

measurement of inhibition of cervical-sympathetic nerve action potential amplitude in the rat (Nickander, R., J. Pharm. & Exper. Ther., 200:245-253, 1977). Dibucaine was the most potent local anesthetic tested, while lidocaine was the least potent. Norpropoxyphene was more potent than propoxyphene, and both were more potent than cocaine in this system.

Compounds possessing local anesthetic activity also modify cardiac conduction. Since electrocardiographic changes have been reported in some cases of propoxyphene overdosage in humans, the possibility arises that the local anesthetic effect of norpropoxyphene (and propoxyphene) might contribute to the toxicity or lethality of propoxyphene overdose, by a deleterious effect on cardiac conducting tissue.

The effects of propoxyphene and of norpropoxyphene on cardiac conduction have been studied *in vivo* and *in vitro* (Holland and Steinberg, Toxicol. & Appl. Pharm., 47:161-171, 1979). Propoxyphene and norpropoxyphene, 10^{-6} to 10^{-4} molar, (0.34-34 $\mu\text{g/ml}$) decreased V_{max} ,¹ action potential duration, and cellular refractoriness of isolated canine Purkinje fibers *in vitro*. Norpropoxyphene was more potent with respect to reduction of V_{max} , while the shortening of the action potential duration (at 95% repolarization) was similar for both propoxyphene and norpropoxyphene. The decrease in the effective refractory period by either compound was approximately equivalent, and thus the ratio of effective refractory period to action potential duration was essentially unaltered by either compound.

Both propoxyphene and norpropoxyphene have negative inotropic and chronotropic effects on guinea pig atria *in vitro*. Atrial rate of contraction (ED_{50}) was slowed 50 percent by propoxyphene $3.5/1.3 \times 10^{-5}\text{M}$ (11.7/4 $\mu\text{g/ml}$) and by norpropoxyphene $5.6/1.6 \times 10^{-5}\text{M}$ (18.7/5.3 $\mu\text{g/ml}$). Atrial tension development was decreased by 50% in the presence of $1.40/0.01 \times 10^{-4}$ (46.7/0.3 $\mu\text{g/ml}$) propoxyphene or $7.9/2.0 \times 10^{-5}$ (26.3/6.7 $\mu\text{g/ml}$) norpropoxyphene. Thus, propoxyphene had a slightly greater negative chronotropic effect and a lesser negative inotropic effects.

Amsterdam et al. (Clin. Res., 25:A204, 1977) observed a decrease in tension developed *in vitro* by cat right ventricular papillary muscle with either propoxyphene or norpropoxyphene at 10^{-4} molar (34 $\mu\text{g/ml}$). After washout, tension was promptly restored with isoproterenol. Neither propoxyphene nor norpropoxyphene altered the time to peak tension of the contracting muscle.

Lund-Jacobson (Acta Pharmacol. & Toxicol., 42:171178, 1978) compared the effects of infusions of equimolar doses of propoxyphene and norpropoxyphene on the ECG in conscious rabbits. Prolongation of QRS, intermitted A-V block and ventricular extrasystoles were observed during both propoxyphene and norpropoxyphene infusion. The ECG changes were determined to be independent of respiratory depression and were viewed as resembling those seen in quinidine intoxication. The QRS prolongation correlated with plasma concentrations of propoxyphene and norpropoxyphene, although direct time comparisons were not made.

The effects of propoxyphene and norpropoxyphene infusions 0.72 to 7.2 $\mu\text{g/kg}$ were studied in unanesthetized dogs. (Signs of central nervous system toxicity appeared in all dogs receiving the 7.2 $\mu\text{g/kg}$ infusion of propoxyphene.) The effects of the 7.2 $\mu\text{g/kg}$ doses of propoxyphene and norpropoxyphene on the P-R interval (atrioventricular conduction time) were similar, i.e., it was increased about 35 milliseconds. Plasma propoxyphene concentrations during the infusion of 7.2 $\mu\text{g/kg}$ were 3.5/0.4 $\mu\text{g/ml}$. Plasma concentrations of norpropoxyphene were one-fourth those of propoxyphene.

When the lower doses of propoxyphene were infused, heart rate diminished, while the 7.2 $\mu\text{g/kg}$ dose increased the heart rate about 25 beats per minute. Norpropoxyphene at the high dose increased heart rate less markedly, that is, about 16 beats per minute. The QT_c ,² increased slightly with increasing doses of propoxyphene, and the QRS duration was not significantly increased.

His bundle conduction, A-H and H-V intervals, were prolonged by both propoxyphene and norpropoxyphene. Norpropoxyphene was significantly more potent in prolonging H-V intervals than propoxyphene.

If the infusion of either propoxyphene or norpropoxyphene was increased beyond 7.3 $\mu\text{g/kg}$ to a total of 16.3 $\mu\text{g/kg}$, second degree A-V nodal block usually appeared.

¹ Maximum rate of rise of the action potential.

² $\text{QT}_c = \text{QT interval divided by (R-R interval)}$.