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Blood Removal and Renal Elimination of a Constant Dose of Ethanol as a Function of Volumes and Concentrations of Solutions Administered to Rats

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DOSSEVI, L , P MARFAING-JALLAT, L A CAMPFIELD AND J LE MAGNEN *Blood removal and renal elimination of a constant dose of ethanol as a function of volumes and concentrations of solutions administered to rats* PHARMACOL BIOCHEM BEHAV **18**(3) 333–339, 1983 —Blood ethanol and urinary excretion were determined in rats following intragastric administration of a constant dose of 3 g per kg of ethanol diluted in five different volumes of aqueous solutions from 30 to 1 87 ml (2 5 to 40% concentrations) In a first experiment, it was shown that administration of the 30 ml of the most diluted solution was followed by a slower and longer lasting rise and by a subsequent more rapid decline of blood ethanol concentration than observed following administration of smaller volumes of more concentrated solutions In experiment 2, measurement of urinary flow after the IG administration of the five solutions and of equivalent volumes of isotonic saline showed that a maximal three hour diuresis was induced by the high volume of the diluted solution By measuring urine ethanol content in a third experiment, it was found that the proportion of the dose of ethanol excreted in urine was seven fold higher following the administration of the 30 ml (2 5%) solution compared to 1 87 ml (40%) solution It is concluded that the drinking of a dose of ethanol in a high volume of a dilute solution is likely less toxic than the drinking of the same dose in a small volume of concentrated solution

Ethanol Ethanol intake Rats Blood ethanol concentrations Renal clearance of ethanol

BLOOD ethanol removal results from the simultaneous action of four different pathways of elimination from the body In addition to ethyl oxidation, cutaneous, pulmonary and renal excretions contribute somewhat to the rate of total elimination According to various investigators ethanol oxidation, mainly in liver, represents 80 to 90% of elimination [7,10] However, this proportion is apparently dependent on the contribution of the other output pathways Cutaneous alcohol elimination through sweating appears to be small It is likely dependent on sweating rate and, thus, on environmental temperature and physical exercise Pulmonary exhalation of ethanol is, as is well known, proportional to the blood ethanol level Consequently, the participation of pulmonary output in total elimination depends on all variables which influence blood ethanol level According to Haggard, Greenberg and others [6, 8, 11, 12] the fraction of total elimination due to pulmonary exhalation would range from 1 to 3% with small doses to 6 to 8% with larger doses

The diuretic property of ethyl alcohol is well known and has been extensively studied [5, 13, 21, 23, 24] By inhibiting pituitary antidiuretic hormone release, ethanol induces water diuresis and thereby a polyuric-polydipsic syndrome [1, 5, 16] In addition to this diuresis promoting action, ethanol is passively filtered by the kidney Like pulmonary elimination, participation of renal excretion in total elimination from the body has been claimed to be dependent on the dose According to various investigators [4,22], it would vary between 2 and 10% The rate and amount of renal elimination may be also affected by another factor, up to now neglected, represented by the volume and concentration of the dose of ethyl alcohol solutions drunk or administered In the present study, the influence of various volumes and concentrations of intragastrically administered solutions containing the same dose of 3 g/kg body wt of ethanol on total renal excretion has been investigated in rats

METHOD

In order to perform gastric administrations of ethanol solution without stressing the animals by oral tubing, rats were implanted with a chronic gastric catheter according to the technique of Kohn [14] as modified by Marfaing-Jallat Under Nembutal anesthesia, a 0 765 mm ID silastic tube terminated by a more rigid polyethylene tube was implanted

through the stomach wall and fixed as described in detail elsewhere [19] The tube was led under the skin and connected at the top of the head to a metal tube fixed on the skull by dental cement After recovery from surgery, rats were placed in Plexiglas cylindrical cages specially equipped for rats bearing chronic catheters The metal head piece was connected to a polyethylene tube and via a swivel-joint to a motor driven pump

Blood ethanol level was determined using the A D H /N A D technique (Boehringer) on blood samples of 0 1 ml taken from the tail vein The same technique was used to determine urine ethanol concentration from 0 1 ml samples Urinary flow was measured in standard metabolic cages Male Wistar rats weighing approximately 250 g were used Except for acute experiments, they were housed under standard laboratory conditions with constant access to laboratory chow and water

