Epinephrine does not reduce the plasma concentration of lidocaine during continuous epidural infusion in children

[L'épinéphrine ne réduit pas la concentration plasmatique de lidocaïne pendant une perfusion péridurale continue chez les enfants]

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Purpose: During continuous epidural anesthesia with lidocaine, plasma monoethylglycinexylidide (MEGX), an active metabolite of lidocaine, increases continuously. We assessed the effect of epinephrine on the absorption of lidocaine and the accumulation of MEGX during continuous epidural anesthesia in children.

Methods: Anesthesia was administered as an initial bolus of 5 $mg \cdot kg^{-1}$ of 1% lidocaine solution followed by continuous infusion at 2.5 $mg \cdot kg^{-1} \cdot hr^{-1}$. Patients in the control group ($n = 8$) received lidocaine alone, while patients in the epinephrine group ($n = 8$) received lidocaine + epinephrine (5 $\mu g \cdot mL^{-1}$). Concentrations of lidocaine and its active metabolite, MEGX, were measured in plasma samples obtained after 15 min, 30 min, and one, two, three, four, and five hours of infusion using high-performance liquid chromatography with ultraviolet detection.

Results: Plasma lidocaine concentrations were higher in samples from the control group for the first hour; however, after two hours the levels were the same in all samples. Plasma MEGX levels increased continuously in both groups and were significantly higher in the control group samples. The sum of lidocaine + MEGX was higher in the control group for the first two hours but there was no significant difference between groups after three hours.

Conclusions: Reduction of the potential for systemic toxicity by the addition of epinephrine to lidocaine is limited, because the reduction of the sum of the plasma concentrations of lidocaine and its active metabolite MEGX is small and limited to the initial phase of infusion.

Objectif : *Pendant l'anesthésie péridurale continue avec de la lidocaïne, le monoéthylglycinexylidide plasmatique (MEGX), un métabolite actif de la lidocaïne, augmente constamment. Nous avons évalué l'effet de l'épinéphrine sur l'absorption de la lidocaïne et l'accumulation de MEGX pendant l'anesthésie péridurale continue chez des enfants.*

Méthode : *L'anesthésie a été administrée par un bolus initial de 5 $mg \cdot kg^{-1}$ d'une solution de lidocaïne à 1 % suivi d'une perfusion continue à 2,5 $mg \cdot kg^{-1} \cdot h^{-1}$. Les patients témoins ($n = 8$) ont reçu de la lidocaïne seule tandis que les autres ($n = 8$) ont reçu de la lidocaïne et de l'épinéphrine (5 $\mu g \cdot mL^{-1}$). Les concentrations de lidocaïne et de son métabolite actif, le MEGX, ont été mesurées dans des échantillons de plasma prélevés après 15 et 30 min, puis une, deux, trois, quatre et cinq heures de perfusion en utilisant la chromatographie liquide haute performance avec détection ultraviolette.*

Résultats : *Les concentrations de lidocaïne étaient plus élevées chez les patients témoins pour la première heure ; cependant, après deux heures, les niveaux étaient les mêmes dans tous les échantillons. Les niveaux de MEGX ont augmenté constamment chez les patients des deux groupes et ont été significativement plus hauts chez les témoins. La somme des concentrations de lidocaïne et de MEGX a été plus élevée dans le groupe témoin pour les deux premières heures, mais il n'y a pas eu de différence intergroupe significative après trois heures.*

Conclusion : *La réduction des possibilités de toxicité générale, par l'ajout d'épinéphrine à la lidocaïne, est limitée, car la réduction de la somme des concentrations plasmatiques de lidocaïne et de son métabolite actif, le MEGX, est faible et n'apparaît qu'à la phase initiale de la perfusion.*

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Accepted for publication January 22, 2002.

Revision accepted March 18, 2002.

ONE of the potential problems during epidural anesthesia is local anesthetic toxicity, especially if the administration of anesthetic is repeated or continuous.[1] We previously reported that, during continuous epidural anesthesia with lidocaine in children, the concentration of plasma monoethylglycinexylidide (MEGX), an active metabolite of lidocaine, increases continuously while plasma lidocaine concentrations remain constant.[2] We hypothesized that it might be helpful to add epinephrine to lidocaine used for epidural administration to prevent the accumulation of MEGX, since the addition of epinephrine reduces peak plasma lidocaine concentrations following administration of a single epidural dose.[3–5] However, the information on the effect of epinephrine on plasma lidocaine concentrations during continuous epidural anesthesia is from adult patients.[6,7] Furthermore, the effect of epinephrine on the plasma concentrations of MEGX during continuous epidural anesthesia in children remains unclear. Thus, the goal of our study was to evaluate the effect of epinephrine on the plasma concentrations of lidocaine and its metabolite during continuous epidural administration in children.

