The Superiority of Enzyme Impregnated Paper for Determining Glycosuria in Patients Receiving Antituberculosis Drug Therapy*

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Qualitative and quantitative analysis of the urine for glucose is generally accepted as a useful measure for the detection of diabetics and for the daily follow up of those with proved diabetes as a rough practical estimation of the degree of control of blood sugar levels. In the past the test commonly employed using Benedict’s Solution depended on the fact that cupric sulfate was reduced in the presence of glucose in the urine to cuprous oxide, an insoluble yellow or red precipitate. More convenient tablets such as “Clinitest” utilize the same principle of copper reduction. It has been known that reducing substances, other than glucose will at times give a false-positive test in the urine using copper reduction method, but generally these instances were infrequently encountered clinically. In addition there has, in the past, been no simple specific test for urine glucose available, so that to prove by further identification that the reducing substance in the urine was actually glucose involved such procedures as paper chromatography, fermentation tests or the osazone test, none of which is particularly adaptable for bedside use.1 Recently the development of a testing paper impregnated with the enzyme, glucose-oxidase, has made available a simple specific test for glucose in the urine.* The enzyme, glucose-oxidase, reacts with glucose to form hydrogen peroxide and gluconic acid. The hydrogen peroxide then reacts with peroxidase and orthotolidine, also impregnated in the paper, to form a light green to blue-black color depending on the concentration of glucose present in the urine.

The present study is submitted to call attention to a clinical situation in which the presence of reducing substances in the urine other than glucose is a relatively common occurrence, namely, in patients receiving antituberculosis drug therapy, and the usefulness of the enzyme impregnated test paper under these circumstances as a test for glycosuria. A survey was made on the tuberculosis service of the Providence Veterans Administration Hospital for the incidence of false-positive tests for glucose in the urine using the copper reduction method. Of 40 patients receiving antituberculosis drugs, 30 (75 per cent) were found to have false-positive tests for glycosuria with the copper reduction Benedict’s test, varying from trace to two plus. None had false-positive tests with the specific enzyme impregnated paper. Blood sugar determinations in the fasting and postprandial states (11 a.m.) were carried out on each patient, all of which were normal. The results are shown in Table I.

Interference of antituberculosis drugs in the testing of urine for glucose with the copper reduction methods has been noted in other studies.

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*Tes-Tape—Eli Lilly and Company.
Neuberg\textsuperscript{2} reported this phenomenon in patients receiving streptomycin. Goldner\textsuperscript{3} noted a reducing substance in the urine as the result of PAS administration. Exact identification of the reducing substance in each instance was not carried out but glucose was excluded. It was considered that the reducing substance was due to drug administration, and was one of the breakdown products or the drug itself. In regard to isoniazid both this drug and its principal breakdown product acetyl isonicotinic acid hydrazide are strong reducing agents. That this drug can give false-positive reducing tests for glycosuria was reported by Luntz and Smith.\textsuperscript{4} It was their opinion, in addition, that isoniazid produced abnormalities in glucose metabolism with a tendency to hyperglycemia, a point which was not substantiated in the present study. In our survey of 40 patients, all those with false-positive tests for glycosuria were receiving both isoniazid in doses of 300 milligrams daily and PAS in doses of 12 grams daily, except in two instances. One patient was receiving streptomycin one gram twice weekly in addition to the two drugs mentioned, and one was receiving streptomycin alone in doses of 0.5 gram daily (other drugs having been interdicted because of sensitivity reactions). It was not considered advisable to discontinue combined treatment in those with false-positive Benedicts' tests to try to further identify which drug or combination of them was responsible for the false-positive test in each case. It seemed clear from a clinical standpoint that significant numbers of patients receiving these drugs have false-positive copper reduction tests for glycosuria, and this is circumvented by the use of the enzyme impregnated paper. The crucial point in the use of the enzyme paper method then became its reliability in detecting glycosuria when glucose in varying concentrations is actually present in the urine. A comparison of the Benedict's test and the paper enzyme test was then carried out by mixing varying amounts of glucose with sugar-free urine so as to obtain concentrations of 0.1 per cent, 0.25 per cent, 0.5 per cent, 1.0 per cent, 2 per cent, 3 per cent, 4 per cent and 5 per cent. The mixture was allowed to stand one hour. A total of 10 specimens were tested at each concentration...
using both Benedict's and the paper enzyme method. The testing was done by technicians following the standard procedure in each test. Those doing the tests were unaware of the actual concentration of glucose in the specimens prior to the test. The average reading at each concentration of glucose by each method is shown in Figure 1. As can be seen, there is a slight tendency to "underread" the paper enzyme test at the higher concentrations of glucose. This is in agreement with the report of Leonards. However, it should be noted that the Benedict's test was not always read as four plus in the higher glucose concentrations. The difficulties in each test concern matching color charts by the eye of the observer. In addition it should be remembered that the amount of glycosuria is at best a rough guide as to be the degree of hyperglycemia. Taking these factors into consideration, it is the opinion of the author that the enzyme impregnated specific test for glucose is superior as a testing material for determination of glycosuria in patients under drug treatment for pulmonary tuberculosis.

