CHRONIC HYPERCALCAEMIA SECONDARY TO HYPERPARATHYROIDISM: A RISK FACTOR DURING ANAESTHESIA?

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SUMMARY

Hypercalcaemia (increased plasma total calcium concentration, \([\text{Ca}]\)) has been associated with serious ventricular arrhythmia and sudden cardiac arrest in patients with hyperparathyroidism. To support our impression that the occurrence of such complications during surgery is rare, we examined the records and e.c.g. of 193 patients with moderate hypercalcaemia \(([\text{Ca}] = 2.89 \pm 0.02 \text{ mmol litre}^{-1}, \text{mean} \pm \text{SEM})\) secondary to histologically demonstrable parathyroid hyperfunction, who were admitted to hospital between 1974 and 1978. We found that ventricular arrhythmia was not recorded for any patient, and A-V junctional rhythm was present at the beginning of operation in two. Before operation a statistically significant although minimal shortening of corrected values of Q-T interval occurred compared with a control group \((n = 60)\). However, duration of the corrected Q-T interval was not diagnostic of increased \([\text{Ca}]\) in a given patient with hyperparathyroidism.

Hypercalcaemia (abnormal increase in total plasma calcium concentration) in patients with hyperparathyroidism may be considered to increase the risk of anaesthesia (Young and Emerson, 1949; Rapoport, Sepp and Brown, 1960; Surawicz, 1966) because of potentially dangerous disturbances in cardiac rhythm. A manifestation of hypercalcaemia on e.c.g. is the shortening of the Q-T interval (Yu, 1952; Bellet, 1955; Surawicz, 1967a, b).

Dangerous cardiac arrhythmia in patients with hyperparathyroidism during anaesthesia for exploration of the neck seemed to us to be rare. Our impression was that, even when arrhythmia of supraventricular origin was present before operation, major complications resulting from ventricular irritability did not occur during anaesthesia or in the recovery phase. We have studied the occurrence of abnormalities in cardiac rhythm in a large group of patients undergoing parathyroid surgery. We also assessed the duration of the Q-T intervals (QTI) and indices of calcium homeostasis.

PATIENTS

Group 1a \((n = 193)\)

Records were reviewed of patients admitted to the Massachusetts General Hospital between 1974 and 1978 with the diagnosis of primary hyperparathyroidism, in whom histological examination of operative specimens revealed the presence of either parathyroid adenoma or hyperplasia. There were 66 male and 127 female patients aged 17-82 yr. Upon admission of each patient, a 12-lead e.c.g. was obtained and venous blood sampled for determination of biochemical variables as part of routine laboratory screening, including plasma total calcium concentration \(([\text{Ca}]\)), inorganic phosphorus \((P_i)\), serum potassium and sodium concentrations \((K^+ \text{ and } Na^+)\), respectively.

Cervical exploration was performed under general anaesthesia. Lead II e.c.g. was displayed on an oscilloscope. Anaesthesia was induced by i.v. infusion of thiopentone (approximately 5 mg kg\(^{-1}\)) and the trachea intubated following administration of suxamethonium 1.5 mg kg\(^{-1}\). Anaesthesia was maintained with appropriate concentrations of inhalation anaesthetics (halothane or enflurane) or a combination of morphine or pethidine, droperidol or diazepam, and a non-depolarizing muscle relaxant (pancuronium, tubocurarine or dimethylcurare) and 60% nitrous oxide in oxygen.

Group 1b \((n = 100)\)

Records were reviewed of patients admitted to the hospital in the same time period with the diagnosis...
of hypercalcaemia unrelated to parathyroid disease. Electrocardiographic and biochemical data were obtained as in group 1a. There were 46 males and 54 females ranging in age between 22 and 86 yr. Conditions associated with hypercalcaemia in these patients are listed in Table I.

**Table I. Clinical conditions associated with hypercalcaemia (group 1b)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>58</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>8</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>7</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
</tr>
</tbody>
</table>

**Group 2 (n = 60)**

To obtain normal values of QTI and some biochemical variables in a patient population similar to that of group 1a, the records were reviewed of a control group of patients (ASA class I) who underwent operation during 1977 for a variety of surgical procedures. The age range was 28–69 yr and there were no known abnormalities of calcium metabolism. Patients were identified by hospital identification number according to a random number generator.

Patients receiving digitalis preparations or quinidine and those with K⁺ or Na⁺ values outside the normal range (3.5–5.0 and 135–145 mmol litre⁻¹, respectively) were excluded.

