The impact of anaesthesia and perioperative antibiotic treatment on postoperative infections

PhD Thesis

István Bátai

Pécs University

Faculty of Medicine

Department of Medical Microbiology and Immunology

Department of Anaesthesia and Intensive Care

Pécs, Hungary

2000.

Program leader: Levente Emődy

Introduction

Whereas in the early days of surgery the major concern of the anaesthetist was merely survival of the patient, whilst providing adequate anaesthesia and analgesia, nowadays the anaesthetist's task has broadened to encompass the protection of the patient against adverse effects of the surgical trauma in general and to help reducing perioperative morbidity.
Infection is still one of the leading causes of perioperative morbidity and mortality. The postoperative infection rate of patients undergoing clean elective surgery can be as low as 0.7%, but after major trauma it can be as high as 80%.
Factors determining the occurrence of postoperative infections include the type and length of surgery, the presence of underlying diseases, perioperative blood transfusion, hypothermia and anaesthesia.

The anaesthetist, in taking care of the patient before, during and after the operation, should have a sufficient knowledge of postoperative infections. Preventing these infections requires an understanding of their pathogenesis.
Bacteria colonising patients in the perioperative period are generally acquired in one of two ways: endogenously from the patient's own flora or exogenously from the immediate hospital environment. Most of the infections in the postoperative period and/or associated with long term ventilation belong to the endogenous infections.

The occurrence of infections most often involves a three-step process: first, colonisation of a patient's mucosa or skin with a potential pathogen; second, access of the pathogen to a site where it may invade tissues, often in association with a foreign body such as an intravascular catheter or an endotracheal tube; and third, an imbalance among the pathogen's virulence factors and the host's defence factors, which eventually results in the infection.

Aims of the Thesis

Anaesthesia has been long suspected to contribute to infection in the postoperative period. So far the main concern has been the depression of the immune system which allows an invading organism to become established. The majority of investigators have studied granulocyte and lymphocyte functions and revealed depressed immune functions.
In the Thesis other possible causes of postoperative infection were discussed.

I. The effect of drugs used in anaesthesia and perioperative antibiotic treatment on the endogenous and exogenous source of postoperative infections.

I/1. What are the effects of atracurium, cisatracurium, glyceryl trinitrate (GTN), and sodium nitroprusside (SNP) on bacterial growth?

I/2. What is the effect of antibiotic treatment – simulating natural circumstances – on the *in vivo* selection of resistant haemolytic *E. coli* clones?

I/3. Could antiblotic treatment enhance the emergence of intergeneric plasmid transfer?

II. Does anaesthesia affect bacterial adherence?

II/1. Does halothane affect bacterial haemagglutination?

II/2. Does halothane affect fimbria mediated bacterial adherence to human epithelial cells *in vitro*?

II/3. Is there any change in human oral bacterial flora following general anaesthesia, surgery, and perioperative antibiotic treatment?

III. Could anaesthesia influence perioperative antibiotic therapy by altering intracellular antibiotic concentrations?

Materials and methods

Bacterial sensitivity to atracurium, cisatracurium, GTN, and SNP was examined on clinical isolates of *S. aureus*, *P aeruginosa* and *E. coli* at 20°C and 37°C.

In vitro and in vivo R plasmid transfer was investigated with *E. coli* J53pTE1 and *E. coli* P673pTE5. Twelve-week-old mice were used for the *in vivo* experiments.

The *in vitro* and *in vivo* Hly plasmid transfer was demonstrated between *E. coli* and *P. morganii*, mice were used for the *in vivo* studies.

Virulence tests.
Mouse lung toxicity assay and chicken embryo virulence assay was used.

Haemagglutination
Mannose sensitive and mannose resistant haemagglutination of *E. coli* was examined.

Adherence assay
The adherence of *E. coli* K88 and *E. coli* NG7C to HEp-2 cells was studied.

Total intravenous anaesthesia (TIVA)
Patients: ASA 1 or 2 female patients aged 16-24 scheduled for scoliosis operation.
Propofol, alfentanil, atracurium, oxygen 40% in air was administered for TIVA. Cefuroxime was given on induction of anaesthesia.

Bacteria adhered to human buccal epithelial cells was determined *in vitro* by light microscopy following Giemsa staining.

Human polymorphonuclear granulocytes (PMN) were isolated by combining centrifugation and sedimentation in ficoll gradient.

Doxycycline isolated from PMN was measured by high pressure liquid chromatography (HPLC) and by a bioassay using *B. subtilis* 6633.

