Products for office pathology testing

An assessment of three test systems

Patricia Ludowyk
Anthony Lea
David Hailey

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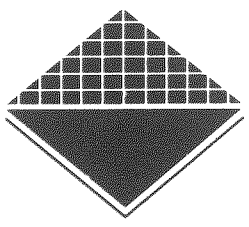

AUSTRALIAN INSTITUTE OF
HEALTH & WELFARE

PRODUCTS FOR OFFICE PATHOLOGY TESTING

An assessment of three test systems

Patricia Ludowyk
Anthony Lea
David Hailey

Comments on the material in this report would be welcome and should be forwarded to:

The Head
Health Technology Division
Australian Institute of Health and Welfare
GPO Box 570
CANBERRA ACT 2601

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CONTENTS

EXECUTIVE SUMMARY

- This report presents preliminary assessments of the performance of three products intended for pathology testing outside the laboratory setting.

- The products considered are: URISCREEN - a test for detection of urinary tract infection (UTI); MICRAL-TEST - a test for detection and semi-quantitative measurement of urinary microalbumin; and the HemoCue Blood-Glucose Test - a analyser for quantitative measurement of blood glucose levels.

- Particular consideration has been given to the analytical performance of the products and their potential for contribution to patient management. Cost factors are briefly discussed.

- The assessments reflect the data available to the Institute from the literature and from distributors of the products. More definitive descriptions of performance and potential impact would require additional information.

- URISCREEN is a low unit cost test which is easy to perform and appears to be a useful method for testing urine specimens for the presence of bacteria. Some questions remain regarding the significance of infection not detected by the test because of low concentrations of bacteria.

  URISCREEN is considered to have the potential to contribute to patient management in general practice and hospital settings. Users of the test should be aware of its level of performance, particularly the relatively high proportion of false positive results. Both URISCREEN and other products for detection of UTI offer equivalent or better performance than microscopy on urine specimens.

- MICRAL-TEST is inexpensive and could offer an effective method of testing specimens within the laboratory. Data from trials indicate that the test has good sensitivity and specificity. There is some uncertainty concerning the number of false positives about the decision point (20 mg/L). The colour generated in the test varies with the depth and time of immersion and the time of reaction. Such variation could decrease the reliability of this product in the hands of operators who do not have laboratory experience.

- The HemoCue Blood-Glucose Test is based on a satisfactory chemistry and on the basis of limited available data appears to be capable of giving appropriate performance in the non-laboratory environment. It is considered that, as is the case with other glucose analysers, pathology accreditation provisions should apply to use of this product.

- While analytical data were available for each product, there was very little information on their performance under routine conditions outside the laboratory. It would be desirable for all products intended for use in the non-laboratory setting to be

subject to properly designed investigations under Australian conditions.

- These products are useful approaches to the development of methods for decentralised testing. The potential for their use outside the laboratory to contribute to effective patient management and to achieve cost savings will depend on a number of factors related to training, reimbursement, patterns of practice and availability of alternative types of testing.

- The extent to which pathology accreditation provisions should apply to kits used outside the laboratory is a matter that might usefully be considered by the National Pathology Accreditation Advisory Council.

INTRODUCTION

This report consists of preliminary assessments of three products intended for pathology testing outside the laboratory setting. This work was undertaken at the request of the Department of Health, Housing and Community Services (HHCS) following submission of the products for consideration by the Pathology Services Table Committee.

The three products considered are: URISCREEN - a test for detection of urinary tract infection (UTI) which is distributed by Medical Industries Australia Pty Ltd; MICRAL-TEST - a test for detection and semi-quantitative measurement of urinary microalbumin which is distributed by Boehringer Mannheim, Australia; and the HemoCue Blood-Glucose Test - an analyser for quantitative measurement of blood glucose levels distributed by Medipac Pty Ltd.

Information on these products was sought from the manufacturers and distributors and from the literature. The contents of the report reflect the data that were available to the Institute. A comprehensive survey and analysis of each of these products has not been attempted at this stage and more definitive descriptions of their performance and potential impact would require additional information.

In assessing the available information, the Institute took particular note of data on the analytical performance of the test methods, results (where available) obtained under non-laboratory conditions, and potential for contribution to patient management through availability of decentralised pathology tests. The speed and robustness of the tests and any training issues were also considered.

Some note has been taken of cost factors and the potential place of each of these products in relation to laboratory investigation. However, this report does not address reimbursement issues, which are the responsibility of HHCS.

Each product is considered separately in the following three sections.

