The Hoesch Test: Bedside Screening for Urinary Porphobilinogen in Patients with Suspected Porphyrina

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A little-known procedure for porphobilinogen screening, the Hoesch test, was examined for sensitivity, specificity, and utility as compared to the Watson–Schwartz test. The data demonstrate that its sensitivity is similar to that of the Watson–Schwartz test. The Hoesch test, however, is without false-positive reactions secondary to urobilinogen, and its simplicity makes it easier to use and more easily interpretable. We conclude that the Hoesch test should replace the Watson–Schwartz test for urine porphobilinogen screening in suspected cases of acute intermittent and variegate porphyria.

Additional Keyphrases: Watson–Schwartz • “reversed Ehrlich reaction” • screening

Acute intermittent porphyria is an inherited defect of porphyrin biosynthesis characterized by an excess of porphyrin precursors in the urine. Although clinical manifestations may vary, the cardinal symptom is abdominal pain. Neuropathy, seizures, coma, psychoses, and electrolyte disturbances may occur. Photosensitivity is not a feature of acute intermittent porphyrin. An indistinguishable acute illness may occur during the course of variegate porphyria and with hereditary coproporphyria.

Diagnosis of acute intermittent porphyria and the acute attack equivalents of variegate porphyria and hereditary coproporphyria is based on the demonstration of increased excretion of porphobilinogen in the urine. Subsequent studies of the patterns of urine and fecal porphyrin excretion are necessary to define the type of porphyria (acute intermittent porphyria, variegate porphyria, or hereditary coproporphyria). The test for urinary porphobilinogen customarily used in this setting is that developed by Watson and Schwartz in 1941 and modified in 1964 (1, 2). Although termed a screening test, it is a multistep procedure, rarely performed on the clinical ward but instead is usually done in the hospital laboratory. We propose that the Hoesch test, first described in 1947 (3) as the “reversed Ehrlich reaction,” replace the “conventional Ehrlich reaction” (Watson–Schwartz). With the same aldehyde reagent originally described by Prösch (4), the Hoesch procedure is simpler, faster, and appears to be more specific and more easily interpreted than is the Watson–Schwartz test. The advantages of this test appear to have been ignored until recently (5–7).

Patients and Methods

The Hoesch test was examined for specificity and sensitivity by comparison with the modified Watson–Schwartz procedure (3) on fresh urine specimens from persons including patients with alcoholic liver disease, hepatitis, porphyria (acute intermittent porphyria and variegate porphyria), normals, and normals treated with phenazopyridine HCl (Pyridium). Urobilinogen was measured in parallel with these two tests, as it has been a well-documented cause of falsely positive Watson–Schwartz tests. Patients treated with Pyridium were included because use of this drug has been reported as a source of potential falsely positive reactions. In addition, quantitative porphobilinogen determinations were compared to the qualitative Hoesch test results.

These screening test procedures (Watson–Schwartz and Hoesch) are outlined in Table 1. We have found that the Ehrlich’s reagent used in the Hoesch test can be stored for at least nine months in a clear-glass container on the shelf without loss of activity.

Results

Specificity of the Hoesch Test

The Watson–Schwartz and Hoesch procedures gave almost identical results (Table 2) for normal persons, normal persons on Pyridium therapy, and for documented cases of acute intermittent porphyria and variegate porphyria. Two cases of the liver-disease group, specifically two with positive urobilinogen tests, produced positive interpretations with the Watson–Schwartz procedure, while the Hoesch test was unreactive.
One of us (T. K. W.) has screened 50 cases of "acute abdominal" problems, resolved with diagnoses other than porphyria—all with a negative Hoesch test. Doss (8) further reported negative Hoesch tests in all of 300 different patients with chronic liver disorders, porphyria cutanea tarda, lead poisoning, and polynuertis.

Sensitivity of the Hoesch Test

During porphyrinic attacks (acute intermittent porphyria), the porphobilinogen concentration in serum will be 10 mg/liter or greater (9). Thus, it is important that a test be unequivocally positive at these diagnostic concentrations of porphobilinogen, but not so sensitive as to detect physiological concentrations of porphobilinogen. Table 3 demonstrates that at low concentrations, not consistent with an acute attack (2.2 mg/liter), the Hoesch test is nonreactive, and at clinically significant concentrations, it is strongly positive.

Discussion

Although they are rare diseases, both acute intermittent porphyria and variegate porphyria are often considered in the differential diagnosis of painful abdominal disorders and certain neuropsychiatric disorders. The availability of a quick, reliable screening procedure is invaluable when the possibility of porphyria is considered. The Watson–Schwartz test has served well as a screening procedure for more than 30 years; however, its use on clinical wards has been restricted by (a) the number of reagents required, (b) time for test performance, and (c) lack of expertise in proper performance and interpretation of the test results.

The Hoesch procedure has also been available for almost 30 years, and it is interesting to note the comparative evolution of these two procedures. Both evolved from the strong red reaction produced by acid solution of p-dimethylaminobenzaldehyde with certain urines, originally described by Ehrlich in 1900. It was not until 1931 that the potential significance of porphobilinogen in urine was appreciated (10–12). In the previous years, interest in the clinical significance of urobilinogen and its detection in urine was the major importance of the Ehrlich reagent (13–18). Hoesch used Ehrlich's original reagent (Table 1). Thus, the essential difference between the Watson–Schwartz and Hoesch procedures is that the former attempts to fully develop and then extract the urobilinogen-attributable color, while the Hoesch discovery of the inverse Ehrlich's reaction (i.e., of maintaining an acid solution by adding a small urine volume to a relatively large reagent volume) eliminated the problem of urobilinogen reaction.

Our data confirm the original observation of
Hoesch that the inverse Ehrlich reaction is specific for porphobilinogen (Table 2). Falsely negative reactions have seldom been a problem with the Watson–Schwartz test, and the same appears to be true for the Hoesch test. With certain indicator compounds such as Pyridium, in the strongly acid Ehrlich's reagent color will commonly form that is not characteristic of either urobilinogen or porphobilinogen. Other possible sources of falsely positive Ehrlich reactions were not examined (19, 20), nor were potential inhibitors of this reaction tested with the Hoesch procedure (21). The Hoesch test does not detect the low concentrations of porphobilinogen that are present in normal urine (Table 3). The value of the Hoesch test lies in screening for suspected acute attacks. In such cases the porphobilinogen concentration in the urine is typically 10 mg/liter. When such an amount is present, the positive Hoesch test is unequivocal (Table 3). The dilemma of interpreting “weakly positive” tests will only arise if the test is extended to a search for carriers. We have encountered several cases of “suspicious” Watson–Schwartz tests that have been negative by quantitative methods. With the Hoesch test the presence of porphobilinogen in urine can be quickly and accurately identified and further investigative procedures instituted to identify the type of porphyria.

We suggest that the Hoesch test replace the Watson–Schwartz test. In no way is it less effective, and in several it is better. It is not our intention to add another test to the diagnostic armamentarium of medicine, rather to improve the methodology for efficient diagnosis. We feel sufficient criteria have been met to warrant replacing the Watson–Schwartz test with the more efficacious Hoesch test.

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References