SUMMARY

1. False-positive tests for glycosuria using Benedict's test were found in 30 of 40 patients receiving antituberculosis drug therapy with isoniazid, para-aminosalicylic acid and streptomycin in a range of trace to two plus.

2. None of the patients had false-positive reaction for glycosuria using a specific enzyme impregnated test paper (Tes-Tape).

3. The use of enzyme impregnated testing paper is recommended for the routine determination of glycosuria in patients receiving the present day commonly used antituberculosis drugs. It appeared sufficiently accurate in detecting true glycosuria when compared with Benedict's reagent in testing urines with known concentrations of glucose.

RESUMEN

1. Se encontraron reacciones positivas falsas de glicosuria usando el reactivo de Benedict, en 30 de 40 enfermos que han recibido drogas antituberculosas con isoniazida, PAS y estreptomicina siendo estos resultados de huellas hasta positivo 2.

2. Ninguno de los enfermos tuvo una reacción positiva falsa cuando se usó una enzima especifica en cinta de papel impregnado.

3. El uso de cinta de papel impregnado de enzima se recomienda para la investigación de rutina de la glicosuria en enfermos que usan las drogas antituberculosas actuales. Parece suficientemente exacta para descubrir la verdadera glicosuria en comparación con el reactivo de Benedict al probar orinas con conocidas concentraciones de glucosa.

RESUME

1. Des réponses faussement positives et même extrêmement positives décélannt la glycosurie selon la méthode de Benedict, furent découvertes chez 30 malades sur 40 en cours de traitement par les médications antituberculeuses avec isoniazide, P.A.S et streptomycine.

2. Aucun des malades n'eut de réaction de glycosurie faussement positive lorsqu'on employa un papier-test imprégné d'un enzyme spécifique (Tes-Tape).

3. L'emploi d'un papier-test imprégné d'enzyme est recommandé pour la détermination courante de la glycosurie chez les malades recevant les médications antituberculeuses communément employées de nos jours. Si on le compare au réactif de Benedect, il semble suffisamment précis pour dépister la vraie glycosurie, lorsqu'on examine des urines contenant des concentrations connues de glucose.

ZUSAMMENFASSUNG

1. Irrige positive Proben zur Glykosurie bei Gebrauch der Benedikt'schen Proben fanden sich bei 30 von 40 Kranken, die eine antituberkulöse Arzneimittelbehandlung erhalten hatten mit INH, PAS und SM, und zwar in Werten von Spuren bis zu 2-fach positiv.


REFERENCES

3 Goldner, M.: The Nature of a Reducing Substance in Urine During PAS Therapy. Minutes of the 8th Streptomycin Conference, p. 105-107, Veterans Administration, Atlanta, Georgia.