Perioperative changes in α₁-acid glycoprotein concentrations in infants undergoing major surgery

P. D. Booker, C. Taylor and G. Saba

Summary

α₁-Acid glycoprotein (AAG) is an acute phase protein that is responsible for binding basic drugs such as bupivacaine. In order to determine how AAG concentrations change in response to surgical stress, arterial blood samples were obtained from 50 infants undergoing major surgery, at induction of anaesthesia and daily for the next 7 days. AAG concentrations were measured using a rate nephelometric technique. The overall mean preoperative AAG concentration was 0.38 (SD 0.16) mg ml⁻¹, although concentrations were significantly greater in infants undergoing urgent surgery compared with those undergoing elective surgery (P = 0.02). There were no significant correlations between gestational or postnatal age and preoperative AAG concentration. Mean AAG concentrations increased to 0.76 (0.18) mg ml⁻¹ by day 4 after surgery and stayed at that concentration thereafter. Infants with preoperative AAG concentrations < 0.38 mg ml⁻¹ showed a greater percentage increase in postoperative AAG concentrations than did infants with preoperative AAG concentrations > 0.38 mg ml⁻¹ (P = 0.001). We conclude that preoperative measurement of AAG may identify those infants most at risk of drug toxicity in the early postoperative period. (Br. J. Anaesth. 1996; 76: 365–368)

Key words

Anaesthesia, paediatric. Protein, α₁-acid glycoprotein. Infants.

Plasma protein binding of drugs may have significant pharmacodynamic implications, because it is the unbound moiety that diffuses most readily across biological membranes, reaches receptor sites to produce pharmacological effects and is available for elimination from the body. Although albumin (ALB) has a greater binding capacity than α₁-acid glycoprotein (AAG), AAG has much greater drug affinity for drugs with pKₐ values of 8 or more, and binding of basic drugs decreases in AAG-deficient plasma [1, 2]. However, changes in protein binding are only important clinically for drugs which are highly bound to plasma proteins, such as bupivacaine (96 % bound) [3], sufentanil and alfentanil (both 92 % bound) [4]. If variations occur in the plasma concentrations of AAG, then the free plasma concentration of the bound drug can vary considerably, whereas the total concentration of the drug in plasma is only slightly affected.

The normal average plasma concentration of AAG in a healthy adult is 77 mg ml⁻¹, although there is great individual variation [5]. Many physiological factors influence AAG concentrations, including time of day [6], age [7, 8], sex [5, 7], pain [9] and nutritional status [10, 11]. Newborn infants may have very low plasma concentrations of AAG (and ALB) which tend to increase with age, to reach adult values by about 10 months of age [12]. Moreover, AAG is one of several plasma proteins synthesized by the liver; its concentration changes in response to various stressful stimuli, such as trauma [13], burns [14], malignancy [15] or infection [12, 16]. Thus the concentrations of “acute phase proteins” would be expected to change after major surgery, as has been shown in adults [17, 18], although this has not been confirmed in infants or children.

The latency period and extent of the change in AAG concentrations may be expected to have significant clinical implications for infants undergoing major surgery, as these patients are most likely to be receiving infusions of local anaesthetic or opioids in the immediate postoperative period. Therefore, in an attempt to define further the changes in plasma protein concentrations that may occur in this group of patients, we measured AAG plasma concentrations in infants requiring major surgery, both before and daily for 7 days after surgery.

Patients and methods

We obtained local Ethics Committee approval and written, informed consent from the parents of 116 infants, aged 3–200 postnatal days, presenting for major abdominal, thoracic or cardiac surgery and expected to require prolonged postoperative intensive care. Patients with tumours or suspected infection were excluded. The clinical notes were examined to determine maturity at birth and the gestational age of each infant at the time of surgery was calculated accordingly.

After induction of anaesthesia, a 0.5-ml arterial blood sample was obtained. This sampling was repeated every morning for the next 7 days or until
the arterial cannula was removed, whichever was sooner. We obtained all eight samples from 50 infants and blood was analysed for AAG using a rate nephelometric immunoassay technique (Beckman Array 360 System), which has a sensitivity of $\pm 3\%$. All patients were given peroperative analgesia using opioids, local anaesthetic drugs, or both; infusions of opioids were continued into the postoperative period for as long as was deemed clinically appropriate.

Daily full blood counts, bacteriological cultures and measurement of C-reactive protein (CRP) were performed routinely. If there was any clinical suspicion of infection together with a $>50\%$ increase in leucocyte count or CRP, or $>50\%$ decrease in platelet count after the second postoperative day, or positive bacteriological cultures, or both, the AAG data for that patient were subsequently discarded. Routine biochemical monitoring of these patients included hepatic function tests every 2 days, or more frequently if indicated clinically. In addition to glucose infusions to maintain normal calorie intake, all patients were given protein supplementation either enterally (formula or breast milk) or i.v. (Primene 10% Clintec) by day 3 after surgery, according to our normal clinical practice.

