# A MATHEMATICAL DESCRIPTION OF THE TOXICITY OF "SERNYL" TO GOLDFISH[1, 2]

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## ABSTRACT

The toxicity of the drug 1- (1-phenylcyclohexyl) piperidine, "sernyl", to goldfish, *Carassius auratus*, was tested. Median tolerance limits, median lethal concentrations (LCt 50) and the relation of the quantity *Ct* to time were calculated. The relation of concentration of sernyl to time of exposure may be expressed by the equation: $Ct=34+23t^{0.43}$. The results indicate that at higher concentrations of sernyl the LCt 50 is less than at lower concentrations. The value of K=34 in the above equation provides a new constant for the tolerance of goldfish to serynl.

## THE TOXICITY OF "SERNYL" TO GOLDFISH

The drug 1- (1-phenylcyclohexyl) piperidine hydrochloride (sernyl) has anesthetic properties in warm-blooded animals and in fish (Chen et al., 1959). It also has psychotropic characteristics in man (Bodi et al., 1959; Luby et al., 1959). Its toxicity in man is of a relatively low order. How toxic it is in cold-blooded animals is obscure.

To ascertain the toxicity of sernyl in fish, the goldfish (*Carassius auratus*) was used as the test animal. This species has long been used effectively in toxicological studies (Powers, 1917). The importance of fish tests in the evaluation of drugs and poisons is well established (Nigrelli, 1953; Valette, 1954).

## MATERIALS AND METHODS

Goldfish, 3 in. in length, obtained from a commercial fish farm were used in all the tests. Ten fish were used for each mean value reported in this paper. The fish were exposed continuously to various concentrations of sernyl dissolved in spring water which was kept at 22 C. Each aquarium held 15 liters in which the 10 fish were exposed. In general the criteria which are accepted in most bioassay procedures involving fish were followed (Doudoroff et al., 1951). The number of dead fish was recorded every 15 min for 24 hr during a test. The criteria for death were those recommended by Doudoroff et al. (1951). Mean values were calculated and the data were plotted in various ways to illustrate the toxic effects of sernyl. All dead fish were removed from each aquarium immediately after recording the fact. Each fish was used in only one test.

The sernyl was supplied by the Parke, Davis Company to whom gratitude is expressed.

## RESULTS AND DISCUSSION

One method of expressing toxicity results is in terms of median tolerance limits TLm. The medium tolerance limit may be defined as the concentration of toxicant in which 50 per cent of the test fish survive for a specified time. Table 1 shows the basic results from which TLm values were derived.

From table 1, by interpolation the median tolerance limits for two times of

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exposure to sernyl were estimated (Doudoroff et al., 1951; fig. 1). These values are shown below:

| *Time of exposure* | *Median tolerance limits* |
|---|---|
| 1.5 hr | 36 mg per liter |
| 2.25 hr | 20 mg per liter |

Extrapolations were made to obtain median tolerance limits for 1.75 and 2.5 hr respectively. These values are shown below:

| *Time of exposure* | *Median tolerance limits* |
|---|---|
| 1.75 hr | 29 mg per liter |
| 2.5 hr | 18 mg per liter |

If the values for the median tolerance limits as obtained are plotted against respective times of exposure a good straight line results

$$Y = 62 - 18X \qquad \text{I}$$

where Y is the median tolerance limit in mg per liter and X is the exposure time in hours.

It is important that time as well as concentration be considered in evaluations of toxicity. This fact needs repeated emphasis because it is often neglected.

TABLE 1

*Results of experiments to evaluate toxicity of sernyl to goldfish*

| Concentration mg per liter | Per cent test fish surviving after | | | | |
|---|---|---|---|---|---|
| | 1 hr | 1.5 hr | 1.75 hr | 2.25 hr | 2.5 hr |
| 15 | 100 | 100 | 100 | 90 | 80 |
| 25 | 100 | 100 | 70 | 10 | 0 |
| 40 | 90 | 40 | 0 | 0 | 0 |

NOTE: Ten fish were used for each concentration.

