Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
High serum procalcitonin concentrations in patients with sepsis and infection

MARCEL ASSICOT  DOMINIQUE GENDREL  HERVÉ CARSIN
JOSETTE RAYMOND  JEAN GUILBAUD  CLAUDE BOHUON

High concentrations of calcitonin-like immunoreactivity have been found in the blood of patients with various extrathyroid diseases. By means of a monoclonal immunoradiometric assay for calcitonin precursors, we have measured serum concentrations of procalcitonin in patients with various bacterial and viral infections.

79 children (newborn to age 12 years) in hospital with suspected infections were investigated prospectively. 19 patients with severe bacterial infections had very high serum concentrations of procalcitonin at diagnosis (range 6–53 ng/mL) in comparison with 21 children found to have no signs of infection (baseline concentrations <0·1 ng/mL). Serum procalcitonin values decreased rapidly during antibiotic therapy. 11 patients with peripheral bacterial colonisation or local infections without invasive sepsis and 18 (86%) of 21 patients with viral infections had concentrations within or slightly above the normal range (0·1–1·5 ng/mL). Among 9 severely burned patients studied in an intensive care unit, the post-traumatic course of procalcitonin concentrations (range 0·1–120 ng/mL) was closely related to infectious complications and acute septic episodes. Concentrations of mature calcitonin were normal in all subjects, whatever procalcitonin concentrations were found.

Concentrations of a substance immunologically identical to procalcitonin are raised during septic conditions. Serum concentrations seem to be correlated with the severity of microbial invasion.

Lancet 1993; 341: 515-18.

Introduction

Increased production of calcitonin by medullary thyroid carcinoma (MTC) is well known, and serum calcitonin is used as a marker of this cancer. High serum concentrations of calcitonin-like immunoreactivity have also been reported in various extrathyroid disorders, including many cancers, acute and chronic inflammatory disease of the lung, acute pancreatitis, renal failure, benign liver disease, and fulminating infantile meningococcaemia.1-9 The presence of several circulating immunoreactive forms of calcitonin and its precursors in MTC patients has been shown by several groups,8,10-13 but the nature of circulating immunoreactive calcitonin species in other disorders remains unknown. However, Ghillani and colleagues8 lately showed that, unlike MTC, which produces both precursors and mature hormones, most of the extrathyroid diseases produce calcitonin precursors in the absence of mature hormone.

We have investigated calcitonin species in patients with severe bacterial infections and sepsis.

Patients and methods

Two groups of patients were studied. The first comprised 79 newborn and older infants and children admitted to a paediatric unit with suspected infections (table) and the second included 9 severely burned patients admitted to an intensive care unit (burn injuries 16–80% of body surface area). Blood samples were centrifuged for 15 min at 1500 g and serum was stored at −20°C until analysis. Procalcitonin was measured with a monoclonal immunoradiometric assay (m-IRMA).8 This assay uses two monoclonal antibodies, one directed against residues 96–106 of procalcitonin, and one recognizing residues 70–76, as the tracer antibody (fig 1). This assay has a detection limit of 100 pg/mL. Serum calcitonin was measured with a commercial m-IRMA (CIS Bio-International, Gif sur Yvette, France) which is specific for mature calcitonin and has a sensitivity limit of 10 pg/mL. Circulating immunoreactive forms of calcitonin were analysed by reverse-phase high-performance liquid chromatography (HPLC). After partial purification on a Sep-Pak cartridge, serum was injected into a C 18-Nucleosil (Macherey-Nagel, Düren, Germany) column equilibrated with 0·1% (by volume) trifluoroacetic acid. The column was eluted at room temperature and at a flow rate of 1 mL per min with a 60 min gradient of 20–70% acetonitrile in 0·1% trifluoroacetic acid.

CLINICAL DATA FOR STUDY CHILDREN

| — — — — — — — — | Age | Clinical details |
| — — — — — — — — | — — — — — — — — | — — — — — — — — |
| Controls (n = 21) | Newborn | 10 yr | Children admitted for various reasons with no infection |
| Newborn infants | Bacterial sepsis (n = 12) | 1–10 days | 10 proven neonatal sepsis (positive blood cultures: Escherichia coli, streptococcus group B, E. coli, Escherichia coli, Listeria monocytogenes); 2 sepsis (L. monocytogenes, Proteus sp) after initiation of treatment (days 4 and 6) |
| | Bacterial colonisation (n = 6) | | Streptococcus group B peripheral colonisation without sepsis |
| | Viral infection (n = 4) | | 2 varicella zoster virus; 2 herpes virus (type 2) |
| Infants and children | Severe bacterial infection (n = 19) | 1 month | 6 bacterial meningitis (3 Haemophilus influenzae, 3 meningococcus); 1 pneumococcal pneumonia; 1 haemophilus septicemia; 1 staphylococcus septicemia and Stevens–Johnson syndrome; 10 severe infection after initiation of treatment (days 2–4) |
| | Local infection (n = 5) | | 3 enteric salmonella; 1 purulent otitis; 1 urinary-tract infection |
| | Viral infection (n = 17) | | 4 lymphocytic meningitis, 3 hepatitis A; 10 various viral infections (high alpha-interferon) |

