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PHARMACODYNAMICS

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Barbiturate coma may promote reversible bone marrow suppression in patients with severe isolated traumatic brain injury

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Abstract *Objectives*: Barbiturate coma is employed in brain-injured patients whenever increases in intracranial pressure remain unresponsive to less aggressive therapeutic regimens. Barbiturate-mediated neuroprotection, however, is weakened by an increased infection rate related to barbiturate-induced immunosuppression. Co-administration of barbiturates with antibiotics known to induce bone marrow suppression could, in turn, potentiate barbiturate-mediated immunosuppression. Adverse drug reactions and interactions of thiopental with antibiotics in terms of leukopenia, infection rate, and bone marrow suppression were investigated.
Methods: White blood cells were measured daily, tracheobronchial secretion and urine were examined for bacterial growth twice a week or if an infection was suspected.
Results: A total of 52 patients with severe isolated head injury were consecutively investigated. Due to increased intracranial pressure (ICP), which did not respond to analgosedation, barbiturate coma was performed in 23 cases. The other 29 patients remained analgosedated. Leukocytes and neutrophils were reversibly and significantly decreased in all patients, mostly sustained under thiopental. The pulmonary infection rate due to Gram-negative organisms was nearly doubled during barbiturate coma. Reversible agranulocytosis and bone marrow suppression attributed to antibiotics developed in six patients after thiopental administration. Mortality rate, however, was not increased by these adverse effects.
Conclusions: Barbiturate coma may cause reversible leukopenia and an increased infection rate. Long-term administration of thiopental may also promote reversible antibiotic-induced bone marrow suppression. The mechanisms and site of interaction between thiopental and antibiotics cannot be assessed by the present study and remain to be clarified. However, during and after barbiturate coma, close monitoring of leukocytes and infections and careful selection of antibiotics is required.

Key words Head injury · Barbiturate coma

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Introduction

During intensive care of patients with severe traumatic brain injury (TBI) increases in intracranial pressure (ICP) often reveal ongoing oedema formation. Secondary brain injury leading to brain oedema is caused by reduced cerebral perfusion [1], disturbed ionic homoeostasis and released excitotoxic transmitters [2], generated free radicals [3] and depleted energy stores [4]. Brain damage due to elevated ICP can be avoided by applying different neuroprotective strategies, such as controlled hyperventilation, moderate hypothermia, and release of cerebrospinal fluid (CSF) [5]. These general measures, however, may fail to reduce high ICP and a more aggressive therapeutic strategy such as the administration of barbiturates may become necessary. The beneficial effect of barbiturates in terms of lowering elevated ICP is thought to be due to decreased cerebral metabolism and blood flow [6, 7]. Continuous infusion of barbiturates, however, is associated with side effects. Haemodynamic instability due to reduced ventricular filling pressures and peripheral vascular resistance is observed during long-term infusion [8, 9] which, however, can be balanced with catecholamines. The immunocompetence of patients under barbiturate coma is down-regulated, resulting in an increased infection rate, with a high prevalence of pneumonia [10]. Altered functions of immunocompetent cells have a marked impact on the infection rate. White blood cells are negatively influenced resulting in a dose-dependent decrease in phagocytosis [11], an attenuated migratory function of leukocytes in bone marrow [12] and a depressed acti-

vation of lymphocytes [13]. In turn, barbiturate-related infections require specific antimicrobial therapy. Antibiotics, however, have been shown to reduce immunocompetence as well by inducing leukopenia [14–17]. Thus, the immunomodulating adverse effects of thiopental and antibiotics could potentiate each other, possibly resulting in severe adverse effects like agranulocytosis, putting the life of these patients at stake.

Our aim was to investigate whether patients with isolated TBI requiring long-term thiopental infusion develop more complications related to altered immunocompetence than analgosedated patients. In particular, we wanted to determine whether there is an association between thiopental as used in clinical routine and the extent of leuko-/granulocytopenia, rate of pulmonary infection, type of Gram-negative organisms, length of intensive care and mortality rate.

