Markers and mediators in the pathophysiology of multiple system organ failure in the critically ill

Ph.D. Thesis

Dr. Molnar Zsolt
POTE, Anaesthesiologiai és Intenziv Therápiás Intézet

Programvezető: Dr Kellermayer Miklós (POTE, Központi Klinikai Kémiai Intézet)

Pécsi Orvostudományi Egyetem

1998

INTRODUCTION

Despite modern intensive care technologies and recent advances in antimicrobial therapies, sepsis and multiple system organ failure (MSOF) are increasingly common causes of morbidity and mortality in critically ill patients on the intensive care unit (ICU). A variable mortality rate of between 20-30% is seen in patients who go on to develop sepsis and MSOF.

Sepsis and MSOF are associated with a high expenditure and enforce a considerable stress upon an already stretched medical and nursing staff because of the relatively long length of stay and poor chance of survival. Therefore, the early detection of markers identifying patients at high risk of developing MSOF would be of great value.

Although the exact pathophysiological mechanisms implicated in the development of MSOF have not been fully elucidated, it has been proposed, that following an insult, such as trauma, systemic infection or major surgery, the development of MSOF is due to a generalised inflammatory reaction, involving activation of leukocytes, endothelial cells and release of inflammatory mediators and oxygen free radicals.

Microalbuminuria is the term used by biochemists to describe the pathological albuminuria in the 30-200 mg/L range, which is undetectable by qualitative urine dipsticks. Clinical and experimental evidence indicates that microalbuminuria is often associated with increased vascular permeability in both acute and chronic conditions. At present the cause of this association in chronic conditions remains unclear, but microalbuminuria is an early feature of increased vascular permeability associated with the acute inflammatory response.

Oxygen-derived free radicals have been proposed to play a central role in the pathophysiology of septic shock and subsequent tissue. In human septic shock, there is thought to be an imbalance in the oxidant/antioxidant status. Furthermore, evidence for free radical activity has been found in acut respiratory distress syndrome (ARDS), septic shock and MSOF.

It is thought that deficiencies in the antioxidant system may mean that tissues no longer have adequate protection from the damaging effects of free radicals. Recently N-acetylcysteine (NAC) has been used as a free radical scavenger in intensive care. It seems to be a potent direct scavenger of certain free radicals such as hypochlorous acid, hydroxyl radical and hydrogen peroxide; and it also increases the intracellular stores of glutathione. There have been encouraging results of benefit in clinical studies of patients with ARDS and sepsis.

AIMS OF THE STUDY

Capillary leak is a major problem in critically ill patients and to monitor its magnitude would be of great value in assessing the severity of the process and possibly to predict outcome. The value of microalbuminuria in a heterogeneous (i.e. normal) ICU population had not been studied before us.

Just as microalbuminuria could reflect the generalised process of MSOF, oxygen free radicals might play a pivotal role at the end of the inflammatory cascade throughout the illness. We suggested, that measuring free radical activity indirectly in critically ill patients could bring us closer to the understanding of the development of MSOF.

We also hypothesised, that reinforcing the organism's own antioxidant defence system by the early administration of NAC, could ameliorate the destructive effects of the oxygen free radicals in excess.

Early detection and markers of critical illness

Our aim was to assess the practicability of the measurement of microalbuminuria in critically ill patients compared to the conventional biochemical marker of acute phase response, C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). In addition, serum total antioxidant potential (TAP), and uric acid (UA) concentration were employed as measures of free radical activity.

The effects of NAC treatment in the critically ill patients

In our second study the effect of prolonged infusion of NAC was investigated whether it could ameliorate the development or progression of MSOF and improve mortality, when commenced immediately after admission to the ICU.

The effects of NAC on the TAP and microalbuminuria

We hypothesised that: a) the free radical scavenging effect of NAC could be observed as either an increase, or an attenuation of a fall in the plasma total antioxidant potential; b) clinical improvement might result in a decrease in urinary albumin excretion as indicated by the urine albumine:creatinine ratio.

MATERIALS AND METHODS

Following regional Ethics Committee approval, critically ill patients admitted to our six bedded teaching hospital ICU were entered the study between October 1995 and May 1997. Those who had chronic organ insufficiency prior to their critical illness, those with isolated head injury or drug overdose and those with an expected ICU stay of less than 24 hours were excluded from the study.

In order to assess the effects of NAC, patients were randomly allocated to receive NAC (treatment group) or placebo (control group). The design was a prospective, randomised, double blinded, placebo controlled clinical trial. Patients in the treatment group received NAC as a 150 mg/kg bolus in 5% dextrose followed by a continuous infusion of 12 mg/kg/hour. Patients in the control group were administered the same volume of 5% dextrose as placebo. The duration of treatment was for a minimum of 3 days up to a maximum of 5 days and was reviewed daily.