URISCREEN

Description of product

URISCREEN is a rapid test for the detection of bacteriuria and somatic cells in urine. The basis of the test is that organisms likely to be found in urine, leucocytes and blood liberate catalase, which splits hydrogen peroxide. The test can be read within two minutes after the addition of urine and peroxide. Interpretation is simple in that if a ring of foam develops on the top of the liquid, the test is positive.

Urine testing in pathology laboratories using bacterial culture takes two days, whereas UTI can be detected with URISCREEN within five minutes. This contributes to prompt diagnosis. Physicians may have to wait 48-72 hours for results from a laboratory and often commence antibiotic treatment prior to these becoming available.

It has been estimated that approximately 80% of tests for UTI are negative. The manufacturer suggests that if only positive-testing urine specimens were subsequently sent to a laboratory, there would be a substantial saving on pathology costs as URISCREEN costs only $3.50 per test.

Analytical performance

The performance of URISCREEN has been compared with standard laboratory procedures and other techniques in a number of studies. Details are given in the Annexe (page 7). The sensitivity (the probability that a person with disease has a positive test) and specificity (the probability that a person without disease has a negative test) are considered stable measures of the performance of a test. The positive predictive value (PPV) and negative predictive value (NPV), which are measures of the probability that a given result is correct, depend on the prevalence of the disease or substance being measured.

With high bacterial concentrations ($>10^5$ CFU/mL), results for sensitivity of URISCREEN reported from various studies range from 82% to 100% and those for specificity from 55% to 83%. Compared with other kits for detecting UTI, URISCREEN has higher or equivalent sensitivity and lower specificity. Values for PPV and NPV average 42% and 94% respectively.

The data for sensitivity suggest that URISCREEN has useful performance for detecting UTI. Users of the test would need to be aware that in a minority of patients infection would not be detected because of false negative results which could contribute to missed diagnoses.

The relatively low specificity reported from most studies suggests that there will be large numbers of false positive results when the test is used in general practice. The high false positive rate could result in missed diagnoses or in unnecessary prescription of

antibiotics. However, use of the test should produce worthwhile gains to health care as expenditure on antibiotics and laboratory testing will be avoided in cases where infection is correctly excluded.

Catalase-negative organisms, such as streptococci, would not be detected by URISCREEN and are a potential source of false negative results. However, about 60% of streptococcal-positive urine specimens also contain leucocytes which are detectable by this system. URISCREEN is unable to distinguish between bacteriuria, pyuria or hematuria and will give a positive result if any of these are present.

The detection limit of 5×10^4 pathogens per mL specified for URISCREEN may not always be appropriate for specimens from men and children. Lower concentrations, of the order of 10^3 pathogens per mL, are considered significant by some pathologists. Lower levels are also considered significant in symptomatic adult females.

The trials reported to date are mostly from hospitals. Clinical trials in the general practice environment using operators without laboratory training are needed to give an indication of the performance of URISCREEN under the conditions for which the product is to be marketed.

The available data suggest that URISCREEN has the potential to provide a useful diagnostic aid in general practice, but that users of the test would need to be aware of its level of performance.

Safety for the operator

The only scheduled poison used in the test is 10% hydrogen peroxide (supplied in 10 mL bottles). The test tubes are plastic and the test is stoppered except when urine and peroxide are being added. There would be the usual hazard of handling potentially infectious urine.

Intended target and scope of the test

Over two million urine samples per year are sent for urinalysis at pathology laboratories in Australia (as measured by Medicare data - Items 2127 and 2128). The high level of negative results obtained in urine testing (approximately 80%) suggests that present procedures are inadequate. URISCREEN is proposed as a rapid test for use as an alternative to laboratory testing.

URISCREEN is intended for use by general practitioners, physicians and hospital staff. It may be useful to laboratories as a preliminary test to reduce workload and costs.

Cost issues

There is potential for cost savings if the test is used instead of bacterial culture at a laboratory. The level of use in general practice would be influenced by the level of reimbursement.

Cost savings to the Australian health care system could possibly result from:

. the elimination of the cost of cultures when bacteruria is correctly excluded;
. a reduction in consultations; and
. a reduction in the prescription of unneeded antibiotics.

Savings would be reduced if:

· there was double-testing of specimens (follow up by a laboratory);
· the reduction in repeat consultations was limited; or
· false negatives resulted in significantly higher treatment costs.

Quality control requirements

Positive and negative controls should be performed on each new pack of tests. These controls are supplied with the kits. There is a need for non-laboratory users to be familiar with the necessary controls and to understand their application and need for any follow up action.

