The effect of changes in arterial CO_2 tension on plasma lidocaine concentration

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The authors studied the effect of changes in arterial carbon dioxide tension on plasma lidocaine concentrations during a constant lidocaine infusion in eight healthy volunteers. With a $PaCO_2$ of 41.4 ± 0.9 mmHg (mean ± SE), total plasma lidocaine concentrations were 3.97 ± 0.20 $\mu g \cdot ml^{-1}$. There was no significant change associated with hypercarbia ($PaCO_2$ = 55.7 ± 1.5 mmHg, lidocaine = 3.93 ± 0.18 $\mu g \cdot ml^{-1}$) or hypocarbia ($PaCO_2$ = 19.5 ± 1.4 mmHg, lidocaine = 4.29 ± 0.25 $\mu g \cdot ml^{-1}$), despite the known effects of changes in CO_2 tension on hepatic blood flow and lidocaine protein binding. During hypercarbia, plasma lidocaine binding decreases while total plasma lidocaine remains essentially constant; therefore, increased CO_2 tensions could cause toxicity if total lidocaine concentrations were in the high therapeutic range (5 $\mu g \cdot ml^{-1}$). Four subjects experienced transient symptoms of mild lidocaine toxicity during acute increases in carbon dioxide tension.

Lidocaine, an amide local anaesthetic, is frequently infused in the operating room and intensive care units to control ventricular arrhythmias. Usual infusion rates range from 20 to 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Because patients receiving lidocaine infusions are frequently critically ill, their arterial CO_2 tensions could vary between 20 and 60 mmHg. We previously demonstrated *in vitro* that significant changes in lidocaine plasma protein binding occur with changes in CO_2 tension;[1] the effect of such changes on the kinetics of a lidocaine infusion *in vivo* has not been evaluated. We designed the present study to determine if the changes in lidocaine protein binding that occur with changes in CO_2 tension affect its blood level or clearance in the steady state.

Key words

ANAESTHETICS, LOCAL: lidocaine; CARBON DIOXIDE: hypercarbia, hypocarbia; PROTEIN: binding, lidocaine.

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Methods

Eight healthy physician volunteers, aged 25–34, gave written informed consent to participate in our study, which was approved by our institutional review committees. The volunteers took no medications for at least three days before the study, refrained from caffeine or alcohol-containing beverages for 12 hours and took nothing by mouth for eight hours before coming to the laboratory. After weighing the subjects, we inserted intravenous and radial artery catheters using local anaesthesia. We monitored arterial pressures and the electrocardiogram throughout the study and infused normal saline at a rate of 100 $ml \cdot hr^{-1}$ through the venous catheter.

After calibrating an Instrumentation Laboratories End TidIL 200® CO_2 analyzer with standard gas mixtures, we administered lidocaine 1.5 $mg \cdot kg^{-1}$ slowly IV over five minutes, while the subjects breathed 100 per cent oxygen. We then began a 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of lidocaine (2 $mg \cdot ml^{-1}$) in normal saline. This regimen has been shown to result in stable plasma lidocaine concentrations of 3.5 ± 0.2 $\mu g \cdot ml^{-1}$ within one hour.[2,3] One hour after the start of the infusion, while subjects breathed 100 per cent oxygen, we drew samples of arterial blood for lidocaine concentration and blood gas analysis. Subjects then breathed mixtures of CO_2 in O_2 from a breathing circuit with variable CO_2 absorption with continuous monitoring of $PETCO_2$. For odd numbered subjects, we adjusted the flow through the CO_2 absorber to maintain a constant $PETCO_2$ of 58 ± 2 mmHg; after maintaining this state for 20 minutes, we sampled arterial blood for gas tension and lidocaine analysis. Then, with maximum CO_2 absorption ($FICO_2$ = 0), these subjects voluntarily hyperventilated to a $PETCO_2$ of 16 ± 2 mmHg for 20 minutes, at which time we obtained a third set of blood samples for analysis. For even numbered subjects, we reversed the sequence of hyper- and hypocarbic determinations. After 20 min of spontaneous ventilation of room air, we drew a

TABLE Plasma lidocaine concentrations (mean ± SEM)

$PaCO_2$ (mmHg)	Plasma lidocaine concentration ($\mu g \cdot ml^{-1}$)
19.5 ± 1.4	4.29 ± 0.25
41.4 ± 0.9*	3.97 ± 0.20*
55.7 ± 1.5	3.93 ± 0.18

*Mean of values obtained during spontaneous ventilation at normocarbia, before and after alterations in CO_2 tension.

final set of blood samples. At the completion of the study, we discontinued the lidocaine infusion and observed the subjects for one hour in the laboratory.

We immediately placed the blood samples on ice, and within one hour measured their pH, PCO_2, and PO_2 using a Corning 168® pH/Blood Gas analyzer, which was calibrated with standard gas mixtures before each determination. We collected the samples for plasma lidocaine determination in heparinized test tubes, and after centrifugation at 5500 × g for 20 min, froze the plasma for subsequent analysis. The Emit-Cad® quantitative enzyme immunoassay (Syva, Palo Alto), determined the total concentration of lidocaine in our plasma samples. This assay is designed for quantitation of concentrations in the 1 to 12 $\mu g \cdot ml^{-1}$ range, with a coefficient of variation of less than five per cent in our laboratory.

There was a small but statistically significant ($p < 0.05$) increase in lidocaine concentration between the initial and final control states; in the analysis, therefore, we used their mean as our best estimate of normocarbic lidocaine concentrations. Two-way analysis of variance and power analysis determined the significance of differences between the eucarbic, hypercarbic, and hypocarbic states.[4] $P < 0.05$ indicated statistical significance.

