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Title: Infant spinal anaesthesia: Do girls need a larger dose of local anaesthetic?

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Abstract:

Background

Gender differences in absorption, distribution and metabolism of a number of anaesthetic agents have been identified in adults. Clinically, adult studies suggest women demonstrate slower onset of opioid analgesic effects, lower spinal and epidural dose requirements and greater sensitivity to neuromuscular blocking agents. Sex-related differences in the pharmacokinetics and pharmacodynamics of local anaesthetics in neonates and infants however have not been well documented. As a result, it is not known whether modification of the dose of local anaesthetic for awake spinal anaesthesia in infants is required.

Aims

Our aim was to determine whether the ED50 and ED95 of local anaesthetics used for infant spinal anaesthesia are different between sexes.

Methods

This was a retrospective analysis of data previously collected during dose response studies of levobupivacaine and ropivacaine spinal anaesthetics. The doses were reanalysed using generalized linear regression analysis to determine whether there is a discernible difference in dose requirements between male and female infants.

Results

One hundred and twenty infant spinal anaesthetics were reviewed. For levobupivacaine the ED50 (95% CI) was 0.49 (0.33-0.65) mg vs 0.69(0.49-0.88) whereas the ED95 (95% CI) was 1.07(0.73-1.41) vs 0.93(0.64-1.22) for girls and boys respectively. For ropivacaine spinal anaesthesia the ED50 (95% CI) was 0.64 (0.35-0.92) mg vs 0.30(-0.32-0.92) whereas the ED95 (95% CI) was 1.30(0.73-1.87) vs 1.66(0.55-2.76) for girls and boys respectively.

Conclusion

There is no evidence that sex differences occur at the ED50 dose range or at the clinically relevant ED95 dose. Modification of spinal anaesthetic dose is not required for infant girls.

Key words: Anesthesia, spinal; Anesthetics, local; Pharmacology, clinical; Levobupivacaine; Infant;

Clinical implications:
What is already known about the topic?

Gender has an influence on drugs commonly used in adult anaesthesia including propofol, neuromuscular blocking agents and opiates. The effect involves physiological, pharmacokinetic and pharmacodynamic parameters and not only alters drug responses but also the incidence of adverse drug responses.

Infants undergo significant changes in pharmacological responses in the first year of life with age dependent maturation of hepatic and renal function results in age dependent clearance and metabolism.

What new information this study adds:

There is no discernible difference in dose requirements at either the ED50 dose or the clinically relevant ED95 dose.

Background and Significance

During infancy and up to the first year of life there are important age dependent changes in body composition, weight, and maturation of hepatic and renal function resulting in extensive interindividual variability of drug disposition(1). Maturational pharmacokinetics describe the changes in drug absorption, distribution, metabolism and elimination while maturational pharmacodynamics describe changes in the concentration effect profile (differences in receptor expression, function or specific tissue /organ sensitivity). Phenotypic variation in metabolism of anaesthetic drugs is based on constitutional, environmental and genetic factors but in early life mainly reflects ontogeny (age dependent maturation)(2). Other uncontrolled factors that impact the maturation related variability in drug disposition include pathological processes (growth retardation, sepsis, cardiac disease and organ failure) or treatment interventions (co-medication, surgery). For age-dependent maturational processes such as clearance the effects of covariates such as post-natal age (PNA), size, comorbidity or genetic polymorphisms have been reported but not sex related differences(3).

Gender differences in pharmacokinetics and pharmacodynamics are either sex dependent or sex specific. Sex dependent changes largely relate to physical differences in body composition such as lean body mass and body water or body fat percentage whereas sex specific changes relate to sex steroid hormones influencing receptor responses, cytochrome enzymes or neurotransmitter expression. As sex specific effects usually become apparent following puberty they are unlikely to play a role in infancy but whether gender affects the developmental expression of enzymes is unknown. In contrast sex is considered an independent factor influencing the pharmacokinetics and pharmacodynamics of anaesthetics in adults (4). Females have 20-30% greater sensitivity to neuromuscular blocking agents vecuronium and pancuronium(4, 5). Females are also more sensitive to opioid receptor agonists as well as a number of kappa receptor agonists (nalbuphine and pentazocine)(6). Some studies, however, have been unable to identify sex-specific differences in anaesthetic drug requirements(7). A pharmacokinetic model of remifentanil demonstrated an effect of age and lean body mass but no influence of sex on any pharmacokinetic or pharmacodynamic parameter (8). In contrast males are more sensitive than females to propofol with a 30-40% reduction
in dose required to achieve similar recovery times(9). The overall effect is that sex adversely impacts the overall quality of recovery from anaesthesia (10).

