Effect of Levallorphan and Nalorphine upon Barbiturate-Induced Respiratory Depression in Rats.* (21970)

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N-allylnormorphine HCl. (nalorphine), and levo-3, hydroxy N-allylmorphinan tartrate, (levallorphan), have been shown to be effective antagonists of analgetic-induced respiratory depression both clinically and experimentally(1-9). However, with respect to the possible use of nalorphine against barbiturate depression the available reports are confusing, for some authors report that nalorphine is an effective barbiturate antagonist(10-12), while others found it to be ineffective(3,13-15). No reports are available concerning the effectiveness of levallorphan as an antagonist to barbiturate depression.

This study was undertaken to determine in rats the effectiveness of both nalorphine and levallorphan as antagonists to the respiratory depressant effects of some of the more commonly used barbiturates.

Procedure. Male albino rats (Sprague-Dawley) 200-300 g in weight were used. All experiments were acute, each animal serving as its own control, and about 50 experiments were carried out. The procedure was similar to that described previously(7), and consisted of cannulation of the trachea under ether, and infiltrating the area with a local anesthetic. The animal was restrained and connected to a one-way valve system to measure tidal air. After a control period, the barbiturate under examination was given, in a dose determined previously to produce 50% respiratory depression, then either nalorphine or levallorphan were administered by intraperitoneal injection at various dosage levels. The barbiturates examined were phenobarbital, barbital, amytal, pentobarbital and secobarbital.

Results. Levallorphan exerted no demonstrable effect in reducing the barbiturate-induced depression of respiration when used in dosage ratios of 1:1 or less of levallorphan to barbiturate. Because of this ineffectiveness of levallorphan a second series of experiments was carried out in the dose of the antagonist was increased. Fig. 1. Levallorphan was effective in diminishing only the pentobarbital-induced respiratory depression, and only when twice as much of the antagonist as depressant was employed. No noticeable stimulatory effects were observed with other barbiturates.

In the experiments with nalorphine only the higher dosage levels were tested, these were identical with doses used in the second series with levallorphan. Again, as with levallorphan, nalorphine was only effective in diminishing pentobarbital-induced respiratory depression, and only when twice as much nalorphine as pentobarbital was used.

Discussion. Both levallorphan and nalorphine were found to be moderately antagonistic to pentobarbital-induced depression but only when very large doses of these 'antagonists' were employed. On the other hand, no stimulatory effects were observed when these 2 compounds were used with phenobarbital, barbital, amytal and secobarbital. This is in marked contrast to the effect of levallorphan and nalorphine upon respiratory depression induced by the narcotic analgetic compounds, where the effective ratio of antagonist to depressant ranged from 1:1 to 1:30 for Dromoran, methadone, morphine, alphaprodine and meperidine. For example, the ratios in the case of morphine sulfate depression are 1:6.7, and 1:5, and in meperidine depression 1:30 and 1:5 for levallorphan and nalorphine respectively(7).

In this present series of experiments leval-

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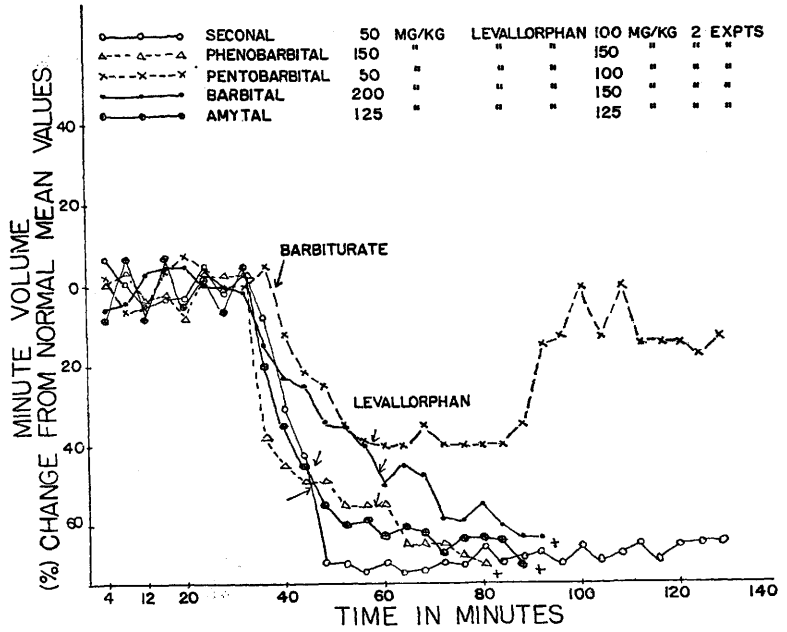