Multiple Organ Dysfunction Scoring System

In order to assess the effects of the treatment on organ function, an altered version of a multiple organ dysfunction scoring system (MODS) was employed and daily scores were obtained of the five main organ systems (cardiovasculas, respiratory, renal, hepatic, haematological) according to physiological parameters. The individual organ scores are summated and a MODS achieved with 0 indicating normal organ function and 20 being the worst possible value. Multiple system organ failure was defined as an average MODS of 4.

Laboratory tests

Determination of serum C-reactive protein levels: Blood samples were collected daily for upto 3 days. Serum CRP concentration was measured by an immunoturbidimetric method.

Determination of the erythrocyte sedimentation rate: Blood samples were collected daily for upto 3 days for the determination of the ESR by a modification of the Westergren technique.

Determination of the urine microalbumin:creatinine ratio: Urine was collected upon admission to the ICU (t=0) and every 6 h for upto 18 hours. Urinary microalbumin was quantitated by automated immunoturbidimetry.

Determination of serum total antioxidant potential: Blood samples were collected from patients upon ICU admission (t=0) and every 6 h upto 18 hours The TAP was determined by using a commercial kit.

Determination of the serum uric acid concentration: Blood samples were collected upon ICU admission (t=0) and every 6 h upto 18 h. Serum UA was determined an automated uricase method.

Statistics

To compare two groups (treatment vs. control or survivors vs. non-survivors) either non-parametric Mann-Whitney U tests or Chi-square tests were used as appropriate.

SUMMARY OF THE MAIN RESULTS

Inflammatory mediators

1) Classic markers of the acute phase response, such as CRP and ESR, could not be used to predict outcome nor the development of sepsis or MSOF in critically ill patients.

2) Microalbuminuria in this context has not been investigated by others. It seems, that it is a rapid, simple, sensitive, specific and relatively cheap biochemical test suitable for a rapid prediction of outcome, and monitoring the progress of severity of critical illness.

3) Serum total antioxidant concentrations observed in this study were in contrast to those observed by others, but significant differences between survivors and non-survivors were evident. The true relevance of this finding in clinical practice remains to be determined as this test is expensive and would not be applicable for a rapid prediction of outcome at present.

4) Serum uric acid concentrations gave a clear differentiation between survivors and non-survivors. Unfortunately, most results were within the reference range, which gives certain limitations to its clinical application for critically ill patients.

Effects of N-acetylcysteine

1) N-acetylcysteine at the dose used in this study could not improve outcome, or effect the progress of critical illness in a heterogenous ICU population.

2) Initiation of NAC treatment after 24 hours of hospital admission may potentially be harmful to such an extent, that it worsens mortality rate.

3) However, early treatment might provide protection against free radical mediated injury, therefore it could ameliorate the development of MSOF, and improve outcome.

Effects of N-acetylcysteine on serum total antioxidant potential and microalbuminuria

1) NAC failed to increase or alter the progression of the serum TAP compared to controls during the first 18 hours of treatment in our heterogenous (i.e. normal) ICU population.

2) Regarding microalbuminuria, there was a continuous decline of the values in both groups after admission to ICU, which was more obvious but non-significant in the NAC treated patients.

Publications:

1. Bogar L, **Molnar Z,** Tekeres M: Altered filterability of human leukocytes, caused by bacterial endotoxin. *Biorheology* 1986; 23: 289

2. Bogar L, **Molnar Z,** Tekeres M: Passive and active mechanical properties of stimulated human polymorphonuclear leukocytes. *Clinical Hemorheology* 1987; 7: 393

3. Bogar L, **Molnar Z,** Tekeres M: The Nuclepore filter holder: New method for cell migration test. *Pediatric Research* 1987; 22: 220

4. Bogar L, **Molnar Z,** Tekeres M: New simplified assay for evaluation of motile activity of human polymorphonuclear leukocytes. *Immunology Letters* 1988; 17: 211-6

5. **Molnár Z**, Shearer E: Rhabdomyolysis on the intensive care unit - an under diagnosed condition. *Care Crit Ill* 1996; 12: 165-8

6. **Molnar Z,** Shearer E: The role of veno-venous haemofiltration in the treatment of sepsis and multiple organ dysfunction syndrome. *Br J Int Care*, 1998; 8:12-20

7. **Molnar Z,** K. L. MacKinnon, E. Shearer, D. Lowe, I. D. Watson: The effect of N-acetylcysteine on total serum anti-oxidant potential and urinary albumin excretion in critically ill patients. *Intensive Care Med* 24 1998; 3, 230-235