The aim of this study was to determine whether sex based difference in the effectiveness of infant spinal anaesthesia exist. If the effect is marked then modification of doses used clinically may be required. Tailoring doses according to sex could then reduce the incidence of local anaesthetic induced adverse events as excessive doses could be avoided.

Method:
Dose response data was obtained from three previously reported studies. Study 1 was a single center trial of infants with mean postmenstrual age (PMA) of 43.4 (SD 4.8, range 32-55) weeks and weight 3.8 (SD 1.0, range, 2.3–6.1) kg received levobupivacaine 0.5% spinal anaesthetic for lower abdominal surgery(11). The minimum local anaesthetic dose (MLAD) was determined by the Dixon Massey Up-down sequential allocation method and probit analysis was also used to determine the ED50 and ED95 by extrapolation into the clinical range. The trial was approved by the Royal Childrens Hospital Ethics and Research committee (EHRC#22117). Study 2 was a second single center trial, infants with mean PMA of 43 (SD 3.1, range 36-50) weeks and weight 3.7 (SD 0.9, range, 1.9–5.5) kg received ropivacaine 0.5% spinal anaesthetic(12). In a two-phase method, the MLAD was determined in the first 25 patients. An expanded dose ranging study was then performed with dose escalation to doses predicted to fall in the ED90-ED95 range. The trial was approved by the Royal Childrens Hospital Ethics and Research committee (EHRC#24122A). Study 3 was a single center pharmacokinetic study, infants with mean PMA of 43.8 (SD 3.2, range 36-52) weeks and weight 4.2 (SD 0.8, range, 2.2-4.7) kg received 1mg.kg\(^{-1}\) of levobupivacaine 0.5% spinal anaesthetic(13). The trial was approved by the Royal Childrens Hospital Ethics and Research committee (EHRC#33045A).

For this study, the terms ‘sex’ and ‘gender’ were considered interchangeable. Whilst the terminology is related, one refers to biological differences (sex) while the other is a psychosocial construct (gender).

Statistics:
Results are reported as means and standard deviations (SD) along with numbers of patients. Demographic data was analysed using the independent t-test. Statistical significance was accepted for p values of <0.05. The ED50 and ED95 doses and respective confidence intervals were estimated using appropriate non-linear combinations with logit and probit regression coefficients using delta method; this was implemented using the nlcom command in STATA (StatCorp, College Station, TX, USA). The ED50 and ED95 and 95% confidence intervals (CI) in each group were calculated. The probable difference between ED50 doses for male and females were evaluated using independent t-test.

Results:
Demographic data is presented in table 1. There were no significant differences between sexes with respect to age, weight or post menstrual age. The dose response curves for levobupivacaine and
ropivacaine are illustrated in Fig. 1A and 1B respectively. The figure illustrates that the dose response curves are not parallel or in the case of males receiving ropivacaine not particularly sigmoid shaped. The calculated ED50 and ED95 values for levobupivacaine and ropivacaine are presented in Table 2. From logit analysis, the estimated ED50 of levobupivacaine was higher in girls (0.69 vs. 0.49 mg.kg\(^{-1}\)) but not significantly different (p=0.15). For ropivacaine the estimated ED50 was also higher for girls than boys (0.64 vs. 0.30 mg.kg\(^{-1}\)) but not significantly (p=0.47).

Similar results were also obtained from the analysis of 95% effective dose, ED95. The estimated ED95 for levobupivacaine was higher in girls compared to boys (1.07 vs. 0.93 mg.kg\(^{-1}\)) but not significantly different (p=0.56). In contrast, the ropivacaine ED95 was higher for boys than girls (1.66 vs. 1.30, p=0.66) but not significantly and with wide confidence intervals.

Values calculated by probit analysis confirm the logit findings.

**Discussion:**

This study was not able to demonstrate significant differences between sexes at the ED50 and ED95 dose. The ED50 dose for levobupivacaine is 41% higher in girls than boys but the effect is less important at the ED95 dose where the difference is only 15%. For ropivacaine the dose response curves are not parallel and as a result the ED50 dose is 113% higher but the ED95 dose is 27% lower in girls compared to boys. The effect at the ED50 dose was small and the precision of the estimate unreliable as judged by the wide confidence intervals. The comparison of the dose response curve of ropivacaine in boys was difficult as it was not a classical sigmoid shape. It has been suggested that dose response curve should be considered a 3 or 4 dimensional rather than the traditional 2 dimensional dose effect models where magnitude of response and time of assessment affect the response relationship (14). This reinforces the difficulty in conducting infant pharmacodynamic studies especially where a defined endpoint in a dichotomous outcome is largely subjective.