**METHODS**

The 12-lead e.c.g. was recorded at a standard paper speed of 25 mm s⁻¹. The duration of the QTI, determined by averaging three complexes in lead II, was identified and measured according to the method of Lepeschkin and Surawicz (1953). The symbols Q-oTᵣ and Q-Tᵣ refer respectively to the origin and end of T-wave deflection, measured from the time of the beginning of the Q-wave deflection. Correction for heart rate was made by dividing the duration of the QTI by the square root of the duration of the R-R interval (Bazzett, 1920). Cardiac arrhythmias were identified.

Plasma total calcium concentration ([Ca]) was determined by atomic absorption spectrometry, inorganic phosphorus (Pᵢ) by spectrophotometry, and sodium and potassium concentration by flame photometry. In a few patients plasma ionized calcium concentration ([Ca²⁺]) was measured by a calcium-selective electrode system (Orion SS 20) at 37 °C as described previously (Drop, Fuchs and Stulz, 1978).

To examine the relationship between QTI and [Ca²⁺], we determined corrected values of QTI and plasma ionized calcium concentration prospectively in three patients with histologically confirmed primary hyperparathyroidism. In each patient, a 12-lead e.c.g. and a venous blood specimen were obtained upon hospital admission, approximately 30 min before the induction of anaesthesia, immediately following completion of surgery, and daily thereafter up to the second day after operation.

The statistical calculations were performed by use of a programmable calculator (Hewlett-Packard HP 67). Group means were compared by use of Student's t test for unpaired data. Values are presented as mean ± SEM.

**RESULTS**

**Group 1a.** Atrial fibrillation was present on the e.c.g. tracing of one patient before operation (ventricular rate: 60 beat min⁻¹), atrial flutter in one (ventricular rate: 95 min⁻¹). Disturbances in conduction were present before operation on the e.c.g. tracings of 12 patients, including A-V block (first degree) in four patients, and bundle branch block in eight. During operation, the anaesthetist diagnosed A-V junctional rhythm in two patients; and in one of these, lignocaine 1.5 mg kg⁻¹ was administered i.v. Ventricular arrhythmias were not identified on any anaesthetic record.

The difference between values of Q-oTᵣ and Q-Tᵣ in the hyperparathyroid group and those in the control group was minimal (table II), although statistically significant. In three patients, [Ca] and [Ca²⁺] values were increased before parathyroid exploration, and both values decreased below normal after operation.

**Table II. Biochemical variables and corrected Q-T intervals**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hyperparathyroidism (group 1a)</th>
<th>Other causes (group 1b)</th>
<th>Control (group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ca] (mmol litre⁻¹)</td>
<td>2.89 ± 0.02*</td>
<td>3.16 ± 0.04*</td>
<td>2.33 ± 0.01</td>
</tr>
<tr>
<td>[Pᵢ] mmol litre⁻¹</td>
<td>0.83 ± 0.01*</td>
<td>1.14 ± 0.04</td>
<td>1.16 ± 0.01</td>
</tr>
<tr>
<td>[K⁺] (mmol litre⁻¹)</td>
<td>4.28 ± 0.03</td>
<td>4.17 ± 0.05</td>
<td>4.28 ± 0.03</td>
</tr>
<tr>
<td>Q-oTᵣ (s)</td>
<td>0.21 ± 0.001*</td>
<td>0.22 ± 0.002</td>
<td>0.22 ± 0.003</td>
</tr>
<tr>
<td>Q-Tᵣ (s)</td>
<td>0.38 ± 0.002*</td>
<td>0.40 ± 0.003</td>
<td>0.40 ± 0.003</td>
</tr>
</tbody>
</table>
HYPERCALCAEMIA AND CARDIAC ARRHYTHMIA