Immunoreactivity of the fractions was tested by four assays: the two described above; a radioimmunoassay based on a polyclonal goat antiserum directed against residues 1–57 of procalcitonin, which recognises both procalcitonin and the putative cleavage peptide N-proCTI-57; and an IRMA that uses the polyclonal antiserum against procalcitonin 1–57 and the monoclonal antibody directed against residues 96–106, which can detect only entire procalcitonin (fig 1).

ADDRESSES: Département de Biologie Clinique, Institut Gustave-Roussy, 94805 Villejuif (Prof M. Assicot, PhD, Prof C. Bohuon, PhD); Département de Pédiatrie (Prof D. Gendrel, MD) and Laboratoire de Microbiologie (J. Raymond, MD), Hôpital Saint-Vincent-de-Paul, Paris; and Centre de Traitement des Brûlés, Hôpital d'Instruction des Armées Percy, Clamart (H. Carsin, MD, J. Guilbaud, MD), France. Correspondence to Prof Claude Bohuon.
Results

Fig 2 shows the distribution of procalcitonin concentrations in the five subgroups of children with and without infection. Procalcitonin was undetectable (<0.1 ng/mL) in 21 children without infection. At the time of diagnosis, 10 newborn infants and 9 older infants or children with severe bacterial infection (100%) had high serum concentrations of procalcitonin (6.5–53 ng/mL). Antibiotic treatment rapidly decreased procalcitonin concentrations (days 2–6 of treatment). Among the 5 infants and children with locoregional infection and the 6 newborn infants with skin bacterial colonisation and no sepsis, procalcitonin concentrations did not exceed 1.5 ng/mL (0.3–1.5 ng/mL). Of the 21 patients with viral infections, 18 (86%) had values within or slightly above the normal range (maximum 1.4 ng/mL); 2 children with gastroenteritis (1 coronavirus, 1 rotavirus) had values of 3.5 mg/mL and 8.0 mg/mL, and a child with acute hepatitis A had concentrations of 17 mg/mL on admission and 2 ng/mL on day 8.

Serum procalcitonin concentrations varied widely among the 9 burns patients from 0.1 to 120 ng/mL. Three subgroups were identified according to the time course of procalcitonin changes (fig 3). 2 patients had peak procalcitonin concentrations of 2 ng/mL and 3 ng/mL within 3 days of the burn; concentrations then fell progressively to normal (subgroup I). These patients did not have any infectious complications during the hospital stay. 3 patients (subgroup II) had higher values, up to 19 ng/mL. The peak concentrations were found at the onset of sepsis, confirmed by clinical and microbiological signs. In subgroup III, serum concentrations of 3 patients were high 1 day after the burn (14 ng/mL, 21 ng/mL, and 78 ng/mL) and continued to rise during the next few days, during acute septic episodes. 1 of these patients, who had severe infectious complications (Escherichia coli positive blood culture on day 4, septic shock on day 6, Pseudomonas aeruginosa positive culture on day 20), had high concentrations of procalcitonin in all serum samples; the highest value (120 ng/mL) was measured during septic shock. The 4th patient in subgroup III had toxic shock syndrome 18 days after the burn, and procalcitonin reached a maximum of 70 ng/mL at that time. Only 1 burns patient (subgroup II) died (pulmonary embolism 57 days after injury). Concentrations of mature calcitonin were normal at all times in both burns patients and children.
Fig 4—Reverse-phase HPLC profile of Sep-Pak C18 extracts of serum from patient with sepsis.

Analysis of serum extracts by reverse-phase HPLC showed a major peak eluting at 37-39 min, as detected by several immunoassays (fig 4). It is likely that this immunoreactive peak corresponded to the whole molecule of procalcitonin. Two other small peaks detected in some samples could not be identified. Calcitonin was consistently undetectable by a specific m-IRMA.

