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Distribution Kinetics of Intravenous Epinephrine. (24916)

MARGARET G. FILBERT AND JOHN M. WELLER*

Clinical Investigation Branch, Chemical Warfare Lab., Army Chemical Center, Md.

Epinephrine given intravenously rapidly disappears from plasma(1). Guyton and Gillespie found that infusion of .0025 mg/kg/min into a dog sustained blood pressure at 200 mm Hg(2). Using constancy of pressure as criterion they calculated that rate of destruction was directly proportional to quantity in the body; the amount destroyed/minute being .631 times that quantity. The following studies were carried out to analyze, by means of fluorometrically determined plasma levels, distribution kinetics and disappearance rate of intravenously injected epinephrine.

Methods. Mongrel dogs of both sexes weighing 8 to 20 kg were anesthetized with intravenous pentobarbital. Six were given rapidly into femoral vein a single injection of 40 μg epinephrine/kg as l-epinephrine bitartrate. Five were similarly injected, then immediately given a constant intravenous infusion of epinephrine to 75 minutes duration. Blood pressures were recorded continuously from a cannula in femoral artery. Heparinized blood was drawn from opposite femoral artery immediately prior to, in some instances during, and at frequent intervals following administration of epinephrine. Plasma epinephrine contents were determined fluorometrically by modification of the method of Lund(1,3).

Results. Immediately following injection of 40 μg epinephrine/kg blood pressures rose to 300-350/200-250 mm Hg, remained for approximately one minute, fell during the next minute to 160-180/100-120 mm Hg, then slowly returned toward pre-injection levels over subsequent 4 minutes. During continuous infusions, blood pressures were maintained at about 200/150 mm Hg, then at cessation fell to 50-70/30-50 mm Hg within 2 minutes.

When epinephrine is given rapidly intravenously, arterial plasma levels reach a peak within several seconds and fall to pre-injection values within 4 to 6 minutes (Fig. 1). Mean half-time for disappearance from the plasma compartment of epinephrine, which is in excess of pre-injection level, is 23 seconds. Mean calculated disappearance rate constant $(k_1)^\dagger$ is −1.77. By extrapolation to zero time the calculated volume of distribution of injected epinephrine averages 45 ml/kg. This approaches the plasma volume of the dog(4).

Five experiments were carried out in which epinephrine was infused at a constant rate following rapid injection of 40 μg/kg. When given at a rate of 11 or 12 μg/kg/min, plasma levels continued to rise at 2 μg/l/min. When administered at a rate of 6 or 7 μg/kg/min more nearly constant levels of about 100 μg/l

* Present address: Dept. of Internal Medicine, Univ. of Michigan Med. School, Ann Arbor.

† k_1 (disappearance rate constant for rapid injection) and k_3 (disappearance rate constant for slow phase after prolonged infusion) $= \frac{2.303}{T_1 - T_2} \times \log \frac{C_{T_1} - C_0}{C_{T_2} - C_0}$; where C_0 is pre-injection plasma epinephrine concentration and C_{T_1} and C_{T_2} are concentrations at T_1 and T_2 minutes, respectively. k_2 (disappearance rate constant for rapid phase after prolonged infusion) $= \frac{2.303}{T_1 - T_2} \times \log \frac{C_{T_1} - C_{Eq}}{C_{T_2} - C_{Eq}}$; where C_{Eq} is plasma epinephrine concentration (21 μg/l) at beginning of slow disappearance phase. Regression lines calculated by method of least squares.

were present after 30 minutes. Six μg/kg/min is somewhat greater than the disappearance rate of epinephrine.

In these experiments the plasma epinephrine level was followed after cessation of infusion. It rapidly fell within 4 or 5 minutes to approximately 5 times average pre-injection concentration (Fig. 2). The calculated half-time of 38 seconds for disappearance of epinephrine, which is in excess of this new "equilibrium" level of about 21 μg/l, is slightly greater than that found following single injection. Mean calculated disappearance rate constant $(k_2)^\dagger$ after cessation of continuous infusion was −1.08.

Occurrence of this new "equilibrium" level by 5 minutes after termination of constant infusion means that the rapid disappearance rate has ceased. Therefore, in one experiment plasma epinephrine level was followed for one hour beginning 5 minutes after constant infusion was discontinued (Fig. 3). Plasma concentration changed very slowly; half-time for decline of plasma epinephrine in excess of pre-injection level in this period was 23 minutes and disappearance rate constant $(k_3)^\dagger$ was −0.030. During this hour 8.64 μg appeared in urine, while during the hour of infusion 2.24 μg were excreted. These were respectively 0.06 and 0.01% of total given.

