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EFFECT OF DOSAGE ON THE RATE OF DISAPPEARANCE OF ETHANOL FROM THE BLOOD OF DOGS

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In 1919 Mellanby, investigating the disappearance of ethanol from the blood stream of dogs after oral administration, came to the conclusion that 'whatever the amount of alcohol in the body, the rate of oxidation is constant'. This was generally accepted, in spite of its being a most unusual behaviour for a metabolite, until controverted by Haggard & Greenberg who, in 1934, published curves of blood-ethanol concentration following intravenous injection of ethanol in the dog. These curves were of exponential form, indicating a rate of metabolism proportional to dosage. Nobody before or since has secured such results, nor have the authors risen in their defence. However, the work was provocative of further investigation of the problem. Newman & Cutting (1935), by means of constant intravenous infusion in man, showed that, with fairly low concentrations of ethanol from 15 to 94 mg./100 c.c. of blood, the amount of ethanol required to maintain a given concentration was independent of the concentration. Neymark & Widmark (1936) published additional curves of blood-ethanol concentration in the dog which had a straight line form, reaffirming the constant rate thesis.

However, in 1937, Newman, Lehman & Cutting reported findings which showed some effect of dosage on rate of ethanol metabolism, after intravenous administration in the dog. In this work they covered a much greater range of concentrations than they had in the previous work with human subjects, using doses of 1, 2, 4 and 6 c.c./kg. They found that, in this range, for each doubling of the dose there was an increase in rate of about 17 %, far less than that reported by Haggard & Greenberg (1934), but still unmistakably significant. In spite of this effect of concentration they felt that the individual curves retained their straight line form, a seeming paradox for which they could offer no satisfactory explanation.

Eggleton, in 1940, re-opened the investigation of the problem with intravenous injection of ethanol. She used cats anesthetized with pentobarbitone. Her results showed that, in accord with the earlier work of Newman *et al.* (1937), the rate of metabolism was higher at higher concentrations, although in no wise proportionally as maintained by Haggard & Greenberg. However, she found that the blood-ethanol curves departed from the straight line form, being less steep as the concentration lessened. Further, she demonstrated that constant infusion of ethanol, at a rate which caused the blood-ethanol concentration to increase when this was at a low level, was insufficient to maintain a high level of concentration without decline.

Clark, Morrissey, Fazekas & Welch in 1941 showed that, in the dog, higher rates of ethanol metabolism were associated with higher dosage, but their published curves show the straight line form, as do also those of Gregory, Ewing & Duff-White in 1943. Thus, it seemed evident at this juncture that there was unanimity of opinion that larger doses of ethanol are metabolized at higher rates, but some divergence regarding the constancy of the rate of decline of blood-ethanol concentration after a single dose. Newman and co-workers offered, as a possible explanation for their findings, that the rate of fall of blood ethanol was in some way conditioned by the highest concentration reached. This cannot be said to explain the results; it does little more than restate their findings in different terms. Because of this apparent divergence of evidence, it was deemed advisable to investigate the problem further.

METHODS

Adult dogs of both sexes were used, without anesthesia. Ethanol was injected intravenously by gravity as a 20% solution in an isotonic solution of sodium chloride. The rate of injection never exceeded 0·5 c.c./kg./min., and for the continued maintenance of an already attained concentration was much less than this. Administration of small divided doses by stomach tube was resorted to for very prolonged maintenance. Samples of blood were secured from leg veins at appropriate intervals and analysed for ethanol by the method of Newman & Abramson (1942).

RESULTS

Thirty-nine single injections were made in ten dogs, using doses of ethanol ranging from 0·75 to 3·0 g./kg. The results are summarized in Table 1. The rate of metabolism is expressed in two ways in this table. First, by extrapolation of the best-fitting line between the points representing ethanol concentrations in the blood at varying intervals after injection to the time base, the length of time that alcohol remained in the blood stream could be estimated. Dividing the dose by this time gave the rate of metabolism in mg./kg./hr. This estimation assumes that the disappearance of ethanol from the venous blood indicates the completion of its metabolism in the body. Secondly, by taking the blood-ethanol concentration about 45 min. after the completion of the injection and subtracting from it the concentration at a subsequent time, preferably when this had approached but not actually reached zero, and dividing the difference by the time elapsed between the two determinations, the rate of fall of blood-ethanol concentration in mg./c.c./min. was obtained. As can be seen from the table, there is quite a constant relationship between the two values, so that little advantage can be claimed for one method over the other, and they are both set down mainly for ease in comparison with the figures of other workers, some of whom use one and some the other means of expression.

