Comparison of Noludar (Methylprylon) and Pentobarbital on Respiratory Minute Volume in Rabbits.*† (22817)

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Noludar (3,3-diethyl-2, 4-dioxo-5-methyl piperidine),‡ has been demonstrated in both animal and clinical trials to be a mild hypnotic and sedative with very few side effects (1,2). It has been suggested clinically that Noludar, when given with morphine, does not add to respiratory depression produced by the opiate and hence would be a desirable agent to be used when combination therapy is necessary.§ The purpose of this study was to compare respiratory depressant effects of Noludar and pentobarbital alone and in combination with morphine on rabbit respiratory minute volume.

Methods. Rabbits, ranging in weight from 1 to 2 kg, were used. Respiratory minute volumes were determined in 2 L. spirometer which collected expired air by means of a Lucite mask fitted with one-way flutter valves. In each experiment, at least 3 control values were determined before injection of the drug. Following control determinations, the drugs, dissolved in normal saline, were injected into marginal ear vein. When morphine was used it was always injected before the hypnotic drug. Minute volume measurements were then taken every 15 minutes for a 2-hour period after injection. Respiratory minute volume depression was expressed as a percentage of control and these percentages summed for the 2-hour period to yield 2-hour total area values(3). All comparisons were made from these values.

Results. Fig. 1 represents the calculated regression plots for morphine (M), Noludar (N), pentobarbital (P) and combinations of

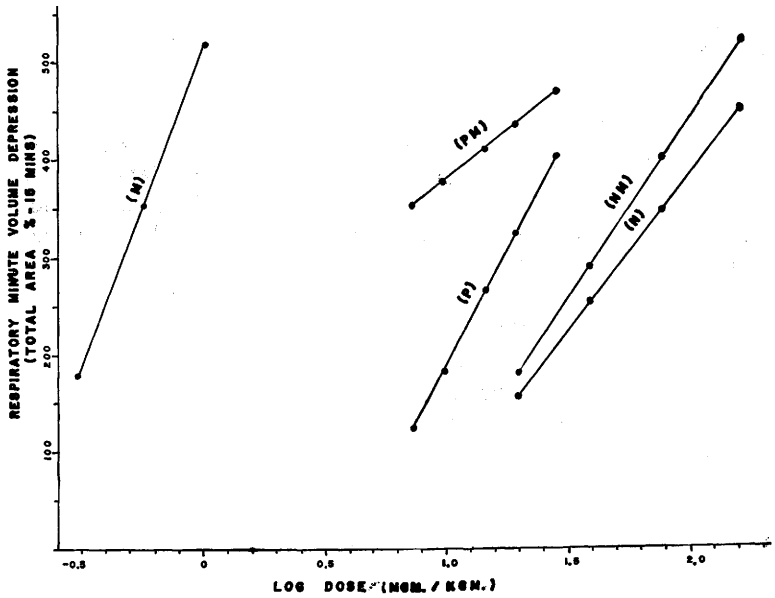

FIG. 1. Calculated regression plots for M (morphine), P (pentobarbital), N (Noludar), NM (Noludar-morphine) and PM (pentobarbital-morphine).

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TABLE I. Regression Statistics for Regression Lines Fig. 1.

Drugs	No. animals/regression line	a*	b	$\bar{x}$†	Linearity of regression F	Significance P
Morphine (M)	18	360.56	566.12	.199	54.66	.001
Pentobarbital (P)	25	271.16	471.35	1.19	27.82	"
Noludar (N)	26	269.62	318.77	1.66	55.53	"
Morphine-pentobarbital (MP)	25	411.64	191.75	1.18	6.66	.05–.01
Morphine-Noludar (MN)	22	336.37	364.91	1.73	35.83	.001

* % total area (15 min. for 2 hr). † Log dose.

Regression equation, $Y = a + b(x - \bar{x})$.

pentobarbital (PM) and Noludar (NM) with 0.608 mg/kg of morphine. The data in each case were tested for linearity of regression and in all cases were found to be significantly linear. These regression statistics (4) are collected in Table I.

Comparisons of slopes of regression lines were conducted by means of t test of regression coefficients. Morphine had a significantly greater slope than Noludar ($t_{(42)} = 0.01>p>0.001$), than pentobarbital-morphine combination ($t_{(39)} = 3.50 p<0.001$) and the Noludar - morphine combination ($t_{(36)} = 2.00$ $0.05>p>0.02$). The slope of pentobarbital alone was greater than that of pentobarbital-morphine combination ($t_{(46)} = 2.41$ $0.02>p>0.01$). Morphine when compared to pentobarbital and Noludar when compared to pentobarbital or Noludar-morphine were not found to be significantly different. The slope of Noludar-morphine, although somewhat greater than that of pentobarbital-morphine, was not significantly greater ($t_{(43)} = 1.80$ $0.10>p>0.05$).