Statistical analysis
Using paired or unpaired Student's t test or analysis of variance where appropriate performed statistical analysis. Individual comparisons between group means were made using Scheffe's procedure. $P < 0.05$ was regarded as significant.

New observations

1. Glyceryl trinitrate infusion is safe as far as infection control is concerned. It reduces the number of *S. aureus*, *E. coli* and *P. aeruginosa* at both 20°C and 37°C.

2. Sodium nitroprusside has less antibacterial activity than GTN and in special circumstances may facilitate the development of postoperative infections. It reduced the bacterial counts of *S. aureus* at both 20°C and 37°C and that of *E. coli* only at 37°C. It is bacteriostatic against *P. aeruginosa* at 37°C and supports its growth at 20°C.

3. Both atracurium and cisatracurium are unlikely to pose a risk for postoperative infection. They killed *P. aeruginosa* after 3 hours at 37°C and after 6 hours at 20°C. They were less effective against *S. aureus*.

4. The antibacterial effect of GTN, SNP, atracurium and cisatracurium is more pronounced at 37°C than at 20°C.

5. Synergistic combination of antibiotics given parenterally following infection can select antibiotic resistant haemolytic transconjugant bacteria *in vivo*.

6. Genetic information of alpha-haemolysin is exchangeable between *E. coli* and *P. morganii in vivo* and antibiotic treatment may select for the transconjugants.

7. The inhalational anaesthetic halothane does not influence the mannose sensitive or the mannose resistant haemagglutination of *E. coli*.

8. The inhalational anaesthetic halothane decreases the adherence of *E. coli* to human epithelial cells *in vitro*.

9. The number of bacteria attached to human oral epithel decreases following surgery under general anaesthesia (TI antibiotic prophylaxis.

10. Halothane decreases the intracellular doxycycline cor human polymorphonuclear leukocytes *in vitro*.

11. Halothane does not influence the antimicrobial effect of dox *in vitro*.

Discussion

In the Thesis GTN, SNP, atracurium and cisatracurium has been a the list of drugs used in anaesthesia and tested concerning t growth. Atracurium cisatracurium and GTN proved to be safe wh supports the growth of some bacteria at room temperature.

Adherence of pathogen bacteria to mucous membranes is thougl the initial step in infection. There are many defence mechanisms against the adherence of potentially pathogenic microorganisr anaesthesia affects most of them. An important host defence mech the presence of the resident micro-flora. Drugs or procedures bacterial adherence influence host defence mechanisms. Howe effects of anaesthesia on this prerequisite of infection have n investigated yet.

Our results suggest that general anaesthesia reduce bacterial adherence to epithelial cells. Data showing changes in the adhesive properties of epithelial cells after anaesthetic exposure may promote better understanding of the pathomechanism of postoperative infections. Commensal flora protects us from colonisation by potential pathogens and it is an essential element of maintaining host defence mechanisms. Any changes in the normal human bacterial flora may result in increased susceptibility to infections.

Questions whether anaesthesia alone can be responsible for changes in the normal protective oral flora or in the adherence of pathogenic bacteria in clinical settings need further investigations.

Should our measures fail to prevent infection in the postoperative period, despite their side effects, antibiotics will provide the basis of treatment. We must always remember that the use of antibiotics, especially their synergistic combinations may help the appearance of multiresistant strains and/or more virulent clones. On the other hand, antibiotics can only help if they get to the site of infection at a sufficient concentration. Anaesthetics may interact with the effect of antibiotics at this level.

List of publications in connection with the Thesis

1. Emődy L, **Bátai I**, Kerényi M, Vörös S. Transfer of *Escherichia coli* haemolysin plasmid into *Proteus morganii* in the mouse intestine. *FEMS Microbiol Lett* 1983; **16**: 35-38.
2. Emődy L, Kerényi M, **Bátai I**. The effect of antibiotic treatment on the in vivo selection of resistant haemolytic *Escherichia coli* clones in mice. *FEMS Microbiol Lett* 1984; **22**: 179-182.
3. **Bátai I**, Vástyán A, Tekeres M, Matus Z. Halotán hatása a granulocyták doxycyclin tartalmára. *Anaesthesiologia és Intenzív Therapia* 1987; **17**: 161-165.
4. **Bátai I**, Kerényi M, Tekeres M. The impact of drugs used in anaesthesia on bacteria. *Eur J Anaesth* 1999; **16**: 425-440.
5. **Bátai I**, Kerényi M. Impact of halothane on bacterial adherence in vitro. *Acta Anaesthesiol Scand* 1999; **43**: 760-763.
6. **Bátai I**, Kerényi M, Tekeres M. The growth of bacteria in intravenous glyceryl trinitrate and in sodium nitroprusside. *Anesth Analg* 1999; **89**: 1570-1572.