TABLE 1. Relationship of dosage to rate of metabolism of ethanol

Dog	Weight	Dose ethanol (g./kg.)	Rate of metabolism mg./kg./hr. *A*	Rate of metabolism mg./c.c. blood/min. *B*
BR	18	3·0	174	0·00364
1	23	3·0	113	0·0024
		1·5	102	0·00223
		1·5	98	0·0021
		1·5	103	0·00228
		0·75	91	0·00222
2	21	3·0	146	0·00288
		3·0	138	0·00257
		1·5	102	0·00203
		1·5	123	0·00252
		1·5	107	0·00237
		0·75	111	0·00218
3	18	3·0	136	0·00308
		1·5	130	0·00273
		1·5	105	0·00233
		1·5	94	0·00218
		0·75	91	0·00213
4	18	0·83	101	0·00237
		0·83	98	0·00213
		0·83	116	0·00233
5	10·5	1·43	102	0·00243
		1·43	104	0·00228
		1·43	106	0·00238
6	14	1·07	133	0·00305
		1·07	133	0·003
		1·07	143	0·00333
A1	17	3·0	156	0·00365
		1·5	122	0·00307
		0·75	103	0·00287
		0·75	91	0·00265
A5	22·5	3·0	95	0·00197
		3·0	101	0·00242
		1·5	82	0·0019
		0·75	71	0·00213
		0·75	83	0·00188
A6	15	3·0	133	0·00312
		3·0	145	0·00297
		0·75	77	0·00223
		0·75	67	0·00177

A, mg./kg./hr., determined by time required for alcohol to disappear from the blood. *B*, rate of fall of blood alcohol concentration in mg./c.c./min.

TABLE 2. Rate of ethanol metabolism after varying dosage. Where more than one trial of a dose was made, the average of the trials is recorded

	Rate of metabolism (mg./kg./hr.)		
Dog	Dosage (0·75–1·07 g./kg.)	Dosage (1·43–1·5 g./kg.)	Dosage (3·0 g./kg.)
BR	—	—	174
1	91	101	113
2	111	111	141
3	91	110	136
4	105	—	—
5	—	104	—
6	136	—	—
A1	97	122	156
A5	77	82	98
A6	72	—	139
Average	98	105	137

Table 2 utilizes the same data, with the rate of metabolism for all trials of similar dosage in each animal averaged. It demonstrates the variability in rate of metabolism at the same dose in different dogs, with, however, a definite increase in rate with increasing dosage.

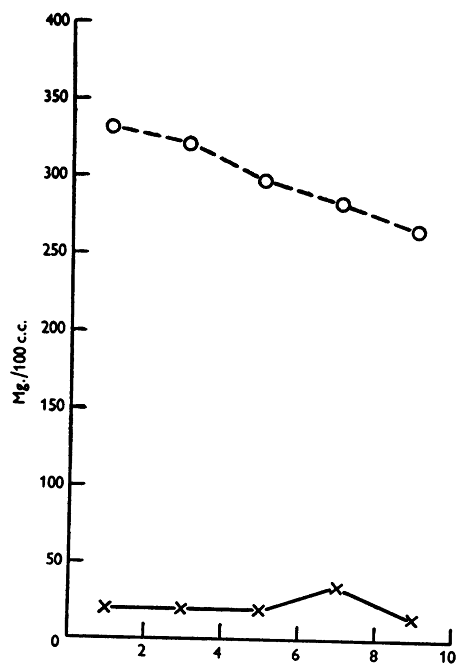

Fig. 1. Blood-ethanol concentration over an 8 hr. period in dog A6, during which period hourly doses of 72 mg./kg. were administered by stomach tube. In the case of the upper curve, an initial dose of 3·0 g./kg. preceded the maintenance dosage, while with the lower curve the initial dose was 0·375 g./kg.