Discussion

Serum calcitonin-like immunoreactivity has been reported in various extrathyroid diseases. Our study shows that serum concentrations of a substance immunologically identical to procalcitonin increase at the onset of infections. In addition, serum concentrations of this substance seemed to be correlated with the severity of the infection. In all but 2 children with procalcitonin concentrations above 5 ng/mL, the diagnosis of severe bacterial sepsis was confirmed microbiologically. The study of burns patients suggests that burn injuries may lead to moderate systemic release of procalcitonin. However, among these patients, very high peak concentrations of procalcitonin were associated with septic complications, although no direct correlation was found between the post-burn course of the procalcitonin concentrations and the size of the burn or pulmonary injury. The correlation of procalcitonin with the severity of infection was confirmed by findings of serum concentrations up to 200 ng/mL (2000 times the normal value) in patients with septic shock (data not shown). Antibiotic treatment lowered procalcitonin rapidly. By contrast, high circulating procalcitonin concentrations persisted in 1 burns patient who had overwhelming microbial invasion and a long septic episode. Do the procalcitonin molecules originate from the thyroid gland or from other tissues in these patients? Thyroid C-cells do not seem to be the production site of procalcitonin; indeed, 1 burns patient who had undergone thyroidectomy 2 years earlier had high procalcitonin values but no secretion of mature calcitonin. The finding that procalcitonin was detectable in the absence of mature calcitonin shows that the procalcitonin-producing cells are unable to process this precursor form to the mature hormone. MTC are capable of producing protein that secretes all the biosynthetic pathway products. Pulmonary neuroendocrine cells in the bronchial epithelium have been reported to be a major source of calcitonin immunoreactivity. However, most of our patients with sepsis did not have pulmonary injury. Others have reported the isolated presence of calcitonin precursors in patients with benign liver diseases (such as hepatitis) or with hepatocellular carcinoma, and also the presence of calcitonin-related RNA in this tumour. Perhaps the liver is the site of procalcitonin production in patients with sepsis. Since serum calcitonin-like immunoreactivity has been described in a wide variety of extrathyroid diseases, it is likely that inflammatory processes other than infection lead to the elaboration of calcitonin-like immunoreactivity by various types of cells. Such immunoreactivity and a clinical picture resembling sepsis have been reported in some patients with acute pancreatitis.

The place, if any, of procalcitonin induction in the cytokine cascade that occurs in sepsis and other inflammatory processes remains to be investigated. Rapid and substantial release of procalcitonin, at the same time as tumour necrosis factor alpha and before interleukin-6, has been observed in patients with renal cancer after intravenous administration of interleukin-2 (unpublished). This observation could help elucidate the mechanism of rapid procalcitonin production in the septic process. Our results, based on several specific immunoassays, strongly suggest that the molecule detected in the serum of patients with sepsis is procalcitonin. However, we cannot exclude the possibility that some of the aminoacids not involved in the recognised epitopes may differ. A second calcitonin messenger, encoding a procalcitonin bearing eight different aminoacid residues on the carboxy-terminal region, has been identified in the thyroid. Concentrations of calcitonin gene-related peptide, the product of the calcitonin gene in nerve cells, are also increased in patients with sepsis.

Further studies are needed to elucidate the importance of procalcitonin production in association with infection and to assess a potential role in diagnosis and follow-up of patients with bacterial sepsis.

We thank Mr Johny Bomble and Mr Lionel Fougeat for excellent assistance; Dr Walter Born (Research Laboratory for Calcium Metabolism, University of Zurich) for proGr 1-57 peptide and polyclonal antiserum; and Dr Jean-Michel Bidart for reviewing the manuscript.

REFERENCES

1. Coombes RC, Hillyard C, Greenberg PB, MacIntyre I. Plasma immunoactive-calcitonin in patients with non-thyroid tumours. Lancet 1974; 1: 1080-83.
2. Milhaud G, Calmette C, Taboulet JJ, Julienne A, Moukhtar M. Hypersecretion of calcitonin in neoplastic conditions. Lancet 1974; 1: 462-63.
3. Becker KL, Nash DR, Silva OL, et al. Increased serum and urinary calcitonin levels in patients with pulmonary disease. Chest 1981; 79: 211-16.
4. Canale DD, Dorabjedian RK. Hypercalcitoninemia in acute pancreatitis. J Clin Endocrinol Metab 1975; 40: 738-40.
5. Gillquist J, Larsson J, Sjodahl R. Serum calcitonin in acute pancreatitis in man. Scand J Gastroenterol 1977; 12: 21-23.
Association of fibrinolytic tests with outcome of acute upper-gastrointestinal-tract bleeding

J. M. A. AL-MOHANA G. D. O. LOWE G. D. MURRAY H. G. BURNS

Endogenous fibrinolysis may play a part in acute upper-gastrointestinal-tract bleeding by causing digestion of haemostatic plugs. We assessed the predictive value of fibrinolytic tests for hospital outcome in a prospective study of 122 patients with acute upper-gastrointestinal-tract bleeding who underwent endoscopy.

