Decrease in white blood cell counts after thiopentone barbiturate therapy for refractory intracranial hypertension: A common complication

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ABSTRACT

Background: Leucopenia has been reported after induction of thiopentone barbiturate therapy for refractory intracranial hypertension. However, the incidence and characteristics are not well described. Aims: We performed a retrospective review to describe the incidence and characteristics of leucopenia after induction of thiopentone barbiturate therapy. Setting and Design: Our centre is a national referral centre for neurotrauma and surgery in a tertiary medical institution. Materials and Methods: We performed a retrospective review of all patients who received thiopentone barbiturate therapy for refractory intracranial hypertension during an 18 month period from January 2004 to June 2005 in our neurosurgical intensive care unit. Statistical Analysis Used: Statistical analysis was performed using SPSS version 15.0. All data are reported as mean ± standard deviation or median (interquartile range). The Chi square test was used to analyze categorical data and student t test done for comparison of means. For paired data, the paired t-test was used. Results: Thirty eight (80.9%) out of 47 patients developed a decrease in white blood cell (WBC) count after induction of thiopentone barbiturate coma. The mean decrease in WBC from baseline to the nadir was $6.4 \times 10^9/L (P < 0.001)$ and occurred 57 (3-147) h after induction. The mean nadir WBC was $8.6 \pm 3.6 \times 10^9/L$. Three (6.4%) patients were leucopenic, with a WBC count of 2.8, 3.1, and $3.6 \times 10^9/L$. None of them were neutropenic. We did not find any association between decrease in WBC count and clinical diagnosis of infection. We did not find any association between possible risk factors such as admission GCS, maximum ICP prior to induction of barbiturate coma, APACHE II score, total duration and dose of thiopentone given, and decrease in WBC count. Conclusions: Decrease in WBC count is common, while development of leucopenia is rare after thiopentone barbiturate coma. Regular monitoring of WBC counts is recommended.

Key words: Barbiturate coma, leucopenia, traumatic brain injury

Introduction

Barbiturate coma is a second tier measure for control of refractory intracranial hypertension.1 While potentially useful in reducing intracranial pressure, multiple adverse effects such as hypotension and hypokalaemia have been reported.2,3 Leucopenia following administration of thiopentone barbiturate coma has been reported,4,5 with increased infections attributed to pharmacological immunosuppression by thiopentone. To define the incidence and characteristics of changes in white blood cell counts after induction of thiopentone barbiturate therapy, we performed a retrospective review of patients who received thiopentone barbiturate therapy for refractory intracranial hypertension in our neurosurgical ICU.

Materials and Methods

Following institutional review board approval, we performed a retrospective review of all patients who received thiopentone barbiturate therapy for refractory intracranial hypertension...
intracranial hypertension in our neurosurgical ICU from January 2004 to June 2005.

Protocol for thiopentone barbiturate therapy
Our institution is a national referral centre for neurotrauma and neurosurgery. A standard protocol for thiopentone barbiturate therapy is applied to patients who have refractory raised intracranial hypertension of more than 25 mmHg despite maximal medical and surgical measures. A loading dose of thiopentone 250 mg is given over 10-20 min and may be repeated up to 1000 mg. This is followed by a maintenance dose of 125-500 mg/h of thiopentone. The primary end point is intracranial pressure (ICP) control of less than 25 mmHg. If this is not achievable, a secondary end point of burst suppression on the electroencephalogram is used. A full blood count is performed at least once daily when on thiopentone barbiturate coma. Leucopenia is defined as a WBC count less than 4 × 10^9/L. Neutropenia is defined as a total neutrophil count of less than 0.5 × 10^9/L. Patients are not actively cooled unless they are hyperthermic. If core temperature falls below 35°C, active warming measures are instituted to correct the hypothermia. Once ICP control has been achieved for 24-36 h, the patients are gradually weaned from the barbiturate therapy. The attending physician may also choose to terminate barbiturate therapy for other reasons, including lack of therapeutic efficacy.