Conclusions

URISCREEN is a low unit cost test which is easy to perform and appears to be a generally acceptable method for testing urine specimens for bacterial infection. However, users of the test should be aware of its level of performance, and the significance of false positive and false negative results.

Some questions remain regarding the significance of infection not detected by the test because of low concentrations of bacteria (particularly in children and men) or a lack of catalase activity.

URISCREEN is considered to have the potential to contribute to patient management in general practice and to achieve cost savings. The extent of any savings will depend on a number of factors. There remains a need for data on the performance of this product under routine conditions outside the laboratory.

A number of other diagnostic kits for UTI are currently marketed. These dip stick products include leucocyte esterase, nitrite and other indicators of UTI. It is considered that both URISCREEN and these competing products offer equivalent or better performance than that of microscopy in the non-laboratory setting.

ANNEXE - SUMMARY OF STUDIES ON ANALYTICAL PERFORMANCE OF URISCREEN

Berger et al. (1) compared the sensitivity, specificity, PPV and NPV of URISCREEN and Dip stick (Ames) with standard laboratory culturing and chamber counts when a significant bacterial concentration (>10^5 CFU/mL) was present:

Test	Sens.	Spec.	PPV	NPV
Dipstick				
Nitrite	42%	92%	68%	82%
Leukocyte	77%	75%	65%	87%
Erythrocyte	66%	76%	60%	73%
URISCREEN	83%	71%	79%	76%

They concluded that the URISCREEN method is sensitive, easy to perform and should prove useful for the detection of UTI.

Larone et al. (2) compared the sensitivity, specificity, PPV and NPV of URISCREEN and UTIscreen (an automated bioluminescent method for the detection of bacterial ATP, Los Alamos Diagnostics) with urine culture:

Test	Pathogens CFU/mL	Sens.	Spec.	PPV	NPV
UTIscreen	10^4	79%	85%	66%	91%
	$5x10^4$	85%	82%	58%	95%
	10^5	90%	81%	53%	97%
URISCREEN	10^4	82%	72%	50%	92%
	$5x10^4$	86%	71%	46%	94%
	10^5	89%	69%	40%	96%

They concluded that both UTIscreen and URISCREEN were acceptable methods for the detection of significant bacteria in clinical specimens.

Pezzlo et al. (3) compared the sensitivity, specificity, PPV and NPV of URISCREEN and UTIscreen with a semi-quantitative plate culture used as a reference method.

Results were obtained using concentrations of $>10^5$ CFU/mL for all organisms (AO) and probable pathogens (PP):

Test	Pathogens	Sens.	Spec.	PPV	NPV
UTIscreen	AO	92%	77%	56%	97%
	PP	95%	75%	44%	99%
URISCREEN	AO	84%	57%	38%	92%
	PP	94%	55%	31%	98%

The overall results were similar for both methods. However, URISCREEN appeared to have more false positives than UTIscreen. This may be explained by the fact that URISCREEN also detects pyuria (the presence of leukocytes in the urine). Pezzlo et al. commented that URISCREEN offers the advantages of no instrumentation, single or batch testing, less technical time and a faster turnaround time.

Pezzlo et al. (4) compared the sensitivity, specificity, PPV and NPV of URISCREEN and Chemstrip LN (a two minute enzymatic dip stick method, BioDynamics) to detect significant bacteriuria and pyuria with a semi-quantitative plate culture used as a reference method:

Test	Pathogens CFU/mL	Sens.	Spec.	PPV	NPV
CHEMstrip	$>10^3$	58%	84%	77%	68%
	$\geq 10^4$	69%	81%	65%	84%
	$>10^5$ AO	85%	77%	50%	95%
	$>10^5$ PP	3%	74%	38%	98%
	WBC>10/µL	70%	92%	86%	81%
URISCREEN	$>10^3$	64%	64%	63%	66%
	$\geq 10^4$	75%	64%	51%	83%
	$>10^5$ AO	87%	61%	37%	94%
	$>10^5$ PP	95%	59%	29%	98%
	WBC>10/µL	86%	67%	65%	88%

The cost for detection of bacteriuria and pyuria was $1.20 less per specimen for the rapid urine tests than for the reference methods. Overall, URISCREEN had a similar sensitivity for the detection of bacteriuria to Chemstrip LN, but higher sensitivity for the detection of bacteriuria at $>10^5$ CFU/mL and for pyuria.

A further evaluation (5) compared URISCREEN with Chemstrip LN. Semi-quantitative plate culture was the reference method:

Test	Pathogens	CFU/mL	Sens.
Chemstrip	AO	10^4_5	87%
	AO	10^5	93%
	PP	10^4_5	83%
	PP	10^5	86%
URISCREEN	AO	10^4_5	90%
	AO	10^5	94%
	PP	10^4_5	88%
	PP	10^5	92%

These results indicated that URISCREEN and Chemstrip are similar in sensitivity for the detection of bacteriuria and pyuria.