Congress abstracts in connection to the Thesis

1. **Bátai I**, Kerényi M, Vástyán A, Matus Z, Tekeres M. The effects of halothane and N_2O on the doxycycline content of human polymorphonuclear leucocytes in vitro. 69th Clinical and Scientific

Congress of the International Anesthesia Research Society. 10-14 March 1995, Honolulu, USA. *Anesthesia Analgesia* **80**:S29. 1995.

2. **Bátai I**, Kerényi M, Tekeres M, Sarang K. Impact of halothane on bacterial adherence *in vitro*. 3rd Congress of the European Society of Anaesthesiologists. CNIT Paris, France, 29 April- 3 May, 1995. *Br J Anaesth* **74**(Suppl. 1.):93. 1995.
3. **Bátai I**, Kerényi M, Kiss A, Tekeres M. The impact of anaesthesia and surgery on oral bacterial adherence. 11th World Congress of Anaesthesiologists. 14-20 April 1996, Sydney, Australia. Abstract Book, p583. (P1199).
4. Kerényi M, **Bátai I**, Kiss A, Tekeres M. Antimicrobial property of atracurium. 11th World Congress of Anaesthesiologists. 14-20 April 1996, Sydney, Australia. Abstract Book, p427. (P735).
5. Kerényi M, **Bátai I**, Tóth V, Emödy L. Antitoxic effect of human and rabbit sera against *Escherichia coli* and *Morganella morganii* lung toxin. International Union of Microbiological Societies. 8th International Congress of Bacteriology and Applied Microbiology Division. Jerusalem, Israel, 18-23 August, 1996. p.146.
6. **Bátai I**, Kerényi M, Kiss A, Tekeres M. Growth of microorganisms in intravenous nitrates or in sodium nitroprusside. 71th Clinical and Scientific Congress of the International Anesthesia Research Society. March 14-18. 1997, San Francisco, USA. *Anesth Analg* 1997; **84**: S467.

Other publications

1. Emödy L, **Bátai I**, Kerényi M, Székely J, Polyák L. Anti-*Escherichia coli* alpha-haemolysin in control and patient sera. *Lancet* 1982; **ii**: 986.
2. Emödy L, Kerényi M, **Bátai I**, Pácsa S, Székely J, Kellermayer M. Haemolytic uraemic syndrome and alpha-haemolytic *Escherichia coli*. *Lancet* 1984; **i**: 1248-1249.
3. Bárdosi L, **Bátai I**. Az emésztőtraktus szelektív dekontaminációja (Kolonizációs rezisztencia; régi ötlet, új gyakorlat). *Anaesthesiologia és Intenzív Therápia*, 1988; **18**: 165-171.
4. **Bátai I**, Bárdosi L. Tekeres M. Laryngeális maszk. *Anaesthesiologia és Intenzív Therápia* 1991; **21**:135-140.
5. Gál J, **Bátai I**, Horváth JA, Brolly M, Tekeres M: Malignus hipertermia kialakulása eseménytelen halotán narkózist követö izoflurán anesztézia során. *Aneszteziológia és Intenzív Terápia* 1997; **27**: 11-18.

Other congress abstracts

1. **Bátai I**, Kerényi M, Kiss A, Tekeres M. Impact of subinhibitory dose of bupivacaine on bacterial adherence. International Symposium on Regional Anaesthesia. 9-11 April Auckland, New Zealand, 1996. Abstract handbook p158.

2. **I. Bátai**. Pipecuronium in the practice of anesthesia and intensive care. 4th Iranian Congress of Anesthesiology and Critical Care. 15-17 May 1996, Teheran, Iran.
3. **Bátai I**, Gáspár T, Kustos T. Laryngealis maszk alkalmazása low flow anaesthesiával. A Magyar Aneszteziológiai és Intenzív Terápiás Társaság Nemzeti Kongresszusa. 1996. Siófok. Abstract 3.01.

Book Chapters

1. Bátai István: Teljes intravénás anaesthesia. In: Aneszthezíológia és intenzív terápia. Szerk: Pénzes István. Medicina Könyvkiadó Rt. Budapest, 1998. 131-134.
2. Bátai István: Alkoholizmus és narkománia. In: Aneszthezíológia és intenzív terápia. Szerk: Pénzes István. Medicina Könyvkiadó Rt. Budapest, 1998. 219-223.