Plasma and salivary thiocyanate in gastric cancer

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EDITORIAL SYNOPSIS This study again shows that the thiocyanate concentration in saliva tends to be low in patients with gastric carcinoma. The low level does not appear to be specifically related to the carcinoma but to secondary factors, and, as there is also a big overlap with the normal range, this measurement is not recommended as a diagnostic test.

Previous studies (Jakobi, Jakobi, and Cavalcanti, 1961) have suggested that the concentration of thiocyanate in the saliva of patients suffering from oesophageal or gastric cancer is unusually low compared with that in normal subjects or patients with peptic ulcer. If this were confirmed the measurement of salivary thiocyanates might provide a screening test for gastric cancer. Salivary thiocyanates have, therefore, been measured in a further series of subjects and some observations have been made on plasma thiocyanate concentration and the changes in plasma levels in response to oral doses of thiocyanate.

METHOD

Thirty-eight patients with gastric cancer, 92 with benign gastric ulcers, and 56 healthy adults were examined.

Subjects were asked to spit into a test tube: stimulants to salivary flow were not administered and no provision was made to collect at a particular time of day. The thiocyanate concentration was determined colorimetrically using ferric nitrate. Distilled water, 6.5 ml., and 2.5 ml. of 20% w/v trichloroacetic acid solution were added to 1 ml. of saliva in a test tube. The contents of the tube were mixed by repeated inversion and allowed to stand for 10 minutes before filtration through Whatman no. 42 filter paper. Then 3 ml. of the filtrate was added to 2 ml. of water, followed by 5 ml. of ferric nitrate reagent. This was prepared by adding 250 ml. of 2 N nitric acid to 80 g. of ferric nitrate: the total volume was then made up to 500 ml. before filtration. The colour change produced was measured colorimetrically at 470 m μ and the results compared with a standard curve obtained by adding ferric nitrate solution to standard thiocyanate solutions.

Plasma thiocyanate concentrations were measured

FIG. 1. For comparison between gastric ulcer and carcinoma.

FIG. 2. For comparison between carcinoma and pernicious anaemia.

FIG. 3. Results of thiocyanate tolerance tests on eight patients with gastric cancer and four normal subjects.

spectrophotometrically on samples deproteinized with 10% trichloroacetic acid (Wilson, 1965) by the method of Aldridge (1945), in which thiocyanate is converted to cyanogen bromide, and forms a coloured complex with pyridine benzidine hydrochloride mixture. Oral thiocyanate tolerance tests were performed in the morning after the subject had fasted overnight, when 0.25 mg./kg. body weight of potassium thiocyanate solution of concentration 0.25 mg./ml. was given by mouth and blood samples were collected before and for up to one hour after the test.

RESULTS

Figure 1 shows the salivary thiocyanate concentrations in the normal subjects and in the patients with (a) gastric cancer and (b) benign gastric ulcer, divided by sex and smoking habits. Subjects were regarded as non-smokers if they had not smoked for at least two months before the test and as smokers if they were continuing to smoke up to the time of the test; others were excluded. On average, smokers in each clinical group had higher salivary thiocyanate concentrations than non-smokers. Gastric cancer patients, however, had significantly lower salivary concentration than gastric ulcer patients or normal subjects, irrespective of their smoking habits ($P < 0.001$ in all cases), but there was considerable overlap between groups.

Figure 2 shows the results of plasma thiocyanate determinations in healthy non-smokers and in non-smokers with (a) treated pernicious anaemia and (b) gastric cancer, and in normal subjects who are non-smokers. The number of estimations is small, but the concentrations in patients with gastric cancer are lower than those in patients with pernicious anaemia or in normal subjects ($P = 0.02$ and $P < 0.01$ respectively), the last two groups showing similar

results. Moreover, it was confirmed that salivary concentrations vary directly with plasma levels.

