Comparison of a new tumour marker, CA 19–9™, with α-fetoprotein and carcinoembryonic antigen in patients with upper gastrointestinal diseases

HANNU JALANKO,* PENTTI KUUSELA, * PETER ROBERTS, † PENTTI SIPPONEN, ‡ CAJ HAGLUND, † OLLI MÄKELÄ*

From the *Department of Bacteriology and Immunology, University of Helsinki, Helsinki, †Fourth Department of Surgery, University Central Hospital, Helsinki, and ‡ the Jorvi Hospital, Espoo, Finland

SUMMARY Serum CA 19–9™ antigen concentrations were measured in 246 patients with benign and histologically confirmed malignant gastrointestinal diseases. The CA 19–9 concentration was above the upper limit of the normal range (0–37 U/ml) in 76% of patients with pancreatic carcinoma, 73% of patients with cholangiocarcinoma, 42% of patients with gastric carcinoma, and 22% of patients with hepatoma. High CA 19–9 concentrations were found mainly in patients with a metastasised cancer, whereas 71% of patients with a localised carcinoma had normal CA 19–9 concentrations. All of the patients with benign gastric diseases had normal CA 19–9 values. Moderately increased concentrations were found in 15–36% of the patients with benign pancreatic, liver, and biliary tract diseases. α-fetoprotein was a better marker for hepatomas than CA 19–9. CA 19–9 was better than carcinoembryonic antigen in differentiating malignant from benign diseases. The results indicate that the CA 19–9 assay is not completely specific for cancer but serves as a valuable adjunct, especially in the diagnosis of pancreatic carcinoma.

CA 19–9™ radioimmunoassay is a new solid phase assay for the measurement of a diagnostic tumour marker defined by a monoclonal antibody. This antibody was originally raised against a human cell line, SW 1116, which was derived from a colorectal carcinoma. The CA 19–9 antigen has been isolated and characterised as sialylated lacto-N-fucopentaose II, an oligosaccharide which is related to Lewis™ blood group substance. Low concentrations of the CA 19–9 antigen are found in the serum of healthy subjects, but serum from patients with gastrointestinal adenocarcinoma, especially those of the pancreas, often contain increased concentrations of CA 19–9. The new test is reported to have a high specificity (98.5%) and a high sensitivity (up to 79%) for patients with gastrointestinal adenocarcinoma.

We have determined the serum CA 19–9 concentration in 246 patients with benign and malignant diseases of the stomach, liver, pancreas, and biliary tract. We have also compared the new antigen with α-fetoprotein, a well established marker for liver cancer, and with carcinoembryonic antigen, which shows increased serum concentrations in patients with various gastrointestinal cancers.

Patients and methods

Patients Serum CA 19–9 concentrations were measured in 104 patients with untreated, histologically confirmed cancer and in 142 patients with benign diseases. The diagnoses, based on clinical and laboratory data and histological findings, were as follows:

Gastric diseases. Adenocarcinoma (45 patients), unclassified carcinoma (five), gastric ulcer (14), chronic gastritis (37 patients, 16 of whom were classified as atrophic gastritis), duodenal ulcer (two), gastric non-malignant polyps (one), hiatus hernia (four), duodenitis (four), oesophagitis (two), bile reflux with normal gastric epithelial surface (five). All of the patients underwent gastroscopy.

Liver diseases. Liver cell carcinoma (18), cirrhosis (15, mostly alcoholic cirrhosis), acute hepatitis (seven), chronic persistent hepatitis (three), primary biliary cirrhosis (two). Blood samples from these
Comparison of a new tumour marker, CA 19-9™, with α-fetoprotein and carcinoembryonic antigen

Serum concentrations of CA 19-9, α-fetoprotein and carcinoembryonic antigen in patients with upper gastrointestinal diseases