Beard et al. (6) evaluated three urine screening systems (Bac-T-screen, UTIscreen and URISCREEN) and compared them to quantitative bacterial culture:

Test	Sens.	Spec.
UTIscreen	73%	78%
Bac-T-screen	57%	87%
URISCREEN	82%	55%

They concluded that UTIscreen and URISCREEN should be used to eliminate the culturing of negative samples.

Fedorko and Congdon (7) evaluated two urine screening systems (Bac-T-screen and URISCREEN) when the level of microorganisms was low (10^4 CFU/mL) and when specimens contained both leukocytes and significant numbers of microorganisms. Standard culture techniques were used as a reference:

Test	Pathogens CFU/mL	Sens.	Spec.	PPV	NPV
Bac-T-screen	10^4	82%	70%	45%	93%
	significant	96%			99%
URISCREEN	10^4	91%	43%	33%	94%
	significant	100%			100%

They concluded that both screening tests were inexpensive and easy to use and would be acceptable for use in clinical microbiology laboratories.

Trevino and Nauschuetz (8) evaluated a catalase screening method (CAT) and a leukocyte esterase-nitrite dip stick (LEN) for efficacy in detecting bacteriuria:

Test	Pathogens CFU/mL	Sens.	Spec.	PPV	NPV
CAT	10^4	89%	78%	37%	98%
	10^5	94%	77%	29%	99%
LEN	10^4	78%	90%	62%	96%
	10^5	83%	89%	52%	98%

They concluded that the catalase screening method was a more sensitive method for detecting bacteriuria than the leukocyte esterase-nitrite dip stick method.

Dimech et al. (9) determined the ability of URISCREEN to detect urinary tract infections in comparison with standard culture, leukocyte esterase activity and nitrite detection:

Test	Sens.	Spec.	PPV	NPV
leucocyte esterase	68%	79%	48%	89%
URISCREEN	74%	83%	56%	92%

Streptococci spp are common urinary pathogens which do not produce catalase. Thirty-two urine specimens yielding significant pure growth of streptococci or enterococci showed leucocyte esterase activity in 17/32 (53.1%) and catalase activity in 12/32 (37.5%). Both enzymes were detected in 9/32 (28.1%) urine samples. Consequently, catalase-negative organisms are a potential source of false negative results for URISCREEN. Dimech et al. (9) state that 'with a NPV of 91.6% it would be a useful indicator of normal urines and therefore aid laboratories in rationalising their urine specimens processing'.

MICRAL-TEST

Background

MICRAL-TEST is an immunological test strip giving a semi-quantitative determination of microalbuminuria.

Microalbuminuria is defined as a urinary albumin concentration of approximately 20 to 200mg/L in patients with normal urine output (10) and is an indicator of renal disease which strongly predicts the development of clinical nephropathy in diabetics and hypertensive persons (11,12,13). It is also indicative of retinopathy, neuropathy, hypertension and abnormal lipid profiles.

If microalbuminuria is detected early (before it reaches an advanced level of more than 100mg/L), then renal damage is reversible. The kidney responds to therapy in the microalbuminuric phase and the progression of the damage can be stopped, preventing serious complications (14).

Method of use

A morning midstream urine specimen is collected, and the MICRAL-TEST strip is dipped into the urine, up to, but not including, the buffer zone, for 5 seconds. The strip is removed from the sample without wiping off excess urine and placed on a flat surface. After 5 minutes the colour formed is compared with the reference colour chart on the vial. Semiquantitative results are determined by comparison with the five colour blocks on the vial label: yellow (0mg/L), light brown (10mg/L), mid-brown (20mg/L), brick-red (50mg/L) and burgundy (100mg/L or more).

The test requires little technical skill. However, it must be timed correctly and a reading taken between 5 and 6 minutes after the strip is dipped in the urine specimen.

Analytical performance

In a number of studies, the performance of MICRAL-TEST has been compared with standard laboratory procedures and other techniques (Table 1). Trial results indicate a sensitivity in the range 85% to 100% and a specificity of between 85% and 97%. The values found for the PPV and the NPV were 66.7% to 86.4% and 93% to 96.5% respectively. The variability in trial results is in part due to the differences in imprecision and inaccuracy of the various comparative methods.