FIG. 1. Effect of levallorphan upon respiratory depression produced by various barbiturates. Effect with nalorphine was essentially the same, and the dosages were identical.

lorphan and nalorphine were not used in doses greater than 150 mg/kg because this would have exceeded the LD_{50} in rats for both compounds, (approximately 180 mg/kg for both levallorphan and nalorphine).

Eckenhoff *et al.*(13) found that nalorphine was ineffective in combating clinical barbiturate depression. However, Belford and Kao (11) and Vivante *et al.*(12) later reported that nalorphine was effective in relieving pentobarbital-induced respiratory depression in the dog. Clinically, Dulfano *et al.*(10) found nalorphine to be effective in combating barbiturate depression in several instances. On the other hand, several recent reports(3,14,15), have pointed out the failure of nalorphine, both experimentally and in man, to relieve respiratory depression from barbiturates.

There are no reports in the literature concerning the ability of levallorphan to combat respiratory depression produced by barbiturates. From the present study it would appear that both levallorphan and nalorphine can restore partially the respiratory minute volume in rats when it has been depressed by pentobarbital. However, this effect could only be achieved with very large doses.

Summary. It was observed that nalorphine and levallorphan were ineffective in antagonizing the respiratory depression produced in rats by large doses of phenobarbital, barbital, amytal and seconal. The two compounds did, in large doses, cause some diminution in the depression produced by pentobarbital.

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Morphology of Characteristic Particles Associated with Avian Erythroblastosis.* (21971)

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Erythroblastosis and myeloblastosis (granuloblastosis)(1) are highly malignant leukemic diseases of viral etiology in the chicken. In the latter condition involvement of the precursors of the myelocytes(2) results in the occurrence in the blood circulation of very large numbers of primitive cells of myeloblastic features. The virus of erythroblastosis presumably affects the progenitors of the red blood cells and the disease is characterized(3) by the presence of many erythroblasts in the circulating blood. That the respective viruses, likewise, are present in the circulation in both conditions is attested by transmissibility of the diseases with filtered blood plasma. By application of ultracentrifugal procedures, the virus of myeloblastosis has been obtained from the plasma of diseased chicks in appreciable amounts in purified preparations for physical, chemical and biological characterization(4,5). The findings with myeloblastosis have stimulated the undertaking of similar studies with the virus of erythroblastosis. Examination of filtered blood plasma from chicks with this disease has revealed characteristic particles, which by virtue of the experience with myeloblastosis, may represent the etiological agent of erythroblastosis. This paper describes results of preliminary investigations on the morphology of these particles observed in electronmicrographs.

Materials and methods. Erythroblastosis virus was obtained from Dr. Astrid Fagraeus of the State Bacteriological Laboratory, Stockholm, who had received it previously from Dr. J. Engelbreth-Holm at the Department of Pathological Anatomy, University of Copenhagen. The agent has been passed in this country by means of filtered plasma injected whole, or diluted, in 0.1 ml volumes in 3-day to 3-month-old chickens. The birds employed routinely were inbred White Leghorns of line 15 developed(6) at the Regional Poultry Research Laboratory, East Lansing, Mich. and the same as those used in the work with myeloblastosis(7). As will be developed in later reports, the strain of erythroblastosis appears to be a characteristic entity entirely distinct from myeloblastosis with respect both to the pathological manifestations and to host-response to the agent. Small chicks with the disease were bled by section of the sagittal sinus and larger ones by heart puncture. The blood was received in chilled tubes containing heparin and cleared of cells by 2 cycles of low speed centrifugation. The plasma was recovered in each case with fine tipped pipettes, then filtered with celite and passed through Selas filters by the technics(8) employed in the work with myeloblastosis. Donor birds were selected on the basis of the number of erythroblasts seen in routine daily blood smears, and bleeding was effected only when the chickens were near death. Once the chicks became obviously ill, as indicated by lassitude or weakness, the condition pro-

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