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Pancreas</th>
<th>Liver</th>
<th>Biliary tract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ca%</td>
<td>Be%</td>
<td>Ca%</td>
<td>Be%</td>
</tr>
<tr>
<td>CA 19-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;37 U/ml)</td>
<td>42</td>
<td>0</td>
<td>76</td>
<td>16</td>
</tr>
<tr>
<td>Carcinoembryonic antigen</td>
<td>(50)</td>
<td>(69)</td>
<td>(25)</td>
<td>(32)</td>
</tr>
<tr>
<td>(&gt;2.5 ug/l)</td>
<td>39</td>
<td>17</td>
<td>68</td>
<td>15</td>
</tr>
<tr>
<td>α-fetoprotein</td>
<td>(46)</td>
<td>(66)</td>
<td>(19)</td>
<td>(26)</td>
</tr>
<tr>
<td>(&gt;25 ug/l)</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ca = patients with a carcinoma.
Be = patients with benign disease.
Values given as percentage of patients with an increased concentration; in parenthesis, the number of patients in the group.

Results

GASTRIC DISEASES

Patients with non-malignant gastric diseases (69 patients) had low serum CA 19-9 concentrations (Fig. 1). Of the 50 patients with a gastric carcinoma, 21 (42%) had concentrations above the recommended cut off point of 37 U/ml (Table). Three of these 21 patients had small localised tumours, but in 18 patients metastases were found. An increased CA 19-9 concentration was found in 15% of patients with cancer with no metastases. All five patients with unclassified (anaplastic) carcinomas had normal CA 19-9 concentrations.

No correlation between the CA 19-9 and carcinoembryonic antigen concentrations was found (Fig. 2a). The carcinoembryonic antigen concentration was increased in 17% of the patients with benign diseases and in 39% of the patients with cancer (Table). Both markers were normal in 46% of the patients with cancer. An increased CA 19-9 value with a normal carcinoembryonic antigen concentration was found in 15% of the sera from patients with cancer, while the opposite was true in another 15%.

PANCREATIC DISEASE

Patients with benign pancreatic diseases had slightly higher CA 19-9 concentrations than patients with gastric diseases, but no value exceeded 100 U/ml (Fig. 1). Seventeen patients with cancer (68%) had values above 100 U/ml and 16 had values of 1000 U/ml or more. A normal CA 19-9 concentration was found in four of the six patients with localised carcinomas (Fig. 2) as well as in two patients with endocrine tumours.

Serum α-fetoprotein concentration was normal in all patients with pancreatic diseases (Table). The carcinoembryonic antigen concentration was increased in 68% of the patients with cancer and in

patients were originally sent for the serum α-fetoprotein assay because of a clinical suspicion of liver malignancy.

Biliary tract diseases. Cholangiocarcinoma (11), cholelithiasis with obstructive jaundice (10) and without jaundice (four).

Pancreatic diseases. Adenocarcinoma (25), endocrine tumour (two), acute pancreatitis (26), chronic pancreatitis (four), chronic pancreatitis with pseudocysts (two). Two patients with cirrhosis also had chronic pancreatitis. Laparotomy was performed on most of the patients with cancer within a few days of the blood sampling. The staging of the cancers was based on the findings at operation and the operative histological specimens. In a few patients with hepatic, in whom no operation was performed at the time of sample collection, the staging was based on other clinical data.

ASSAYS

CA 19-9 antigen concentration (expressed as U/ml) was determined by a solid phase assay of Centocor (Malvern, PA, USA). A cut off value of 37 U/ml was used; 0-6% of normals have concentrations above this value. The samples had been stored at −20°C for one to 18 months before the CA 19-9 measurements. Serum α-fetoprotein was measured by the method of Ruoslahti and Seppälä. Double antibody radioimmunoassay for carcinoembryonic antigen was performed using anti-carcinoembryonic antigen antiserum from Dakopatts a/s (Copenhagen, Denmark) as the first antibody. The values in our assay showed good correlation (r = 0.997) with the values obtained by Abbot-CEA-RIA Diagnostic Kit (Abbott, Wiesbahn, West Germany) as tested with 100 serum samples containing carcinoembryonic antigen in concentrations ranging from normal up to 60 500 ug/l. Cut off values of 25 ug/l and 2.5 ug/l were used for α-fetoprotein and carcinoembryonic antigen, respectively.
15% of patients with benign diseases. A weak correlation \((r = 0.803)\) between the CA 19-9 and carcinoembryonic antigen concentrations was found (Fig. 2b).