Data extraction
The patients were identified from a database of all patients admitted to the neurosurgical ICU. From patient charts and electronic records, we extracted the following data: Demographics, aetiology, admission Glasgow Coma Scale (GCS), maximal intracranial pressure (ICP) prior to induction of thiopentone barbiturate coma, APACHE II scores, admission radiological findings, duration of barbiturate therapy (time period between induction and cessation of infusion) and WBC counts. As this was a retrospective review, we were unable to apply a standardised criteria for diagnosis of infections. An infection was deemed present if a clinical diagnosis had been made by the ICU team and documented in the chart. Based on physiological and pharmacological mechanisms as well as our clinical experience, we performed an exploratory univariate analysis of variables which may be associated with a decrease in WBC count. These include admission GCS, maximum ICP prior to induction of barbiturate coma, APACHE II score, total duration and dose of thiopentone given.

Statistics
Statistical analysis was performed using SPSS version 15.0. All data are reported as mean ± standard deviation or median (interquartile range). The Chi square test was used to analyze categorical data and Student t-test done for comparison of means. For paired data, the paired t-test was used.

Results
During the study period, 47 patients received thiopentone barbiturate therapy for refractory intracranial hypertension. Patient demographics and characteristics are reported in Table 1. Characteristics and outcomes of the thiopentone barbiturate therapy are shown in Table 2.

Changes in white blood cell count after induction of thiopentone barbiturate therapy
The mean pre induction WBC count was 14.5 ± 4.6 × 10^9/L. No patient was leucopenic prior to induction. Thirty eight (80.9%) patients had a decrease in WBC count after induction. Among these patients, the mean decrease in WBC from baseline to the nadir was 6.4 ± 10^9/L (P < 0.001) and occurred 57 (3-147) h after induction. The mean nadir WBC was 8.6 ± 3.6 × 10^9/L. Three (6.4%) patients were leucopenic, with a WBC count of 2.8, 3.1, and 3.6 × 10^9/L. None of them were neutropenic. An example of WBC trend vs time for one of these three patients is illustrated in Figure 1.

Table 1: Patient demographics and characteristics

| Age | 47±14 |
| Total | 100 |
| Male | 33 (70.2) |
| Female | 14 (29.8) |
| APACHE | 25±5 |
| Post resuscitation GCS | |
| 9-15 | 12 (25.5) |
| 6-8 | 17 (36.2) |
| 3-5 | 18 (38.3) |
| Mechanism of injury | |
| Traumatic | |
| Assault | 1 (2.1) |
| Fall from heights | 7 (15.6) |
| Road traffic accident | 19 (40.4) |
| Non–traumatic | |
| Haemorrhagic stroke | 1 (2.1) |
| Ischaemic stroke | 4 (8.5) |
| Postoperative unknown | 2 (4.3) |
| Primary radiological lesion | |
| Extradural haemorrhage | 4 (8.5) |
| Subdural haemorrhage | 8 (17.0) |
| Subarachnoid haemorrhage | 7 (14.9) |
| Intracranial haemorrhage | 8 (17.0) |
| Diffuse axonal injury | 18 (38.3) |
| Contusion | 2 (4.3) |

GCS: Glasgow coma scale, APACHE: Acute Physiology and Chronic Health Evaluation
Association with decrease in WBC count and clinical diagnosis of sepsis

Twenty seven patients had a new clinical diagnosis of infection during the phase of thiopentone barbiturate coma, of which there were 24 patients with pneumonia, 2 with urinary tract infections and 1 with pneumonia and wound infection. All three leucopenic patients had a clinical diagnosis of pneumonia. We did not find any association between a decrease in WBC count and a clinical diagnosis of infection [Table 3].

Univariate analysis of variables associated with decrease in WBC count

The exploratory univariate analysis did not find any significant associations between a decrease in the WBC count and possible risk factors such as admission GCS, maximum ICP prior to induction of barbiturate coma, APACHE II score, total duration and dose of thiopentone given [Table 4].