The differences in slope among the various drugs and combinations do not allow direct comparisons of potency. We have therefore compared the differences between low and high doses of pentobarbital alone and with morphine and similarly low and high doses of

TABLE II. Comparison of Low (N–NM), High (N–NM), Low (P–PM) and High (P–PM).

Log dose (x)	Comparison	$t_{(df)}$	Significance P
.933	P_1–PM_1	$6.01_{(46)}$	.001
1.569	P_2–PM_2	$.74_{(46)}$	.50–.40
1.285	N_1–NM_1	$.58_{(44)}$	.60–.50
2.226	N_2–NM_2	$1.42_{(44)}$	.20–.10

TABLE III. Effect of Intermittent Injections of Pentobarbital and Noludar in Normal and Morphine-Treated Rabbits.

No. of doses of depressant	Morphine pretreatment, mg/kg	Noludar* treatment† effect
6	0	Survived
8	0	"
7	.608	Died 60 min. post-inj.
8	.608	Survived
4	1.220	"
7	1.220	"
8	1.220	Died 60 min. post-inj.

* All pentobarbital animals died at end of last dose.

† Each pentobarbital dose contained 10 mg/kg and each Noludar dose 35.5 mg/kg as calculated from regression lines as producing equivalent respiratory minute volume depression. Inj. rate was 1 dose/min.

Noludar alone and with morphine. These comparisons are detailed in Table II. Noludar-morphine combinations do not differ significantly from Noludar alone at either high or low doses. Pentobarbital-morphine combinations are, however, significantly more depressant than pentobarbital alone at low dose but not at high doses.

In view of the apparent lack of difference between pentobarbital and Noludar at high doses, an attempt was made to compare pentobarbital and Noludar as to toxicity (*i.e.* cessation of respiration). Simultaneous intermittent injections of equidepressant doses of Noludar and pentobarbital were given to rabbits with and without morphine pretreatment. The results are summarized in Table III.

Discussion. There is some indication from the toxicity data that Noludar is less toxic than pentobarbital at equally depressant doses of the hypnotics alone and in combina-

tion with morphine. However, in evaluating these data, it must be considered that Noludar is a much longer acting hypnotic than pentobarbital and hence discrepancies in the time necessary to produce respiratory arrest might be expected. Nevertheless, 4 out of 7 animals survived for 4 hours or longer following Noludar while all 7 animals receiving equi-depressant doses of pentobarbital expired.

Summary. Noludar and pentobarbital alone and in combination with morphine were compared as to their respiratory minute volume depressant effects in rabbits. No statistically significant difference could be found between Noludar alone and in combination with 0.603 mg/kg of morphine. Pentobarbital, on the other hand, was significantly more depressant in combination with morphine at low pentobarbital doses but not at anesthetic levels.

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Carbohydrate Metabolism and Phosphate Turnover Rate in Scorbutic Guinea Pigs. (22818)

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Metabolism of carbohydrate is altered in ascorbic acid deficiency. Banerjee *et al.*(1-4) and Bacchus and Heiffer(5) observed decreased glucose tolerance in scorbutic guinea pigs. Murray *et al.*(6) and Stewart *et al.*(7) reported diminished glucose tolerance in scorbutic monkeys. Liver glycogen content was lower in such animals than in paired fed normal controls. Banerjee *et al.*(3,8,9) ascribed the decreased carbohydrate metabolism to diminished insulin content of the pancreas in scurvy. Recently Banerjee and Ghosh(10) reported diminished hepatic and muscle hexokinase activity in scorbutic guinea pigs possibly due to decreased insulin synthesis and supply in such animals. Insulin was shown to stimulate hexokinase(11) and reduce liver glucose-6-phosphatase activities(12). Considering the possible role of ascorbic acid in the biosynthesis of insulin and the functions of insulin at these levels of glucose metabolism, the glucose-6-phosphatase activity was determined in tissues of scorbutic and paired fed normal guinea pigs. Decrease in hexokinase activity and increase in glucose-6-phosphatase activity might consequently lead to diminished phosphorylated intermediates of the glycolytic system. The changes in phosphorylation and dephosphorylation processes might eventually alter inorganic phosphorus content of tissues in scurvy. Studies were, therefore, carried out to elucidate the pattern of metabolic changes in relation with carbohydrate metabolism in scorbutic guinea pigs. The hexokinases are known to be sulfhydryl enzymes, and it is now well accepted that ascorbic acid protects and maintains the sulfhydryl groups of the enzymes(13). As an introduction to further study on the role of ascorbic acid in carbohydrate metabolism, fructokinase activity of the brain tissue of scorbutic and paired fed normal guinea pigs was determined.

Methods. Female well-growing guinea pigs of weights varying between 230 and 260 g were distributed into 16 pairs. Feeding a scorbutic diet, with or without supplement of ascorbic acid, by paired feeding technic and care of animals were the same as described previously(14). Pairs of animals were sac-