LIVER DISEASES
An increased serum CA 19-9 concentration was found in 15% of the patients with benign liver diseases and in 22% of the patients with hepatomas (Fig. 1). No difference in the median values between these groups was found. Serum \(\alpha\)-fetoprotein concentration was increased above 25 \(\mu\)g/l in 16 of the 18 patients with cancer. No correlation between the CA 19-9 and \(\alpha\)-fetoprotein concentrations was found (Fig. 2c).

BILIARY TRACT DISEASES
Pathological CA 19-9 concentrations were found in eight of the 11 patients with cholangiocarcinoma and in 35% of the patients with benign biliary tract diseases (range 5-3-440 U/ml). Liver metastases were found in 10 of the 11 patients with cancer. All of the patients with choledocholithiasis and increased CA 19-9 concentrations had obstructive jaundice.

Serum \(\alpha\)-fetoprotein was slightly increased in one of the patients with cancer (56 \(\mu\)g/l); the other patients had normal values (Table). Raised carcinoembryonic antigen values were found in both benign and malignant biliary tract disease and in liver disease (Fig. 2b, Table).

Discussion
Serum CA 19-9 concentration was most consistently increased in patients with pancreatic cancer (76%) or cholangiocarcinoma (73%). DelVillano et al.1 studied patients with pancreatic carcinoma and patients with non-malignant pancreatic diseases. Our findings in patients with cancer agree with their findings, but our patients with non-malignant pancreatic diseases had moderately increased values more often than their patients (16 v 0%). This discrepancy may be due to differences in the patients studied. All our patients with pancreatitis and increased CA 19-9 concentrations had a highly fulminating haemorrhagic disease. DelVillano et al may not have included such patients in their study.

Some patients with benign hepatobiliary disease, especially those with obstructive jaundice, showed a moderately increased CA 19-9 concentration. This may be a problem as many patients with pancreatic cancer or cholangiocarcinoma also have obstructive jaundice. The highest CA 19-9 value in patients with benign disease was 440 U/ml. Higher values were found in 64% and 56% of the patients with
Comparison of a new tumour marker, CA 19-9™, with α-fetoprotein and carcinoembryonic antigen

pancreatic and biliary tract carcinomas, respectively. Thus in patients with moderately increased CA 19-9 values, additional tests are obviously required to distinguish between benign and malignant diseases.

Measurement of serum α-fetoprotein is a well established test in the diagnosis of liver cancer, and our results suggest that α-fetoprotein is a more sensitive and more specific marker for hepatoma than CA 19-9. Increased α-fetoprotein concentrations are found in 80% of patients with liver cell cancer and substantially increased values are rarely found in patients with benign liver disease or other gastrointestinal malignancies. The CA 19-9 concentration, on the other hand, was higher than 37 U/ml in 15% of the patients with benign liver disease and in only 22% of the patients with hepatoma. Two patients with cancer had normal α-fetoprotein concentrations and both also had normal CA 19-9 values. Thus it seems unlikely that the CA 19-9 antigen would be a reliable marker in patients with hepatoma with normal α-fetoprotein concentrations.

