ANAESTHESIA AND CONGENITAL AGRANULOCYTOSIS: INFLUENCE OF ANAESTHETIC AGENT ON NEUTROPHIL NUMBERS IN A PATIENT WITH KOSTMANN’S SYNDROME

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SUMMARY

We describe a 14-month-old male patient with congenital agranulocytosis who received general anaesthesia on three separate occasions during a 6-week period for minor surgery. Granulocyte colony stimulating factor was commenced after the second anaesthetic. Each anaesthetic was followed by profound reductions in neutrophil numbers, irrespective of the agent used. Even the third anaesthetic, which avoided all the common agents thought to have a marrow suppressant effect and given during granulocyte colony stimulating factor therapy, was associated with a marked decrease in neutrophil numbers.

KEY WORDS

Kostmann’s syndrome, described by R. Kostmann in 1956, is a rare, autosomal recessive congenital neutropenia [1]. There is usually a history of parental consanguinity. Other congenital abnormalities are commonly associated with this condition [2]. Kostmann’s syndrome presents in the first few months of life, with repeated bacterial infections of the skin and respiratory tract. The condition is characterized by the presence of a persistently depressed neutrophil count with variable degrees of thrombocytosis, eosinophilia or monocytosis. The bone marrow from patients with Kostmann’s syndrome shows an arrest of myelocyte maturation at the promyelocyte stage. The interaction of anaesthetic agents with neutrophil numbers in Kostmann’s syndrome has not been described before. The case presented here describes the effects of three different anaesthetic regimens on the neutrophil count in a child with Kostmann’s syndrome.

CASE REPORT

A 14-month-old Asian male, weighing 9.45 kg, was admitted initially with acute varicella zoster infection and secondary infection of some of the vesicular skin lesions. One lesion in the groin had progressed to a cutaneous abscess. The patient, born of a consanguineous partnership, had a history of recurrent upper and lower respiratory tract infections. At another hospital, this history, together with the results of laboratory investigations, had led to the provisional diagnosis of Kostmann’s syndrome [1].

The patient received three anaesthetics during a 44-day period; the first of these, for incision and drainage of the dermal abscess and bone marrow biopsy, was preceded by 3 days of parenteral antibiotics. Before the first anaesthetic, investigations revealed iron-deficiency anaemia (haemoglobin 8.3 g dl⁻¹) and neutropenia (leucocyte count 12.7 x 10⁹ litre⁻¹; neutrophil count 0.6 x 10⁹ litre⁻¹). Chest x-ray showed right upper lobe consolidation with partial collapse.

First anaesthetic (GA1)

Premedication with trimeprazine 2 mg kg⁻¹ orally was followed by induction of anaesthesia with thiopentone 2.6 mg kg⁻¹ i.v. Suxamethonium 1.6 mg kg⁻¹ i.v. was given to facilitate tracheal intubation. Anaesthesia was maintained by spontaneous ventilation of 50% nitrous oxide and isoflurane (up to 2%) in oxygen with a fresh gas flow of 7 litre min⁻¹ via an Ayres’ T-piece with a heat and moisture exchanger. Anaesthesia lasted 35 min and recovery was uneventful. The
neutrophil count decreased from $0.6 \times 10^9 \text{ litre}^{-1}$ before this anaesthetic, to less than $1 \times 10^6 \text{ litre}^{-1}$, 4 days later (table I).

Second anaesthetic (GA2)

Eight days after the first anaesthetic, anaesthesia was required for rigid bronchoscopy because of persistent right upper lobe collapse. Premedication, consisting of atropine 40 |ig kg$^{-1}$ orally, preceded gaseous induction with 50% nitrous oxide and halothane (up to 5%) in oxygen. After induction, nitrous oxide was discontinued because of persistent arterial desaturation associated with an $FiO_2$ of less than 1.0. Anaesthesia was maintained with halothane (up to 5%) in oxygen, with spontaneous and manually assisted ventilation using a fresh gas flow of 6 litre min$^{-1}$ via an Ayres' T-piece. Anaesthesia lasted 30 min and recovery was uneventful. The neutrophil count increased from less than $1 \times 10^6 \text{ litre}^{-1}$, 4 days before the second anaesthetic to $0.62 \times 10^9 \text{ litre}^{-1}$, 3 days after it (table I).