The values obtained for the sensitivity and specificity indicate that this test would be suitable when performed under laboratory conditions for investigation of symptomatic patients, and would be useful in ruling out microalbuminuria. There would be some additional testing on timed specimens because of false positive readings.

Table 1: Summary of sensitivity and specificity data for MICRAL-TEST

Comparison method	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Comments
Nephelometry(15)	86	97			elevated
RIA(16)	95	96			elevated
Nephelometry(17)	85	97			20 mg/L
Mixed comparison(18)	90	87	82	93	
RIA Immunoturb(19)	92	92	86		False positive 37.8% (20 mg/L)
RIA(20)	91	91	85	95	20 mg/L
Immunoturb(21)	92	82	67	97	>20 mg/L
Immunoturb(22)	91	97			
RIA (23)	100	91		>50 mg	sens. = 100% spec. = 88%

Muller and Schlipfenbacher (18) assessed the performance of MICRAL-TEST when it was used by 15 persons who had had no experience with the test. Of 45 tests, 42 were performed and interpreted correctly. Two of the three incorrect tests led to false results being obtained.

Robustness of the test

Results obtained by Schlipfenbacher et al. (16) suggest there is no interference from other urinary proteins or drug treatment. Results were not altered significantly by changes in urine osmolality, pH, and sodium and potassium concentration. No interference was found from leucocytes, nitrite, pH, glucose ketones, urobilinogen, bilirubin and blood (17).

However, extremes of temperature altered the rate of colour development. Also, the depth at which the strip was dipped into the sample and the time at which the colour was read were found to be critical. The colour intensity increases rapidly and if reading time is delayed by one minute, there will be a positive error in albumin concentration of approximately 40%.

Marshall et al. (23) found that significantly low results would occur if the MICRAL-TEST strips were read after four minutes as opposed to the five minutes specified by the manufacturer. They also reported significant differences if the test strips were read at six minutes. They also investigated the effects of reducing the time of immersion in urine and found that, if the time was reduced to two seconds rather than the five seconds specified, significant underestimation of the albumin concentration would result. They concluded that MICRAL-TEST is a sensitive and specific test which compares well with other on-site methods but is critically time dependent and must be performed on fresh urine samples. They also stated that this test may not be sufficiently accurate to allow follow up of patients with microalbuminuria during therapeutic intervention.

Marshall et al. (23) tested 36 urine samples, stored these at 20^{o}C for 14 days, thawed the specimens and then repeated the MICRAL-TEST. Thirteen of the 36 samples gave significantly different results, with three showing an increase and 10 a decrease in microalbumin concentration.

Schlipfenbacher et al. (16) found no interference from long-term storage of MICRAL-TEST strips. Jury et al. (22) found the stability of the MICRAL-TEST strips on storage was good, with regard to temperature, light and humidity. Lim-Tio et al. (17) found that strips stored incorrectly for one week did not produce discrepant results.

Safety for the operator

There would be the usual hazard of handling potentially infectious urine.

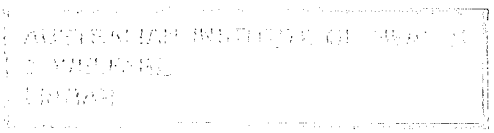
Intended target and scope of the test

MICRAL-TEST would be made available to general practitioners and endocrinologists. Potentially, it could also be used by diabetic educators, cardiologists, nephrologists and laboratory staff.

MICRAL-TEST could be used to determine the level of microalbuminuria in:

- established Type I and Type II diabetics
- newly diagnosed diabetics
- hypertensive patients
- patients undergoing chronic treatment with drugs which show nephrotoxic effects.

In Australia, an estimated 257,000 persons suffer from diabetes or hyperglycemia (24) and 1.5 million persons suffer from hypertension (25). Fifteen per cent of diagnosed diabetics have Type I-Insulin Dependant Diabetes Mellitus (IDDM) and 85% are Type II-Non-Insulin Dependant Diabetes Mellitus (NIDDM). Diabetic nephropathy occurs in 40 to 50% of Type I diabetics and 20 to 40% of Type II diabetics (11,12,26).



Cost considerations

The cost per MICRAL-TEST strip is less than two dollars. Cost savings to the Australian health care system could result from:

- elimination of the need for a more expensive laboratory test, particularly if the microalbuminuria levels were normal during a consultation;
- the early detection of elevated microalbumin levels and consequent treatment preventing some patients from developing nephropathy and possibly reaching ESRD.

Sharp (27) has noted that the strip method is also useful as a guide to laboratories for deciding what dilution to use in the RIA test.

