The effect of hypermagnesaemia on serum immunoreactive calcitonin levels in normal human subjects

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Abstract. The effect of hypermagnesaemia on serum levels of immunoreactive calcitonin was studied in normal human subjects. After iv administration of magnesium sulphate over 120 min, the mean (± SEM) serum magnesium concentration rose from the baseline level of 0.9 ± 0.1 to 2.6 ± 0.3 mmol/l (P < 0.01), and thereafter remained higher than the baseline level. The magnesium infusion caused a significant increase in serum immunoreactive calcitonin levels (P < 0.01). The rise in serum magnesium concentration was accompanied by a significant decrease in the concentrations of corrected serum calcium and whole blood ionized calcium (P < 0.01, P < 0.01, respectively). Our results suggest that hypermagnesaemia causes an increase in serum immunoreactive calcitonin levels in normal human subjects despite a decrease in the concentrations of corrected serum calcium and whole blood ionized calcium.

Although calcium is the principal regulator of the thyroid C-cell function, magnesium has also been observed to have an important role. All reports of in vitro and in vivo animal studies indicate that magnesium, like calcium, stimulates the release of calcitonin (CT) from the thyroid gland (Radde et al. 1969; Bell 1970; Care et al. 1971; Littledike & Arnaud 1971). However, the effect of hypermagnesaemia on serum CT has not been extensively studied in normal human subjects. Some investigators demonstrated no significant change of serum immunoreactive CT (iCT) levels during magnesium infusion in pre-eclamptic women (Cruikshank et al. 1979), whereas others found a marked increased level of serum iCT during magnesium administration (Deftos et al. 1978). On the other hand, Anast et al. (1975) reported that magnesium administration caused a decrease in circulating iCT in patients with thyroid medullary carcinoma. To study the effect of hypermagnesaemia on serum iCT levels in normal human subjects, we analysed changes in serum iCT levels, and concentrations of corrected serum calcium and whole blood ionized calcium during and after iv administration of magnesium sulphate.

Subjects and Methods

Seven healthy men ranging in age from 20 to 34 years (mean 26 years) participated in the study. Informed consent was obtained from each subject. Our investigation was conducted in accordance with the principles of the Declaration of Helsinki II and was approved by our institutional review board. While the subjects were...
supine in bed, a cannula for infusion was inserted into the antecubital vein in one arm, and another cannula for blood sampling was inserted into the other arm. Magnesium sulphate heptahydrate of 0.58 ± 0.01 (mean ± SEM) mmol/kg body weight in 250 ml of 5% dextrose in water was given iv over 2 h. For 1 h before and 3 h after magnesium infusion, 5% dextrose in water was administered at 125 ml per h. Blood samples were obtained just before, 30, 90, 120, 150, 210 and 270 min after the magnesium infusion began. Sera were frozen and stored at -20°C until analysed. Serum values of magnesium, calcium, and total protein were measured with a multichannel autoanalyzer technique (TBA-880, Toshiba, Tokyo, Japan). All values of serum calcium were corrected for total serum protein concentration (Husdan et al. 1973). The whole blood ionized calcium concentration was measured with an ionized calcium analyzer (ICA1, Radiometer Co, Copenhagen, Denmark). Serum CT was measured with an Eiken RIA kit (Eiken Immunochemical Laboratory, Tokyo, Japan). The limit of detection was 20 ng/l and normal baseline CT levels were less than 100 ng/l. The intra-assay coefficient of variation was 8.5%. A series of blood samples was always analysed in the same assay, thus eliminating the effect of inter-assay variation. A two-way analysis of variance was used for the estimation of the effect of magnesium on serum iCT levels and concentrations of corrected serum calcium and whole blood ionized calcium, and the Bonferroni method was used for the statistical analysis of timed measurements during and after magnesium infusion in comparison to baseline values.

