Influence of Myocardial Infarction on Serum Manganese, Copper, and Zinc Concentrations

Jacques Versleek, Fabrice Barbier, Albert Speecke, and Julien Hoste

Reportedly, serum manganese concentrations increase after myocardial infarction, closely correlated with increased serum aspartate aminotransferase activity. However, these conclusions are apparently based on analyses of contaminated samples. Serum manganese concentrations after myocardial infarction have been re-investigated by neutron activation analysis, and no significant increase could be demonstrated. Because serum copper and zinc could be determined simultaneously, analyses for these trace elements are also reported, which confirm the findings of others. After myocardial infarction a statistically significant (0.02 < $P < 0.05$) increase in serum copper and a statistically significant (0.001 < $P < 0.01$) decrease in serum zinc were observed.

Additional Keyphrase: neutron activation analysis

Abnormal values for serum manganese, copper, and zinc after myocardial infarction have been described (1–8). However, the early publication reporting an increase of serum manganese (1) must be discounted because the conclusions are apparently based on analyses of contaminated samples. Indeed, serum manganese concentrations in normal subjects (9–13) are about 20-fold lower than those determined by Hedge et al. (1) in their control series.

We developed a sampling method and analytical technique (12, 14) for determination of serum manganese, copper, and zinc, and have reported our values for normal subjects (13, 15) and for patients with acute and chronic hepatitis and postnecrotic cirrhosis (16). Here, we describe our results for patients with myocardial infarction.

Materials and Methods

Subjects. We studied 46 control subjects. Of these, 29 were examined during a stay in the hospital (in the ophthalmologic, orthopedic, or internal medicine ward), and 17 during a clinical examination for recruitment of university personnel. All were free of any obvious medical disease. Twenty-five were men, 21 women. Women taking oral contraceptives were not included as it is known that these drugs influence values for serum copper (17–20) and zinc (18).

We studied 16 patients with acute myocardial infarction. From eight (six men and two women, age 33 to 84 years, mean age 63 years), blood samples were collected on admission to the hospital. Chest pain had started 2 h to 3.5 days (mean, 28 h) before. From the eight others (all men, age 42 to 68 years, mean age 58 years), blood samples were collected while they were under treatment in the intensive-care unit. Chest pain had started 27 h to 4.5 days (mean, 52 h) before. Treatment included analgesics and sedatives and in some cases sodium warfarin, lanatoside C, furosemide, or chlorthalidone. In one case, betamethasone and aminophylline were also administered because of associated bronchial asthma. All patients were also given intravenous glucose (50 g/liter, 1 to 1.5 liters per 24 h).

Every case of acute myocardial infarction was documented by electrocardiogram and increased serum enzyme activity (aminotransferases, lactate dehydrogenase, creatine kinase).

In the case of control subjects and the patients hospitalized in the intensive-care unit, blood was sampled between 0800 and 1000 h, after an overnight fast.

Four of the hospitalized controls received intravenous glucose, as did the patients with myocardial in-
Serum manganese, copper, and zinc were determined before and at the end of the infusion.

**Techniques.** Serum manganese, copper, and zinc were determined by neutron activation analysis. Collection of blood specimens, sample and standard handling, irradiation, chemical separations, and measurements were carried out as described elsewhere (12). However, the blood samples were collected with a plastic cannula trocar (Intranele, 110 16, Vygon Sterile) instead of with a disposable steel needle (Terumo, 18 G 1½) as mentioned in the original report (12). It is of paramount importance to take the utmost care to avoid all possible sources of contamination (9, 11, 13, 15). The serum samples were irradiated for 4 h in the Thetis reactor of Ghent University at a flux of $1.9 \times 10^{12}$ n·cm$^{-2}$·s$^{-1}$. The neutron spectrum of the reactor being stable, a copper wire, co-irradiated with the samples was used as a flux monitor (single comparator method). Beforehand, we evaluated the ratios of the specific photopeak activities of the isotopes investigated to the specific photopeak activity of the copper monitor measured in well-defined experimental conditions (21). All samples were analyzed in duplicate and the mean value was calculated.

**Statistical methods.** The values obtained for healthy subjects were tested for outlying observations according to the criteria of Grubbs (22). The normality of the distributions in healthy subjects was checked by the chi-square test (23). Standard statistical techniques (24) were used to determine means and standard deviations (SD) and to calculate the correlation coefficient ($r$) between serum manganese concentration and aspartate aminotransferase (EC 2.6.1.1) activity. The two sample $t$-test (comparison of two means, unpaired case) (24) was used to test the significance of differences in mean concentrations.

**Precision and accuracy of the assays.** The reproducibility of the assays for the trace elements involved was checked in two ways.

First, it was determined by carrying out repeated (six) analyses of four normal serum samples and calculating the percent standard deviation. Values between 6.9% and 9.7% were obtained for manganese, between 1.5% and 4.6% for copper, and between 4.1% and 7.9% for zinc (12).

Secondly, the percent difference ($d$) between the two results of the duplicate determinations also permitted an estimate of the standard deviation. The calculations were made as follows (25):

$$\text{estimate of SD} = \frac{\sqrt{\sum x^2}}{2n}$$

where $n$ is the number of duplicate determinations performed. We obtained the following values for manganese: $s = 12.9$% (controls) and 12.8% (patients with acute myocardial infarction); for copper the values were respectively $s = 5.6$% and 5.1%; and for zinc they were $s = 7.3$% and 6.5%.