Toxicologists who evaluate the effect of agents in air breathed by mammals use the Ct value which is the product of concentration of agent in air times the actual exposure time in hours or minutes. A similar Ct can be calculated for fish exposed to a toxicant in water.

The LCt 50 is, then, the product of concentration and time at which 50 per cent of the test fish are killed. It differs from LD 50 because no specification of the amount of agent actually entering the fish is made. In fact no such specification can be made in experiments in which the toxicant is added to water. Hence, the LD 50 term would be meaningless.

The LCt for sernyl was derived by first plotting time in hours against per cent dead at each quarter hour. The result was a separate curve for each concentration of sernyl used. The time to kill 50 per cent of the test fish at each concentration was then obtained by interpolation. Table 2 shows these results.

It is evident that the product of concentration and time which results in a specified biological result (in this case death of 50 per cent of the fish) is not a constant. At higher doses the LCt 50 is less than at lower doses. This fact suggests that the toxic action of sernyl is more effective at higher concentrations.

The relationship of dose of a toxicant to time of exposure is expressed in the following general form (Silver, 1945):

$$Ct = K + at^{b+1} \qquad \text{II}$$

where C is the concentration of the toxicant in appropriate units, t the time of exposure, K the constant related to species susceptibility, a is a constant related to the magnitude of rate of detoxication, and b a constant related to change in rate of detoxication. Clearly, if the constants K, a, and b are known the relation between dosage (Ct) and time (t) to produce a specified physiological effect may be calculated.

A graphical method of analysis facilitates estimation of the various constants. Equation II is rearranged as follows:

$$Ct-K=at^{b+1} \qquad \text{III}$$

If logarithms of both sides are taken, a straight line is invariably obtained when log (Ct−K) is plotted against log t; the slope of the resulting line will be (b+1);

TABLE 2

*Median Lethal concentration, LCt 50, for sernyl in goldfish*

| Concentration, C mg per liter | Time, t to kill 50%; hr | LCt 50 mg hr per liter | LCT 50 mg min per liter |
|---|---|---|---|
| 15 | 4.8 | 72 | 4300 |
| 25 | 2.0 | 50 | 3000 |
| 40 | 1.3 | 52 | 3100 |

log a is equal to the intercept on the log (Ct−K) axis when t=1. By using log-log paper to plot these values, all terms may be read directly from the chart without conversion to logarithms.

An estimate of K is obtained by plotting Ct against t on regular coodinate paper. If K (the intercept on the Ct axis when t is zero) is difficult to locate, because of curvature of the resulting line, a plot of log (Ct−K) against log t which gives the straightest line will approximate K adequately.

Using the graphic method referred to, the relation of dosage of sernyl to time of exposure, with goldfish as the test species, is expressed by the following:

$$\log (Ct-K)=1.3424+0.43 \log t \qquad \text{IV}$$

In terms of equation II the relation is

$$Ct=K+23t^{0.43} \qquad \text{V}$$

The value of K was found to be 34. Hence for goldfish exposed to sernyl with 50 per cent death of the exposed fish as the biological criterion desired

$$Ct=34+23t^{0.43} \qquad \text{VI}$$

From equation VI it can be seen that if t is 1.5 hr, Ct is 61.4 and C is 41—a value essentially identical with the experimental value of 40 mg per liter.

At no concentrations of sernyl used in the study was excitation observed. The goldfish, in all concentrations, were depressed; they reacted sluggishly to visual and auditory stimuli; they tended to remain still in the water rather than swim around as did the controls. Siamese fighting fish (*Betta splendens*) reportedly react similarly to sernyl (Chen et al., 1959).

SUMMARY

The toxicity of sernyl to goldfish was tested. Median tolerance limits, median lethal concentrations (LCt 50) and the relation of Ct to time were calculated. The relation of dosage of sernyl to time of exposure may be expressed by the equation: $Ct=34+23t^{0.43}$. The value of K=34 provides a new constant for the tolerance of goldfish to sernyl.

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