THE ROLE OF ENDOTHELIUM-DERIVED RELAXING FACTOR IN THE ANALGESIC EFFECT OF LIDOCAINE

Hülya ÇELEBİ , M.D., Sevim ERCAN*, M.D., Füsun BOZKIRLI, M.D., Sami EREN*, M.D.

Gazi University, Faculty of Medicine, Departments of Anesthesiology and Pharmacology*, Ankara, Turkey
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SUMMARY : *The purpose of this study is to evaluate the effect of lidocaine, an amid group anesthetic agent, on endothelium-derived relaxing factor (EDRF).*

For this study, adult rabbit aorta has been used. The response of intact strips and denuded strips to acetylcholine before and after the lidocaine has been added to the media has been meausered separately.

The same procedure has been carried out with aspirin, with or without the presence of procaine and prilocaine.

Statistically analyzed by Student's t test, addition of lidocaine to the medium caused a significant increase in the relaxation response to acetylcholine in intact strips but not in the denuded strips.

Neither procaine nor prilocaine change the relaxation induced by acetylcholine.

In conclusion, long lasting analgesic effect of high dosage iv lidocaine has been attributed to the release of EDRF and analgesic effect of factor nitric oxide (NO) which is a kind of EDRF.

Key Words : *EDRF, Lidocaine.*

INTRODUCTION

Lidocaine, is one of the most widely used local anesthetic. The anesthetic role of lidocaine has been mainly limited to direct application to nervous tissue, although there have been reports of pain relief after systemic administration (5). It has been considered unlikely that analgesia after systemic administration is due to a direct effect on the excitability of peripheral nerves since it has been shown that neither afferent receptors nor peripheral nerve fibers are significantly blocked by non-toxic doses of lidocaine (9). A possible explanation for the analgesic effect of systemically administered local anesthetics is their central anticonvulsant property (1).

Endothelial cells also produce a vascular smooth muscle relaxant, known as endothelium-derived relaxing factor (EDRF) (3). Although the chemical nature of EDRF is still unknown, some studies indicate that one of the EDRF might be nitric oxide (NO) (7). Recently it has been shown that NO has an analgesic effect and therefore it is one of the analgesic mediator of the organism (4).

It seemed interesting to us to investigate whether lidocaine had an effect on the release of EDRF from vascular endothelium.

MATERIAL AND METHOD

Aortae were taken from adult rabbits of both sexes (1.5-2.5 kg) anesthetized with sodium pentobarbital (30 mg/kg) dissected free of fat and surrounding tissues and the strips (4 mm width and 2 cm length) were prepared. The endothelium was either left intact or removed by rubber or wooden stick. The strips were then suspended in a jacketed organ bath and isometric contractions were recorded on a GRASS POLYGRAPH (Model 7D) by force displacement transducer (FT-03) under 1.0 g initial tention. Submaximal contication of the strips (% 70 of maximum) was elicited by phenylephrine (10^{-7} M) and the concentration-response curve of acetylcholine were determined in both endothelium intact and denuded strips before and after adding lidocaine to the medium. Experiments were also repeated in the presence of aspirin added to the medium containing lidocaine in order to eliminate the possible interaction of cyclo-oxygenase products of arachidenic acid in vascular wall. Aortic segments were allowed to contact with lidocaine and aspirin for 15 minutes, then the tests were repeated. In another series of experiments, after control measurements on the aortic strips, procaine and prilocaine were added to the bath and the responses to acetylcholine were repeated.

The bathing medium was Krebs solution at the following composition (mM) : NaCl 112; KCl 5; $NaHCO_3$ 25; NaH_2PO_4 1; $CaCl_2$ 2.5; $MgCl_2$ 0.5; dextrose 11.5. Krebs solution was continuously gassed with 95 % O_2 and 5 % CO_2 mixture and warmed at 37°C.

The results were statistically analyzed by using Student's t test and presented as mean ± SEM.

RESULTS

Acetylcholine produced a concentration-dependent relaxation in endothelium-intact rabbit aortic strips precontracted with phenylephrine. This relaxation was completely abolished in endothelium-denuded strips.