Discussion. Rate of disappearance of epinephrine from plasma following single injection or immediately following termination of constant infusion is very rapid. Radiosulfate has a half-time of 4 minutes(5). The speed with which potassium leaves the circulation approaches that of epinephrine(6). Weil-Malherbe and Bone found physiological amounts of epinephrine in platelets(7). While our methods did not necessarily include epinephrine in platelets, this substance is not readily taken up by platelets *in vivo*(8). Storage by platelets therefore is not apt to accelerate the rate of disappearance from plasma. Epinephrine is almost completely bound to plasma proteins, especially albumin(9). However, such binding does not appear to retard seriously the disappearance of epinephrine from plasma.

Utilization or degradation of epinephrine would give an accelerated rate of disappearance compared to substances not so metabolized. On the basis of arterial-venous differences in human plasma, rate of utilization has been calculated to be 0.033 μg/kg/min(10). Rate of degradation by certain organs is high. Lund calculated that rabbit liver destroys up to 10 mg/kg/min, while the intact dog eliminated 10 μg/kg/min(11). He postulated that epinephrine could 1) be destroyed by oxidative deamination, 2) diffuse into tissues, 3) be oxidized through the adrenochrome stage, and 4) be excreted by the kidneys. Although degradation by amine oxidase has been considered important, Corne and Graham found that inhibition of this enzyme in the cat with 1-isonicotinyl-2-isopropyl hydrazine did not alter pressor response to infused epinephrine (12). Inhibition did raise urinary excretion of free epinephrine from 2.5 to 5.2%. As methylation to metanephrine probably precedes oxidative deamination by monamine oxidase, inhibition of this enzyme does not lead to a significant increase in unmetabolized epinephrine in urine(13).

Circulating epinephrine is removed by hind leg, liver and kidney(14). It is not known how much is destroyed by or diffuses into these tissues. Little enters or is metabolized by red blood cells(15). No gross change in disappearance rate is found when circulation is shut off to major organs(16). Similarly evisceration, hepatectomy, and nephrectomy do not markedly alter the rate(15). Only a small fraction of infused epinephrine appears in urine, although slightly larger percentages have been reported(17,18).

Rate of removal of epinephrine following single injection of 20 μg/kg has been calculated to be 3 to 5 μg/kg/min(15). This rate is similar to that reported here. As amount destroyed is proportional to quantity present, a more general description, based on the rate constant derived, is that 0.83 times the amount present in plasma disappears each minute. The disappearance rate immediately following cessation of constant infusion is slightly less than that after single injection. Jones and Blake utilizing shorter infusion periods found a similar rate during this time (14). Their calculated distribution volume of epinephrine was at least twice plasma vol-