8. **Molnár Zs**, Shearer E, Lowe D: Az elektív hemofiltráció, mint járulékos terápia a többszervelégtelenség kezelésében. *Anaeszteziologiai és Intenzív Terápia* 1998; 18: 10-19

9. **Molnar Z,** Shearer E, Lowe D: N-acetylcysteine treatment in the prevention of multisystem organ failure: A prospective, randomised, placebo controlled trial. *Crit Care Med* (Accepted for publication, May, 1998)

10. McGowan PR, May H, **Molnar Z,** Cunlliffe M. A comparison of three mathods of analgesia in children having day case circumcision. *Pediatric Anaesthesia* 1998; 8: 403-407

Conferences, presentations:

1. Anaesthetic Research Society, 21st/22nd November, 1996:
   Molnar Z, Shearer E, Lowe D: Sequential veno-venous haemofiltration in the treatment of multisystem organ failure

2. Association of Merseyside Intensive Care Units "Registrar's Prize" Competition, 13th December, 1996 (1st prize winning presentation):
   Molnar Z, Shearer E, Lowe D, MacKinnon K: The prophylactive use of N-Acetylcysteine in the prevention of multisystem organ failure

3. Liverpool Society of Anaesthetists "Registrar's Prize" Competition, 14th February, 1997 (2nd prize winning presentation):
   Molnar Z, Shearer E, MacKinnon K, Lowe D. The effects of N-Acetylcysteine on the total plasma antioxidant potantial during the first day of treatment

4. North West Region of the Association of Clinical Biochemists "Members Papers Evening", 27th January, 1997 (1st prize winning presentation):
   MacKinnon K, Watson I, **Molnar Z**, Shearer E. Is microalbuminuria an indicator for the development of sepsis and multiple system organ failure?

5. 3rd International Conference on Sepsis in the ICU. A Masterclass Symposium. Maastricht, The Netherlands, 24-26 June 1997:
   Molnar Z, MacKinnon K, Shearer E, Lowe D: The effects of N-Acetylcysteine on the total antioxidant potential during the initial hours of critical illness.

6. Anaesthetic Research Society Meeting, Bristol, 3-4 July 1997:
   Molnar Z, Shearer E, Lowe D: The prophylactic use of N-Acetylcysteine in the prevention of multisystem organ failure.

   Molnar Z, Charters P: Lanz tube as alternative for ICU hyperbaric oxygen therapy.

   MacKinnon K, **Molnar Z,** Watson I, Shearer E, Lowe D: The use of microalbuminuria as an indicator for the development of sepsis and multiple system organ failure

7. Magyar Anaesthesiologiai és Intenziv Terápiás Társaság Kongresszusa, Siófok, 1998. Június 3-6:
   Molnár Zs, Shearer E, Lowe D. Az N-acetylcysteine profilaxis hatása a többszervi elégtelenség kialakulására.

8. 20th Annual Meeting of the European Academy of Anaesthesiology, Heraklion Crete, 1998 3-5 September:

Molnar Z, Shearer E, Lowe D. N-acetylcysteine in the critically ill: friend or foe?

9. A MAITT Dél-Dunántúli szekciójának szepszis konferenciája, 1997, november, Pécs: **Molnár Zs.** A mikroalbuminuria prediktiív szerepe szepszisben.

10. A MAITT Dél-Dunántúli szekciójának szepszis konferenciája, 1998, november, Héviz: **Monár Zs.** A szepszis monitorozásának lehetőségei

Abstracts:

1. **Molnar Z**, Shearer E, Lowe D: Sequential veno-venous haemofiltration in the treatment of multisystem organ failure. *Br J Anaesth* 1997; 78: 464P

2. **Molnar Z,** MacKinnon K, Shearer E, Lowe D: The effects of N-Acetylcysteine on the total antioxidant potential during the initial hours of critical illness. *Clin Intensive Care*, 1997; 8: 9

3. **Molnar Z,** Shearer E, Lowe D: The prophylactic use of N-Acetylcysteine in the prevention of multisystem organ failure. *Br J Anaesth* 1997,79: 678.

4. **Molnar Z,** Charters P: Lanz tube as alternative for ICU hyperbaric oxygen therapy *Br J Anaesth* 1997,79: 678.

5. MacKinnon K, **Molnar Z,** Watson I, Shearer E, Lowe D: The use of microalbuminuria as an indicator for the development of sepsis and multiple system organ failure. *Br J Anaesth* 1997,79: 678

6. **Molnar Z,** Shearer E, Lowe D. N-acetylcysteine in the critically ill: friend or foe? *Eur J Anaesth* 1998;O-18: 64

Currently submitted publication:

1. MacKinnon KL, **Molnar Z,** Lowe D, Watson ID, Shearer E: The use of microalbuminuria as a predictor of outcome in critically ill patients. *Crit Care Med*