TENNANT STUDY

Propoxyphene napsylate has been evaluated by Tennant (J. Natl. Med. Assn., *66*:23–27, 1974; J.A.M.A., *232*:1019–1022, 1975) for heroin detoxification and maintenance. Under double-blind conditions, 29 adults were admitted to a 180-day maintenance program. About ¼ of the patients remained in the study more than 90 days; a few remained for as long as two years. The maximum daily dose of propoxyphene napsylate was 1200 mg, starting with 400 mg per day. Patients who received a single dose of 600 mg reported short-term dysphoria, but otherwise no serious toxic effects were noted. Electrocardiograms, chest X-ray, and electroencephalograms were evaluated before and at the third and sixth month of the study. The ECG tracings were reviewed by a cardiologist and no changes were observed, nor were changes observed in the other examinations.

ECG MONITORING

The electrocardiographic effects of propoxyphene were observed in two male volunteers, ages 56 and 60, admitted for study to the Lilly Clinic, Wishard Memorial Hospital, Indianapolis. The twenty-four-hour ECG was recorded for each subject, using Holter monitors. After a six-day control period, a single 300 mg dose of propoxyphene napsylate was given, and blood samples were obtained at various intervals over the next 48 hours. Maximum concentrations of propoxyphene and norpropoxyphene observed in these two subjects were 0.25 and 0.37 (propoxyphene) and 1.1 and 1.4 (norpropoxyphene) micrograms/ml, respectively. From day 9 through day 15 the subjects received propoxyphene napsylate 10 mg every 4 hours (i.e., 600 mg/day). Day 16 through day 25 served as the posttreatment control period. Neither subject manifested any change in P–R, QRS, or QT_c during the period of propoxyphene administration, in comparison with pretreatment or posttreatment control tracings. Ventricular premature beats were observed slightly more frequently in one subject during treatment, while a slight decrease in ectopy was noted in the other. Neither change is significant.

GENERAL COMMENT

Bigeminal cardiac rhythm has been described relatively frequently in cases of propoxyphene overdose, and it is of some interest to note that in the case reported by McCarthy and Keenan "a bigeminal rhythm developed but it responded well to intravenously administered procaine amide hydrochloride"—an antiarrhythmic agent with potent local anesthetic effects.

Serial ECG tracings in heroin addicts on propoxyphene napsylate detoxification-maintenance programs involving large doses of propoxyphene for periods of many weeks to several months do not indicate any effects on conduction or other aspects of cardiac electrophysiology. Twenty-four-hour Holter ECG monitoring of volunteers on usual therapeutic doses of propoxyphene for several days yields no indication of any effect of propoxyphene on cardiac conduction or function.

The possibility that norpropoxyphene cardiotoxicity plays a role in propoxyphene toxicity merits further study. Certainly there are measurable, although relatively minor, effects on myocardial conduction, demonstrable by *in vitro* and *in vivo* animal experiments. Reports of human toxicity that provide cardiac and electrocardiographic commentary strongly suggest that cardiocirculatory problems—such as cardiac arrest, ventricular fibrillation, and arrhythmias—arise mainly from severe anoxia, due to respiratory depression and apnea, acidosis, which may be severe, and electrolyte imbalance. Central nervous system depression *per se* may directly interfere with cardiopulmonary and circulatory function. The impression is gained that prompt correction of acidosis has not received the therapeutic attention that it merits. Management of any cardiac dysfunction in these cases would be greatly enhanced by correction of acidosis.

While the local anesthetic effects of nonpropoxyphene on cardiac conduction might assume somewhat greater significance in an individual severely toxic from drug overdose, the major threats to adequate cardiac function in this situation remain, namely, anoxia and acidosis and, later on, electrolyte imbalance.

RESPONSE TO ITEM NO. 2

Sales volume of Lilly propoxyphene in major population areas, and the dollar volume of sales of Lilly propoxyphene per unit of population in the 24 Standard Metropolitan Statistical Areas comprising the DAWN system.