as much again. Similar conclusions have been reached by other authors.^{2,3}

Because a test is relatively expensive does not necessarily mean that it is not cost effective. Cost effectiveness in medicine cannot be quantified accurately but depends on the speed of obtaining results, the interpretation and clinical use made of them, and, above all, their analytical reliability.

The analytical reliability of urine testing should have improved because commercial strips eliminate the need for test tubes and incorporate standardised reagents. Unfortunately, the clear instructions and warnings issued by manufacturers (for example, Miles Laboratories⁴) about storage and use are often ignored, and multi-

reagent strips are especially liable to be used incorrectly.⁵ Strips may be kept on the wards too long after the bottles have been opened, but rarely are they or their users subjected to the quality control procedures now routine in hospital laboratories.

The interpretation and clinical use of results often depends on the philosophy of the investigator. If testing is used to answer a specific clinical question (for example, is hypoalbuminaemia due to gross proteinuria?) the results are likely to be noted, interpreted correctly, and acted on. If, however, testing is used to screen an unselected population for subclinical disease such as diabetes mellitus in the vague hope that something may turn up the results, in my experience, are more likely to be unreliable, ignored, and, if noted, misinterpreted.

Clinical value of urine testing

The possible clinical value of testing urine varies for each biochemical constituent.

GLUCOSE

Glucose can be detected by routine testing at urinary concentrations of about 5 mmol/l. Glycosuria of this degree occurs either in the usually harmless and relatively common condition of renal glycosuria or if the plasma glucose concentration has exceeded about 11 mmol/l at some time since the last urine specimen was passed (usually due to diabetes mellitus). The diagnosis of renal glycosuria requires proof that the renal threshold for glucose is below 11 mmol/l (198 mg/100 ml).

In a severe diabetic plasma glucose concentrations above 11 mmol/l at all times of day cause thirst and constant glycosuria with polyuria; thirst, polyuria, and other symptoms suggest the need to assay plasma glucose. In such severe disease glycosuria is rarely an unexpected finding. In less severe, often asymptomatic cases plasma concentrations may be high enough to cause glycosuria only after eating; the diagnosis may be missed if reliance is put on screening a random urine specimen, which may have been passed long after a meal. In the least severe cases there may be no

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Based on a paper prepared at the request of the Association of Clinical Biochemists' Scientific Committee Working Party for Clinical Investigation which first appeared in *An Clin Biochem* 1982;19:8-11.