Thiocyanate tolerance tests were performed on eight patients with gastric cancer (one non-smoker and seven smokers) and four normal subjects (three non-smokers and one smoker) and the results are shown in Figure 3. In all the normal subjects and six of the gastric cancer patients the plasma thiocyanate concentration rose by at least $0.7 \mu\text{mole}/100 \text{ ml}$. after the test dose, but the two remaining gastric cancer patients (one smoker and one non-smoker), who had the lowest initial plasma concentrations, showed maximum rises of only $0.3 \mu\text{mole}/100 \text{ ml}$. It may be, therefore, that in some gastric cancer patients thiocyanate absorption is reduced or delayed.

DISCUSSION

The results confirm the observation that salivary thiocyanate concentrations tend to be unusually low in gastric cancer patients (Jakobi *et al.*, 1961). There is, however, so much overlap between clinical groups, even when smoking habits are taken into account, that estimation of salivary thiocyanate concentration would not be of much use as a screening test for cancer of the stomach. In the few measurements made, plasma thiocyanate concentration also tended to be low in gastric cancer patients so that the cause of the low salivary concentrations is unlikely to be a defective salivary concentrating mechanism.

Thiocyanate present in body fluid is derived from two main sources: first, from alimentary absorption of pre-formed thiocyanate from foods such as milk and vegetables (*e.g.*, Støa, 1957; Wilson, 1965), and secondly, from detoxication of cyanide, *e.g.*, from tobacco smoke (see Støa, 1957, for review and summary). Low plasma thiocyanate could therefore, result either from reduced cyanide detoxication or from defective net intake of thiocyanate. The former seems unlikely since one would expect evidence of chronic cyanide toxicity in the most exposed subjects, that is, in smokers. Moreover, as judged by the relative increase in the concentrations of salivary thiocyanate in smokers compared with non-smokers with gastric carcinoma, cyanide conversion does not appear to be defective.

Anorexia is a prominent symptom in gastric cancer and, therefore, the thiocyanate available for absorption could be diminished by a poor diet (Støa, 1957). The thiocyanate tolerance tests, however, also suggest that absorption of thiocyanate may be diminished or delayed in some patients. This is probably associated with the presence of the carcinoma rather than with gastric atrophy since plasma thiocyanate concentrations are almost normal

in treated pernicious anaemia. The results of tolerance tests must, however, be interpreted with caution, since in one patient with a benign antral gastric ulcer and complete pyloric obstruction, as judged by the recovery of a test meal containing an unabsorbable phenol red marker, the plasma thiocyanate concentration did not change in response to oral thiocyanate. It is possible, therefore, that obstruction rather than any other property of the cancer is the cause of the flat thiocyanate tolerance curves noted.

Another, and possibly more important, consequence of obstruction would be the loss through vomiting of salivary and gastric juice containing high concentrations of thiocyanate, which could deplete body thiocyanate stores very quickly (Støa, 1957). A low thiocyanate intake in the diet of an anorexic patient, coupled with a loss of gastric and salivary secretions, could explain our findings in most gastric cancer patients, but the clinical details in a few cases are inconsistent with this hypothesis, and suggest that some other factor, such as failure of alimentary absorption, may be contributory.

An example is provided by the history of one patient, a man of 58, who had a 30-year history of abdominal pain and occasional vomiting. When he was first seen a barium meal showed the appearances of a benign antral gastric ulcer. Following a course of treatment with carbenoxolone sodium, his symptoms remitted for six months before there was a return of moderate occasional epigastric pain, but no return of vomiting. At this time, when he had stopped smoking for six months, his salivary thiocyanate concentration was only $1.75 \text{ mg. \%}$. At operation a malignant gastric ulcer was found.

SUMMARY

The salivary thiocyanate concentration was found to be significantly lower in patients with gastric cancer than in those with benign gastric ulcer, or in normal subjects, but the differences were not sufficiently marked for thiocyanate determination to be of value as a screening test for gastric cancer. The low salivary concentration in cancer was probably due, in most cases, to a combination of depleted body stores through vomiting of gastric juice and swallowed saliva, and inadequate replacement through anorexia, but occasional patients were encountered in whom low saliva concentrations could not be accounted for on this basis.

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