Savings would be reduced if:

- there was little or no substitution for laboratory tests
- incorrect results were obtained by users of the test, particularly false negatives, which could delay appropriate management of patients.

Conclusions

The performance of this product in the laboratory appears to be good on the basis of most studies, but results are somewhat variable and may depend upon the comparison method chosen.

The fact that the colour generated depends on the depth and duration of immersion and the time of reaction may decrease the reliability of this product in the hands of the unskilled operator. It is conceivable that in a non-laboratory setting the requirement for meticulous adherence to strict timing might not be rigorously observed and erroneous results could result.

The study by Muller and Schlipfenbacher (18) gives limited data on the performance of this test in the hands of those with no familiarity with the test, although no mention of the participants' experience or training is made. Further studies are required to establish the place of this technology in the non-laboratory setting.

This test is inexpensive and could offer a cost-effective method of testing specimens within the laboratory. There remains a question concerning the number of false positives about the decision point (20mg/L) and further work needs to be undertaken on this topic. Medical practitioners working in diabetic clinics are used to patients' results being determined on timed specimens and the results being expressed in excretion per unit time. The acceptance of this product would in part depend on whether such practitioners would prefer to maintain this practice.

ANNEXE - SUMMARY OF STUDIES ON ANALYTICAL PERFORMANCE OF MICRAL-TEST

Manegold et al. (15) compared MICRAL-TEST results with nephelometrically measured values. Pathologically elevated albumin concentrations (>20mg/L) were recorded with a sensitivity of 86% and specificity of 97%. No interference was observed due to long-term storage or bacterial contamination of the urine.

Schlipfenbacher et al. (16) compared MICRAL-TEST with the Albumin-radioimmunoassay (RIA, Pharmacia, FRG) method for the detection of microalbumin levels. Pathologically elevated albumin concentrations (>20mg/L) were recorded with a sensitivity of 95% and specificity of 96%.

Sharp (27) compared 109 patient urine specimens using the MICRAL-TEST with the Diagnostic Products RIA test and conducted a regression analysis ($y=0.02+0.96x$, $r=0.974$) which shows reasonably good agreement given the semi-quantitative design of the MICRAL-TEST. He suggested it was useful in estimating albumin content and also could be used to decide what dilution to use in RIA. Sharp concluded that if patients and paramedical staff use MICRAL-TEST, it will be important for them to follow correct procedure; also, that abnormal urines should be sent to a laboratory for quantitative immunoassay.

Lim-Tio et al. (17) compared MICRAL-TEST with nephelometric measurements. At a detection level of 20mg/L, sensitivity was 85% and specificity 97%. At 30mg/L sensitivity was 97%. All MICRAL-TEST estimates of <10mg/L were confirmed on nephelometry. They suggested that MICRAL-TEST is simple and convenient, and has acceptable sensitivity and specificity at low detection levels.

Muller and Schlipfenbacher (18) compared MICRAL-TEST with nephelometry, turbidimetry, RIA and ELISA methods:

Comparison method	MICRAL-TEST (ca.mg/L) 0	10	20	50	100
Nephelometry	4.0	12.0	20.0	49.5	97.5
	2.5	9.5	20.0	38.0	nd
	<8.8	<8.8	17.9	34.5	>280
Photometry	4.0	9.0	26.0	56.0	224
Turbidimetry	6.6	10.8	27.1	50.4	179.6
RIA	1.4	3.4	12.6	119.6	300
	3.7	7.5	20.9	37.0	370
ELISA	4.0	4.4	27.5	157.7	642

MICRAL-TEST was found to record pathological urinary microalbumin concentrations with a sensitivity of 90.1%, specificity of 87.2%, NPV of 93% and PPV of 82%. They concluded that MICRAL-TEST is a highly

sensitive, specific test for monitoring of microalbuminuria and is easy to use.

Gilbert et al. (19) compared MICRAL-TEST with RIA and immunoturbidimetry and found that MICRAL-TEST had an overall sensitivity of 92.2%, specificity of 92.3% and PPV of 86.4%. They reported that 65% of the patients in this study had microalbumin levels below 20mg/L, 24% had microalbumin levels between 20-200mg/L, and the remaining 11% had concentrations greater than 200mg/L. However, at the threshold value of 20mg/L, MICRAL-TEST showed a high false positive rate of 37.8% when compared with RIA.

There is high variability in urinary albumin excretion rate and timed urine collections are the traditional way of measuring albuminuria. The development of a semi-quantitative dip stick which allows determination at sites which do not have access to sophisticated laboratory facilities would increase the convenience of detection of microalbumin. Gilbert et al. concluded that MICRAL-TEST was a useful screening method for the detection of microalbuminuria. However, at the threshold value of 20 mg/L, the test gave false positive results in 37.8% of samples (as compared with RIA). They suggested that positive tests be confirmed by a timed urine collection using established methodology and that patients whose MICRAL-TEST is negative be subjected to annual testing.