Methods

Sixteen patients, one to five years old, undergoing abdominal or thoracic surgery participated in this study. Our protocol was approved by the local Ethics Committee, and informed parental consent was obtained. The patients were alternately assigned to one of two groups: patients in the control group (n = 8) received epidural lidocaine alone, and patients in the epinephrine group (n = 8) received lidocaine and epinephrine.

No premedication was administered. Mask anesthesia was induced using sevoflurane, nitrous oxide, and oxygen. After obtaining an *iv* route, vecuronium (0.15 $mg \cdot kg^{-1}$) was given to facilitate endotracheal intubation, and anesthesia was maintained with oxygen (33%), nitrous oxide (67%), and sevoflurane (0–1%). Next, the epidural space was located using a 19-gauge Tuohy needle (Portex Minipak®; Hythe, Kent, England) between the T11–12 and the L3–4 interspace and a 22-gauge epidural catheter inserted into the epidural space. A radial artery was cannulated using a 22- or 24-gauge cannula for continuous monitoring of blood pressure and blood sampling.

In the control group (n = 8), an initial bolus of 1% lidocaine (5 $mg \cdot kg^{-1}$) was administered over a 60-sec period, followed by a continuous lidocaine infusion at a rate of 2.5 $mg \cdot kg^{-1} \cdot hr^{-1}$. The protocol for anesthesia in the epinephrine group was identical except that 5 $\mu g \cdot mL^{-1}$ epinephrine were added to the lidocaine solution. The infusion was delivered by a motor-driven syringe pump (Terumo®, Tokyo, Japan). The systolic arterial blood pressure was maintained above 90 mmHg during the study period by adjusting the inhaled sevoflurane concentration and/or the administration of lactated Ringer's solution or ephedrine. Arterial blood samples were drawn after 15 min, 30 min, and one, two, three, four, and five hours of infusion. The plasma was separated by centrifugation at 4°C and stored at -20°C until analyzed.

Plasma lidocaine and MEGX concentrations were measured using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection;[8] a variable wave length UV detector (Model UV-8020, Tosoh®, Japan) set for 210 nm was used in the chromatography. The HPLC column (TSKgel ODS-80TS) was equilibrated with a mobile phase consisting of acetonitrile, methanol, and 0.05 M phosphate buffer adjusted to pH 4.0 (10:30:60, v/v) at a flow rate of 0.6 $mL \cdot min^{-1}$. Lidocaine concentrations were assessed from peak-height ratios in comparison to an internal standard. With this assay method, the extraction recoveries from plasma for lidocaine and MEGX were 98 and 90% at 10 $\mu g \cdot mL^{-1}$, respectively. The maximum coefficient of variation value for within-run or between-run precision was 3.3%; detection limits for lidocaine and MEGX were 10 $ng \cdot mL^{-1}$ using 250 µL of plasma sample.

Plasma α_1-acid glycoprotein (AAG) is an acute-phase protein that is responsible for binding basic drugs such as lidocaine. We measured AAG concentrations at 30 min and 60 min of infusion of lidocaine, and averaged values were compared between groups. Plasma AAG concentrations were analyzed by radial immunodiffusion kit (NOR-Partigen, Hoechst Japan Inc., Tokyo, Japan) as described before.[9]

Patient characteristics, plasma AAG, the amount of Ringer's lactate, and the amount of ephedrine are expressed as median (range) and were analyzed using Mann-Whitney U test. Plasma lidocaine and MEGX are expressed as the mean ± SD. Differences between the groups with respect to plasma lidocaine and MEGX were analyzed by two-way analysis of variance for repeated measures. Pairwise comparison of the mean values were then assessed by the Scheffe F test. Values of $P < 0.05$ were considered significant.