Two sample $t$ tests were used to compare mean AAG concentrations between male and female infants, between infants with preoperative AAG concentrations $<0.38$ mg ml$^{-1}$ and infants with preoperative AAG concentrations $\geq 0.38$ mg ml$^{-1}$, and between infants requiring urgent and elective surgery. Kendall’s tau-b rank correlation coefficient was used to assess associations between age and preoperative AAG concentrations.

**Results**

The mean preoperative plasma AAG concentration was 0.38 (SD 0.16) mg ml$^{-1}$, although there was wide inter-patient variation (range 0.07–0.78 mg ml$^{-1}$). Figure 1 shows the poor correlation between preoperative AAG concentration and gestational age (correlation coefficient, $r = 0.09; P = 0.09$); a similar correlation existed for AAG concentration and postnatal age ($r = 0.07; P = 0.14$).

There was a significant difference between the sexes in mean AAG concentrations ($P = 0.002$) (table 1). Female infants had a mean gestational age of 49.6 (11.1) weeks compared with males who had a mean gestational age of 45.5 (8.0) weeks ($P = 0.03$). There were similar differences in postnatal age between the sexes ($P = 0.05$). There was an increase in mean AAG concentration, to 0.76 (0.18) mg ml$^{-1}$, by day 4. Thereafter, AAG concentrations remained at or around this elevated concentration for the duration of the study (fig. 2).

Patients ($n = 29$) in whom preoperative values of AAG were less than the mean (0.38 mg ml$^{-1}$) were compared with those patients ($n = 21$) in whom preoperative AAG values were at or greater than the mean value (obtained from 116 infants). These data show that those infants with low preoperative AAG values had a much greater increase in postoperative values than did the group with higher preoperative AAG values ($P = 0.001$) (table 2).

Table 3 shows the mean perioperative AAG concentrations in infants requiring urgent compared with those requiring general surgery; there was a significant difference between the groups in preoperative values, despite the gestational age in the elective surgery group being significantly older than in the urgent surgery group. AAG concentrations after surgery did not differ significantly between the

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**Table 1** Gestational age, postnatal age and preoperative plasma protein concentration (mean (SD or range) in males and females. AAG = $\alpha_1$-acid glycoprotein

<table>
<thead>
<tr>
<th></th>
<th>Male ($n = 64$)</th>
<th>Female ($n = 52$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>45.5 (34–71)</td>
<td>49.6 (32–89)</td>
<td>0.03</td>
</tr>
<tr>
<td>Postnatal age (weeks)</td>
<td>6.69 (0.0–31.4)</td>
<td>10.4 (0.0–51.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>AAG concn (mg ml$^{-1}$)</td>
<td>0.42 (0.17)</td>
<td>0.33 (0.14)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Figure 2** Mean (SD) plasma concentrations of $\alpha_1$-acid glycoprotein before ($n = 116$) and after ($n = 50$) major surgery in young infants.
Perioperative changes in α1-acid glycoprotein in infants

Table 2 Differences in mean AAG concentrations between postoperative values and preoperative concentration expressed as percentage change (SD). Patients (n = 29) in whom preoperative values were less than the mean (0.38 mg ml⁻¹) (group A) were compared with those patients (n = 21) in whom preoperative values were at or greater than the mean (group B).

<table>
<thead>
<tr>
<th>Day after surgery</th>
<th>% Change in group A</th>
<th>% Change in group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85.5 (50.3)</td>
<td>27.9 (19.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>167.1 (97.1)</td>
<td>45.5 (29.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>209.1 (109.5)</td>
<td>57.1 (35.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>198.4 (94.2)</td>
<td>60.3 (32.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>5</td>
<td>241.1 (114.3)</td>
<td>74.5 (57.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>6</td>
<td>230.7 (123.7)</td>
<td>80.2 (69.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>7</td>
<td>262.2 (121.2)</td>
<td>83.5 (62.9)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Discussion

The therapeutic safety margin for many analgesic drugs is reduced in infancy, because of increased sensitivity to the respiratory depressant effects of opioids [19], immature drug elimination pathways [19, 20] and, as we have now confirmed indirectly, a reduction in the plasma protein binding of drugs [21, 22]. Although the provision of postoperative analgesia in this age group is receiving increasing attention [23, 24], there are few data on plasma protein binding of analgesic drugs in infancy.

This study has confirmed previous neonatal studies [12, 16] showing that mean plasma concentrations of AAG in infants are about 50% of those in healthy adults. The large inter-patient variation seen in AAG concentrations reflects not only general individual variation but also the diversity in preoperative "stress". We compared preoperative AAG concentrations in infants who required elective surgery with those requiring urgent surgery, and found a significantly lower concentration in the elective surgical group (P = 0.02). Although these infants were significantly older (P = 0.001), a factor which should have increased the AAG concentration, they were less sick and presumably less "stressed" than those infants requiring urgent surgery. As would be expected, the type of surgery had no significant effect on preoperative AAG concentrations.