In dog A6, which showed the greatest variability in rate of metabolism with dosage of any of the animals tested, observations were made on the amount of ethanol required to maintain the blood ethanol level constant at differing levels. An initial intravenous dose of 0·375 g./kg. produced a blood-ethanol concentration of 20 mg./100 c.c. at the end of 1 hr. At this time, and every hour thereafter for a total of eight doses, the dog was given a dose of ethanol of 72 mg./kg. by

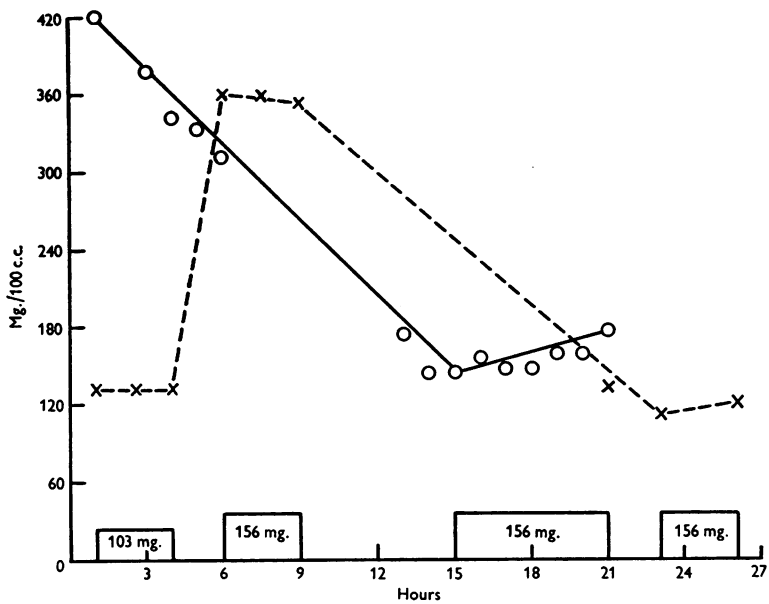

Fig. 2. Curves of blood-ethanol concentration in dog A1. An initial intravenous dose of 0·75 g./kg. was given, and after an hour a constant infusion at the rate of 103 mg./kg./hr. was continued for 3 hr. Then a second large dose was given to raise the concentration to 360 mg./100 c.c., at which level the larger maintenance dose of 156 mg./kg./hr. for 3 hr. failed to maintain this concentration. The concentration was then allowed to fall to a lower level, and the same maintenance dose of 156 mg./kg./hr. resulted in a definite rise in concentration in 3 hr. In a second trial, shown in the solid line, the maintenance dose of 156 mg./kg./hr. was continued for 6 hr. after the concentration had been allowed to drop from an initial value of 420 mg./100 c.c., and again a very definite rise in concentration resulted.

mouth, this being its estimated rate of ethanol metabolism at low blood-ethanol levels. As can be seen from Fig. 1, this dosage was successful in maintaining the blood-ethanol level very nearly constant for the 8 hr. period. On a subsequent day the same procedure was repeated, except that the initial dose of ethanol was 3·0 g./kg., giving a concentration at the first hour of 330 mg./100 c.c. In this instance the hourly doses of 72 mg./kg. were inadequate to maintain the blood concentration constant at this high level, and a fall of 65 mg./100 c.c. in the 8 hr. resulted.

In dog A1, which also showed a considerable effect of dosage on rate of ethanol metabolism, an initial intravenous dose of 0·75 mg./kg. resulted in a blood ethanol concentration of 132 mg./100 c.c., as seen in Fig. 2. This was maintained very nearly constant for a period of 3 hr. by a constant intravenous infusion at the rate already found for this level of blood-ethanol concentration in this dog, 103 mg./kg./hr. At the end of the 3 hr. period the blood-ethanol concentration was raised by a second rapid infusion to 362 mg./100 c.c., and again the constant infusion started, this time at the rate previously found for an initial dosage of 3·0 g./kg., namely 156 mg./kg./hr. This proved to be inadequate to prevent a slight drop in concentration over the 3 hr. period, the blood-ethanol concentration falling to 352 mg./100 c.c. No further ethanol was then given for 14 hr., by which time the concentration had fallen to 112 mg./100 c.c. Then a constant infusion was again started, at the same high rate of 156 mg./kg./hr., with the result that the blood-ethanol concentration rose in 3 hr. to 120 mg./100 c.c. On another occasion, in the same animal, an initial dose resulting in a concentration of 420 mg./100 c.c. was given, as seen in the solid line in Fig. 2. The concentration was allowed to decline to 144 mg./100 c.c., and then the constant infusion at the rate of 156 mg./kg./hr. started. At the end of 6 hr. the concentration had risen to 176 mg./100 c.c.