Serum fibrin degradation products (FDP) were above the normal range in 32% (95% CI 21–44%) of patients who survived and did not require transfusion or surgery, in 53% (37–69%) of patients who survived without surgery but required transfusion, and in 100% (82–100%) of patients who required surgery or died. Multivariate analysis showed that after adjustment for the effects of established risk factors (age, pulse rate, blood pressure, and haemoglobin on admission), serum FDP was a powerful independent predictor of outcome (p = 0.003). Doubling of serum FDP was associated with a 59% increase in the risk of a poor outcome (95% CI 14–120%).

These findings are consistent with roles for endogenous fibrinolysis in gastrointestinal-tract bleeding, for fibrinolytic tests in prediction of adverse outcome, and for fibrinolytic inhibitors in treatment.

Lancet 1993; 341: 518–21

Introduction

About 3000 of the 30 000 people admitted to hospital in the UK each year for acute upper-gastrointestinal-tract bleeding will die.1 Prognostic indicators for outcome include: age, pulse rate, blood pressure, and haemoglobin at admission, and findings at endoscopy, such as presence, site, and nature of a bleeding lesion, and stigmata of recent bleeding.2 4 One factor that may promote continued bleeding and hence an adverse clinical outcome is the fibrinolytic activity of the upper gastrointestinal tract, because fibrinolysis may lead to digestion of haemostatic plugs.5 Consistent with this possibility, Poller and colleagues6 demonstrated increased serum fibrin degradation products (FDP) in a small series of patients with acute upper-gastrointestinal-tract bleeding; however, the prognostic value of serum FDP concentrations has not been reported in a prospective study. We therefore investigated the prognostic value of both serum FDP concentrations (a measure of in-vivo fibrinolysis) and the fibrin plate lysis area (FPLA) of the plasma euglobulin fraction,6 an in-vitro global test of the fibrinolytic potential of blood.

Patients and methods

We studied 122 patients with acute upper-gastrointestinal-tract bleeding (haematemesis and/or melaena in the preceding 24 h) who were admitted between April, 1986, and April, 1988, to the medical receiving unit of Glasgow Royal Infirmary and who underwent emergency endoscopy. Because of the known diurnal variation in FPLA,7 patients were assessed and blood sampled between 0900 h and 1000 h at the time of assessment for endoscopy. Patients who had emergency endoscopy before this time or who were assessed on Saturday or Sunday mornings were not included in the study. Patients were also excluded if they had haemostatic disorders or were receiving anticoagulant, antifibrinolytic, or recent thrombolytic therapy. Clinical prognostic factors recorded included age, pulse rate, blood pressure, and haemoglobin on admission. Endoscopic findings were recorded. Patients were followed up until either discharge or death in hospital, and outcome was recorded in increasing order of adversity—ie, no blood or red cell transfusion, acute surgery, or death (group 1); blood or red cell transfusion only (group 2); or surgery and/or death (group 3).

A venous blood sample was taken from the arm contralateral to the terminal region of preprocalcitonin. J Clin Endocrinol Metab 1983; 56: 802–07.

1. Born W, Beglinger C, Fischer JA. Diagnostic relevance of the amino-terminal cleavage peptide of procalcitonin (PAS-57), calcitonin and calcitonin gene-related peptide in medullary thyroid carcinoma patients. Regul Pept 1991; 32: 311–19.

2. Colon JM, Grinellus L, Thim L. Structural characterization of a high-molecular-mass form of calcitonin [procalcitonin-(60-116)-peptide] and its corresponding N-terminal flanking peptide [procalcitonin-(1-57)-peptide] in a human medullary thyroid carcinoma. Biochemistry 1988; 256: 245–50.

3. Becker KL, Monaghan KG, Silva OL. Immunocytochemical localization of calcitonin in Kulchitsky cells of human lung. Arch Pathol Lab Med 1980; 104: 196–98.

4. Minvielle S, Girard-Dartevelle S, Cohen R, et al. A novel calcitonin carboxy-terminal peptide produced in medullary thyroid carcinoma by alternative RNA processing of the calcitonin/calcitonin gene-related peptide gene. J Biol Chem 1991; 266: 2647–31.

5. Joyce CD, Ficus RR, Wang X, et al. Calcitonin gene-related peptide levels are elevated in patients with sepsis. Surgery 1990; 108: 1097–101.