Previous studies have shown that AAG concentrations increase with increasing gestational age between 28 weeks and term [12, 16, 25], reaching adult concentrations by about 10–12 months of age [12, 26]. Our results agree with the previous findings of Bienvenu and colleagues [12] who found that, from the third postnatal day, the influence of gestational age on AAG concentrations was insignificant. Our finding of a significant difference in preoperative AAG concentrations between males and females is in contrast with previous neonatal [16] and adult [4] studies which showed little difference between the sexes, but supports a larger adult study [5]. This apparent anomaly may be explained by one neonatal study [25] which found no significant difference between the sexes at birth but a difference after the fourth day of life. Although our females were significantly older than the males, they had significantly lower mean preoperative AAG concentrations; this age difference in our male and female groups thus makes the AAG concentration difference between the sexes meaningful.

We have shown that most infants had an increase in AAG concentration in response to major surgical trauma, and by 4 days after surgery the AAG concentrations had doubled to 0.76 mg ml⁻¹, irrespective of the type or urgency of the surgery. Infants with preoperative AAG concentrations > 0.38 mg ml⁻¹ showed a smaller percentage increase in the postoperative period than those infants with preoperative AAG concentrations < 0.38 mg ml⁻¹.

We postulate that the higher preoperative values in the more stressed infants undergoing urgent surgery, reflects a sharp increase in hepatic AAG production that occurred before operation. The rate of increase in AAG production thereafter was consequently less than in those individuals who began to increase their hepatic AAG production only in response to surgical stress. However, the sickest neonates, particularly those with clinically and biochemically significant signs of hepatic dysfunction, exhibited little change and concentrations remained less than 0.5 mg ml⁻¹, often decreasing from their preoperative value. Low numbers of such patients and the lack of a widely accepted objective scoring system precluded separate

Table 3 Gestational age (mean (range)) and perioperative AAG concentrations (mean (SD) mg ml⁻¹) of infants requiring elective surgery compared with those requiring urgent surgery and in infants requiring abdominal surgery compared with those requiring cardiac surgery. AAG = α1-acid glycoprotein.

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Elective surgery (n = 89)</th>
<th>Urgent surgery (n = 27)</th>
<th>P</th>
<th>Cardiac surgery (n = 90)</th>
<th>General surgery (n = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>0.37 (0.18)</td>
<td>0.47 (0.19)</td>
<td>0.02</td>
<td>0.38 (0.16)</td>
<td>0.36 (0.20)</td>
<td>0.69</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.50 (0.12)</td>
<td>0.58 (0.20)</td>
<td>0.19</td>
<td>0.52 (0.13)</td>
<td>0.54 (0.22)</td>
<td>0.82</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.63 (0.17)</td>
<td>0.71 (0.21)</td>
<td>0.23</td>
<td>0.64 (0.17)</td>
<td>0.73 (0.25)</td>
<td>0.43</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.75 (0.18)</td>
<td>0.66 (0.20)</td>
<td>0.21</td>
<td>0.74 (0.18)</td>
<td>0.68 (0.24)</td>
<td>0.38</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.76 (0.18)</td>
<td>0.76 (0.20)</td>
<td>0.97</td>
<td>0.75 (0.18)</td>
<td>0.87 (0.25)</td>
<td>0.64</td>
</tr>
<tr>
<td>Day 5</td>
<td>0.78 (0.18)</td>
<td>0.78 (0.19)</td>
<td>0.99</td>
<td>0.79 (0.19)</td>
<td>0.77 (0.24)</td>
<td>0.27</td>
</tr>
<tr>
<td>Day 6</td>
<td>0.80 (0.20)</td>
<td>0.78 (0.21)</td>
<td>0.38</td>
<td>0.78 (0.22)</td>
<td>0.74 (0.20)</td>
<td>0.34</td>
</tr>
<tr>
<td>Day 7</td>
<td>0.83 (0.21)</td>
<td>0.75 (0.16)</td>
<td>0.22</td>
<td>0.81 (0.22)</td>
<td>0.78 (0.19)</td>
<td>0.23</td>
</tr>
</tbody>
</table>
analyses of patients on the basis of severity of sickness in the postoperative period. However, one adult study has suggested that AAG concentrations decrease in proportion to the degree of hepatic dysfunction [27]. We suggest that preoperative measurement of AAG concentration should be performed in all infants undergoing elective major surgery who are expected to receive prolonged bupivacaine infusions in the postoperative period. Bupivacaine toxicity is not unknown in this age group [28] and this phenomenon may be related to low plasma protein concentrations. The maximum bupivacaine dose should be reduced in infants with preoperative AAG concentrations <0.3 mg ml\(^{-1}\) and in infants with significant hepatic dysfunction.

Acknowledgement

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References