Materials and methods

Study population

Fifty-two patients with severe isolated TBI, admitted to the University Hospital in Zürich from 1994 to 1996, were consecutively included in the present study. Patients aged 16–75 years were investigated, provided that they did not have any history of bone marrow dysfunction, immunopathology, splenectomy, tumour growth and/or pregnancy.

Neurointensive care

After admission all patients were taken to the operation room for evacuation of any haematomas and implantation of pressure monitoring devices. Thereafter, the intubated and mechanically ventilated patients were treated according to a standard protocol [5]. The critical care management goal was to maintain cerebral perfusion pressure above 70 mmHg, which was accomplished by maintaining intracranial pressure below 20 mmHg and mean arterial pressure above 90 mmHg. Analgosedation was performed in all patients with fentanyl and midazolam, and relaxation was achieved with pancuronium. Patients who had persisting ICP values exceeding 20 mmHg received thiopental intravenously, provided that ICP could not be lowered by routine measures such as drainage of CSF or controlled hyperventilation. Barbiturate coma was induced by giving thiopental (Pentothal, Abbott Laboratories, Switzerland) 5–11 mg kg^{-1} body weight as a bolus, followed by continuous infusion of 4–6 mg kg^{-1} h^{-1} to maintain a burst-suppression pattern of 4–6 bursts min^{-1}. The thiopental dosage was adjusted according to the burst-suppression pattern. Barbiturate coma was stopped once ICP remained below 20 mmHg for 24 h. Enteral nutrition was started in all patients on the first day until oral intake of food was adequate and sufficient. Prophylactically, all patients received cefuroxime intravenously to reduce the risk of central nervous system infections due to implanted pressure monitoring devices. Cefuroxime was started pre-operatively and administered three times daily (1.5 g) until removal of the catheters.

Study protocol

Prospectively, patients in need of barbiturate coma were compared to analgosedated patients. Blood was drawn every morning and was assayed for leukocytes and neutrophils. Twice a week, or whenever an infection was suspected, tracheobronchial secretions sampled with a sterile suction device from the lower pulmonary tract and urine were examined for bacterial growth. Infection was diagnosed whenever isolation of pathogens in the different specimens coincided with leukocytosis (>11.000 cells/μl^{-1}), a significant increase of C-reactive protein (CRP) and fever (>38.5 °C).

Statistical analysis

All data are presented as mean with (SEM) or median values where appropriate. Comparisons of leukocytes and neutrophils over time were made using one-way, repeated-measures analysis of variance and Student Newman-Keul's test or the Friedman repeated analysis of variance on rank test for non-parametric data. Comparisons of haematological parameters over time between control patients and those receiving thiopental were made using two-way, repeated-measures analysis of variance and Student Newman-Keul's test. Comparisons of non-parametric infection parameters (infection rate, type of Gram-negative organisms) between the different patient groups were made using the Mann-Whitney rank-sum test. Differences were rated as significant at $P < 0.05$.

Results

Clinical data

Barbiturate coma was required in 23 patients, while 29 were analgosedated (Table 1). Patients receiving thiopental were significantly younger [27 (3) vs 44 (3) years; $P < 0.01$]. Barbiturate coma was begun as early as the first post-traumatic day and was maintained for an average of 7 days (3–12 days). Hospitalization was significantly prolonged in patients receiving long-term infusion of thiopental [28 (2) vs 18 (3) days; $P < 0.02$] with an equal mortality rate among the investigated patients (17% in each group).

