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## Histamine Release into the Circulation by Meperidine (Demerol®).* (26477)

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Hypotension is the primary cardiovascular effect of meperidine. This pharmacologic action has been demonstrated in the dog with various intravenous doses, both small and large. This fall in blood pressure has been attributed to a number of mechanisms, including vasodilatation by direct action, central vasomotor depression and perhaps, ganglionic blockade. Schacter(1) measured increases in free histamine in cat muscle and skin after treatment with meperidine. Subsequently, the possibility that histamine release contributes in part to the mechanism of meperidine induced hypotension has been suggested by several workers(2,3). Since there is no quantitative information concerning this effect in the intact dog, this study was done to find out if this drug is a histamine releasing agent in the dog and if so, whether enough histamine is released to cause hypotension.

*Methods.* Anesthetized (pentobarbital, 35 mg/kg) mongrel dogs received artificial ventilation through a cuffed endotracheal tube by means of a Starling pump. Blood pressure was recorded continuously from a catheter in the femoral artery connected to a Statham pressure transducer. The tracing was obtained on an Offner direct writing recorder. After a steady state was obtained, meperidine 5 mg/kg of a 10% solution, was injected rapidly into the femoral vein, followed with 1 ml of isotonic saline. Prior to and at one, 3 and 5 minutes after injection, samples of venous blood were taken into siliconized syringes containing 1:100 of 10% disodiumethylenediaminetetraacetate. Histamine was measured by the method of Shore and co-workers(4) with one modification; a Farrand photofluorometer, model A was employed instead of a spectrophotofluorometer. The approximate activating and fluorescent wave lengths were isolated by use of Corning glass filters, primary no. 5860 and secondary no. 3389. The sacrifice of some selectivity was replaced by the gain in ease of measuring duplicate specimens. Quenching occurred at a lower final concentration of histamine but the latter was proportional to fluorescence over the range .005 μg/ml to .165 μg/ml. All measurements were performed on duplicate specimens. Three dogs received intravenous injections of histamine, .03 mg/kg. The dose was calculated from the average increase in blood histamine found at the one minute interval after meperidine injection in 5 dogs. Blood histamine was measured in only one of the 3 dogs.

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† Markle Scholar in Medical Science.

TABLE I.

| Dog wt, kg | Blood histamine, μg/ml, after meperidine, 5 mg/kg I.V. Control | 1 min. | 3 min. | 5 min. | Blood pressure after meperidine, 5 mg/kg I.V. Control | 1 min. | 3 min. | 5 min. |
|---|---|---|---|---|---|---|---|---|
| 1-15 | .12 | .57 | .30 | .27 | 174/126 | 40/18 | 34/12 | 42/18 |
| 2-16 | .18 | .61 | .54 | .29 | 182/120 | 48/24 | 42/24 | 60/30 |
| 3-14 | .12 | .45 | .43 | .37 | 162/ 94 | 27/12 | 27/18 | 36/25 |
| 4-15 | .06 | .39 | .25 | .18 | 182/126 | 48/28 | 54/32 | 66/42 |
| 5-13 | .05 | .53 | .41 | .37 | 162/108 | 50/28 | 42/24 | 48/30 |
| Avg* | .11 ±.06 | .51 ±.11 | .39 ±.14 | .30 ±.10 | 172/115 | 43/22 | 40/22 | 50/29 |
| 6-13† | .06 | .76 | .12 | .08 | 174/115 | 54/30 | 90/64 | 130/100 |

Comparisons of significance of change between control and post-meperidine averages reveal $p < .001$.

* ± includes 95% confidence interval.

† Received histamine .03 mg/kg I.V.

*Results.* Rapid injection of meperidine into the circulation is followed by a marked lowering of arterial pressure and a rise in concentration of blood histamine to approximately 5 times control level (Table I). Mean concentration of blood histamine at control and post injection intervals varied between 0.11 μg/ml prior to injection and 0.30 μg/ml after 5 minutes. The largest increase occurred at the one minute period and the average was 0.51 μg/ml. The differences between control and post-injection values for histamine are significant, p being much lower than .001 for the 3 comparisons.

The temporal relationships between these changes are illustrated in Fig. 1 The nadir of blood pressure depression occurs during the interval of maximal velocity of histamine release.