Results

The results of magnesium infusion are shown in Table 1. The iv administration of magnesium sulphate caused a marked hypermagnesaemia over 270 min (P < 0.01). The mean (± SEM) serum magnesium concentration rose from normal baseline levels of 0.9 ± 0.1 to 2.6 ± 0.3 mmol/l (P < 0.01) at 120 min, and thereafter remained higher than the baseline level up to 270 min (Fig. 1A). The magnesium infusion caused a significant increase in serum iCT levels (P < 0.01). The serum iCT level increased significantly from the baseline level of 43.7 ± 5.4 to 60.0 ± 7.0 ng/l (P < 0.01) at 150 min and to 54.0 ± 8.2 ng/l (P < 0.05) at 210 min (Fig. 1B). The rise in serum magnesium concentration was also accompanied by a significant decrease in the concentrations of corrected serum calcium and whole blood ionized calcium (P < 0.01, P < 0.01, respectively); the corrected serum calcium concentration decreased progressively from the baseline level of 2.49 ± 0.03 to 2.22 ± 0.03 mmol/l (P < 0.01) at 270 min after start of the magnesium infusion (Fig. 1C), and the whole blood ionized calcium concentration, which did not change during the magnesium infusion, decreased from baseline levels of 1.24 ± 0.01 to 1.21 ± 0.01 mmol/l (P < 0.01) at 150 min, and reached a nadir of 1.17 ± 0.01 mmol/l (P < 0.01) at 270 min after start of the magnesium infusion.

Table 1.
Effects of magnesium infusion on concentrations of serum magnesium, serum immunoreactive calcitonin, corrected serum calcium, and whole blood ionized calcium in normal human subjects.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Serum magnesium (mmol/l)</th>
<th>Serum immunoreactive calcitonin (ng/l)</th>
<th>Corrected serum calcium (mmol/l)</th>
<th>Whole blood ionized calcium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.9 ± 0.1</td>
<td>43.7 ± 5.4</td>
<td>2.49 ± 0.03</td>
<td>1.24 ± 0.01</td>
</tr>
<tr>
<td>30</td>
<td>1.6 ± 0.1**</td>
<td>45.1 ± 5.6</td>
<td>2.43 ± 0.03*</td>
<td>1.27 ± 0.03</td>
</tr>
<tr>
<td>90</td>
<td>2.2 ± 0.1**</td>
<td>48.3 ± 8.5</td>
<td>2.34 ± 0.03**</td>
<td>1.26 ± 0.03</td>
</tr>
<tr>
<td>120</td>
<td>2.6 ± 0.3**</td>
<td>50.7 ± 7.6</td>
<td>2.36 ± 0.03**</td>
<td>1.26 ± 0.02</td>
</tr>
<tr>
<td>150</td>
<td>2.2 ± 0.1**</td>
<td>60.0 ± 7.0**</td>
<td>2.28 ± 0.03**</td>
<td>1.26 ± 0.01</td>
</tr>
<tr>
<td>210</td>
<td>1.8 ± 0.1**</td>
<td>54.0 ± 8.2*</td>
<td>2.26 ± 0.03**</td>
<td>1.21 ± 0.01</td>
</tr>
<tr>
<td>270</td>
<td>1.6 ± 0.1**</td>
<td>39.4 ± 8.8</td>
<td>2.22 ± 0.03**</td>
<td>1.19 ± 0.01**</td>
</tr>
</tbody>
</table>

Normal range

0.8-1.1
< 100
2.20-2.60
1.10-1.30

Values given as mean ± SEM. * P < 0.05, ** P < 0.01 as compared with baseline level.
Our results in normal human subjects demonstrate that administration of magnesium sulphate leads to an increase in serum iCT levels despite a decrease in the concentrations of corrected serum calcium and whole blood ionized calcium. Thus, compared with calcium, the effect of magnesium on CT secretion appears to be slower and weaker in normal human subjects. Why did the serum iCT level increase in the late period of hypermagnesaemic state? We do not have a clear explanation about the delayed response of the hormone to magnesium. Part of the explanation may be that the effect of magnesium per se on CT release was not so strong as that of calcium (Care et al. 1967, 1971; Pento et al. 1974), and furthermore, the slower rate of the increase in serum magnesium concentration in our study, compared with those of previous studies (Littlelie & Arnaud 1971; Pento et al. 1974; Anast & Gardner 1985).