Haematological parameters

Leukocytes

Patients receiving thiopental revealed a significant decrease in leukocytes on the first day after the start of barbiturate coma. During long-term thiopental infusion

Table 1 Clinical data of the patients suffering from isolated severe head injury who were in need of barbiturates to reduce intracranial pressure compared with the patients who could be treated with benzodiazepines and opioids. *ICU* intensive care unit

Parameters	No thiopental	Thiopental
Number of patients	29	23
Age in years	44 (3)	27 (2)
Start of barbiturate coma in days (range)	–	2 (1) (1–3)
Length of barbiturate coma in days (range)	–	7 (1) (3–12)
ICU in days (range)	18 (3) (4–60)	28 (2) (6–39)
Infection rate in percent	40% (12/29)	90% (21/23)
Mortality rate in percent	17% (5/29)	17% (4/23)

leukocytes remained unchanged at reduced levels which were significantly lower than under analgosedation. After thiopental was stopped, leukocytes reached high normal values and remained stable thereafter (Fig. 1a).

In analgosedated patients leukocytes declined significantly during the first 7 days after trauma, followed by a significant increase during the following 5 days, with a further decrease during the last 2 weeks (Fig. 1b).

Neutrophilic granulocytes

During barbiturate coma, neutrophils were significantly decreased compared with pre-infusion values and compared with analgosedated patients. After thiopental infusion was stopped, neutrophils increased to high normal values (Fig. 1a). Under analgosedation neutrophils decreased significantly during the first week, followed by a subsequent increase by day 12, and a decrease to lower but normal values by the end of hospitalization (Fig. 1b).

Infection parameters

Infection rate as assessed by radiological pneumonia-typical findings and identification of bacterial colonization in tracheobronchial secretions from the lower respiratory tract was significantly increased in patients receiving barbiturates (90% vs. 40%, $P < 0.005$). Gram-negative organisms were *Klebsiella* pneumonia, *Enterobacter cloacae*, *Serratia marcescens*, *Escherichia coli*, *Pseudomonas aeruginosa* (Table 2). *K.* pneumonia was equally distributed during the entire investigation period in analgosedated patients. *E. cloacae* peaked during the first 2 weeks of hospitalization in all groups. *S. marcescens* was not isolated until 2 weeks after admission to the intensive care unit (ICU) and was predominantly found in the thiopental group. E. coli was equally distributed in barbiturate patients and isolated only in one thiopental-free patient. *P. aeruginosa* was isolated in the thiopental group a week prior to the analgosedated group.

Antibiotics

Apart from routine prophylactic administration of cefuroxime, specific antimicrobial therapy was not started until the relevant infection was diagnosed and the specific sensitivity was tested according to the antibiogram. Overall, cefuroxime was the most commonly applied antibiotic in all patients with a similar length of appli-