Results

The patients median (range) age and weight, and male/female ratio in control and epinephrine groups were 35 (12–72) and 31 (12–56) months old, 14

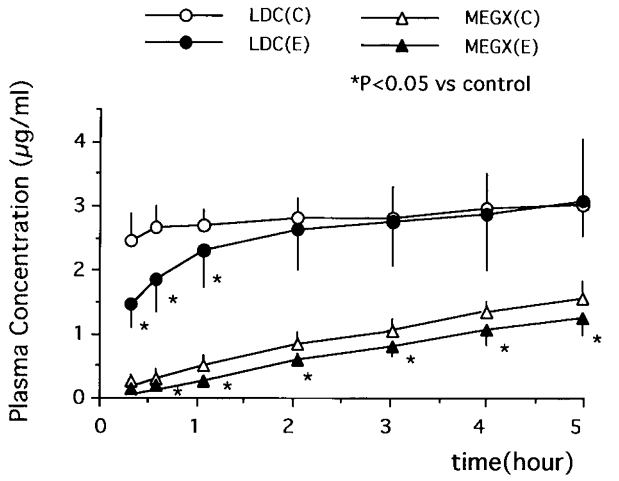

FIGURE 1 Mean plasma concentrations of lidocaine (LDC) and monoethylglycinexylidide (MEGX) during continuous epidural infusion of LDC. In the control group (C), LDC was administered alone. In the epinephrine group (E), LDC was administered in combination with epinephrine. Values are mean ± SD. See text for details.

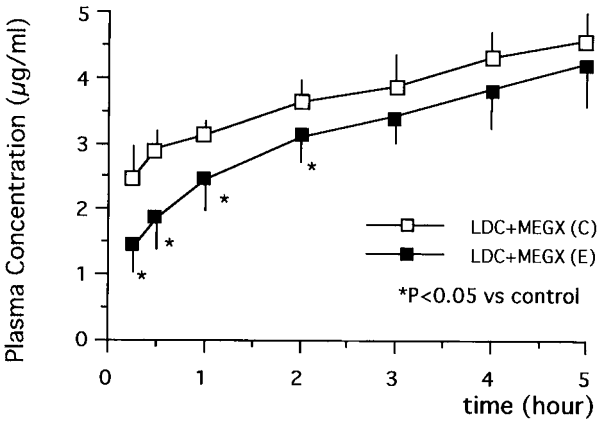

FIGURE 2 The sum of the plasma concentrations of lidocaine and monoethylglycinexylidide (MEGX) during continuous epidural infusion of lidocaine (LDC) without (C) control group or with (E) epinephrine group. Values are mean ± SD. See text for details.

(10–19.5) and 14 (10–18) kg, and 6/2 and 5/3 respectively. There were no statistically significant differences between groups. The median amount of Ringer's lactate administered during study in the control and epinephrine groups were 550 (360–800) and 560 (300–900) mL, respectively. The median amount of ephedrine during study in the control and epinephrine groups were 0 (0–3) and 0 (0–2) mg, respectively The median plasma AAG concentrations in the control and epinephrine groups were 62.5 (34.0–78.0) and 65.0 (47.5–123.5) $mg \cdot dL^{-1}$, respectively. These values were not statistically different.

The mean plasma lidocaine concentration was significantly higher in the control group than in the epinephrine group during the first one hour of the lidocaine infusion. After two hours there was no significant difference in the lidocaine concentration between groups (Figure 1).

The mean plasma concentration of MEGX increased continuously during the lidocaine infusion (Figure 1). MEGX levels were significantly higher in the control group than in the epinephrine group throughout the five-hour test period (Figure 1). The sum of the plasma lidocaine and MEGX concentrations in the control group was significantly higher than in the epinephrine group for the first two hours. However, after three hours the sum of lidocaine and MEGX concentrations did not differ between the two groups (Figure 2).

Discussion

The present study shows that the addition of epinephrine to epidural lidocaine does not contribute to the reduction of the mean concentration of plasma lidocaine except during the first hour in children. The plasma MEGX concentrations were lowered by adding epinephrine for five hours and the sum of the plasma lidocaine and MEGX concentrations decreased statistically as a result of adding epinephrine during the first two hours. However the differences in the sum of lidocaine and MEGX are small and this sum increased continuously even when epinephrine is added to epidural lidocaine. This suggests that the potential for the reduction of systemic toxicity by adding epinephrine to lidocaine during continuous epidural anesthesia in children is limited.

There are two possible mechanisms by which the addition of epinephrine to epidural lidocaine can affect the plasma concentration of lidocaine. One is a local effect such as a reduction of the absorption of lidocaine and the other is a systemic effect such as an increase in clearance and volume of distribution (VOD).

