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Plasma concentrations of alpha-1-acid glycoprotein in preterm and term newborns: influence of mode of delivery and implications for plasma protein binding of local anaesthetics

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Abstract

Background: Alpha-1-acid glycoprotein (AAGP) is an acute-phase protein with high affinity for amide local anaesthetics (LAs), and a major determinant of free and potentially toxic concentrations of LAs in plasma. Neonates are known to have lower plasma concentrations of AAGP than adults, and are at risk of developing high free concentrations of LAs. Data regarding AAGP in newborns are so far sparse. The aim of this study was to determine plasma concentrations of AAGP after delivery of preterm and term infants, and to investigate correlations between AAGP and gestational age, birth weight, gender, and mode of delivery.
Methods: In this prospective observational study, blood was sampled from umbilical cords of 70 newborn infants born at gestational weeks 27–42 immediately after delivery. Blood samples were subsequently analysed for AAGP plasma concentrations with an immunoturbidimetric assay.
Results: We found higher concentrations of AAGP in infants born vaginally compared with those who were delivered by elective Caesarean section [median (inter-quartile range) 0.189 g litre^{-1} (0.142–0.263 g litre^{-1}) *vs* 0.110 g litre^{-1} (0.094–0.157 g litre^{-1}; P=0.0003)], respectively. There was a correlation between gestational age and AAGP concentrations (r=0.50; P=0.011), with significantly higher concentrations in the more mature infants. Gender and birth weight did not appear to influence the plasma concentrations of AAGP.
Conclusions: Alpha-1-acid glycoprotein concentrations in newborns are influenced both by gestational age and mode of delivery. Thus, when dosing local anaesthetics in a parturient, these factors should be taken into account.

Keywords: anaesthesia; local; glycoproteins; infant; newborn

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Editor's key points

- The acute-phase-protein alpha-1-acid glycoprotein (AAGP) has a high affinity for amide local anaesthetics.
- Lower AAGP concentration is associated with reduced binding of amide local anaesthetics, and may increase the risk for local anaesthetic toxicity.
- Newborns have lower AAGP concentrations than adults, and AAGP concentrations increase after 260 days of gestation.
- AAGP concentrations can also increase during stressful situations, such as a normal vaginal delivery or Caesarean section, and could therefore influence the free concentration of local anaesthetics and the development of local anaesthetic toxicity.

The administration of local anaesthetics (LAs) by epidural or wound catheter infusion represents valid options to provide good postoperative analgesia after major surgery in both term and preterm newborn infants.[1–5] However, excessive dosage, unintentional intravascular administration, or rapid systemic absorption of LAs may cause serious complications, such as seizures and haemodynamic collapse.[6–8] Relevant safety issues need to be addressed before recommending the widespread use of regional anaesthesia in these patient categories.

LAs have a high affinity for plasma proteins making the free fraction of key concern regarding potential LA systemic toxicity (LAST). Alpha-1-acid glycoprotein (AAGP), an acute-phase protein, is mainly responsible for the plasma binding of LAs.[9] Low concentrations of AAGP are associated with reduced binding of LAs and result in higher free plasma concentrations of LAs that, in turn, will increase the risk for LAST. It has been shown that plasma concentrations of AAGP in newborns are approximately half of adult levels.[10] LAs also bind to albumin and red blood cells.[11] As albumin concentrations also are reduced in newborn and especially preterm infants, it will probably not provide any additional safety regarding LAST. The high haematocrit of newborn infants is only of limited importance.[12] To our knowledge, AAGP concentrations have not been determined in the very preterm population; furthermore, the effect on AAGP concentrations caused by mode of delivery (vaginal delivery *vs* Caesarean section) remains unexplored. This is useful knowledge to avoid LAST and make dosage suggestion in these patient categories.

The aim of this prospective observational study was to determine AAGP plasma concentrations in preterm and term newborns, and whether there was a correlation between AAGP concentrations and gestational age, birth weight, gender, and mode of delivery.

Methods

Study population

Ethical approval for this study (Dnr:2014/64-31/2) was provided by the ethical committee of Karolinska Institutet, Stockholm, Sweden on April 19, 2014. After written parental informed consent, 70 newborn infants were included in the study.

Blood sampling and measurements

Immediately after delivery, 1 ml blood was sampled from the umbilical artery attached to the placenta. The blood was collected in micro-cuvettes (Microvette® 500 K2-ethylenediaminetetraacetic acid (EDTA) 500 ml; Sarstedt AG and Co., Nümbrecht, Germany) and sent for further handling in the hospital laboratory. In the laboratory (Karolinska University Hospital, Huddinge, Sweden, accredited in accordance with the International Standard ISO 15189:2012), the micro-cuvettes were centrifuged at 20°C for 10 min using the Sigma 1–14K centrifuge (LABEX Instrument AB, Osterode am Harz, Germany). Plasma AAGP (orosomucoid) was analysed in EDTA plasma with an immunoturbidimetric assay, cobas C system (Roche Diagnostics, Mannheim, Germany). The lower limit of quantification was 0.1 g litre^{-1}, defined as three standard deviations above the lowest standard. The total coefficient of variation was 5%.

Investigated parameters

The AAGP concentrations were analysed in relation to gestational age, birth weight, gender, and mode of delivery (vaginal delivery *vs* Caesarean section).

Statistical analyses

Median values and inter-quartile range (IQR) were used when describing AAGP concentrations. Kruskal–Wallis test was used to compare concentrations of AAGP between infants born with different modes of delivery. To investigate the correlation between AAGP and gestational age, the Spearman correlation test was used. Statistics were evaluated by GraphPad InStat 3.10 (GraphPad Software, La Jolla, California, USA).

Results

The patient characteristics of the included newborns are presented in Table 1. Six infants were excluded because of

Table 1 Patient characteristics. AAGP, alpha-1-acid glycoprotein; IQR, inter-quartile range.

	Modes of delivery		
	Vaginal	Elective Caesarean section	Acute Caesarean section
Number of infants (*n*)z	31	26	13
Gender (male/female)	17/14	16/10	7/6
Gestational age at birth (days) (median: minimum–maximum)	273 (191–295)	265 (222–279)	263 (190–293)
Body weight (g) (median: minimum–maximum)	3363 (1734–4630)	3439 (1234–4790)	2873 (1058–4000)
AAGP concentration (g litre^{-1}) (median: IQR)	0.189 (0.142–0.263)	0.110 (0.094–0.157)	0.182 (0.121–0.376)