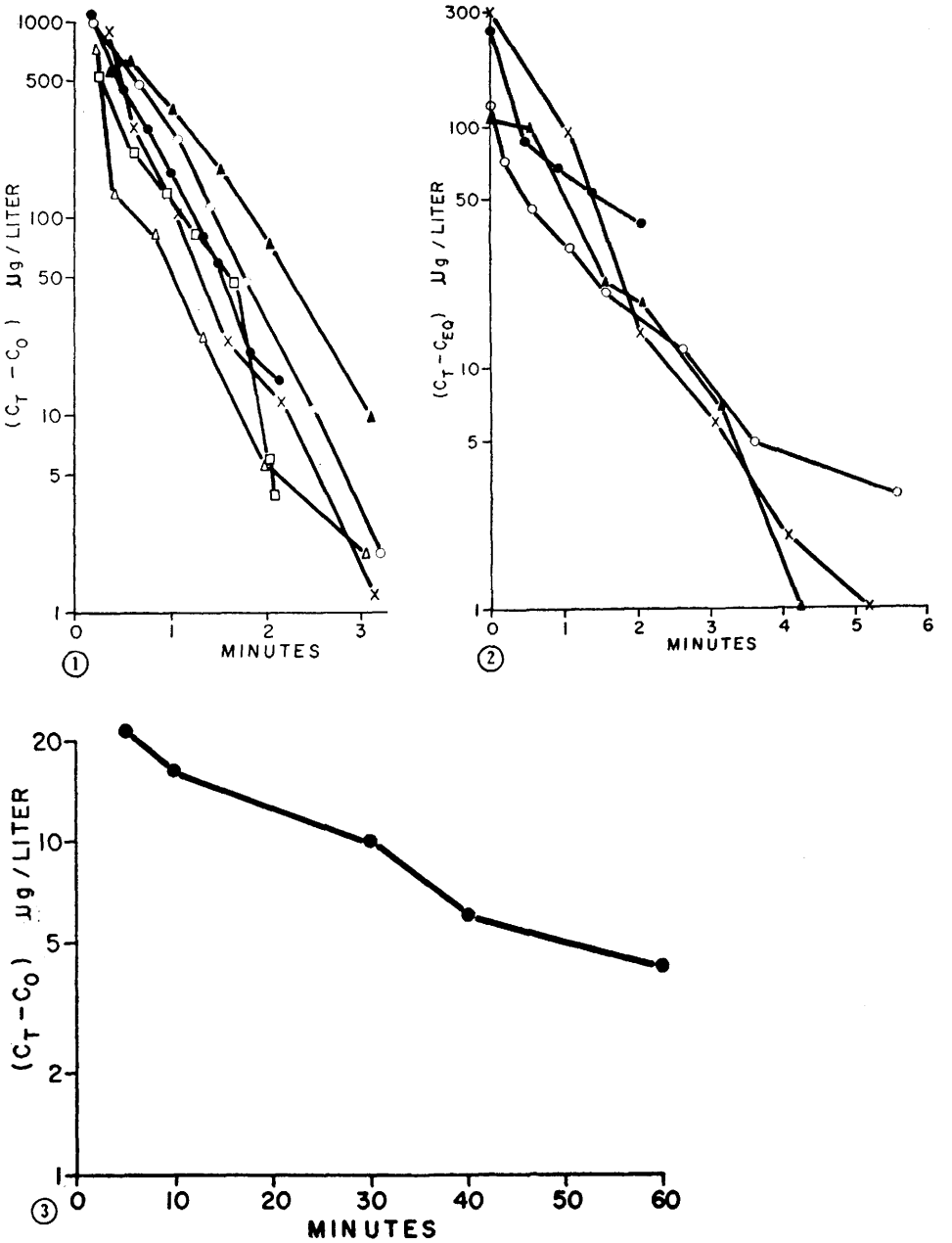

FIG. 1. Disappearance of epinephrine from dog's arterial plasma following rapid intrav. administration of 40 µg/kg. Difference between arterial plasma concentration of epinephrine at each time (C_T) and pre-inj. level (C_0) is plotted logarithmically against time. Lines connect logarithms of actual values obtained from each dog. Calculated regression line for entire group is $Y = 2.964 - 0.770\ X$. Individual slopes differ significantly from mean regression coefficient.

FIG. 2. Disappearance of epinephrine from arterial plasma immediately following discontinuance of constant infusions given at rate of 12.51 µg/kg/min. for 35 min. (●); 11.22 µg for 35 min. (×); 7.34 µg for 60 min. (○), and 6.38 µg for 75 min. (▲). Difference between arterial plasma concentration of epinephrine at each time (C_T) and "equilibrium" concentration (C_{Eq}) reached at 4 or 5 min. is plotted logarithmically against time. Lines connect logarithms of actual values. Calculated regression line for entire group is $Y = 2.169 - 0.471\ X$. Mean regression coefficient of these dogs is significantly different ($0.001 > p < 0.005$) from that of dogs shown in Fig. 1.

FIG. 3. Disappearance of epinephrine from arterial plasma during hour following a constant infusion of 7.12 μg/kg/min. for 60 min. Difference between arterial plasma concentration of epinephrine at each time (C_T) and pre-inj. plasma level (C_0) is plotted logarithmically against time. Calculated regression line is $Y = 1.358 - 0.013\ X$. This regression coefficient is significantly different ($p < 0.0005$) from that of groups in both Fig. 1 and 2.

ume, but less than total extracellular fluid volume. Removal rates indicate that it is not simply distribution into classical fluid compartments, *i.e.*, disappearance from plasma compartment after single injection and from total extracellular fluid compartment after continuous infusion, but other compartments or removal mechanisms are involved.

Plasma disappearance rate following single injection and that within 5 minutes after termination of infusion of epinephrine, as well as maintenance of a nearly constant plasma level when infusion is at the rate of 6 μg/kg/min, demonstrate a rapid rate of catabolism. On the other hand, in the single experiment in which it was followed, the slow rate of disappearance from 5 to 60 minutes after discontinuance of constant infusion suggests slow release of epinephrine from a reservoir, such as might occur following binding to proteins and platelets or entry into cells. Alternative possibilities are that the precipitous fall in blood pressure following cessation of continuous infusion may have been stimulus for release of endogenous catechol amines, thereby prolonging elevation of plasma levels, or may have reduced perfusion of liver and other organs so that destruction of epinephrine was impaired.

Extreme importance of awareness of prompt rate of disappearance of epinephrine is apparent. In animal experimentation or clinical investigation, transiently elevated plasma levels will remain undetected unless appropriately timed samples are analyzed. This has been stressed in diagnosing pheochromocytoma (19).

Summary. Epinephrine (40 μg/kg) injected rapidly, intravenously, disappears from plasma of anesthetized dog in 4 to 6 minutes. Mean half-time for this disappearance rate is 23 seconds. Epinephrine administered by continuous intravenous infusion approaches constant plasma levels in 30 minutes when given at 6 μg/kg/min. Following cessation of a constant infusion, plasma epinephrine concentration falls rapidly for 4 or 5 minutes, then slowly during subsequent hour. Half-time for rapid fall is 38 seconds and for the slow phase, 23 minutes. Inconsequential amounts of epinephrine are excreted in urine.

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