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TITLE: A COMPARISON OF TWO EPIDURAL ALPHA-2-AGONISTS, GUANFACINE AND CLONIDINE, IN REGARD TO DURATION OF ANTINOCICEPTION, AND VENTILATORY AND HEMODYNAMIC EFFECTS

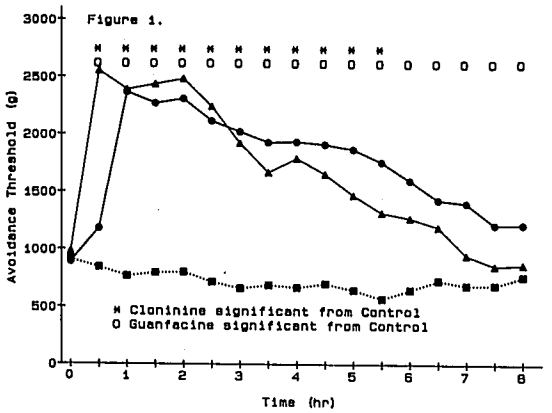
AUTHORS: B.D. Smith, M.D., L.J. Baudendistel, M.D., Ph.D., J.J. Gibbons, M.D., J.F. Schweiss, M.D.

AFFILIATION: Department of Anesthesiology, St. Louis University School of Medicine, St. Louis, MO

Epidural clonidine(C) produces analgesia in humans with acute and chronic pain.[1,2] However, it's use appears to be limited because of short lasting analgesia, hemodynamic depression,[1] sedation and respiratory depression.[3] A comparison of intrathecal guanfacine(G) and C has shown G to have longer duration of action.[4] This study compares these two agents epidurally.

Approval was obtained from the Animal Care Committee. 5 Nubian goats, 45-55 kg, were instrumented with pulmonary and carotid artery and epidural catheters. Each goat received epidural injections of G 5 mg in 10 ml normal saline(NS), C 750 mcg in 10 ml NS, and a 10 ml NS control on 3 separate days, in an open label fashion. Antinociception [avoidance threshold, (AT)] was tested by using a point pressure device[5] attached to the goats hind limb in which force was gradually applied until limb withdrawal. AT, blood pressure (BP), heart rate (HR), cardiac output (CO), wedge pressure (PCWP), central venous pressure (CVP), and arterial and venous blood gases were measured at baseline and then every 30 minutes after epidural injection for 8 hrs. Statistical significance ($p < 0.05$) was determined with an analysis of variance with repeated measure design.

G and C produced similar increases in the AT, however, G lasted significantly longer than C (G-8 hrs. vs. C-5.5 hrs)(Fig.1). Increases in pCO_2 were greater and much more frequent in the C group. There were no marked differences between G and C in regard to decreases in HR, BP, CO, PCWP, CVP, or venous admixture during periods of increased AT. Epidural pretreatment with the alpha-2-antagonist idazoxan 30 min prior to epidural guanfacine prevented the increase in AT.



To our knowledge this is the first study to document the antinociceptive effects of epidural guanfacine. Because of longer duration of antinociception and less respiratory depression, epidural guanfacine may be a superior drug for postoperative analgesia and chronic pain syndromes.

References:

1. Eisenach, JC, et al., Anesthesiol 71:640-646, 1989.
2. Eisenach, JC, et al., Anesthesiol 71:647-652, 1989.
3. Penon, C, et al., Anesthesiol 71:A649, 1989.
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TITLE: EFFECTS OF CLONIDINE ON C-FIBER ACTION POTENTIAL, INTERACTION WITH LIDOCAINE

AUTHORS: D. Gaumann, M.D.; P. Brunet, Ph.D.*; P. Jirounek, Ph.D.*; D. Morel, M.D.; B. Volet*

AFFILIATION: Dept. Anesthesiology, Dept. Pharmacology*, Univ. Geneva, 1211 Geneva, Switzerland