Some researchers theorize that, when administered together with epidural lidocaine, epinephrine reduces plasma lidocaine concentrations by constricting local blood vessels, thereby inhibiting lidocaine's absorption into the general circulation.[10] Single-dose epidural studies generally find that the addition of epinephrine to lidocaine solutions consistently reduces

peak plasma concentrations by 30–40%, as compared to injection of lidocaine alone.[3,5,11]

Sharrock *et al.*[12] has shown that a reduction in local anesthetic plasma concentration is achieved if epinephrine is administered intravenously, presumably because low-dose epinephrine increases the clearance and/or the VOD of lidocaine. Ward *et al.*[13] demonstrated epidural blocks with epinephrine-containing solutions result in an increase in cardiac output and a decrease in peripheral resistance due to the ß-stimulating effects of epinephrine. Based on these reports, it is possible that decreases in the plasma concentration of lidocaine during epidural anesthesia with epinephrine-containing lidocaine are due to systemically absorbed epinephrine. However, it has been shown also that epinephrine added to epidural lidocaine has no effect on the clearance of lidocaine.[14]

In this study the addition of epinephrine to epidural lidocaine did not reduce the mean concentration of plasma lidocaine, except during the first hour in children. In adults, during the continuous infusion of lidocaine, we[7] and others[6] demonstrated that epinephrine decreased plasma lidocaine concentration only transiently. The results of the present study in children are in agreement with those findings in adults.

Our results did not enable us to determine why the effect of epinephrine is lost during the continuous epidural infusion of lidocaine. One possibility might be tachyphylaxis to epinephrine's vasoconstricting effects. It has been reported that the intrathecal injection of epinephrine (200 μg) reduces dural blood flow for 40 min,[15] but the effect of an epidural infusion of epinephrine on epidural vessels or dural blood flow is unknown.

Plasma concentrations of the principal metabolite of lidocaine, MEGX, were lower in the epinephrine group, suggesting that the addition of epinephrine to lidocaine solutions is effective in reducing the accumulation of the active metabolite of lidocaine during continuous epidural anesthesia. This may have resulted from the lower plasma lidocaine concentrations during the first hour of infusion, which would be expected to result in lower MEGX accumulation.

MEGX is an active metabolite having the same convulsant potency as lidocaine itself.[16] Since lidocaine is metabolized to MEGX during infusion of lidocaine, Blumer *et al.*[16] estimates plasma levels of 15.4 $\mu g \cdot mL^{-1}$ of lidocaine in combination with 3.6 $\mu g \cdot mL^{-1}$ of MEGX are equipotent in convulsant efficacy to a plasma level of 18.7 $\mu g \cdot mL^{-1}$ of MEGX. Therefore, accumulation of MEGX contributes to local anesthetic toxicity even when blood lidocaine concentrations remain within the therapeutic range.[17–19] We reported previously that during continuous epidural anesthesia in infants and children with plain lidocaine, MEGX accumulation occurred even when plasma lidocaine was maintained within the normal range.[2] From this study we conclude it is also true that MEGX accumulation may occur after several hours of infusion of lidocaine, regardless whether epinephrine is present or not.

The plasma levels of lidocaine at the onset of convulsions are 15.4 $\mu g \cdot mL^{-1}$ in rats[16] and 18–26 $\mu g \cdot mL^{-1}$ in monkeys.[20] Therefore the levels of lidocaine and MEGX in this study were well below the convulsive threshold. However toxic symptoms such as light headness, tinnitus, visual disturbance are reported at concentrations of 5 $\mu g \cdot mL^{-1}$ of lidocaine.[20] Therefore it is possible that accumulation of lidocaine and MEGX might affect the recovery of general anesthesia even at low concentrations.

The plasma AAG is an acute-phase protein that is responsible for binding basic drugs such as lidocaine. We reported previously that plasma AAG concentration correlated with the steady-state lidocaine concentration and inversely correlated with the accumulation rate of MEGX.[9] In this study the plasma AAG concentrations were not different between groups.

We measured the plasma concentrations of lidocaine and MEGX during epidural lidocaine infusion for five hours. It would be valuable to perform a study over a longer period of time such as 24 or 48 hr and we speculate that the accumulation of MEGX would reach toxic levels. However the dose we administered was for surgery, and smaller doses should be chosen for postoperative pain relief.

This study was performed under general anesthesia. Since hepatic blood flow may decrease during general anesthesia, the metabolism of lidocaine might have been decreased. Therefore, we cannot apply our results directly to awake patients.

We conclude that, during continuous epidural anesthesia for surgery in children, reduction of the potential for systemic toxicity by the addition of epinephrine to lidocaine is limited because the reduction of the sum of the plasma concentrations of lidocaine and its active metabolite MEGX is small and limited to the initial phase of infusion. Further studies of the potential toxicity of epidural lidocaine for postoperative pain relief (i.e., a prolonged administration in awake patients) in pediatric patients would be of interest.

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