Third anaesthetic (GA3)

This anaesthetic, 5 weeks after the second, was for a further bone marrow biopsy to assess the effects of the recombinant human granulocyte colony stimulating factor (GCSF) therapy, which had been started after the second anaesthetic. Before operation, it was decided to avoid any anaesthetic agents thought likely to cause bone marrow suppression, in order to maximize the possible benefits which the patient may obtain from the GCSF therapy. After premedication with atropine 20 |ig kg$^{-1}$ i.m., anaesthesia was induced with midazolam 100 |ig kg$^{-1}$ i.v. and ketamine 2.5 mg kg$^{-1}$ i.v. An additional bolus of ketamine 1 mg kg$^{-1}$ i.v. was required for maintenance. Anaesthesia lasted 25 min and was uneventful. Recovery, in a quiet, well illuminated room, was marked by much more restlessness than had characterized recovery from either of the two previous anaesthetics. The neutrophil count decreased from $4.66 \times 10^9 \text{ litre}^{-1}$ before the third anaesthetic, to $2.9 \times 10^9 \text{ litre}^{-1}$ after 4 days, to less than $1 \times 10^6 \text{ litre}^{-1}$ after 8 days (table I).

The patient had two bone marrow biopsies. The first, at the time of the first anaesthetic before GCSF therapy had been started, showed few neutrophils of a maturation later than that of promyelocyte. The lymphocyte line was normal in number. Monocytes were prominent. These changes were thought consistent with a diagnosis of Kostmann's syndrome with iron deficiency in addition. The second biopsy demonstrated that granulocytes were still markedly reduced, but less so than in the first bone marrow sample and with more at a mature stage. These changes were

### Table I. Haemoglobin, white cell, neutrophil, granulocyte and platelet counts in a patient with Kostmann's syndrome during the period when three different anaesthetics were administered

<table>
<thead>
<tr>
<th>Day</th>
<th>Haemoglobin (g dl$^{-1}$)</th>
<th>White cells ($\times 10^9 \text{ litre}^{-1}$)</th>
<th>Neutrophils ($\times 10^9 \text{ litre}^{-1}$)</th>
<th>Granulocytes ($\times 10^9 \text{ litre}^{-1}$)</th>
<th>Platelets ($\times 10^9 \text{ litre}^{-1}$)</th>
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<tr>
<td>1</td>
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<td>12.7</td>
<td>0.6000</td>
<td>0.8540</td>
<td>821</td>
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<tr>
<td>3</td>
<td>6.9</td>
<td>7.9</td>
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<tr>
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<td>1.0600</td>
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</tr>
<tr>
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</tr>
<tr>
<td>17</td>
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<td>1.1300</td>
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<tr>
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<td>20.3</td>
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<td>0.6100</td>
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</tr>
<tr>
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<td>28</td>
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<td>23.3</td>
<td>1.6300</td>
<td>2.7950</td>
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thought to be consistent with a response to GCSF therapy. Serum vitamin B$_{12}$ and folate concentrations measured on two occasions during this 44-day period were within normal limits. Reticulocyte counts were not performed, even though some of the blood films demonstrated polychromasia. The total white cell, neutrophil and granulocyte counts and their temporal relation to the three anaesthetics over this period are shown in figure 1.

DISCUSSION

Kostmann's syndrome is characterized by the arrest of neutrophil maturation at the promyelocyte stage [1, 2]. The resultant profound neutropenia leads to an increased susceptibility to and severity of bacterial infections from early infancy onwards. Affected individuals suffer from repeated episodes of infections such as otitis media, skin abscesses, pneumonia and urinary tract infections [1, 2]. These infections progress frequently to systemic illness and septicaemia, hence the serious morbidity and mortality associated with this condition. Management is aimed primarily at prompt treatment of infections [2], including surgical drainage of any abscesses. Bone marrow transplantation has been reported to effect a cure in this syndrome [3]. The beneficial use of recombinant human GCSF in Kostmann's syndrome has been reported [4]. A dose-dependent increase in neutrophil count is seen within 48 h of starting GCSF therapy in normal individuals, although there is a latent period of 8 or 9 days before this increase occurs in patients with Kostmann's syndrome [4]. The increase occurs in a cyclical manner at periods of 7–16 days. This may be the explanation for the dramatic decreases in neutrophil numbers observed over this period in our patient, although we do not believe this to be the case. Apart from the anaesthetics administered over this period, there does not appear to have been any other likely causative agent or incident that would explain these changes.

Following the first anaesthetic (thiopentone, suxamethonium, nitrous oxide and isoflurane in oxygen), neutrophil count decreased to unrecordable values, but with preservation of total leucocyte numbers. Subsequent to the second anaesthetic (nitrous oxide and halothane in oxygen) there was a delayed, moderate increase in neutrophils. However, this observation is complicated by the initiation of GCSF therapy on the day of operation. The dose of GCSF was doubled 22 days before the third anaesthetic, following which there was a rapid increase in the neutrophil count reaching a peak 3 days before the third anaesthetic. This anaesthetic (midazolam, ketamine and oxygen) was followed by a further dramatic reduction in the neutrophil count to unrecordable numbers, accompanied by a marked decrease in total leucocyte count. These reductions in neutrophil and leucocyte counts occurred concurrently with continuing GCSF therapy.