Experiment 1 Blood Ethanol Level

Five adult rats were food deprived the night prior to the experiment Water was removed one hour before the test At 9 a m , rats received through the chronic gastric catheter a dose of 3 g/kg of ethanol, contained in volumes of either 30 ml, 15 ml, 7 5 ml, 3 75 ml or 1 87 ml of water, i e in solutions at concentrations (w/v) of 2 5, 5, 10, 20 and 40% respectively These volumes of ethanol solutions were randomly administered in successive tests three days apart By changing the programmed flow rate the five solutions were administered over a constant interval of 10 min Blood samples were drawn 10, 20, 40, 70, 130, 190, 310 and 370 min after the beginning of the intragastric administrations

Experiment 2 Urinary Flow

Ten adult rats were placed in metabolic cages After a period of adaptation, they were food deprived overnight The same volumes of 3 g/kg ethanol solutions employed in the above experiment and five identical volumes of isotonic NaCl solution, were intragastrically administered according to a latin square design Water had been removed one hour prior to the infusions Urine volumes were determined one and three hours after the infusion of ethanol or saline solutions

Experiment 3 Urine-Ethanol Content

In this experiment, treatments were limited to three solutions namely 30 ml (2 5%), 7 5 ml (10%) and 1 87 ml (40%) administered according to a latin square design in nine rats 0 1 ml samples of urine were taken 30, 60, 120, 180 and 300 min after ethanol administrations

RESULTS

Experiment 1

Changes in blood ethanol levels determined from 10 to 370 min after the intragastric administrations of the five solutions are illustrated in Fig 1

A computer analysis determined that the experiment data best fit (using a least squares criterion) by the following formula

$$C_t = C_o\,(1-\bar{e}^{k_1 t})\,(\bar{e}^{k_2 t})$$

where C_t=blood ethanol concentration at time (t), C_o=blood ethanol concentration at the end of absorption assuming no elimination, k_1=absorption rate constant k_2=elimination rate constant

TABLE 1

PARAMETERS VALUES AND ESTIMATES FROM COMPUTER FITS OF BLOOD ETHANOL DATA

Ethanol concentration (%)	C_o (mg)	k_1 (min^{-1})	k_2 (min^{-1})	C_{max} (mg/ml)	T_{max} (min)	T_o (min)
2 5	9 20	0 00885	0 00513	3 26	113	365 8
5	3 87	0 0325	0 00357	2 71	71 1	410 1
10	3 51	0 0357	0 00300	2 61	71 6	478
20	4 24	0 0276	0 00314	2 94	82 5	465 9
40	4 22	0 0267	0 00307	2 91	85	486 8

C_o, k_1 and k_2 are defined in the text

C_{max} is the maximum predicted blood ethanol concentration

T_{max} and T_o are the times of maximum and zero blood ethanol concentrations, respectively Data are means

The mean values of C_o, k_1, k_2, and the estimated maximum concentrations, and the time of the peak and zero concentrations are given in Table 1

Experimental points and data extrapolated from the computed curves show that

(1) Blood ethanol concentration increases at a slower rate, and the time to peak concentration was longer after administration of the most diluted solution, 30 ml (2 5%), than after the administration of the four other concentrations The duration of this rising phase of blood ethanol level lasted 113 min for the most diluted solution vs 71 to 85 min with the four other solutions The estimated peak of blood ethanol concentrations ranged from 2 61 to 3 26 mg/ml (Table 1)

(2) Experimental data indicate a faster fall of blood ethanol concentration with the 30 ml (2 5%) solution than with the other solutions The duration of the fall in blood ethanol from the peak until an extrapolated 0 level was 365 8 min with the dilute solution vs 410 1, 478, 465 9, and 486 8 min respectively with more concentrated solutions

(3) Despite the slower rate and longer duration of the increasing phase the time elapsed from intragastric administration to total elimination was significantly shorter after the delivery of the 30 ml (2 5%) solution than after the three most concentrated solutions However, the total duration was approximately identical with the two most diluted solutions

In summary, intragastric administration of a dose of 3 g/kg of ethanol leads to a longer increase in blood ethanol level at a slower rate and to a more rapid subsequent decline when administered in a volume of 30 ml at the concentration of 2 5% compared to administration of the same dose in lower volumes and more concentrated aqueous solutions In contrast, appearance and disappearance rates of blood ethanol are not significantly different after the IG administration of the constant dose in volumes from 15 to 1 87 ml and concentrations from 5 to 40%

Experiment 2

Urinary flow observed after the intragastric administration of 1 87 to 30 ml of saline solution demonstrates the classical water diuresis (Fig 2) The volume of urine excreted during the first hour and the two subsequent hours

