PHARMACOKINETICS AND DISPOSITION

Khaled Abou-Hatab · Kandasamy Ganeshalingam
M. Sinead O'Mahony · Fathi Giurani
Sarju Patel · Kenneth Woodhouse

The effect of community-acquired pneumonia on plasma esterases in older people

Received: 17 April 2000 / Accepted in revised form: 28 November 2000 / Published online: 21 February 2001
© Springer-Verlag 2001

Abstract Introduction: Pneumonia is a major cause of morbidity and mortality in older people. The poor outcome of older pneumonia patients despite treatment is still not understood.

Objective: The aim of this study was to examine the effect of community-acquired pneumonia on enzymes of drug metabolism in older people.

Methods: Fifteen patients (median age 67 years) with a clinical and radiological diagnosis of community-acquired pneumonia and 14 healthy volunteers matched for age and gender (median age 75 years) were recruited. Plasma activities of benzoylcholinesterase, butyrylcholinesterase, acetylcholinesterase and aspirin esterase were determined spectrophotometrically at three time points in pneumonia patients – within 24 h of admission to hospital, 2 days later and 10 days later. Monocyte aryl hydrocarbon hydroxylase (AHH) activity was determined spectrophotometrically at the same time points. Enzyme activities were measured at one time point in healthy controls.

Results: Mean plasma benzyolcholinesterase activity was significantly lower in pneumonia patients on admission to hospital (mean ± SEM 848 ± 100) and after 10 days of treatment (mean ± SEM 925 ± 114) than in healthy controls (mean ± SEM 1333 ± 84, P < 0.05). Similarly, plasma acetylcholinesterase activity was significantly lower in pneumonia patients on admission (P = 0.007) and after 10 days of treatment (P = 0.01) than in controls. Butyrylcholinesterase activity was lower in pneumonia patients on admission (P = 0.029) than in healthy controls, but improved slightly after treatment so there was no longer a significant difference at 10 days compared with controls (P = 0.077). In contrast there were no significant differences in plasma aspirin esterase activity or induced monocyte AHH activity between pneumonia patients and healthy controls. The activities of benzoylcholinesterase (r = −0.536, P = 0.04), butyrylcholinesterase (r = −0.638, P = 0.01), acetylcholinesterase (r = −0.583, P = 0.022) and aspirin esterase (r = −0.624, P = 0.013) correlated inversely with the British Thoracic Society pneumonia poor prognostic index.

Conclusion: The activities of several esterases are reduced in older pneumonia patients. Other enzymes including aspirin esterase and induced monocyte AHH activity are unaltered in pneumonia. There was a significant inverse relationship between the activities of all esterases studied and the British Thoracic Society pneumonia poor prognostic index.

Key words Esterases · Cytochrome P450 · Pneumonia

Introduction

Pneumonia is common in older people and advancing age is associated with increasing morbidity and mortality. The outcome of pneumonia varies widely, from full physiological and functional recovery to death, despite the use of intensive measures in treating this illness [1]. Differences in outcome can be explained by complex interactions between several factors, both host factors such as age, underlying illnesses, nutritional status and immunocompetence, and disease factors such as micro-organism virulence [2, 3]. Interactions between drug metabolising systems and host defences may also contribute to variations in the outcome of this illness. Pharmacokinetic studies have shown that drug distribution is altered in pneumonia [4, 5] and antipyrine clearance is also impaired [6]. No studies have been undertaken examining enzymes of drug metabolism directly in pneumonia patients.