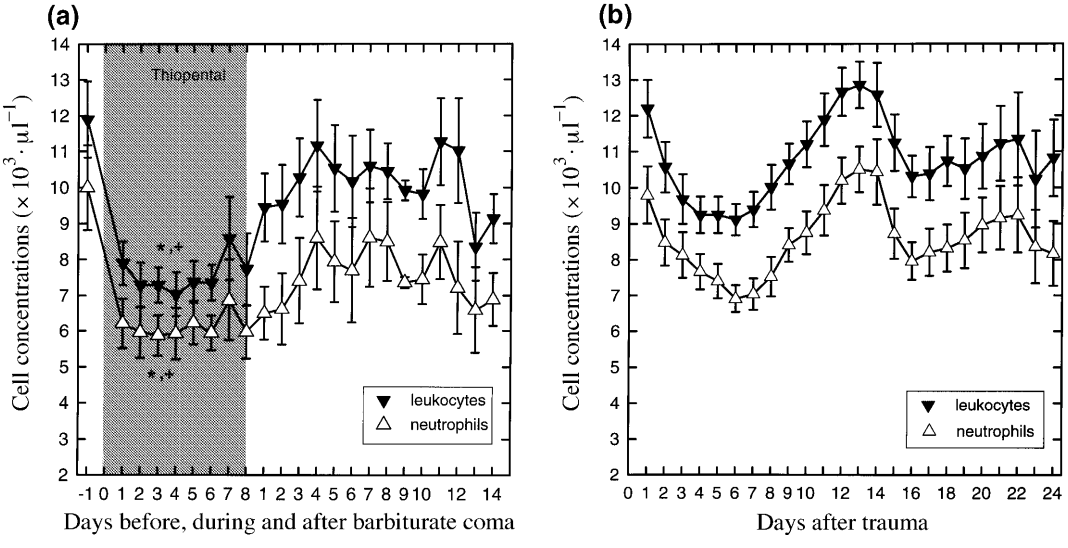

Fig. 1 Changes in leukocytes and neutrophils in 23 patients requiring barbiturate coma (**A**) and in 29 analgosedated patients (**B**) suffering from isolated traumatic brain injury. Decreases in white blood cells compared with levels before barbiturate coma (*) and analgosedated patients (+) are significant ($P < 0.05$)

Table 2 Post-traumatic spectrum, frequency and time of occurrence of Gram-negative organisms found to cause pneumonia in brain-injured patients under analgosedation and during barbiturate coma

Bacteria	Frequency of isolation		Maximum after trauma (days)	
	No thiopental	Thiopental	No thiopental	Thiopental
Klebsiella pneumonia	6	2	4–26	5
Enterobacter cloacae	14	15	4, 10, 15	5, 10, 15
Serratia marcescens	1	12	13	12, 16
E. coli	1	6	5	4–20
Pseudomonas aeruginosa	7	15	24–28	15–17

cation 15 ± (2) days. According to spectrum and frequency of isolated Gram-negative organisms, cotrimoxazol, netilmicin, and ciprofloxacin were given significantly more often in patients requiring thiopental (thiopental: cotrimoxazol/netilmicin/ciprofloxacin: 10/7/5 vs no thiopental: 6/3/2 patients; $P < 0.04$). Amoxicillin and teicoplanin were given in similar frequencies. Tazobactam/piperacillin and vancomycin were only given in a few cases. Length of antimicrobial therapy did not differ in the subgroups (Table 3).

Mitochondrial liver enzyme GOT

During barbiturate coma the hepatic enzyme GOT, normally confined to mitochondria, was significantly increased in serum compared with analgosedated patients [thiopental: 52 (18) (day 1) to 148 (49) U l^{-1} (day 8); no thiopental: 32 (5) (day 1), 48 (8) U l^{-1} (day 8); $P < 0.008$]. After thiopental infusion was stopped GOT tended to normalize during the following 11 days.

Bone marrow suppression

Of the 23 patients treated with thiopental, six developed severe but reversible leukopenia and agranulocytosis. In four patients iliac bone marrow was sampled and studied histologically. Two patients showed complete bone marrow suppression with absent differentiation of neutrophils beyond the stage of myelocytes. Another patient revealed partially suppressed bone marrow with intact differentiation but reduced neutropoesis. Occurrence of viral infections [Cytomegalovirus (CMV), Epstein-Barrvirus (EBV), herpes simplex virus (HSV) and hepatitis] was excluded serologically in all patients. These six patients revealed a repetitive pattern: barbiturate coma was induced as early as the first day after trauma and was maintained between 7 and 12 days; during long-term thiopental infusion reversible leukopenia and granulocytopenia were observed. One to 7 days after thiopental administration had been stopped, antimicrobial therapy was commenced in four patients with pneumonia related to Gram-negative organisms. One patient (Fig. 2) received tazobactam/piperacillin (3 × 4.5 g/d i.v.), and the other was given ornidazole (3 × 0.5 g/d i.v.). During antimicrobial therapy peripheral leukopenia and agranulocytosis was observed. Upon termination of administration of tazobactam/piperacillin and ornidazole and substitution with ciprofloxacin, leukopoiesis was regained followed by leukocytosis with values as high as 28 000 cells μl^{-1}. Thereafter, white blood cells tended to normalize. In one patient antimicrobial therapy with netilmicin (1 × 0.5 g/d i.v.) was started during the infusion period of thiopental. Again, peripheral leukocytes decreased dramatically and agranulocytosis developed. The antibiotics were changed to ciprofloxacin. Unfortunately, the patient died a few days later due to malignant intracranial hypertension.

