

Propranolol Reduces Bupivacaine Clearance

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Propranolol reduces the clearance of lidocaine by both reducing hepatic blood flow and inhibiting lidocaine metabolism. The authors investigated the possibility that propranolol reduces the clearance of bupivacaine as well. Bupivacaine, 30-50 mg, was administered intravenously to six normal human volunteers, over 10-15 min on two occasions, at least 2 weeks apart. Propranolol, 40 mg orally every 6 h, was used on one occasion, beginning 24 h prior to the bupivacaine administration. The sequence of the sessions was randomized. Twenty-two venous blood samples were obtained over 36 h in order to determine bupivacaine clearance, terminal elimination rate constant, and volume of distribution. All subjects experienced mild CNS toxicity, consisting of tinnitus, facial tingling, or subtle visual disturbances, associated with peak venous plasma concentrations of 0.81 to 2.7 $\mu\text{g/ml}$. Mean bupivacaine clearance was 0.33 ± 0.12 l/min for the control session and 0.21 ± 0.12 l/min during propranolol use, a significant 35% reduction ($P < 0.01$). The terminal elimination rate constant (beta) was 0.27 ± 0.16 h⁻¹ for the control session and 0.14 ± 0.069 h⁻¹ with propranolol ($P < 0.05$); terminal elimination half-lives were 2.6 and 4.9 h, respectively. Volume of distribution was unchanged. Because bupivacaine clearance should be relatively insensitive to hepatic perfusion, it appeared that propranolol caused a substantial inhibition of bupivacaine metabolism at the level of the hepatocyte. These data suggest that concomitant use of propranolol could result in the accumulation of a toxic concentration of bupivacaine. (Key words: Anesthetics, local: bupivacaine; toxicity. Interactions, drug: bupivacaine; propranolol. Pharmacokinetics. Pharmacology: propranolol.)

PROPRANOLOL REDUCES clearance of a variety of drugs by at least two mechanisms. First, propranolol reduces hepatic blood flow, thereby limiting the delivery of drugs to the organ that is, for many drugs, the major site of drug metabolism. The amount of reduction in hepatic blood flow is variable, but appears to be no greater than 25%.¹⁻⁴ Some drugs, such as lidocaine, are so extensively metabolized that virtually all of the drug entering the hepatic circulation is cleared; reduction of hepatic blood flow causes a directly proportional reduction in the clearance of these drugs.¹ Second, propranolol interferes with drug metabolism within the hepatocyte.⁵⁻¹¹ Lidocaine clearance by rat liver is reduced in the presence of propranolol even when hepatic perfusion is maintained at a constant level by artificial means, demonstrating inhibition of drug metabolism within the liver.⁶ Also, isolated rat

and human liver microsomes are inhibited by propranolol, as well as several other beta adrenergic blocking drugs.⁹⁻¹¹ In humans, propranolol causes lidocaine clearance to be reduced to a much greater degree (46%) than would be predicted from a maximum 25% reduction in hepatic blood flow, implying that drug metabolism with the liver has been affected.⁵

Whether propranolol reduces the clearance of amide local anesthetic agents other than lidocaine is not known. We have examined the effect of propranolol on bupivacaine clearance for several reasons. First, there is considerable concern that bupivacaine may be an unusually cardiotoxic local anesthetic.¹² We have shown previously that reduced lidocaine clearance may result in the accumulation of toxic concentrations of lidocaine during serial reinjection of a continuous epidural block. § If bupivacaine clearance is similarly reduced, patients treated with propranolol for hypertension or coronary disease could be at increased risk for bupivacaine toxicity during continuous epidural block. However, bupivacaine clearance is relatively insensitive to changes in hepatic blood flow (extraction ratio approximately 0.2) compared with lidocaine (extraction ratio > 0.9).¹³ Therefore a substantial reduction in bupivacaine clearance would support the hypothesis that propranolol inhibits amide local anesthetic metabolism within the hepatocyte.