K. Abou-Hatab · M. S. O'Mahony (✉) · F. Giurani
S. Patel · K. Woodhouse
Department of Geriatric Medicine,
Academic Centre, Llandough Hospital,
Penarth, CF64 2XX, U.K.
Email: omahonymys@cf.ac.uk
Tel.: +44-29-20716986; Fax: +44-29-20711267

K. Ganeshalingam
Department of Respiratory Medicine,
Llandough Hospital, Penarth,
CF64 2XX, UK
We know from animal studies that there are considerable interactions between host defences and drug metabolism [7]. In previous clinical studies, we found plasma esterase activities are significantly reduced in patients during infective exacerbations of cystic fibrosis [8] and following elective hip replacement or fracture neck of femur [9]. Plasma esterases are involved in metabolising a number of drugs, including aspirin, heroin, procaine and anaesthetic drugs such as mivacurium [10] and suxamethonium [11] as well as the antidementia drug rivastigmine [12]. These enzymes are readily measured in blood. Aryl hydrocarbon hydroxylase (AHH) is a cytochrome P₄₅₀-dependent enzyme expressed in monocytes and also therefore readily measured in blood.

We have undertaken a prospective study of older patients with community-acquired pneumonia to detect the effect of this illness on the activities of enzymes of drug metabolism. In this study, we measured plasma esterase activities and monocyte AHH following in vitro induction with benzo[a]anthracene. The esterases we measured included benzoylecholinesterase, butyrylcholinesterase, acetylcholinesterase and aspirin esterase. We also examined the relationship between clinical severity of pneumonia and enzymes of drug metabolism.

### Methods

#### Subjects

Fifteen patients (median age 67 years, range 50–85 years) admitted to hospital with community-acquired pneumonia and 14 healthy volunteers matched for age and gender (median age 75 years, range 50–85 years) were recruited. All patients were reviewed within 24 h of admission. Patients were eligible for the study only if they were diagnosed both clinically and radiologically. The radiological diagnosis was of pulmonary shadowing either segmental or present in more than one lobe, which was neither pre-existing nor of other known cause [13].

Written informed consent was obtained and three 45-ml samples of blood were taken: within 24 h of admission, 2 days later and 10 days later. The severity of pneumonia was scored using the British Thoracic Society pneumonia poor prognostic index [13]. The British Thoracic Society predictors of poor outcome are age over 60 years, high respiratory rate of more than 30, diastolic blood pressure less than 60 mmHg, confusion, raised blood urea of more than 7 mmol/l, oxygen tension less than 8 kilopascals, white cell count less than 4 or greater than 30, and serum albumin less than 35 g/l. The presence of each of these factors on admission was given a score of one point, to give a maximum poor prognostic score of 8.

Following written informed consent, 45 ml of venous blood was obtained from healthy volunteers once. This study was given ethical approval by Bro Taf local research ethics committee.

#### Measurements

Monocytes were separated from 40 ml whole blood using density gradient centrifugation followed by culturing in polystyrene culture plates. AHH was then induced by adding benz(a)anthracene to two-thirds of the cultures for 24 h, the remaining cultures acting as controls. Monocytes were incubated with reduced nicotinamide adenine dinucleotide phosphate (NADPH), nicotinamide adenine dinucleotide phosphate (NADP), bovine serum albumin (BSA) and benz(a)pyrene in phosphate buffered saline (PBS) for 40 min at 37°C, and the products of the reaction were extracted with N-hexane and sodium hydroxide. AHH activity was determined spectrophotometrically by measuring the production of 3-OH benzo(a)pyrene from the substrate benzo(a)pyrene [14]. Induced AHH activity was expressed as nanomoles product produced per million cells per hour of incubation.

For the measurement of plasma esterases, 5 ml blood was centrifuged and separated immediately following venesection and the plasma was stored at −80°C until the time of enzyme activity assay. All assays were done in triplicate, assay conditions having already been fully validated and published [15, 16, 17]. Plasma benzylocholinesterase activity was measured in vitro by monitoring the disappearance of the substrate benzoylcholine iodide spectrophotometrically at a wavelength of 240 nm. Enzyme activity was expressed as nanomoles substrate utilised per millilitre plasma per minute of incubation [15]. Plasma butyrylcholinesterase and acetylcholinesterase activities were measured in vitro separately by monitoring spectrophotometrically at a wavelength of 412 nm, the production of thioclycine iodide from the substrates S-butyrylthiocy...