The effects of anaesthetic agents on leucocyte and, in particular, neutrophil function in Kostmann's syndrome have not been described, although there is much information from in vitro and in vivo studies of neutrophil function and of the complex neuroendocrine effects of surgery and anaesthesia upon this function in humans [5, 6]. The complicating effects of the surgical stress response upon the human immune system, of which the neutrophils form a vital part, make the study of the in vivo effects of anaesthetic agents difficult to interpret. Most of the literature deals with in vitro experimentation, observing effects on such aspects of neutrophil functioning as chemoluminescence, random and chemotactic migration, phagocytosis and bacterial killing. After surgery there is normally an increase in leucocyte count, mainly as a result of increased neutrophils, despite a decrease in lymphocyte
numbers. This increase is evident at the end of surgery and frequently lasts for several days [5–7]. This neutrophilia and some of the adverse effects on leucocytes observed in response to surgery under general anaesthesia may be attenuated by regional anaesthesia [7, 8].

The effects of nitrous oxide on vitamin B₁₂, bone marrow and neutrophils have been investigated extensively in the past 30 years. The principal action of nitrous oxide is oxidation of the cobalt moiety of vitamin B₁₂. This prevents vitamin B₁₂ from functioning as a vital co-enzyme to methionine synthetase, required for tetrahydrofolate and DNA synthesis [8]. As little as 2 h of exposure to anaesthetic concentrations of nitrous oxide may induce megaloblastic marrow changes [9]. The consensus of evidence indicates that short exposures to nitrous oxide in healthy patients have little clinically deleterious effect. However, this cannot be stated with certainty in the case of “sick” patients [10]. The pro-myelocyte stage is the predominant phase of neutrophil maturation affected by this action [11]. It is of interest that this is the same stage of neutrophil development at which maturation arrest occurs in Kostmann’s syndrome [1, 2].

The balance of in vitro evidence indicates that, at clinical concentrations, all the inhalation agents in common use (halothane, enflurane and isoflurane) have significant, reversible, depressant effects on neutrophil chemotaxis, phagocytosis and bacterial killing. Isoflurane appears to have the least depressant action of these three agents [8].

The effect of i.v. anaesthetic agents is less well documented. Thiopentone, the i.v. agent studied most, has an inhibitory action on neutrophil action in the concentrations that would be found soon after a bolus dose [7, 12] but, again, not all studies have confirmed this finding. The evidence for other commonly used agents is less definite. Methohexitone probably depresses neutrophil function [7, 12]; benzodiazepines, particularly diazepam, have a slight inhibitory effect [12, 13]; the evidence for significant reversible inhibition of neutrophil function by etomidate is even more equivocal [7]. Ketamine has been found to cause a slight, but significant, inhibition of neutrophil phagocytosis [12] and chemotaxis [13]. However, in both of these studies the concentrations used were greater than those likely to be encountered clinically beyond the initial bolus phase of i.v. dosage, making extrapolation to the in vivo situation difficult to interpret. In a study using a clinically relevant concentration of ketamine, Ruud, Benestad and Opdahl found no depression of neutrophil oxygen consumption or coagulation [14]. The authors are unaware of any report of profound neutropenia following ketamine anaesthesia. The neuromuscular blocking agents appear to have no effect [12]. Few of the opioid drugs have been studied; morphine may have a slight inhibitory effect [12], although this is by no means accepted [14].

The first and third anaesthetic techniques used in our patient were associated with dramatic reductions in neutrophil numbers. This is contrary to the usual increase in neutrophil numbers seen in normal individuals undergoing anaesthesia of similar duration. Following the second anaesthetic, there was a relatively small increase in neutrophil numbers, but this was still not to normal values. In addition, this increase was complicated by having occurred after initiation of GCSF therapy which would, itself, be expected to cause an increase in neutrophil numbers.

In conclusion, this report demonstrates that, in the rare cases of congenital agranulocytosis such as Kostmann’s syndrome, there is a marked depression of neutrophil numbers associated with minor surgery and anaesthesia using agents with possible bone marrow suppressive effects, such as nitrous oxide. It appears likely that exposure to volatile anaesthetics for a short time may also have adverse effects even when GCSF therapy is administered. Furthermore, the use of ketamine may be associated with detrimental effects on the bone marrow of patients with this condition. It would seem prudent, therefore, to use anaesthetic techniques based on conduction block whenever possible in patients with this type of bone marrow aplasia.

REFERENCES
4. Bonilla MA, Gillio AP, Ruggeiro M, Kernan NA,


