The nicotinic acid provocation test and unconjugated hyperbilirubinaemia

W Dickey, J J A McAleer, M E Callender

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SUMMARY
It has been suggested that the nicotinic acid provocation test is useful in the diagnosis of Gilbert's syndrome. We compared the response to intravenous nicotinic acid of patients with Gilbert's syndrome and with chronic liver disease. There was no significant difference in the mean rise in unconjugated serum bilirubin between the two groups. A sensitivity of 70% and specificity of 60% were obtained. All of 5 patients with chronic liver disease and a raised fasting unconjugated serum bilirubin had positive tests. We suggest that the nicotinic acid test is positive in unconjugated hyperbilirubinaemia regardless of cause. It is of no value in differentiating Gilbert's syndrome from liver disease.

INTRODUCTION
Gilbert's syndrome is characterised by mild unconjugated hyperbilirubinaemia increased by stress or fasting, in the absence of significant haemolysis or liver disease. The differentiation of this benign condition from chronic liver disease can be difficult without liver biopsy. The administration of nicotinic acid intravenously produces a rise in serum unconjugated bilirubin which is greater and more sustained in patients with Gilbert's syndrome than in normal controls, and it has been suggested that nicotinic acid provocation is a useful diagnostic test. However, evidence that this test differentiates Gilbert's syndrome and liver disease is lacking. We have compared the effects of nicotinic acid provocation on patients with Gilbert's syndrome and with chronic liver disease.

PATIENTS AND METHODS
We studied 15 patients with biopsy-proved chronic liver disease (10 with hepatitis B surface antigen (HBsAg) negative chronic active hepatitis, 3 with alcoholic hepatitis and 2 with cirrhosis), and 20 patients with Gilbert's syndrome which was diagnosed on the following criteria: intermittent or sustained unconjugated hyperbilirubinaemia for more than six months, normal serum liver enzyme activities and no evidence of significant haemolysis (normal haemoglobin concentration,

Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA.
W Dickey, BSc, MD, MRCP (UK), Registrar.
J J A McAleer, MB, MRCP (UK), Registrar.
M E Callender, MB, MRCP (UK), Consultant Physician.
Correspondence to Dr Callender.

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The reticulocyte count, serum lactate dehydrogenase, plasma haemoglobin and haptoglobin, and negative Coombs' test). Serum total and direct (conjugated) bilirubin concentrations were assayed using modified Jendrassik-Grof techniques (diazotised sulphanilic acid-based methods) and unconjugated bilirubin concentrations calculated from the difference (normal total and unconjugated bilirubin concentrations ≤18 μmol/l).

Informed consent was obtained from all patients and the nicotinic acid test was performed as described. After an overnight fast, patients received fifty milligrams of nicotinic acid by slow intravenous injection. Blood samples were taken for total and conjugated serum bilirubin assay at 30 minute intervals over three hours. A positive result has been defined as a rise of greater than 17 μmol/l in unconjugated bilirubin during the test.

RESULTS

The figure shows the rise in unconjugated bilirubin three hours after administration of nicotinic acid for each patient. The mean rise in patients with Gilbert's syndrome was 21.55 (± 9.43) μmol/l (range 3–46) compared with 17.3 (± 18.9) μmol/l (range 0–77) in those with liver disease: this difference was not statistically significant.

Figure. Rise in unconjugated bilirubin (μmol/l) 3 hours after administration of nicotinic acid. (Positive test-rise greater than 17 μmol/l).
A positive result, (a rise in unconjugated bilirubin of greater than 17 µmol/l), was obtained in 14 of 20 patients with Gilbert’s syndrome and in 6 of 15 with chronic liver disease: the sensitivity of the test for Gilbert’s disease was thus 70% and the specificity was 60%. Five patients, although previously diagnosed as having Gilbert’s syndrome, had a normal fasting unconjugated serum bilirubin (≤18 µmol/l) immediately before receiving nicotinic acid. Of these, three had a negative test. All five patients with chronic liver disease and a raised unconjugated fasting bilirubin had a positive test (range 19–77 µmol/l; mean 35).

Of 20 patients in total who had a raised unconjugated fasting bilirubin, irrespective of diagnosis, 18 had a positive test, compared with 3 of the 15 remaining patients: thus, the sensitivity of the nicotinic acid test for unconjugated hyperbilirubinaemia was 90% and specificity was 80%.

DISCUSSION

Mattei3 first observed that serum unconjugated bilirubin rises after the intravenous injection of nicotinic acid. The mechanism is unclear but alterations in the erythrocyte membrane may occur making red cells more susceptible to splenic haemolysis. The rise in bilirubin is abolished after splenectomy.4 Fromke and Miller5 reported that serum unconjugated bilirubin rose characteristically three-fold 120 minutes after the injection of nicotinic acid in patients with Gilbert’s syndrome compared with a twofold peak after 90 minutes in normal controls. Davidson et al1 compared the rise in bilirubin in 16 patients with Gilbert’s syndrome and six normal controls. Levels in the control patients reached a plateau at 90 minutes: in contrast, peak values for the Gilbert’s syndrome patients were higher and occurred later at 180 minutes. The mean increase in bilirubin at 180 minutes was significantly higher in the patients with Gilbert’s syndrome than in controls (23·3 ± 8·9 µmol/l v. 6·5 ± 4·8 µmol/l: p < 0·001). The authors concluded that a single measurement of plasma bilirubin 180 minutes after the administration of nicotinic acid could distinguish patients with Gilbert’s syndrome from normal subjects. Yet data for patients with liver disease are scanty. Fromke and Miller5 described 2 patients with primary biliary cirrhosis and raised fasting total serum bilirubin levels who had response curves typical of Gilbert’s syndrome. Ohkubo et al2 compared the rise in bilirubin following intravenous nicotinic acid in patients with Gilbert’s syndrome and with chronic hepatitis. They concluded that a rise in unconjugated bilirubin of more than 17 µmol/l was “highly suggestive” of Gilbert’s disease, but the initial fasting bilirubin levels in patients with liver disease were not stated.

In our study, the nicotinic acid test failed to discriminate between patients with Gilbert’s syndrome and those with a raised fasting unconjugated hyperbilirubinaemia due to chronic liver disease. All five patients with chronic liver disease and a raised fasting unconjugated bilirubin had a positive test. We suggest that an exaggerated response to nicotinic acid occurs in patients with a raised unconjugated bilirubin regardless of cause. This is supported by the finding that the response in patients with hyperbilirubinaemia due to haemolytic anaemia does not differ significantly from that of Gilbert’s syndrome.2 The nicotinic acid provocation test is thus unreliable for the diagnosis of Gilbert’s syndrome. We agree with the suggestion6 that the diagnosis may be made, without the need for
invasive tests, in patients with unconjugated hyperbilirubinaemia after careful history, examination, blood tests to exclude haemolysis and liver disease and 12–18 month follow-up.

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