Discussion

A MEDLINE search from 1966 to Nov 2011, using the search terms leucopenia, neutropenia, barbiturate and thiopentone identified only two prior reports of leucopenia after induction of thiopentone barbiturate coma. Frenette published a case report on two patients with traumatic brain injury who developed neutropenia of 0.1 × 10⁹/L and 0.8 × 10⁹/L after induction of thiopentone barbiturate coma.[5] In another case series of 23 head injured patients receiving thiopentone barbiturate coma for refractory intracranial hypertension, all developed a decrease in WBC counts and 6 developed neutropenia. Four of these patients received bone marrow biopsy, with two showing complete marrow suppression with absent differentiation and another showing partial bone marrow suppression with intact differentiation between reduced neutropoiesis.[4]

Our results show that a decrease in WBC count is common after induction of thiopentone barbiturate coma for refractory intracranial hypertension, occurring in 81% of patients. However only 6.4% of our patients were leucopenic, and none were neutropenic. Many in vitro mechanisms for the decrease in WBC count following induction of thiopentone barbiturate coma have been described. It has been proposed that thiopentone-mediated inhibition of nuclear factor κ B,[6] may induce granulocyte apoptosis in response to TNF-α stimulation.[7] Thiopentone may also induce a dose dependent reduction in NFAT DNA binding via calcineurin inhibition.[8]

The role of WBC as a marker for infection in the brain injured population is difficult to define. A baseline leucocytosis is common following traumatic brain injury, due to induction of chemokine synthesis, resulting in

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**Table 2: Characteristics and outcomes of patients undergoing thiopentone barbiturate therapy**

| Number (%)/Mean±SD | Maximum ICP before barbiturate therapy (mmHg) | Duration of barbiturate coma (h) | Outcome of barbiturate therapy | Success in ICP control | Failure | No surgery done | Decompressive craniectomy | ICP controlled | ICP not controlled |
|--------------------|-----------------------------------------------|---------------------------------|---------------------------------|------------------------|--------|----------------|--------------------------|---------------|---------------------|
| 44±14              | 57.0±39.7                                     | 25 (53.2)                      | 15 (31.9)                      | 2 (4.3)                | 5 (10.6) |

ICP: Intracranial pressure

**Table 3: Association between decrease in WBC and clinical diagnosis of infection**

| Clinical diagnosis of infection | No clinical diagnosis of infection |
|---------------------------------|-------------------------------------|
| Decrease in WBC | 22 | 16 |
| No decrease in WBC | 5 | 4 |

P=0.553, WBC: White blood cell

**Table 4: Univariate analysis of risk factors for decrease in WBC**

|                        | Decrease in WBC | No decrease in WBC | P     |
|------------------------|-----------------|--------------------|-------|
| Admission GCS         | 7±3             | 6±2                | 0.345 |
| Max ICP (mmHg)        | 42±21           | 52±20              | 0.158 |
| APACHE II             | 24±5            | 25±5               | 0.483 |
| Total duration of barbiturate coma (h) | 56±40 | 62±37 | 0.649 |
| Total dose of thiopentone (g) | 12±9 | 16±8  | 0.219 |

GCS: Glasgow coma scale, WBC: White blood cell, ICP: Intracranial pressure, APACHE: Acute Physiology and Chronic Health Evaluation
leucocyte mobilisation in the blood, liver, brain.\cite{9,10} Fever trends may be obscured by active cooling measures taken to prevent the deleterious effect of hyperthermia on the injured brain.\cite{1} If thiopentone barbiturate coma is utilized, the iatrogenic decrease in WBC count makes interpretation even more difficult. Other markers of infection in brain injury, such as procalcitonin,\cite{11} may help with diagnosis, but further studies are still needed to clearly define their role.

It is not entirely clear if the decrease in WBC counts contributes to an increased risk of clinical infection during barbiturate therapy. An association between barbiturate therapy and infections, usually pneumonia, has been described in previous studies and is attributed to a dose-dependent pharmacological inhibition of lymphocytic function.\cite{2,12,13} In these studies, the quantitative change in WBC counts were not reported.

We however were unable to demonstrate any associations between decrease in WBC and clinical diagnosis of infections, nor identify any risk factors for decrease in WBC counts. At the same time we recognize that the small sample size of our study limit our ability to analyse the association between WBC changes and development of sepsis as well as risk factors for decrease in WBC count. In addition, the retrospective nature of the data precludes a standardised diagnosis of sepsis.

In conclusion, a decrease in WBC count is common in patients receiving thiopentone barbiturate coma for refractory intracranial hypertension. Regular and frequent monitoring of the WBC count is therefore recommended. The development of leucopenia and neutropenia is a rare complication but should lead the neurointensivist to reassess the risk benefit profile of further barbiturate therapy.

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