Fig. 2 Comparison of the CA 19-9, carcinoembryonic antigen and α-fetoprotein concentrations. (a) Gastric diseases; (b) pancreatic (circle) and biliary tract (triangle) diseases; (c) liver (circle) and biliary tract (triangle) diseases. Open symbol, benign disease; closed symbol, carcinoma.
CA 19–9 resembles carcinoembryonic antigen in that, although both markers were originally found in colorectal carcinoma, various different gastrointestinal adenocarcinomas produce them. It is generally accepted that carcinoembryonic antigen is a poor diagnostic tumour marker since high serum concentrations occur mainly in patients with metastasised cancer and, in addition, increased concentrations are found in patients with benign diseases. The specificity of the carcinoembryonic antigen assay, of course, increases if a high cut off value is used. In our study, the use of a limit of 5 ug/l would have decreased the percentage of false positives in gastric diseases from 17% to 8% and in pancreatic diseases from 15% to 8%. This, however, would have decreased the sensitivity in these cancers from 39% to 28% and from 68% to 57%, respectively. The use of a cut off level of 5 ug/l or 10 ug/l does not appreciably increase the value of the carcinoembryonic antigen measurement as a diagnostic test for cancer. A relatively poor sensitivity is evident also with the CA 19–9 assay. The CA 19–9 concentration was increased in only 15% of patients with localised gastric carcinoma. In pancreatic cancer, a substantially increased CA 19–9 concentration (3200 U/ml) was found in only one of the six patients with no sign of metastases at laparotomy. This patient had an inoperable tumour with a diameter of 20 cm. Similar results have previously been obtained in colorectal cancer, where increased CA 19–9 concentrations were found in 46% of patients with advanced cancer but in only 8% of patients with a Dukes A or B carcinoma.

Important differences between CA 19–9 and carcinoembryonic antigen seem to exist. The new marker is more specific for cancer and, in patients with cancer, the increase is often more pronounced in CA 19–9 values than in carcinoembryonic antigen values. The median CA 19–9 concentration in patients with pancreatic cancer was 86 times higher than the cut off level, and 68% of the patients with cancer had higher values than any of the patients with benign disease. The median carcinoembryonic antigen value in patients with pancreatic carcinoma was 2.9 times higher than the cut off level and only 26% of the patients with cancer had higher values than any of the patients with pancreatitis. In patients with gastric diseases, all of those with benign diseases had normal CA 19–9 values. Increased carcinoembryonic antigen concentrations, on the other hand, were found in benign diseases, and only 17% of the patients with gastric cancer had carcinoembryonic antigen values higher than any of the patients with benign diseases.

Atkinson et al. have recently studied the expression of the CA 19–9 antigen in normal and malignant gastrointestinal tissues. The antigen was found by immunoperoxidase staining in 40% to 80% of carcinomas from gall bladder, stomach, pancreas, and colon. Interestingly, only one of the 11 hepatomas stained for the antigen. This agrees with the low percentage of CA 19–9 positive sera in our patients. The CA 19–9 antigen was also present in 37% to 70% of the normal tissue specimens from upper gastrointestinal organs, including the liver. This may explain why increased serum CA 19–9 concentrations are found in some patients with benign diseases.

The CA 19–9 assay is the first commercially available cancer marker system defined by a monoclonal antibody. The precise value of the new test in clinical practice remains to be determined. We found that the test had a lower sensitivity (50-0%) and lower specificity (90-1%) for cancer than reported by DelVillano et al. It seems, however, that the new assay serves as a valuable adjunct to other clinical tests, especially in the diagnosis of pancreatic cancer.

The work was supported by the Finnish Cultural Foundation. We thank Ms Sirpa Kuisma for excellent technical assistance.

This report is publication no. 11 of the Tumor Biology Unit, University of Helsinki, Helsinki.

References


Requests for reprints to: Dr Hannu Jalanko, Department of Bacteriology and Immunology, University of Helsinki, Haartmaninkatu 3, 00290 Helsinki 29, Finland.
Comparison of a new tumour marker, CA 19-9, with alpha-fetoprotein and carcinoembryonic antigen in patients with upper gastrointestinal diseases.

H Jalanko, P Kuusela, P Roberts, P Sipponen, C A Haglund and O Mäkelä

doi: 10.1136/jcp.37.2.218

Updated information and services can be found at:
http://jcp.bmj.com/content/37/2/218

**Email alerting service**

*These include:*

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/