Payne and Fitchett (1965) have suggested that chronic hypercalcaemia is among factors that may be responsible for serious cardiac complications during anaesthesia for surgery in patients with hyperparathyroidism. Sudden death has been reported in patients with hypercalcaemia secondary to parathyroid hyperfunction (Young and Emerson, 1949; Rapoport, Sepp and Brown, 1960). It has been postulated that such fatal events occur secondary to ventricular fibrillation (Surawicz, 1966). Hypercalcaemia in the experimental animal has also been associated with ventricular premature beats and ventricular fibrillation (Surawicz, 1966). It is known that the duration of the plateau phase (phase 2) of the cardiac action potential is shortened with hypercalcaemia (Surawicz, 1967b). A manifestation of this change in duration of cardiac action potential on e.c.g. is a shortening of QTI (Yu, 1952; Bellet, 1955; Surawicz, 1967a, b). Furthermore, the effective refractory period is shortened and the excitability threshold of the ventricle is increased with hypercalcaemia (Surawicz, 1967a). The combination of decreased conduction velocity (Goodman and Gilman, 1970), increased ventricular excitability and shortening of the ventricular refractory period (Surawicz, 1967a) could facilitate re-entry and the occurrence of ventricular rhythms. If such changes in excitability and conduction occurred, one might expect QTI shortening and potentially serious disturbances in ventricular rhythm in patients with hypercalcaemia. Yet, QTI values in the hyperparathyroid group were shortened only minimally in our study, despite a moderate increase of [Ca] and ventricular arrhythmia was not encountered. It is unlikely that serious disturbances in cardiac rhythm were present but not detected. E.c.g. tracings before operation were interpreted by staff cardiologists from the Cardiac Unit, who always report the presence of ventricular arrhythmias and abnormalities in the duration of the QTI, and by the authors, who were specifically looking for changes in rhythm and time intervals. Even if ventricular arrhythmias were missed on admission to hospital they would be most unlikely to disappear before continuous e.c.g. display during operation. Although it is acknowledged that the anaesthetist may have difficulties in the identification of each occurrence of A-V junctional rhythm from a continuous oscilloscope display of the e.c.g., in this analysis we were interested in the occurrence of any serious cardiac arrhythmias during cervical exploration. If such rhythm disturbances did occur, their appearance and treatment would have been identified.

Fig. 1. Time course of corrected Q–T intervals in three patients with hypercalcaemia secondary to parathyroid adenoma. Each data point and each symbol represents one patient. The shaded areas represent the 95% confidence limits of normal. Note that there was no consistent relationship between [Ca] and corrected duration of Q–T interval. [Ca] = ionized calcium; [Ca] = total calcium.

Group b. Abnormalities in cardiac rhythm were identified in two patients (atrial fibrillation with a ventricular rate of 60 and 80 beat min⁻¹); first degree A–V block in one patient, and bundle branch block in seven. [Ca] was greater than in the control group (P<0.001) and than in group 1a (P<0.001) (table II). However, Q–To values and Q–To values were not different from the mean values obtained in the control group.

DISCUSSION

In patients with moderate hypercalcaemia secondary to hyperparathyroidism, who underwent surgical exploration of the neck under general anaesthesia, arrhythmia of potential concern occurred in two patients, but ventricular arrhythmia was not recorded.
on the anaesthetic record. The increase of \([\text{Ca}]\) in the hyperparathyroid group was moderate (\(\text{[Ca]} = 2.89 + 0.02 \text{ mmol litre}^{-1}\)). However, mean \([\text{Ca}]\) in the patients of group \(1b\) was greater and mean values of QTI in this group were not different from those recorded in the control group. No ventricular arrhythmias were detected on e.g. recordings made on admission of these patients. It is possible that more conspicuous changes in QTI and ventricular arrhythmias may occur at \([\text{Ca}]\) concentrations substantially greater than those encountered in the present study. Such a possibility would be consistent with previous reports; Yu (1952) reported that QTI shortening was most consistent at \([\text{Ca}]\) values that exceeded 3.75 mmol litre\(^{-1}\), while Bronsky and others (1961) found a consistent QTI shortening in patients with \([\text{Ca}]\) values ranging from 3.8 to 6 mmol litre\(^{-1}\). Although the evaluation of the effect of hypercalcemia on the e.g. pattern and the development of cardiac arrhythmias has been difficult in certain circumstances, complete heart block with ventricular escape rhythm at a rate of 40 beat min\(^{-1}\) has been described in a patient with \([\text{Ca}]\) of 3.87 mmol litre\(^{-1}\) (Ginsberg and Schwartz, 1973), and sudden death has been reported in patients with \([\text{Ca}]\) values of 4.5 (Jennings et al., 1965) and 5.5 mmol litre\(^{-1}\) (Rapport, Sepp and Brown, 1960).

The serum potassium concentration is known to be a determinant of calcium-induced changes on the duration of Q-T intervals (Surawicz, 1967a). Therefore, in our assessment of e.g. manifestations of hypercalcemia, patients with abnormalities in K+ concentration were excluded, as were those receiving digitalis (Eliot and Blount, 1961) or quinidine.

In view of the range of corrected QTI values recorded in both control and hyperparathyroid groups (table I), corrected QTI values are not diagnostic of the occurrence of a chronic, moderately increased \([\text{Ca}]\). Similar limitations seem to apply to the reliability of QTI as an index of plasma total calcium during acute changes. Bronsky and others (1961a) found that corrected values of QTI were altered minimally in two patients following calcium loading, increasing \([\text{Ca}]\) from 2.8 to 3.5 mmol litre\(^{-1}\). Conversely, Bradlow and Segel (1956) found that QTc decreased in a patient in whom \([\text{Ca}]\) decreased from 5.2 to 3.45 mmol litre\(^{-1}\) following parathyroid surgery.