Methods

Six healthy volunteers, five men and one woman, were studied after obtaining institutionally approved informed consent. They were 26-37 yr of age and weighed 50-86 kg. Fifty milligrams of bupivacaine was given intravenously over 10 min on two occasions, once without propranolol, and once during concomitant use of propranolol. Propranolol tablets, 40 mg, were taken every 6 h starting 24 h prior to bupivacaine administration and continued until blood sampling was complete. This propranolol dosing schedule has been shown to reduce lidocaine clearance by 46% and to result in propranolol blood concentrations in the therapeutic range.⁵ The sequence was randomized, and the sessions were separated by at least two weeks. The ECG was monitored, and oxygen was administered during the infusion. The dose of bupivacaine was reduced to 30 mg in the female subject,

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who weighed 50 kg, due to concern for possible toxicity. On two occasions bupivacaine infusion was stopped temporarily due to mild CNS symptoms (tinnitus, facial tingling), but infusions were completed by 15 min. Venous blood samples were drawn from a catheter in the contralateral arm at 0 (the time at the end of bupivacaine infusion), 5, 10, 15, 20, 30, 45, 60, 90, and 120 min, then hourly at 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 30, and 36 h.

Bupivacaine plasma concentration was determined by a gas-liquid chromatography (GLC) assay in routine use in our laboratory.¹⁴ The coefficient of variation is about 5%. The terminal elimination rate constant (β) was determined by fitting the data to a two-compartment model with the aid of a program for microcomputers.¹⁵ Area under the curve (AUC) was determined by the trapezoidal rule and by extrapolation with the terminal elimination rate constant. Clearance (Cl) was calculated as dose/AUC (area under the concentration vs. time curve). Volume of distribution ($V_{d_{area}}$) was calculated as Cl/β . Statistical comparisons were performed with the Wilcoxon rank sum test. Variation was expressed as the standard deviation of the mean.

Results

Bupivacaine infusion was well tolerated, but mild, transient symptoms of local anesthetic CNS toxicity occurred during or just after completion of infusion in all subjects. Symptoms consisted of tinnitus, facial tingling, or subtle visual disturbances. No ECG abnormalities were observed. Drug infusion was lengthened from 10 to 15 min on two occasions in order to minimize the intensity and duration of symptoms. Peak venous serum concentrations measured at the end of the infusions were between 0.81 and 2.7 $\mu\text{g}/\text{ml}$ during the control session and between 1.1 and 2.6 $\mu\text{g}/\text{ml}$ during concomitant use of propranolol. Bupivacaine concentrations for a typical subject are shown in figure 1. For the entire group, mean bupivacaine clearance was 0.33 ± 0.12 l/min for the control session and 0.21 ± 0.12 l/min during propranolol use, a significant 35% reduction ($P < 0.01$). The reduction in clearance occurred in all subjects (fig. 2). The terminal elimination rate constant (β) was 0.27 ± 0.16 h^{-1} for the control session and 0.14 ± 0.069 with propranolol ($P < 0.05$); half-lives were 2.6 and 4.9 h, respectively. $V_{d_{area}}$ was not significantly altered (89.6 ± 51.1 l control vs. 94.7 ± 26.2 l with propranolol).

Discussion

Bupivacaine clearance was significantly reduced in subjects taking propranolol. Moreover, bupivacaine is a low-extraction drug (extraction ratio about 0.2) and clearance should be relatively insensitive to hepatic perfusion.¹³ Therefore it would appear that the propranolol resulted in a reduction in clearance by a substantial in-