Results

The values of arterial PCO_2 and plasma lidocaine concentration during normo-, hypo-, and hypercarbia are shown in the Table. Although plasma lidocaine concentrations during hypocarbia exceeded those during hypercarbia by 0.36 $\mu g \cdot ml^{-1}$, this difference was not statistically significant. Power analysis revealed a probability of 0.95 ($\beta < 0.05$) that we would have found a significant difference ($p < 0.05$) had changes in CO_2 tension altered plasma lidocaine concentration by more than 0.68 $\mu g \cdot ml^{-1}$. Alternatively, increasing our sample size from 8 to 12 would have only provided an 80 per cent chance of finding that the observed differences among our experimental phases were significant at the 0.05 level.

During the transition from low to high CO_2 tensions, four subjects noted tinnitus or circumoral numbness, similar to the sensations they experienced during the lidocaine bolus. In the two cases where we obtained blood samples, there was no associated increase in total plasma lidocaine concentration.

Discussion

The binding of drugs in plasma influences their pharmacokinetics and pharmacodynamics. Only that fraction of a drug that is not bound to plasma proteins is available to exert a pharmacologic effect by binding to receptor sites, to cause CNS toxicity by crossing the blood brain barrier, or to be metabolized.

On a theoretical basis, hypocarbia should decrease lidocaine metabolism compared with hypercarbic states via two mechanisms, both involving availability of lidocaine to the liver. Lidocaine metabolism is almost exclusively hepatic, consisting of dealkylation by hepatic mixed function oxidases to monoethylglycylxylidine and glycine xylidide.[5] Because lidocaine extraction by the liver is highly efficient, lidocaine clearance should approach hepatic blood flow.[6] Hepatic blood flow is, in turn, significantly affected by changes in CO_2 tension; Scholtholt and Shirashi demonstrated a 51 per cent decrease in canine hepatic blood flow when $PaCO_2$ changed from 60 to 21 mmHg.[7] A decrease in the free fraction of lidocaine also occurs with hypocarbia; according to our previous *in vitro* data, the free fraction of lidocaine (not bound to α-1 acid glycoprotein) should decrease from 45.8 to 31.0 per cent when PCO_2 decreases from 55.7 to 19.5 mmHg.[1] Thus, hypocarbia might be expected to decrease hepatic extraction, resulting in increased total lidocaine levels. The absence of a significant change in total lidocaine blood levels between hyper- and hypocarbic states suggests that hepatic lidocaine extraction is so efficient that it is unaffected by changes in protein binding or blood flow.

There are two possible explanations for our observation that acute increases in CO_2 tension caused symptoms of lidocaine toxicity. First, even though total plasma lidocaine concentrations remained unchanged, there may have been an acute increase in the fraction of unbound lidocaine available to cross the blood-brain barrier (*vide supra*).[1] This mechanism could also explain Englesson's observation of increased lidocaine toxicity in hypercarbic cats.[8] However, our plasma samples could not be fractionated anaerobically; therefore their gas tensions were altered, and the extent of *in vivo* lidocaine binding could not be determined. Secondly, there may have been a selective increase in lidocaine delivery to inhibitory centres of the brain as CO_2 tensions were rising. This is consistent with the finding that early lidocaine toxicity is related to differential suppression of inhibitory and excitatory centres in the CNS.[9]

Because carbon dioxide readily crosses biological membranes, equilibration of CO_2 tensions is virtually complete within nine minutes (three half-times) of achieving a new end-tidal CO_2 tension.[10] To be conservative, we allowed our subjects to equilibrate for 20 minutes – the maximum time that they could comfortably tolerate the required degrees of hyper- or hypocarbia. (Engelsson also allowed 20 minutes after achieving the desired CO_2 tension before beginning measurements.)

In conclusion, we have found that acute changes in CO_2 tension do not cause clinically significant changes in total plasma lidocaine concentrations during constant lidocaine infusion. Since plasma lidocaine binding decreases during hypercarbia, increased CO_2 tensions could cause lidocaine toxicity, especially if total lidocaine concentrations are in the high therapeutic range ($5\ \mu g \cdot ml^{-1}$).[11] In our subjects, symptoms of toxicity occurred when CO_2 tension increased acutely from hypo- to hypercarbic levels.

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Résumé

Les auteurs ont étudié, chez huit volontaires en santé, l'effet des changements de la pression du gaz carbonique artériel sur les concentrations plasmatiques de lidocaïne, durant une infusion constante de lidocaïne. Avec une $PaCO_2$ de 41.4 ± 0.9 mmHg ($\bar{x} \pm SE$), les concentrations plasmatiques totales de lidocaïne étaient de $3.97 \pm 0.20\ \mu g \cdot ml^{-1}$. Il n'y avait pas de changement significatif associé à l'hypercarbie ($PaCO_2 = 55.7 \pm 1.5$ mmHg, lidocaïne $= 3.93 \pm 0.18\ \mu g \cdot ml^{-1}$) ou à l'hypocarbie ($PaCO_2 = 19.5 \pm 1.4$ mmHg, lidocaïne $= 4.29 \pm 0.25\ \mu g \cdot ml^{-1}$), malgré les effets connus que produisent les changements de pression du CO_2 sur le débit sanguin hépatique et sur la liaison protéinique de la lidocaïne. Pendant l'hypercarbie, la liaison plasmatique de la lidocaïne diminue tandis que la lidocaïne plasmatique totale demeure essentiellement constante; donc, il se pourrait qu'une augmentation des pressions de CO_2 produisent une toxicité si des concentrations totales de lidocaïne se trouvaient dans l'échelle thérapeutique supérieure ($5\ \mu g \cdot ml^{-1}$). Quatre sujets ont ressenti de symptômes transitoires de toxicité légère à la lidocaïne, pendant des augmentations aiguës dans la pression du gaz carbonique.