Comparative tracings of the occurrence of hypotension after meperidine and histamine injections are seen in Fig. 2. Blood pressure falls more precipitously after histamine but recovers more rapidly. This is a reproduction of the tracing reported from Dog 6 (Table I). The 3 recordings from the dogs

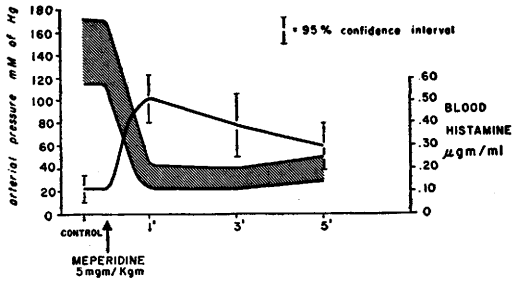


FIG. 1. Time relationship of blood histamine and blood pressure changes (avg from 5 dogs).

receiving histamine were virtually identical.

*Discussion.* Assuming an average blood volume in the dog of 75 ml/kg, a conservative estimate(5), then the change in amount of circulating histamine induced in one minute by administration of meperidine is equivalent to .03 mg/kg of histamine base. This is sufficient to produce the peripheral vasodilatation and hypotension commonly attributed to meperidine *per se* (Fig. 2). In addition

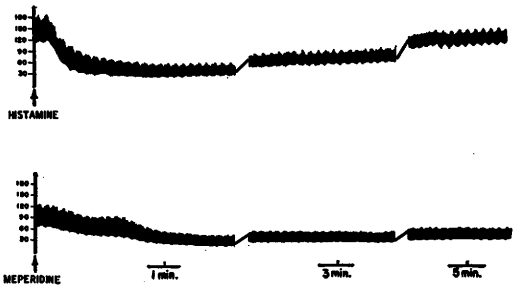


FIG. 2. Effects of histamine and meperidine on blood pressure.

the velocity of change in both parameters occurs simultaneously (Fig. 1), thus the temporal as well as quantitative requirements of such a relationship are satisfied. These conclusions are at some variance with those of Schacter(1), who reported that the ability of meperidine to release histamine is a property incidental to its major pharmacologic actions. While such deductions may be valid from observations in the eviscerated cat, they cannot be applied indiscriminately to all species. For example, the ability of meperidine to reverse histamine induced bronchial spasm in the isolated and perfused guinea pig lung is not sufficient evidence to classify the drug as a gen-

eral anti-histaminic agent. In the anesthetized dog, the major cardiovascular effects of meperidine appear to be mediated through release of histamine, although a combined effect of meperidine and histamine on the peripheral vascular system is not ruled out. Administration of anti-histaminic drugs in large doses has failed to separate these effects and other means are being considered to settle this point.

The differences in configuration of the tracings illustrating the effects of histamine and meperidine (Fig. 2) probably have two causes. First, the initial drop in the histamine tracing is more precipitous because more histamine is perfused per unit of time. These animals received the amine in one or 2 seconds whereas the meperidine group released this amount of endogenous histamine over a one minute period. The return to normal is more rapid in histamine treated animals because there is no prolonged release of the amine. This is evident by the rapid return of the blood values to control levels (Table 1).

*Summary.* Meperidine is a potent histamine releasing agent in the anesthetized dog. The quantitative and kinetic aspects of this phenomenon strongly suggest that it is responsible for the cardiovascular effects of this drug.

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## Employment of Polyethylene Tubing for Production of Intra-Arterial Thrombi in Rabbits and Rats.* (26478)

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Recently we have described(1) a simple method of inducing thrombi of approximately uniform size and weight in both the arteries and veins of rabbits and rats. This technique consisted of insertion into the lumen of a vessel of a small coil of Mg-Al wire previously treated with $ZnCl_2$. The thrombi form within a few hours, apparently triggered by the rapid electrolytic dissociation of the coil.

Other methods were sought for inducing intravascular thrombosis in an intact vessel without interrupting flow of blood, however, because a less fulminant, slower forming thrombus might offer certain advantages in various experimental studies. The present report describes a new method which is simple, relatively reliable and produces thrombi of approximately uniform size, weight and content.

*Methods.* It was discovered accidentally that small segments of polyethylene tubing† will serve as a nidus for thrombus formation. Further studies indicated that if these segments of tubing are split lengthwise and the resulting gutter-like segments inserted, thrombus formation almost invariably occurs within 72 hours in the trough of the segments.

Accordingly, 30 young male rabbits were anesthetized with pentobarbital and their aortae isolated below the exit of the renal arteries. Each aorta was gently occluded by traction upon ligatures approximately 2 cm apart and a very small incision made. Through this incision was inserted a 0.5 inch segment of polyethylene tubing (i.d. = 0.045″ and

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† Clay-Adams PE-160, Intramedic (Medical Formulation PHF) polyethylene tubing.