Sex-related differences in the pharmacokinetics and pharmacodynamics of local anaesthetics in neonates and infants have not been well documented. Aarons et al developed a population pharmacokinetic model of ropivacaine and its active metabolite pipercoloxylidide (PPX) from six studies of caudal or epidural anaesthesia in neonates and infants(15). In a non-linear mixed effect model (NONMEM) unbound and total ropivacaine and PPX plasma concentrations were associated with the covariates ethnic origin, post-natal age, weight and total dose but not sex(15, 16). Deng has demonstrated a 34% higher ropivacaine ED50 in preschool aged children compared to school age children (0.143% vs 0.107%) but did not report a sex difference(17). There have been no other paediatric studies specifically addressing sex as a covariate in epidural or spinal anaesthetic response.

In adults, the effect of sex on local anaesthetic requirements has produced conflicting results. Camorcia demonstrated that intrathecal bupivacaine requirements change with sex and pregnancy(18). The ED50 required to produce motor block in females undergoing elective lower limb surgery is 25% less than males and a further 25% less in pregnancy even when controlled for age, height and weight. The minimum local anaesthetic concentration (MLAC) of ropivacaine for caudal anaesthesia in adults is 31% higher in females compared to males (0.39% vs 0.3% respectively)(19).
In contrast, there were no significant sex related differences in the MLAC for adult ropivacaine supraclavicular brachial plexus blocks and analgesic duration was similar (20).

The mechanisms proposed to explain this variability include both pharmacokinetic (absorption, distribution, metabolism, and elimination) and pharmacodynamic factors (differences in receptor expression and function or specific tissue maturational sensitivity). Amide local anaesthetics are metabolised in the liver by the cytochrome P450 (CYP) enzyme superfamily which demonstrate small differences in their developmental expression (21, 22). There is no difference in hepatic CYP3A activity between female and male neonatal rats in the first two weeks of life but there is a six-fold increase in male rats between the second to ninth week of life (a phase considered to be equivalent to human infant development). Weight normalised clearance of drugs metabolised by CYP3A is 20-30% higher in young women compared to young men but whether this effect occurs in infants is not known (23, 24). Levobupivacaine undergoes extensive metabolism by CYP3A4 and CYP1A2 respectively (25) whereas ropivacaine is mainly metabolised by CYP1A2 and to a minor extent to PPX by CYP3A4 (26). CYP3A4 has a limited activity in the fetus (10% of adult values, increasing to 30-40% of adult activity after 1 month) but most of its biotransformation activities are achieved by CYP3A7, which is a major enzyme in the foetus. The development of CYP1A2 is more protracted and it becomes readily detectable by 1-3 months of age, approaching adult levels after 1 yr. (27, 28). Hamon demonstrated a sex-dependent difference in hepatic glutathione metabolism enzymes in very preterm infants (29). Even though glutathione plasma levels were similar shortly after birth in baby boys and girls, enzymes involved in its synthesis and regeneration were significantly higher in baby girls.

Pharmacodynamic differences in neonates are poorly described with little data on receptor expression and sensitivity and no description of sex effects. Numerous rat studies have demonstrated that whilst there are developmental changes in spinal cord receptors there is no specific sex differences (30-32). Landau has demonstrated that pharmacodynamic differences in intrathecal opioid requirements in women are dependent on the expression of a specific mu opioid receptor (μOR) (33, 34). Women identified as having the 304A allele of OPRM1 gene (which encodes the μOR) needed much more epidural fentanyl to achieve labour analgesia. The incidence of genetic polymorphisms varies according to racial background but has not been demonstrated to be different between sexes and whether this is clinically relevant is unproven (33, 34).

In adults, individual variability in cerebral spinal fluid (CSF) volume affects both spinal anaesthetic success and duration with differences in volume affecting predictability of repeated spinal bupivacaine spinal anaesthetics (35, 36). The effect of variability in CSF volume in infants on spinal anaesthesia has not been explored but a recent study suggests removal of small volumes of CSF prior to paediatric spinal anaesthesia appears to not affect success spread or duration of block (37). Rochette demonstrating that the CSF volume determined by MRI calculation is closely correlated with weight and post conceptional age but not correlated to sex or gestational age (38). Other factors considered to contribute to the sex effect include weight and body fat composition. Sex differences in weight occur with the mean % body fat always higher in female than in male infants but this difference was only significant at 4.5 months (39). Weight and body fat increase is also profoundly altered by
premature birth with ex preterm term infants reaching term have significantly lower body weight, length, whole body and regional lean body mass compared to term born infants. Both body fat composition and body water content impact on the distribution volume of both lipophilic and hydrophilic anaesthetic drugs. Adult studies suggest the higher adipose content in women affects theoretical compartment size and may result in alterations in the plasma concentration and the duration of action of lipid-soluble drugs such as propofol.