DISCUSSION

The results set forth in Table 1, and summarized in Table 2, demonstrate the degree of variability in the rate of metabolism of ethanol in different dogs at the same dosage level. Equally is shown the definite increase in rate when the dosage is increased from the vicinity of 0·75 g./kg. to 1·5 g./kg. and finally to 3·0 g./kg. Since the average blood ethanol value for the entire period that ethanol remained in the blood stream after the 0·75 g./kg. dose was about 50 mg./100 c.c., and that after the 3·0 g. dose was 200 mg./100 c.c., it is seen that the 40% increase in rate of metabolism brought about by this increase in average concentration of 150 mg./100 c.c. is not far out of line with the 30% increase for an increase of 100 mg./100 c.c. reported by Eggleton. We have thus confirmed her work, and incidentally our own previous experiments.

Reference to Table 1 shows also the relatively constant rate of metabolism for a given dose in a given dog. The reduction in rate at lower concentrations is much more apparent in some animals than in others. Thus an increase in dose from 0·75 to 3·0 g./kg. caused an increase in rate of metabolism of 93% in dog A6 and only 24% in dog. 1.

The data presented in Fig. 1 demonstrate that the same divided dose of ethanol at frequent intervals which is capable of maintaining the blood-ethanol level constant at low concentrations is incapable of so doing when the concentration in the blood is at a high level. This confirms the observation of Eggleton, and extends it to the unanaesthetized dog.

Newman and co-workers (1935, 1937, 1942), while demonstrating the increase in rate of ethanol metabolism with increasing dosage, nevertheless found difficulty in reconciling this finding with the apparent straight line form of their curves of blood ethanol. They presented the hypothesis that the rate of ethanol metabolism was in some way conditioned by the highest concentration to be reached in the blood, so that this high rate characteristic of high dosage would be maintained even when the concentration fell during the course of metabolism. Eggleton showed that a dose of ethanol administered by infusion at a constant rate which was more than capable of maintaining a low blood-ethanol concentration was inadequate for this purpose when the blood-ethanol concentration was subsequently raised to a high level, and this has been confirmed by our present work. However, this demonstration does not of itself invalidate the hypothesis of 'conditioning' put forth by Newman and co-workers, since the low concentration was the first tested, and thus the 'conditioning' by a preceding high level had not had a chance to take place. However, if the hypothesis were correct, it should be possible to maintain the blood-ethanol concentration constant at a low level by the constant infusion of a dose of ethanol equal to that required at a much higher level, if the constant infusion was given after the blood-ethanol level had been raised to this high level initially, and then allowed to drop to the desired low level before the constant infusion was begun. The results of such an experiment are shown in Fig. 2. This shows conclusively that a constant infusion of ethanol at a rate slightly less than that required to maintain the blood-ethanol concentration constant at a high level will result in an increase in blood-ethanol concentration at a lower level, even though this lower level has been reached by decline from a much higher one. We must, therefore, accept the fact that under all circumstances ethanol is metabolized at a slower rate at low concentrations than at high, and that the apparent straight line form of the published curves of a number of workers, including ourselves, must be explained by the finding that the rate of fall of blood-ethanol concentration has sufficient irregularity to obscure the relatively small decrease in rate of metabolism with declining concentration.

CONCLUSIONS

The rate at which ethanol is metabolized in the dog bears a relationship to the concentration of the alcohol in the animal body, the higher the concentration the higher the rate. This relationship is not, however, a strict proportionality. It varies considerably from one animal to another. The relatively small degree of the effect of dosage, and the inherent irregularity of disappearance of alcohol from the blood are sufficient to account for the apparent straight line form of the published curves of concentration against time.

SUMMARY

1. The rate of decline of ethanol concentration in the blood of dogs after intravenous injection of varying doses was determined. The amount of ethanol per unit time required to maintain the blood-ethanol concentration constant at varying levels was also found.

2. There is a definite relationship between dose and rate of ethanol metabolism, a 40% average increase in the latter resulting from an increase in blood-ethanol concentration of 150 mg./100 c.c.

3. In view of these findings, the apparent linearity of blood ethanol curves in published work must be due to the relatively minor effect of dosage on rate of decline, coupled with the inherent irregularity in the rate of disappearance of ethanol from the peripheral blood.

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