Administration of clonidine together with lidocaine for peripheral nerve block significantly prolongs the local anesthetic (LA) effect, possibly by a direct action on the nerve (1, 2). The present study examined the effect of clonidine and its interaction with lidocaine on C-fiber action potential in the vagal nerve preparation of the rabbit. Rabbit vagus nerves were desheathed and mounted in a sucrose-gap apparatus. The stimulation chamber was either perfused with Locke solution or with $5x10^{-4}$ M lidocaine. Various concentrations of clonidine ($5x10^{-8}$ M to $5x10^{-3}$ M) were either added to the Locke or lidocaine solution. The preparation was stimulated by single supramaximal square wave pulses of 0.4 msec. The compound action potential (AP) of the C-fiber component was analyzed with regard to area, peak amplitude and time interval from stimulation to peak.

Clonidine added to Locke solution, at concentrations from $5x10^{-8}$ M to $5x10^{-5}$ M, had no effect on AP, while concentrations of $5x10^{-4}$ M and $5x10^{-3}$ M significantly decreased AP area (Table 1). When clonidine was added to a lidocaine solution ($5x10^{-4}$ M), a low concentration of $5x10^{-7}$ M significantly decreased AP area. Clonidine at concentrations of $5x10^{-4}$ M and $5x10^{-3}$ M, in the presence of lidocaine, led to a significant decrease in AP area as compared to clonidine treatment alone (Table 1). Local anesthetic effects of clonidine ($5x10^{-4}$ M) were compared to lidocaine ($5x10^{-4}$ M, Table 2). There was no difference between the two drugs with regard to their effects on AP area. Clonidine evoked a less pronounced decrease in AP amplitude and delay of AP peak than lidocaine.

Clonidine alone exhibits LA effects above concentrations of $5x10^{-5}$ M. LA effects of clonidine ($5x10^{-4}$ M) do not differ from those of lidocaine ($5x10^{-4}$ M) with regard to the probability of fiber blockade, as indicated by AP area. Clonidine, however, slows fiber conduction less than lidocaine, resulting in a higher peak AP. In the presence of lidocaine, clonidine has synergistic local anesthetic effects at concentrations of $5x10^{-7}$ M and above $5x10^{-5}$ M. The synergistic effect of the low concentration of clonidine ($5x10^{-7}$ M) with lidocaine ($5x10^{-4}$ M), might explain the clinical observation that clondine prolongs the action of lidocaine in peripheral nerve block, where it is administered at approximately 1000-fold lower concentrations than lidocaine (1, 2).

References: 1) Anesthesiology 71: A644, 1989
2) Anesthesiology 73: A821, 1990

Table 1: Effects of clonidine on area of action potential (AP) in the presence of Locke or lidocaine solution

Pretreatment	Concentration of Clonidine					
	$5x10^{-8}$ M	$5x10^{-7}$ M	$5x10^{-6}$ M	$5x10^{-5}$ M	$5x10^{-4}$ M	$5x10^{-3}$ M
Locke	96.9±3.6 (n=5)	103±3.0 (n=5)	97.0±2.3 (n=6)	88.5±5.9 (n=7)	83.1±3.4† (n=11)	71.9±3.2† (n=5)
Lidocaine ($5x10^{-4}$M)	98.1±3.5 (n=4)	86.1±5.6*† (n=5)	95.5±4.9 (n=5)	89.0±9.7 (n=5)	63.2±8.8*† (n=4)	17.5±4.8*† (n=4)

Effects of clonidine expressed as % of pretreatment value (mean ± SE). *p<0.05 beween group comparison, †p<0.05 within group comparison to pretreatment value.

Table 2: Effects of clonidine or lidocaine at equimolar concentration ($5x10^{-4}$ M) on action potential (AP)

Drug	AP Peak Amplitude (%)	AP Area (%)	AP Peak Delay (msec)
Lidocaine (n=8)	41.3 ± 3.1†	75.8 ± 9.4	8.4 ± 0.9†
Clonidine (n=5)	58.5 ± 2.4*†	82.2 ± 5.9	2.6 ± 0.4*†

Drug effects as % or difference (mean ± SE) of control value with Locke solution. *p< 0.05 between group comparison. †p<0.05 within group comparison to control value.