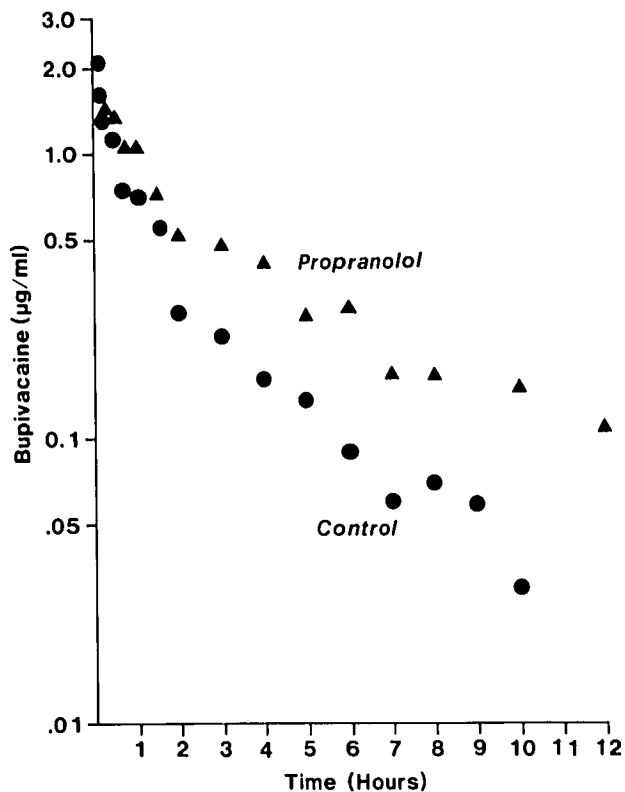


FIG. 1. Plasma bupivacaine concentrations from a typical subject. Time 0, represents the end of the 10-min bupivacaine infusion. Circles are from the control session; triangles are from the propranolol session.

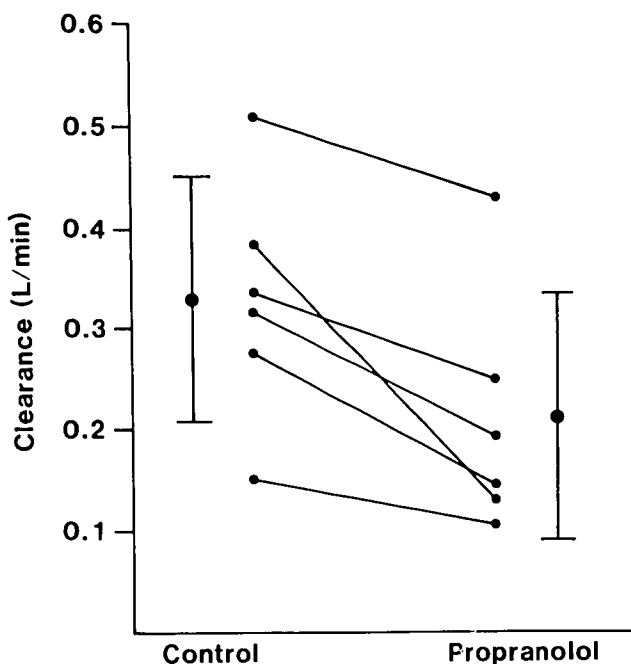


FIG. 2. Bupivacaine clearance during control and propranolol sessions are shown for each subject. Clearance was lower with propranolol in all subjects. Mean clearances and standard deviations are also shown. Mean clearance declined 35% with propranolol ($P < 0.01$).

hibition of bupivacaine metabolism at the level of the hepatocyte. Conrad *et al.* found a 46% reduction in lidocaine clearance during a schedule of propranolol administration identical to ours.⁵ Because hepatic blood flow is maximally reduced 25% by propranolol,⁴ they concluded that propranolol probably affects this change in clearance both by reducing liver blood flow and by inhibition of drug metabolism.

Bupivacaine is highly bound to plasma protein (over 90%), with alpha-1-acid glycoprotein (AAG) the most important binding protein.¹⁶ Because clearance of drugs with low-extraction ratios is inversely related to plasma protein binding,¹³ an increase in bupivacaine binding caused by propranolol could explain a reduction in clearance. However, AAG levels have been shown to be unaffected by propranolol.⁵ Therefore, a change in binding is not a likely explanation for the change in clearance.