The accuracy of the neutron activation technique for determining copper and zinc in serum was checked by comparing the results with those obtained by atomic absorption in a same pooled serum. The mean value determined by neutron activation was 3.9% higher (for copper) and 5.6% lower (for zinc) (14).

**Results**

The individual values for serum manganese, copper, and zinc in controls and in patients with acute myocardial infarction are plotted in Figure 1A, B, and C.

In the controls the distributions are normal but the following values are outlying: 1.01 and 1.04 µg/liter (manganese) and 1.99 mg/liter (copper).

In the patients with acute myocardial infarction, the mean serum manganese, copper, and zinc values on admission do not significantly differ from the mean values during hospitalization, so all the patients are treated as one group.

The means ±1 SD for the controls are 0.57 ± 0.13 µg/liter (serum manganese), 1.07 ± 0.24 mg/liter (serum copper), and 0.94 ± 0.13 mg/liter (serum zinc). These results were previously reported in this journal (16).

The means ±1 SD for the patients with myocardial infarction are 0.64 ± 0.10 µg/liter (serum manganese), 1.23 ± 0.25 mg/liter (serum copper), and 0.81 ± 0.13 mg/liter (serum zinc).

The difference in the mean serum manganese concentration between controls and patients with acute myocardial infarction is not significant ($t = 1.89; 0.05 < P < 0.10$). The difference in the mean serum copper concentration is slightly significant ($t = 2.25; 0.02 < P < 0.05$). The difference in the mean serum zinc value is significant ($t = 3.40; 0.001 < P < 0.01$).

The correlation coefficient ($r$) between serum manganese and aspartate aminotransferase activity is -0.156 (not significant, 0.50 < $P < 0.60$).

Glucose infusion did not modify the serum manganese, copper, or zinc concentrations in the four controls.

**Discussion**

**Manganese.** An earlier report by Hedge et al. (1) describing an increased serum manganese after myocardial infarction is based on analyses of contaminated samples. It now has been proved that the true serum manganese concentration in normal subjects (9–13) is about 0.600 µg/liter, not 10 µg/liter (1).

Our results show that serum manganese concentrations do not significantly increase after myocardial infarction and that no significant correlation exists between serum manganese and aspartate aminotransferase. Thus, in our experience serum manganese values do not provide an indication of myocardial damage.

**Copper.** The serum copper concentration reportedly increases in acute myocardial infarction (2, 3),
ordinarily beginning on the second or third day (3), reaching a maximum on the fourth to the sixth day (2) or on the fifth to the eleventh day (3), and gradually decreasing to normal within three (2) or several (3) weeks. In the present study a slight but statistically significant increase in serum copper was found. The highest two values obtained were 1.62 mg/liter (65-year-old man, 48 h after onset of chest pain) and 1.74 mg/liter (42-year-old man, about 4 days after onset of symptoms). Possible explanations for the increase of serum copper are discussed by Khandekar et al. (2).

Zinc. It now seems firmly established that the serum zinc concentration decreases after myocardial infarction (4–8). Halsted and Smith (4) say that the value decreases within 24–48 h. Davies et al. (26) mention six patients with coronary infarction who had a serum zinc value within the normal range; this must not be interpreted as contradictory—their samples were taken "within the first two weeks" after the acute infarction. Halsted and Smith (4) and Wacker et al. (8) report that low values persist for two weeks. More recently, however, Handjini et al. (5) reported that the mean concentration increases again on the fifth day and that all values exceed the minimal normal by the tenth day, which agrees with the findings of Lindeman et al. (6), who have also shown that the mean concentration increases again on the fourth and fifth day, reaching again control values. Our findings are in good agreement with those of others (4–8). The comparison of the mean serum zinc concentration shows a statistically significant decrease. In only three of our cases was the serum zinc value greater than 0.95 mg/liter. In one case (male, 33 years) the blood was collected about 4 h after onset of symptoms, in another (male, 65 years) about 48 h, and in the third (female, 61 years) 3.5 days after the onset of chest pain. The lowest three serum zinc values obtained are 0.69 mg/liter (male, 53 years, 4 h after onset of symptoms), 0.68 mg/liter (male, 53 years, 27 h after onset), and 0.56 mg/liter (male, 69 years, 12 h after onset).

Because plasma zinc responds to food intake (26–28), we were careful in the case of the patients examined on admission that no blood specimens were collected within 3 h after the last meal. However, in these eight patients a possible diurnal variation could also influence the results. Significant diurnal variations have both been described (29, 30) and denied (4). An intravenous glucose load can cause plasma zinc to decrease (26, 27). However, glucose infusion, as in the hospitalized patients with myocardial infarction, did not significantly influence serum zinc values.

To our knowledge it has not been described that therapeutic doses of the drugs used during this study influence the concentrations in serum of the trace elements involved. Wester (31) reports investigations concerning the influence of chlorthalidone on the concentrations in serum of a number of trace elements. The drug (50 mg per os daily) did not influence serum copper or zinc values. As stated before, there is no statistically significant difference between the mean values obtained in our patients on admission and in those under treatment in the intensive-care unit. Possible explanations for the decrease of serum zinc after myocardial infarction are discussed by Halsted and Smith (4) and Lindeman et al. (6, 32).

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