Another possibility is: ionized Mg$^{2+}$ + protein-calcium $\rightarrow$ protein-magnesium + Ca$^{2+}$, which after a proper incubation time would lead to a transitory increase in blood ionized calcium concentration, thereby stimulating CT. However, this hypothesis is unlikely, because our results showed a significant decrease in the concentrations of whole blood ionized calcium and corrected serum calcium after the end of the magnesium infusion, when the increase in serum iCT levels was observed. Therefore, these findings indicate that calcium is not involved in an increase in serum iCT levels caused by the magnesium infusion.

Considering the hypocalcaemia associated with hypermagnesaemia, it is also possible that this condition attenuates the effect of magnesium per se on CT release, resulting in the delayed response of the hormone to magnesium.

Discussion

Our results in normal human subjects demonstrate that administration of magnesium sulphate leads to an increase in serum iCT levels despite a decrease in the concentrations of corrected serum calcium and whole blood ionized calcium. Thus, compared with calcium, the effect of magnesium on CT secretion appears to be slower and weaker in normal human subjects. Why did the serum iCT level increase in the late period of hypermagnesaemic state? We do not have a clear explanation about the delayed response of the hormone to magnesium. Part of the explanation may be that the effect of magnesium per se on CT release was not so strong as that of calcium (Care et al. 1967, 1971; Pento et al. 1974), and furthermore, the slower rate of the increase in serum magnesium concentration in our study, compared with those of previous studies (Littlelie & Arnaud 1971; Pento et al. 1974; Anast & Gardner 1985).

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Few previous studies have examined the effect of magnesium on serum iCT levels in human subjects. Cruikshank et al. (1979) studied the effect of magnesium sulphate infusion over 24 h on calcium metabolism in twenty women at term with mild to moderate pre-eclampsia and found no significant change in serum iCT levels after the infusion. The disparity between their findings and ours may be partly explained by the earlier time points monitored in our study and/or by the intrinsic pathophysiologic differences between pregnant women and healthy men. Anast et al. (1975) demonstrated that magnesium administration produced rapid and striking falls in the circulating iCT level in patients with thyroid medullary carcinoma. Their results might indicate an intrinsic pathophysiologic difference between tumour cells and normal cells. Our findings is not necessarily consistent with the preliminary report by Deftos et al. (1978), who demonstrated that a progressive increase in serum CT levels occurred during magnesium administration.
Since the details concerning subjects, the method of magnesium administration, and changes in serum concentrations of magnesium and calcium were not shown in their study, we cannot compare our results with theirs.

On the other hand, the development of hypocalcaemia in response to hypermagnesaemia has been well documented in a number of clinical studies (Monif & Savory 1972; Mountokalakis et al. 1972; Cruikshank et al. 1979; Donovan et al. 1980; Cholst et al. 1984; Suzuki et al. 1986). Our previous study in normal human subjects demonstrated that hypocalcaemia associated with hypermagnesaemia was mainly due to an increase in urinary calcium excretion and partly due to the suppression of parathyroid function by the direct action of magnesium (Suzuki et al. 1986). However, the role of CT in the development of hypocalcaemia associated with hypermagnesaemia remains unclear. CT has previously been reported as the major factor responsible for the hypocalcaemic effect of magnesium in animal studies (Radda et al. 1969; Nielsen 1970; Littledike & Arnaud 1971). However, our results showed that a progressive decrease in serum calcium concentrations was not accompanied by an increase in serum iCT levels at least during the first 120 min. Therefore, CT may not play a critical role in the development of hypocalcaemia associated with hypermagnesaemia in normal human subjects.

In summary, our data in vivo in normal human subjects suggest that: a) hypermagnesaemia causes an increase in serum iCT levels despite a significant decrease in the concentrations of corrected serum calcium and whole blood ionized calcium, and: b) unlike CT in animals, CT in normal humans may not play a critical role in the development of hypocalcaemia associated with hypermagnesaemia.

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References


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