April 6 hearing

FORENSIC TOXICOLOGY OF PROPOXYPHENE FATALITIES

A statement to be read before a Food and Drug Administration public hearing on propoxyphene, April 6, 1979, 1:40 - 2:00 PM, at the Department of Health, Education and Welfare, North Building, Room 5051, 330 Independence Avenue, S.W., Washington, D.C.

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I am currently Associate Professor in the Department of Pathology at the University of California School of Medicine at Davis, and Director of the Toxicology and Drug Analysis Laboratory at the UC Davis Medical Center in Sacramento. From 1975 to 1978 I was Chief Toxicologist for the Medical Examiner's Office of the State of Connecticut, and from 1973 to 1975 I was Research Toxicologist at the San Francisco Medical Examiner's Office. My interest in propoxyphene was a result of the very frequent occurrence of this drug in fatal cases investigated by these offices; excluding alcohol, propoxyphene remains the most frequently encountered single agent in deaths recorded in the jurisdictions of San Francisco County, the State of Connecticut and Sacramento County. I have reviewed the numerous literature reports of propoxyphene-related fatalities through 1975 in a publication from the San Francisco office (1) and through 1978 in a recent book (2). From my practical experience and knowledge of the literature I can respond to several of the questions raised for discussion at this hearing.

The question regarding the relative proportion of propoxyphene-induced

suicides, accidental deaths resulting from drug abuse and accidental deaths during normal drug usage would be answered in quantitatively dissimilar terms by representatives of different medicolegal jurisdictions and even by different medical specialists from the same jurisdiction. This is so because the classification of mode of death which appears on a death certificate is often a political decision rather than a scientific judgement. The toxicologist deals only with the evidence found at the scene of the death, the pathological findings and his own chemical findings in reaching a conclusion regarding the cause of death; he may make suggestions to the medical examiner as to the mode of death (accident versus suicide), yet the medical examiner, who has the final authority for this determination, may feel compelled to place more reliance on the testimony of the decedent's friends and relatives or on other situational factors. The study which I personally place the most confidence in consists of a series of 29 propoxyphene-related deaths which occurred during a one-year period in San Francisco (1); these cases were classified as 31% suicide, 45% accidental-drug abuse, 14% accidental-normal usage and 10% unknown or due to natural causes. Thus, 14% of the deaths or four individual cases can be considered to have resulted from normal usage of the drug; even here, however, there is room for differences of opinion, since three of these individuals exhibited blood alcohol concentrations of 0.15-0.26% and the fourth was receiving large doses (600-800 mg daily) of propoxyphene in a narcotic maintenance program. Nevertheless, the apparent potential of this drug for causing death in unsuspecting subjects is highly significant. Similar instances of accidental death have been recorded in the office of Dr. Elliot Gross, Chief Medical Examiner for the State of Connecticut, during the

three years in which I was employed there.

Blood concentrations of propoxyphene and norpropoxyphene in cases which involved normal usage of the drug but in which death was due to unrelated causes have been as high as 0.8 and 1.1 mg/L, respectively (1). These concentrations are in agreement with those observed in living subjects following chronic daily administration of 195 mg of propoxyphene (2,3). The blood concentrations of propoxyphene and norpropoxyphene in fatalities attributed solely to propoxyphene have, in my experience, ranged from 0.4-17 mg/L and from 0.8-30 mg/L and have averaged 3.8 and 6.5 mg/L, respectively. The presence of ethanol does not appear to affect these fatal levels, but the presence of other depressant drugs appears to substantially lower the concentrations of propoxyphene and norpropoxyphene observed in fatalities (1,2). These results have been corroborated by workers in Baltimore (4). Although the blood concentrations seen following therapeutic usage and fatal overdosage of propoxyphene overlap and therefore cannot be used as the sole index of drug toxicity, concentrations of propoxyphene exceeding 1 mg/L are considered indicative of potentially serious toxicity and concentrations exceeding 2 mg/L are consistent with death. It has also been observed that the liver/blood concentration ratios for both propoxyphene and norpropoxyphene usually exceed 10 following acute overdosage and are substantially lower during therapy. These concentration ratios can be very useful in distinguishing these two situations and should be determined routinely in postmortem toxicology investigations.

In order to arrive at a conclusion regarding the overall safety of an analgesic drug, a toxicologist must consider the efficacy of the agent in re-

lieving pain, the population for which the drug is intended, the frequency and quantity of administration, the kinetics of its disposition, its potential for abuse, its apparent toxicity in humans and its toxicity in animals relative to other similar drugs. The scientific literature indicates to me that, although propoxyphene has enjoyed great popularity among a large segment of the U.S. population, its efficacy as an analgesic has been seriously questioned. According to literature studies, the acute lethality of propoxyphene in experimental animals is nearly identical to that of codeine (5,6), yet propoxyphene is considerably less effective than codeine. Furthermore, propoxyphene produces a metabolite, norpropoxyphene, which is equally as toxic and has a much longer plasma half-life than its parent; the resulting accumulation of this toxic metabolite with chronic usage produces plasma drug levels of propoxyphene and norpropoxyphene which in combination amount to at least four times the level expected after an equivalent regimen of codeine (2,3). This accumulation of drug sets the stage for accidental overdosage; one or two additional depressant drugs, such as alcohol or diazepam, may be sufficient even in normally used amounts to cause death in susceptible persons. It has been argued that if propoxyphene is removed from the market that another therapeutic agent will quickly take its place as a vehicle for suicide; this is a very myopic viewpoint, since it is our civic charge as scientists to provide an ever safer environment by the replacement of dangerous, ineffective chemicals with safe and effective ones. Several clinicians of my acquaintance who are involved in drug abuse treatment have argued for the continued availability of propoxyphene as a drug for the detoxification of narcotic addicts; again, more effective agents are available and it is only the easy accessibility of pro-

poxyphene which makes it desirable for this purpose.

In conclusion, I strongly recommend that propoxyphene be strictly controlled as an agent which demonstrates substantial human toxicity and abuse liability and which has limited therapeutic usefulness.

References

1. R.C. Baselt, J.A. Wright, J.E. Turner and R.H. Cravey. Propoxyphene and norpropoxyphene tissue concentrations in fatalities associated with propoxyphene hydrochloride and propoxyphene napsylate. Arch. Toxicol. 34: 145-152, 1975.

2. R.C. Baselt. Disposition of Toxic Drugs and Chemicals in Man. Volume 1, Centrally-Acting Drugs. Biomedical Publications, Canton, Connecticut, 1978, pp. 34-37.

3. R.C. Baselt and R.H. Cravey. A compendium of therapeutic and toxic concentrations of toxicologically significant drugs in human biofluids. J. Analyt. Toxicol. 1: 81-103, 1977.

4. Y.H. Caplan, B.C. Thompson and R.S. Fisher. Propoxyphene fatalities: blood and tissue concentrations of propoxyphene and norpropoxyphene and a study of 115 medical examiner cases. J. Analyt. Toxicol. 1: 27-35, 1977.

5. R. Nickander, Pharmacological Research Department, Eli Lilly and Company, Indianapolis, Indiana 46206. Personal communication, October 31, 1974.

6. H.E. Christensen and T.T. Luginbyhl. Toxic Substances List, HEW Pub. No. (NIOSH) 74-134, 1974, p. 218.