Phillipou (20) compared the MICRAL-TEST with RIA and found a high proportion of misclassifications between the 0 to 10mg/L thresholds, but if a threshold of 20mg/L or more was chosen, the sensitivity was 91.2%, specificity was 91.1%, the PPV was 84.9% and the NPV was 95%. The threshold of 20mg/L was important, as readings at or above this level suggest a pathological elevation in the albumin concentration. It was concluded that the MICRAL-TEST was a satisfactory procedure for the initial semiquantitative screening of diabetic samples, detecting urinary albumin levels of 20mg/L or more.

Bangstad et al. (21) compared MICRAL-TEST with a quantitative immunoturbidimetric method. The correlation coefficient between the new semiquantitative method and the immunoturbidimetric reference method was 0.82. At the threshold of 20mg/L or more, MICRAL-TEST had a sensitivity of 92.3%, specificity of 82.1%, PPV of 66.7% and NPV of 96.5%. The low PPV implies many false positive results and means that many patients have to deliver additional urine samples. They concluded that MICRAL-TEST is useful for in-clinic screening and monitoring for elevated urinary albumin concentration.

Jury et al. (22) compared MICRAL-TEST with a quantitative immunoturbidimetric method and found that at 20mg/L MICRAL-TEST had a sensitivity of 91% and specificity of 97%. In contrast to the work of Gilbert et al. (19), Jury et al. found more false negatives than false positives at the 20 mg/L level. They reported a PPV of 96.8% and a NPV of 89%. They suggested that MICRAL-TEST was robust, sensitive and specific, would be suitable for use by non-laboratory personnel and is capable of producing analytically acceptable results for use in diabetes clinics, small laboratories and general practice - particularly where the resources for establishing RIA and immunoturbidimetric assays are unavailable.

HEMOCUE BLOOD-GLUCOSE TEST

The HemoCue Blood-Glucose Test is a portable whole blood glucose testing device which works on 'dry chemistry' principles. The Australian distributor suggests the test is intended primarily for laboratory use and when testing needs to be done accurately at a clinical facility.

Principles and method of operation

The disposable microcuvette used in the device serves as pipette, test tube and reaction vessel. The sample is obtained by fingerstick or venepuncture, and the microcuvette automatically draws up 5µL of blood by capillary action, producing a chemical reaction on contact with blood.

The chemical reaction is based on the glucose dehydrogenase reference method and quantified photometrically. Enzymatic methods using glucose dehydrogenase have been found to be more accurate than other tests as there is no auxilliary reaction and no protein precipitation required (28).

The microcuvette is inserted into a photometer and the absorbance of the solution measured at 660nm and 840nm. The result is displayed within 40-240 seconds, depending on the glucose concentration. Operators of this instrument may need to be aware of the possibility of air bubbles within the specimen being drawn into the micro-cuvette. Such air bubbles could lower the values obtained.

Like the hemoglobinometer developed by HemoCue AB, this instrument has a control cuvette to check the calibration of the photometer. The use of the control cuvette is restricted to checking the inaccuracy of the photometer and unskilled users need to be aware that performing this check does not constitute a satisfactory quality control regimen.

Analytical performance

Bitzen et al. (29) compared the HemoCue system with the the Yellow Springs Instrument Analyser (YSI) as a reference method. Regression analysis gave the acceptable relationship $y = -0.2 + 1.01 x$ ($r=0.99$). Comparison of imprecision gave 3.3% for the HemoCue Blood-Glucose Test as opposed to 1.0% for the YSI. They concluded that the HemoCue device was simple and safe to use and showed levels of imprecision and inaccuracy which permitted use in the diagnosis of diabetes mellitus.

Data from HemoCue AB indicate that within-run imprecision of between 2.2 to 3.5% over the range of 4.3 mmol/L to 21 mmol/L is achievable in a laboratory setting. These imprecision results are acceptable on the basis of data available from an Australian study (30) in which a limit for coefficient of variation of 6% was used as the criterion for glucose estimations. Between-day imprecision for the HemoCue Blood-Glucose Test reported by the company was 1.9 to 2.7% over the range 2.6 to 10.8 mmol/L, which also meets the criterion used for same-day imprecision (30).