Many studies suggest that the gender effect is largely dependent on sex specific hormones. Increased production of progesterone during the luteal phase of the menstrual cycle and pregnancy can decrease anaesthetic drug requirements. The effect is expected to be negligible in infant girls but changes in pain responses have been demonstrated to occur near puberty(40-42). Female sex hormones, particularly progesterone, might be involved, with premenopausal women having faster recovery time but poor overall recovery(7).

Limitations:
The retrospective nature of the study does not allow for balanced allocation of male and female infants in the analysis. This will be a confounder even in a prospective trial due to the preponderance of male infants presenting for neonatal surgery(43). Preterm birth is both more common in boys with around 55% of all preterm births occurring in males, and is associated with a higher risk of dying when compared to girls born at a similar gestation (44). Among survivor’s males are overrepresented in studies describing neonatal surgery with a 6:1 ratio.

All of the pharmacokinetic factors associated with response to local anaesthetics (particularly volume of distribution and clearance and metabolism) are subject to large inter individual variation in the neonatal population(2, 45). Given that the effect of sex is likely to be small only a study with substantially larger sample sizes than what is standard in current paediatric studies will have sufficient power to detect sex differences(46, 47).

Conclusions:
There is no evidence that sex differences occur at the ED50 or the more clinically relevant ED95 dose for either levobupivacaine or ropivacaine. As such there is no requirement to modify the dose in infant females presenting for surgery under spinal anaesthesia.

Disclosures:
Ethics approval was obtained for the three papers used to provide data. All funding was provided by departmental research funds. The authors declare no conflict of interest.

References:
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3 Chalkiadis GA, Anderson BJ. Age and size are the major covariates for prediction of levobupivacaine clearance in children. Paediatr Anaesth 2006; 16: 275-282.

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Levobupivacaine

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=39</td>
<td>35.0 (4.6)</td>
<td>37.3 (3.9)</td>
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</tbody>
</table>

Ropivacaine

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td>n= 40</td>
<td>35.4 (4.1)</td>
<td>35.1 (4.1)</td>
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Gestational age (Wks)
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<th>Post menstrual age (Wks.)</th>
<th>42.6 (4.6)</th>
<th>44.8 (4.1)</th>
<th>42.6 (3.5)</th>
<th>43.5 (3.0)</th>
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<tbody>
<tr>
<td>Current age (Wks)</td>
<td>7.8 (3.7)</td>
<td>7.5 (4.0)</td>
<td>7.2 (3.5)</td>
<td>8.1 (3.9)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>3.82 (0.9)</td>
<td>3.97 (0.9)</td>
<td>3.72 (0.8)</td>
<td>3.72 (0.6)</td>
</tr>
</tbody>
</table>

Table 1. Demographics of infant spinal anaesthesia with isobaric levobupivacaine or ropivacaine. All values presented as mean (standard deviation).

Figure 1. Sex specific dose response curves for levobupivacaine (Fig 1A) and ropivacaine infant spinal anaesthesia (Fig 1B) calculated from logistic regression (logit). The median effective dose (ED50) and 95% effective dose (ED95) are demonstrated for boys and girls.

<table>
<thead>
<tr>
<th>ED 50</th>
<th>Estimation method</th>
<th>Female Mean (95% CI)</th>
<th>Male Mean (95% CI)</th>
<th>Mean difference (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Logit</td>
<td>0.69 (0.49-0.88)</td>
<td>0.49 (0.33-0.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probit</td>
<td>0.68 (0.47-0.90)</td>
<td>0.47 (0.27-0.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Logit</td>
<td>0.64 (0.35-0.92)</td>
<td>0.30 (-0.32-0.92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probit</td>
<td>0.62 (0.23-1.00)</td>
<td>0.24 (-0.51-0.98)</td>
</tr>
<tr>
<td>ED 95</td>
<td></td>
<td>Logit</td>
<td>1.07 (0.73-1.41)</td>
<td>0.93 (0.64-1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probit</td>
<td>1.06 (0.77-1.36)</td>
<td>0.95 (0.68-1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Logit</td>
<td>1.30 (0.73-1.87)</td>
<td>1.66 (0.55-2.76)</td>
</tr>
</tbody>
</table>

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Table 2. The median effective dose (ED50) and 95% effective dose (ED95) of local anaesthetics used for infant spinal anaesthesia calculated by probit regression analysis and logistic regression (logit). The mean differences in dose of boys compared to girls at ED50 and ED95 are calculated with 95% confidence intervals.

| Probit       | 1.41 (0.82-2.0) | 1.68 (0.62-2.74) | 0.27 (-1.33, 1.86) |
Fitted curves (logit model) levobupivacaine

Figure 1A

Probability of success

ED95

ED50

Male

Female

Concentration (mg/kg)

pan_13219_f1a.jpg
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