Plasma total calcium concentration includes the physiologically active (ionized calcium) and inactive components (complexed and protein-bound calcium) (McLean and Hastings, 1934). Since phase 2 of the cardiac action potential is mainly determined by calcium ion movements across the cardiac cell membrane, changes in the QTI might be expected to correlate with those in plasma ionized calcium concentration (\([\text{Ca}^{2+}]\)). Results shown in figure 1 are compatible with data by Rumancik and others (1978) who found that QTI was an unreliable index of \([\text{Ca}^{2+}]\) in patients during anaesthesia for major surgery in whom rapid fluctuations occurred in \([\text{Ca}^{2+}]\) secondary to rapid citrated blood transfusion and calcium chloride infusion. These authors postulated that the Q-T response to rapid \([\text{Ca}^{2+}]\) fluctuations might differ from that observed with more gradual \([\text{Ca}^{2+}]\) changes such as those recorded in the present study. Our findings cast some doubt on the importance of the time course of \([\text{Ca}^{2+}]\) changes in the QTI response to such \([\text{Ca}^{2+}]\) changes.

REFERENCES


HYPERCALCAEMIA AND CARDIAC ARRHYTHMIA


HYPERCALCEMIE CHRONIQUE DECOULTANT DE L’HYPERPARATHYROIDISME: FACTEUR DE RISQUE PENDANT L’ANESTHESIE?

RESUME
L’hypercalcémie (augmentation des concentrations de calcium total dans le plasma [Ca]) a été associée à une sérieuse arythmie ventriculaire et à un arrêt cardiaque soudain chez les malades souffrant d’hyperparathyroïdisme. Pour appuyer l’impression que nous avions, à savoir que l’apparition de ces complications pendant les interventions chirurgicales est rare, nous avons examiné les dossiers et les électrocardiogrammes de 193 patients souffrant d’hypercalcémie modérée ([Ca] = 2,89 ± 0,02 mmol litre⁻¹, moyenne ± erreur type des moyennes) corollaire d’une hyperfonction parathyroïdienne histologiquement démontrée, et qui étaient entrés à l’hôpital entre 1974 et 1978. Nous avons trouvé qu’aucune arythmie ventriculaire n’avait été enregistrée pour aucun malade, et que le rythme de la commissure auriculo-ventriculaire était présent chez deux personnes au début de l’intervention. Avant l’opération, il s’est produit un raccourcissement d’une importance statistique, des valeurs corrigées de l’intervalle Q–T, bien que celui-ci ait été minimal par rapport au groupe témoin (n = 60). Toutefois, la durée de l’intervalle Q–T corrigé n’a pas été un diagnostic d’augmentation du [Ca] sur un malade donné souffrant d’hyperparathyroïdisme.

HYPERKALZÄMIE SEKUNDÄR ZU HYPERPARATHYREOIDISMUS: GEFAHRENFAKTOR WÄHREND NARKOSE?

ZUSAMMENFASSUNG

HIPERCALCEMIA CRONICA COROLARIA AL HIPERPARATIROIDISMO: UN FACTOR DE RIESGOS DURANTE LA ANESTESIA?

SUMARIO
Se ha relacionado la hipercalemia (concentración total creciente de calcio en el plasma [Ca]) con arritmia ventricular grave y paro cardíaco repentino en pacientes con hipoparatiroidismo. Para apoyar nuestra impresión de que la ocurrencia de tales complicaciones durante operaciones quirúrgicas es rara, examinamos los registros y e.e.g. (electrocardiogramas) de 193 pacientes con hipercalemia moderada ([Ca] = 2,89 ± 0,02 mmol litro⁻¹, promedio ± SEM) corollaria de una hiperfunción paratiroidea histológicamente demostrable, los cuales entraron en el hospital entre 1974 y 1978. Encontramos que no habia ninguna arritmia ventricular registrada en relación con algún paciente, un ritmo de junción A–V (auricular–ventricular) se manifestó en dos pacientes al principio de la operación. Antes de la operación, un acortamiento mínimo aunque estadísticamente significativo de los valores corregidos del intervalo Q–T ocurrió en comparación con el grupo de control (n = 60). Sin embargo, la duración del intervalo del Q–T corregido no constituía un diagnóstico del incremento del [Ca] en un paciente dado con hipoparatiroidismo.