HemoCue AB have provided data comparing their analyser against an acceptable laboratory method. The regression analysis of these data shows an acceptable relationship ($y=0.3+1.00$; $r=0.995$) over the range 1.8 to 21.5 mmol/L. No details of the method of regression analysis are given and a value for the standard error of the estimate, Syx (31) is not included.

Robustness of the test

Details of the effects of inappropriate storage of microcuvettes or use of these beyond their expiry date are not available.

Safety for the operator

The operator would need to observe the usual safety precautions when handling and taking blood specimens.

Intended target and scope of the test

Medipac suggest that the test is primarily intended for laboratory use. It could also be used by general practitioners, physicians and hospital ward staff.

Blood glucose is a common test in the general practice environment (32). The HemoCue Blood-Glucose Test is considerably cheaper than other 'dry chemistry' analysers although it only offers one analyte. A number of other glucose analysers are competing for the home, hospital ward and doctor's office markets.

Costs considerations

The instrument costs $1200 (including transformer, batteries and control cuvette). Cuvettes cost $120 per pack of 80 and their shelf life is 6 months.

As with other office pathology products, potential cost savings to the Australian health care system could result from:

- a possible reduction in the number of consultations; and
- earlier interventions that might prevent hospitalisation or other more expensive treatment.

However, these technologies also have the potential to increase costs if a large degree of substitution (non-laboratory for laboratory testing) does not occur.

Technical expertise required

As with a number of analysers aimed at the non-laboratory market, this analyser would not require major skills on the part of the operator. However, experience from an Australian study (30) has indicated that operators without laboratory experience need to be taught simple volumetric skills to accurately prepare standard solutions from freeze-dried concentrates. An appreciation of the need for quality

control and its implications is also required. As certain basic skills and an appreciation of quality control measures are needed to successfully provide services with a glucose analyser, it would seem appropriate for users of this instrument to meet pathology accreditation requirements.

Quality control requirements

Medipac states that controls should be performed on each new kit of tests. These controls are supplied with the kits and daily quality control takes one minute with the supplied control cuvette. The company also claims that recalibration is rarely needed. On the basis of earlier Australian experience and recommendations (30,32), it would appear appropriate that use of this product be subject to the quality control procedures specified under pathology laboratory accreditation requirements.

Conclusions

The analytical performance of this instrument appears to be adequate for use in the non-laboratory environment. However, there are no data available to establish how well this instrument performs in the hands of operators without laboratory experience.

A number of competing glucose analysers are currently available for use in the home, general practitioners' offices and hospital wards. These include both single-analyte devices and analysers which offer a number of biochemical tests.

The National Health Technology Advisory Panel considered that non-laboratory facilities using such instruments should be required to meet pathology laboratory accreditation standards (32). It is considered that users of the HemoCue Blood-Glucose Test should also be subject to accreditation requirements.

CONCLUDING COMMENTS

All three products represent useful approaches by the manufacturers in the development of systems for decentralised testing. While analytical data were available for each product, little information could be obtained on their performance under routine conditions outside the laboratory. The conclusions in this report must therefore be regarded as tentative.

Unfortunately, the lack of information on performance of non-laboratory tests under routine conditions is widespread. It would be appropriate for all diagnostic products intended for use in the non-laboratory setting to be subject to properly designed investigations to determine their performance (effectiveness) when used by persons without a background in laboratory work. In the case of the products considered here, it is suggested that investigation of their routine performance and potential under Australian conditions would be highly desirable.

Although sensitivity and specificity are regarded as consistent properties of a diagnostic test, these properties are dependent on the group of patients chosen for evaluating the test. As noted by Lachs et al. (33), the diagnostic performance of a test may be distorted by spectrum bias when sensitivity and specificity values are obtained from patients with different manifestations of disease. It would therefore be appropriate during future investigations on performance of diagnostic tests to also take account of the clinical characteristics of the selected patients.

Each of the products is considered to have the potential to contribute to patient management. However, all have some technical limitations which would need to be taken into account in reaching decisions on their use under non-laboratory conditions.

Use of such products might achieve cost savings, but the extent of any savings would depend on a number of factors including levels of reimbursement, extent of substitution for laboratory tests and patterns of practice.

The effectiveness and potential economic impact of each product need to be considered in the context both of existing pathology services and of other products that are intended for the same application in a non-laboratory setting.

Consideration of products such as URISCREEN and MICRAL-TEST raises the question of the extent to which pathology accreditation provisions should apply to kits used outside the laboratory. The National Health Technology Advisory Panel noted that accreditation of pathology services which are providing only tests based on use of kits may not be realistic (32). It is suggested that this matter might be considered further by the National Pathology Accreditation Advisory Council.

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