Whether beta adrenergic blocking drugs other than propranolol inhibit bupivacaine elimination is unknown. However, metoprolol has been shown to reduce lidocaine clearance in humans.⁵ Also, a linear correlation has been found between the degree of inhibition of lidocaine metabolism by rat liver microsomes and the lipid solubility of 13 beta blockers.⁹⁻¹¹ Presumably, bupivacaine as well as lidocaine would be affected by a variety of beta adrenergic blocking drugs because the metabolic pathways are similar. The clearance of amide local anesthetics other than lidocaine and bupivacaine is also likely impaired. Further studies are required to delineate those amide local anesthetics and those beta adrenergic blocking drugs in addition to propranolol that result in significant interactions in humans. It is possible that in some patients (particularly those with clearance or volume of distribution values less than the mean), concomitant use of propranolol might contribute to clinical local anesthetic toxicity. We suggest that caution be exercised in the administration of multiple doses of bupivacaine or lidocaine to patients receiving propranolol.

References

1. Branch RA, Shand DG, Wilkinson GR, Nies AS: The reduction of lidocaine clearance by dl-propranolol: An example of hemodynamic drug interaction. *J Pharmacol Exp Ther* 184:515-519, 1973
2. Hansson L, Zweifler AJ, Julius S, Hunyor SN: Hemodynamic effects of acute and prolonged beta-adrenergic blockade in essential hypertension. *Acta Med Scand* 196:27-34, 1974
3. Bonelli J, Waldhausl W, Magometschnigg D, Schwarzmeier J, Korn A, Hitzberger G: Effect of exercise and or prolonged oral administration of propranolol on haemodynamic variables, plasma renin concentration, plasma aldosterone and c-AMP. *Eur J Clin Invest* 7:337-343, 1977
4. Weiss YA, Safar ME, Lehner JP, Levernson JA, Simon A, Alexandre JM: Propranolol clearance, an estimation of hepatic blood flow in man. *Br J Clin Pharmacol* 5:457-460, 1978
5. Conrad KA, Beyers JM, Finley PR, Burnham L: Lidocaine elimination: Effects of metoprolol and of propranolol. *Clin Pharmacol Ther* 33:133-138, 1983
6. Chen C, Bu CT, Cohen SD: Lidocaine uptake in isolated rat hepatocytes and effects of dl-propranolol. *Toxicol Appl Pharmacol* 55:162-168, 1980
7. Conrad KA, Nyman DW: Effects of metoprolol and propranolol on theophylline elimination. *Clin Pharmacol Ther* 28:463-467, 1980
8. Daneshmend TK, Roberts CJC: The short term effects of propranolol, atenolol and labetalol on antipyrine kinetics in normal subject. *Br J Clin Pharmacol* 13:817-820, 1982
9. Deacon CS, Lennard MS, Bax NDS, Woods HF, Tucker GT: Inhibition of oxidative drug metabolism by β -adrenoceptor antagonists is related to their lipid solubility. *Br J Clin Pharmacol* 12:429-431, 1981
10. Bax NDS, Lennard MS, Al-Asady S, Deacon CS, Tucker GT, Woods HF: Inhibition of drug metabolism by β -adrenoceptor antagonists. *Drugs* 25(Suppl 2):121-126, 1983
11. Tucker GT, Bax NDS, Lennard MS, Al-Asady S, Bharaj HS, Woods HF: Effects of β -adrenoceptor antagonists on the pharmacokinetics of lidocaine. *Br J Clin Pharmacol* 17:215-285, 1984
12. Marx GF: Cardiotoxicity of local anesthetics—the plot thickens. *ANESTHESIOLOGY* 60:3-5, 1984
13. Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. *Clin Pharmacol Ther* 18:377-390, 1975
14. Mather LE, Tucker GT: Meperidine and other basic drugs: General method for their determination in plasma. *J Pharm Sci* 63:206-207, 1974
15. Yamaoka K, Tanigawara Y, Nakagawa T, Uno T: A pharmacokinetic analysis program (multi) for microcomputer. *J Pharmacobiodyn* 4:870-885, 1981
16. Denson DD, Thompson G, Myers JA: Alpha₁-acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther* 35:409-415, 1984