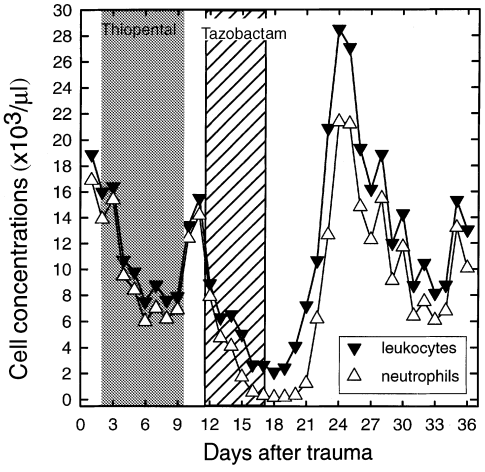

Fig. 2 Illustrative case showing reversible leukopenia and granulocytopenia during barbiturate coma followed by bone-marrow suppression upon adding tazobactam/piperacillin to treat a case of pneumonia caused by *Enterococci*. Bone marrow function was restored after stopping tazobactam/piperacillin and administering ciprofloxacin

Table 3 Antimicrobial therapy, mean duration of intravenous application and frequency of bone marrow suppression during analgosedation (*AS*) and barbiturate coma (*BC*)

Antibiotic	Analgosedation		Thiopental		Cases of bone marrow suppression	
	n	Days	*n*	Days	AS	BC
Netilmicin (1 × 0.45 g i.v.)	3	6 (3)	7	7 (1)	0	2
Tazobactam/piperacillin (3 × 4.5 g i.v.)	–	–	3	5 (3)	0	2
Ornidazol (3 × 0.5 g i.v.)	–	–	2	5–8	0	2
Cefuroxime (3 × 1.5 g i.v.)	29	13 (2)	23	13 (2)	0	0
Cotrimoxazol (3 × 0.96 g i.v.)	6	5 (1)	10	6 (1)	0	0
Ciprofloxacin (2 × 0.4 g i.v.)	2	4–9	5	5 (1)	0	0
Amoxicillin (3 × 2.2 g i.v.)	4	5 (1)	4	8 (3)	0	0
Ceftazidime (3 × 2 g i.v.)	4	5 (2)	3	6 (2)	0	0
Vancomycin (2 × 1 g i.v.)	1	2	2	2–8	0	0
Teicoplanin (1 × 0.4 g i.v.)	2	4, 6	1	7	0	0

Discussion

Long-term infusion of thiopental in brain-injured patients suffering from elevated intracranial pressure caused reversible leukopenia and granulocytopenia. Despite its transient nature, this decrease in white blood cells is of clinical importance because a sustained perturbation of immunocompetence in patients with isolated TBI was associated with an increased infection rate. These results are in line with others showing that barbiturate coma is associated with an increased rate of pneumonia due to Gram-negative organisms [18, 19].

There is substantial evidence that thiopental alters immunocompetence by reducing phagocytic activity of leukocytes, decreasing activation of peripheral lymphocytes [11, 13] and diminishing mobility of white blood cells located in bone marrow [12, 20]. Since white blood cells are the first line of immunological defense, it is obvious that an alteration of these cells will reduce the patient's ability to combat invading pathogens, resulting in an increased infection rate. The exact target and mechanisms of thiopental on immunocompetent cells, however, cannot be assessed by the present study. The decrease in circulating leukocytes and neutrophilic granulocytes could be influenced by an alteration of their pro-genitor cells in bone marrow. The increase in white blood cells after long-term thiopental infusion was stopped reflects thiopental-induced and reversible depression of stem cells.