Addition of lidocaine to the incubation medium at the concentration of 10^{-6} M for 15 minutes caused a significant increase in the relaxation response to acetylcholine (Fig 1). Aspirin did not change these responses.

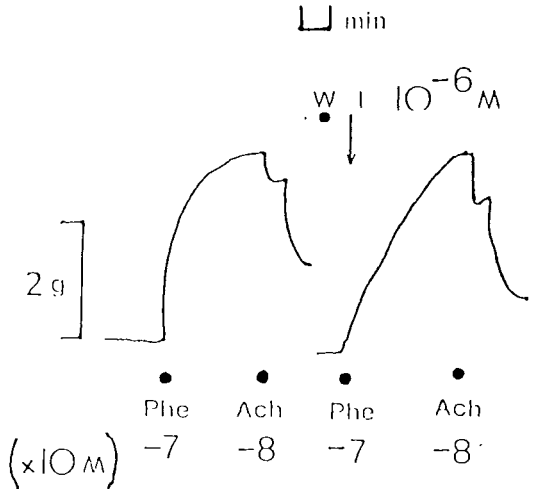

Fig - 1 : Recorder tracing showing the effect of lidocaine (L) on acetylcholine (Ach)-induced relaxation in phenylephrine (Phe) precontracted aortic strip. A significant increase was observed to Ach in presence of L.

In endothelium denuded strips, however, the response to acetylcholine was completely abolished and this unresponsiveness was still present in lidocaine-pretreated strips. Contractile responses to phenylephrine were slightly increased by 10 % in endothelium denuded strips.

Addition of procaine and prilocaine to the medium of precontracted endothelium intact aortic strips, the relaxation induced by acetylcholine did not change.

The results are summarized at Table 1.

	Control	In presence of lidocaine 10^{-6}M
Acetylcholine 10^{-8} M	a) 13.4±1.6 (8)	b) 32.6±3.4 (8)
Acetylcholine 2x 10^{-8} M	c) 53±3.6 (8)	d) 70.4±4.8 (8)

* a-b $p < 0.001$
* c-d $p < 0.05$
(8) number of experiments

Table 1 : Percent of maximum relaxation induced by acetylcholine in aortic strips precontracted with phenylephrine (10^{-7} M). The potentiation in the relaxing responses of acetylcholine by lidocaine in endothelium-intact strips (mean±SEM).

DISCUSSION

The data presented in this study indicate that lidocaine enhanced the relaxing effect of acetylcholine in the isolated rabbit aortic strips. The potentiation by lidocaine of the relaxing effect of acetylcholine apparently originated from the vascular endothelium since acetylcholine responses completely disappeared in endothelium-denuded aortic strips. It is well known that vascular endothelial cells release the cyclooxigenase derivative of arachidonic acid, PGI_2, which exerts and inhibitory influence on vascular smooth muscle (8). On the other hand, it has been shown that lidocaine causes the release of endogenous PGI_2 from heart (6).

Thus one can assume that the potentiation by lidocaine of the relaxing effect of acetylcholine in the aortic segment may be mediated through endogenous PGI_2. But this is unlikely since the enhancement by lidocaine of the relaxing effect of acetylcholine was altered by cyclooxigenase inhibitor, aspirin and it has previously been shown PGI_2 and its stable analogue, iloprost, failed to produced a relaxing effect in precontracted strips (2). Another possibility is the increased release of EDRF by acetylcholine in presence of lidocaine.

Although the chemical structure of EDRF is unknown, some studies indicate that one of the EDRF might be NO. Since NO has analgesic effect and lidocaine causes the release of EDRF, it can be assumed that the long-lasting and more extensive analgesia obtained by lidocaine might be due to its releasing effect of EDRF.

Correspondence to : Dr.Hülya ÇELEBİ
Gazi Üniversitesi Tıp Fakültesi
Anesteziyoloji ve Reanimasyon
Anabilim Dalı
Beşevler
06500 ANKARA - TÜRKİYE
Phone : 312 - 214 10 00 / 6844

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