Original Paper

Pancreatology

Pancreatology 2007;7:451–458
DOI: 10.1159/000108962

Received: August 7, 2006
Accepted after revision: December 1, 2006
Published online: October 1, 2007

Early Prediction of Severity in Acute Pancreatitis Using Infrared Spectroscopy of Serum

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Key Words
Acute pancreatitis · Prediction of severity · Infrared spectroscopy

Abstract
Background: One of the main problems in the management of acute pancreatitis (AP) is the scarcity of accurate predictors of disease severity. ***Methods:*** In a prospective design, we compared APACHE II score, C-reactive protein (CRP) level, and infrared (IR) spectral absorption of serum (wavelength 940 nm) in 167 consecutive patients with AP, 34 with predicted severe and 133 with mild form. ***Results:*** The IR spectral absorption levels on admission and at 24 h after admission were significantly ($p < 0.05$) lower in patients with severe AP. On admission, the sensitivity was 74, 56, and 44%; the specificity was 82, 83, and 81%; the positive predictive value was 51, 45, and 37%, and the negative predictive value was 92, 88, and 85%, for IR spectroscopy, APACHE II, and CRP, respectively. At 24 h, the sensitivity, specificity, positive predictive value, and negative predictive value was 82, 74, 44, and 94%; 65, 72, 37, and 89%; 68, 73, 39, and 90%, for IR spectroscopy, CRP, and APACHE II, respectively. ***Conclusions:*** IR spectroscopy seems to be useful for early detection of severe AP and, in turn, for identifying patients requiring treatment in the intensive care unit and who can benefit from novel therapies.

Dr. M.S. Petrov is a holder of the patent 'Stratification of severity in acute pancreatitis by means of infrared spectroscopy' (RU 2253868, G01N33/49). Effective date for property rights: 29/03/2004.

Introduction

Early identification of patients with severe acute pancreatitis (AP) is acknowledged to be an important aspect of both current and future management algorithms [1–3]. Large-cohort studies have shown that a high percentage of deaths are clustered early in the course of the disease [4, 5]. Further, early intensive monitoring and support, as well as enteral feeding started on admission may be beneficial in severe AP [6–8]. In addition, early prediction of severity allows for heightened vigilance toward early detection of complications and selection of patients for transfer to specialized centers.

However, clinical assessment of severity on admission has been found to be unreliable [9]. The search for a tool that would improve clinical assessment has been going on for decades. Several biochemical parameters [10–12],

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instrumental methods [13, 14], machine-learning techniques [15, 16], and multiple clinicobiochemical scores [17, 18] have been used to assess the severity of AP. An ideal prognostic method should be easily applicable, relatively simple, inexpensive, and highly accurate in the early phase of the disease [19]. Such a method is not yet available.

Infrared (IR) spectroscopy has the potential to satisfy many of these criteria, and its role in biomedical research is increasing [20–22]. The interpretation of IR spectra of serum in particular diseases has been shown to identify disease-specific signatures, e.g., for diabetes mellitus [23], rheumatoid arthritis [24], and human immunodeficiency virus infection [25]. The clearest advantage of this method is that it does not require specific reagents. Thus, automated, repetitive analyses can be carried out at very low cost [20–22].

Although the analysis of biological fluids has long provided information to suggest or corroborate diagnoses, a complementary technique for the interpretation of the IR spectra is emerging. Rather than deriving analytic levels explicitly from the spectra, they may be viewed as fingerprints that correlate directly with disease severity. Because the spectra are complex, patterns characteristic of specific diseases are not always discernable from visual examination of the spectra. However, multivariate analytical methods may identify subtle patterns distinguishing the spectra corresponding to specimens from patients with mild disease from those corresponding to those from patients with severe disease.

On the basis of the above-mentioned facts, we designed the present study to test the hypothesis that the IR spectra of serum could be useful as an early predictor of severe AP.

Patients and Methods

Selection of Patients

Patients admitted to the Department of Surgery of Nizhny Novgorod State Medical Academy with the diagnosis of AP were prospectively entered into a database in an unselected fashion. Of these, 167 consecutive patients who were hospitalized within 48 h of onset of symptoms were enrolled in this study. The diagnosis of AP was based on both clinical (upper abdominal pain) and biochemical presentation (serum amylase concentration at least 3 times the upper limit of the reference range) [1]. AP was defined as severe if an Acute Physiology And Chronic Health Evaluation (APACHE) II score was $\geq$8 and/or a C-reactive protein (CRP) level was >150 mg/l [26, 27]. Exclusion criteria were age <18 years, infection with hepatitis or human immunodeficiency virus, chronic pancreatitis, and pregnancy. This research project was approved by the local Ethics Committee, and written informed consent was obtained from all patients.

Local complications of AP were defined according to the Atlanta criteria [28]. The Marshall score was used [29] to assess organ failure. Intervention was indicated when infection of pancreatic necrosis was proven by fine-needle aspiration or when sepsis persisted despite maximal support in the intensive care unit. Patients with infected pancreatic necrosis were operated on (necrosectomy and open packing or closed continuous lavage).

Study Design

Blood samples were collected routinely on admission from all patients with suspected AP. Patients who met the inclusion criteria were entered into the study and provided additional blood samples 24 and 48 h after admission to the hospital. Blood samples for determination of IR spectra were centrifuged immediately, and serum was stored at –70°C until it could be shipped to a central biochemical laboratory (Institute of Organic Chemistry, Nizhny Novgorod, Russia) in dry ice and analyzed in one series using the same batch number of kits. CRP in plasma was measured in the hospital laboratory by standard assays. The variables required for calculation of the APACHE II score were also determined in the hospital's clinical laboratories.

Infrared Spectroscopy

After serum samples were thawed, 3 ml was pipetted onto each of three disposable silicon sample carriers. The triplicate pipetting improved detection of failures or outliers, which may occur because of variations in the surface properties of the sample carrier, the dispensing probe head, and/or the sample itself. The samples were then left to dry in the analyzer for 30 min. The drying stage helps suppress the strong background absorption of water that is usual in aqueous fluids and frequently interferes with the reproducibility of spectroscopy in the IR region. Upon drying, the serum sample forms a homogeneous film 6 mm in diameter and a few micrometers thick. The thickness of the film has been optimized to give reasonably large IR absorbance signals in the spectral regions of interest while still remaining well within the minimum volume capabilities of the liquid-handling system.

Spectra were acquired with a Perstorp NIR Systems model 6500 scanning spectrometer (Silver Springs, Md., USA). One of two trained individuals performed the scans. They were blinded to individual diagnoses at the time of spectral measurements and at subsequent analysis. Three scans were done for each patient, and these triplicate spectra were collected at the wavelength between 800 and 1,000 nm at a resolution of 2 nm. This near-IR region is the most useful region for analyzing blood samples because the overwhelming absorption of hemoglobin and water at a wavelength <800 and >1,000 nm, respectively, limits spectroscopic studies in these regions [30]. Moreover, our previous study showed that IR spectroscopy in this range successfully distinguished AP from acute abdominal disorders of extrapancreatic origin and from control specimens [31]. Before any further analysis, triplicate spectra from each patient were averaged and the median value for each wavelength was used, giving a total of 846 data points per spectrum. The latter spectra were classified by linear discriminant analysis (LDA) of the optimal set of spectral subregions. An LDA algorithm was used to recognize the patterns in these subregions, which were characteristic of mild and severe AP [21, 23].