There is no current explanation for the bone marrow suppression observed in six patients receiving different antibiotics (netilmicin, tazobactam/piperacillin and ornidazole) after long-term infusion of thiopental. It appears that the likelihood of bone marrow suppression is increased among patients who are concomitantly treated with thiopental and antibiotics which are known to have a bone-marrow suppressing effect. A prospective study revealed normal doses of antimicrobial agents to initiate bone marrow suppression in patients suffering from end-stage liver disease [21]. Barbiturates are known to alter mitochondrial function by uncoupling oxidation from phosphorylation [22], and to reversibly liberate liver enzymes located in hepatic mitochondria and cytoplasm resulting in increasing serum levels [10]. In the present study serum GOT was significantly increased in patients receiving thiopental compared with analgosedated patients and normalized after thiopental infusion was stopped. It is speculated that apart from the induction of enzymes, cellular leakage, possibly influenced by an altered fluidity of hepatic phospholipid membranes [23], must occur at the same time to increase serum enzyme levels. Assuming observed elevated serum GOT levels depict functionally and structurally altered hepatic mitochondria, decreased metabolism of antibiotics could lead to increased serum levels. The elevated serum levels and decreased hepatic elimination of other possibly toxic substances could interfere with bone marrow function, eventually resulting in bone marrow suppression. Antimicrobial agents belonging to the family of nitroimidazol-nitrofuran antibiotics such as ornidazole and metronidazole are substantially metabolized by hepatocytes (90%) and hardly excreted in urine [24, 25]. Functional hepatic alteration will result in a prolonged plasma half-life of these agents [26] and repetitive administration will cause accumulation of certain metabolites in serum [27]. Apart from barbiturate-induced altered liver function, thiopental could also liberate antibiotics from their protein binding or decrease their renal excretion. Teicoplanin bound to plasma protein up to 90–95% [28] could be displaced by thiopental which is protein-bound by 70–85% [29]. This, in turn, could increase serum teicoplanin levels as long as thiopental is measurable in serum. Netilmicin and tazobactam are neither hepatically metabolized nor is there any significant protein binding. They are, however, eliminated renally by 80–90% [30, 31]. A decreased glomerular filtration such as that caused by thiopental [32] could result in increased serum levels of these agents.

Apart from these distant interactions, thiopental and antimicrobial agents might also mutually sustain their ability to cause leukopenia and granulocytopenia on a direct cellular basis within bone marrow. Analysis of antibiotic levels in serum and urine during and after long-term administration of thiopental might confirm or rule out the different targets such as protein binding, renal excretion, and hepatic metabolism, which could account for the bone marrow suppression observed in six patients treated with thiopental and different antibiotics.

References

1. Miller JD, Stanek A, Langfit TW (1971) Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. Brain Res 34: 411–432
2. Katayama Y, Becker D, Tamura T, Hovda DA (1990) Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. J Neurosurg 73: 889–900
3. Bondy SC, LeBel CP (1993) The relationship between excitotoxicity and oxidative stress in the central nervous system. Free Radiol Biol Med 14: 633–642
4. Sutton LN, McLaughlin AC, Kemp W et al (1987) Effects of increased ICP on brain phosphocreatinine and lactate determined by simultaneous ^{1}H and ^{31}P NMR spectroscopy. J Neurosurg 67: 381–386
5. Stocker R, Bernays T, Kossmann T, Imhof HG (1995) Monitoring and treatment of acute head injury. In: Goris RJA, Trentz O (eds) The integrated approach to trauma care. Springer Verlag, Berlin Heidelberg New York, pp 196–210
6. Michenfelder JD (1974) The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 41: 231–236
7. Donegan JH, Traystman RJ, Koehler RC, et al (1985) Cerebrovascular hypoxic and autoregulatory responses during reduced brain metabolism. Am J Physiol 249: H421–H429
8. Epstein B, Li TH (1955) Hemodynamic changes during thiopental anesthesia in humans: cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume. J Clin Invest 34: 500–510

9. Todd MM, Drummond JC, Sang H (1987) Hemodynamic effects of high dose pentobarbital: studies in elective neurosurgical patients. Neurosurgery 20: 559–563
10. Schálen W, Messeter K, Nordstrom CH (1992) Complications and side effects during thiopentone therapy in patients with severe head injuries. Acta Anaesthesiol Scand 36: 369–377
11. Moudgril GC (1981) Effects of premedications, intravenous anaesthetic agents and local anaesthetic agents on phagocytosis in vitro. Can Anaes Soc J 28: 597–602
12. Kress HG, Segmuller R (1987) Intravenous anesthetics and human neutrophil granulocyte motility in vitro. Anaesthesist 36: 356–361
13. Neuwelt EA, Kikuchi K, Hill SA et al (1982) Barbiturate inhibition of lymphocyte function. Differing effects of various barbiturates to induce coma. J Neurosurg 56: 254–259
14. White CM, Price JJ, Hunt KM (1980) Bone marrow aplasia associated with metronidazole. BMJ 280: 647
15. Mandl DL, Garrison MW, Palpant SD (1997) Agranulocytosis induced by vancomycin or ticarcillin/clavulanate. Ann Pharmacother 31: 1321–1324
16. Neftel KA, Hauser SP, Müller MR (1985) Inhibition of granulopoiesis in vivo and in vitro by β-lactam antibiotics. J Infect Dis 152: 90–98
17. Olaison L, Alestig K (1990) A prospective study of neutropenia induced by high doses of β-lactam antibiotics. J Antimicrob Chemother 25: 449–453
18. Eberhardt KEW, Thimm BM, Spring A, Maskos WR (1992) Dose-dependent rate of nosocomial pulmonary infection in mechanically ventilated patients with brain oedema receiving barbiturates: a prospective case study. Infection 20: 16–22
19. Sato M, Tanaka S, Suzuki K, et al (1989) Complications associated with barbiturate therapy. Resuscitation 17: 233–241
20. Kress HG, Eberlein T, Hörber B, Weis KH (1989) Suppression of neutrophil migration and chemiluminescence is due to the sulfur atom in the thiobarbiturate molecule. Acta Anaesthesiol Scand 33: 122–128
21. Singh N, Yu VL, Mieles LA, Wagener MM (1993) β-lactam antibiotic-induced leukopenia in severe hepatic dysfunction: risk factors and implications for dosing in patients with liver disease. Am J Med 94: 251–256
22. Cohen PJ (1973) Effect of anesthetics on mitochondrial function. Anesthesiology 39: 153–164
23. Rosenberg PH, Jansson S-E, Gripenberg J (1977) Effects of halothane, thiopental, and lidocaine on fluidity of synaptic plasma membranes and artificial phospholipid membranes. Anesthesiology 46: 322–326
24. Bourget P (1989) Pharmacokinetics of ornidazole in patients with acute viral hepatitis, alcoholic cirrhosis, and extrahepatic cholestasis. Clin Pharmacol Ther 45: 373–379
25. Horber FF, Maurer O, Probst PJ et al (1989) High haemodialysis clearance of ornidazole in the presence of a negligible renal clearance. Eur J Clin Pharmacol 36: 389–393
26. Farrel G, Baird-Lambert J, Cuejic M, Buchanan N (1984) Disposition and metabolism of metronidazole in patients with severe liver failure. Hepatology 4: 722–726
27. Schneider MU, Reimann JF, Laudage G (1984) Serum concentrations of metronidazole and its main metabolite in patients with active Crohn's disease: correlation with disease activity and therapeutic efficacy. Chemotherapy 30: 345–532
28. Rowland M (1990) Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet 18: 184–209
29. Burch PG, Stanski DR (1983) The role of metabolism and protein binding in thiopental anesthesia. Anesthesiology 58: 146–152
30. Wise R, Logan M, Cooper M, Andrews JM (1991) Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. Antimicrob Agents Chemother 35: 1081–1084
31. Chiu PJS, Miller GH, Brown AD et al (1977) Renal pharmacology of netilmicin. Antimicrob Agents Chemother 11: 821–825
32. Lebowitz PW, Cote ME, Daniels AL, Bonventre JV (1983) Comparative renal effects of midazolam and thiopental in humans. Anesthesiology 59: 381–384