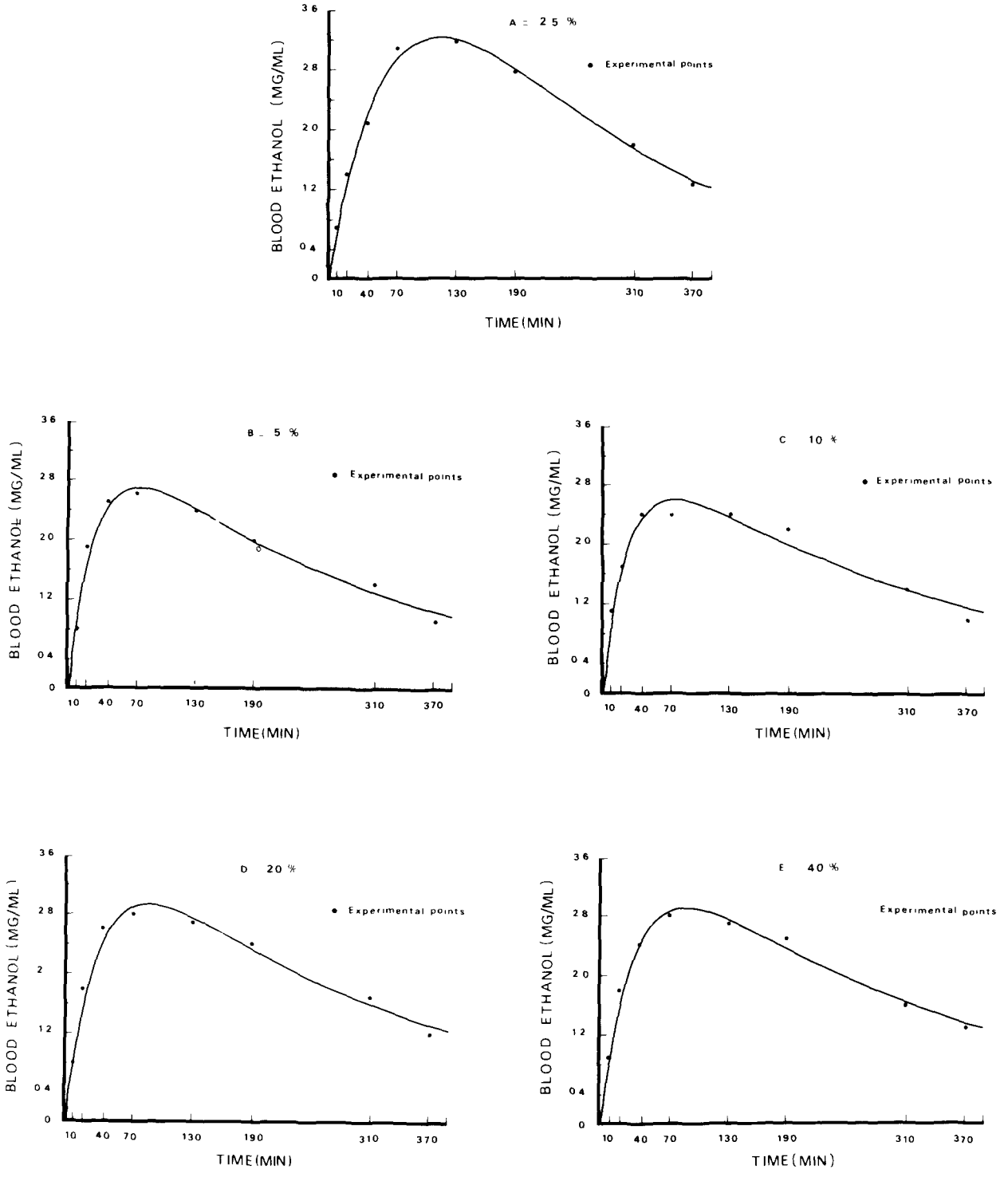

FIG 1 Computer generated curves of blood ethanol as a function of concentration and time (N=5)

markedly increases when the volume of the infusate was greater than 7 5 ml This level is thus apparently the threshold of onset of hypervolemia-induced water diuresis The difference in urine volumes after identical volumes of ethanol or saline indicates the specific diuretic effect of ethanol (Fig 2)

The observed and so determined diuresis due to ethanol content of the solution increased with increasing volumes up to a volume of 7 5 ml (10%) during the first hour At larger volumes, the portion of the diuresis due to ethanol declines

Differences in urine volume during the first hour following the administration of ethanol or saline were statistically

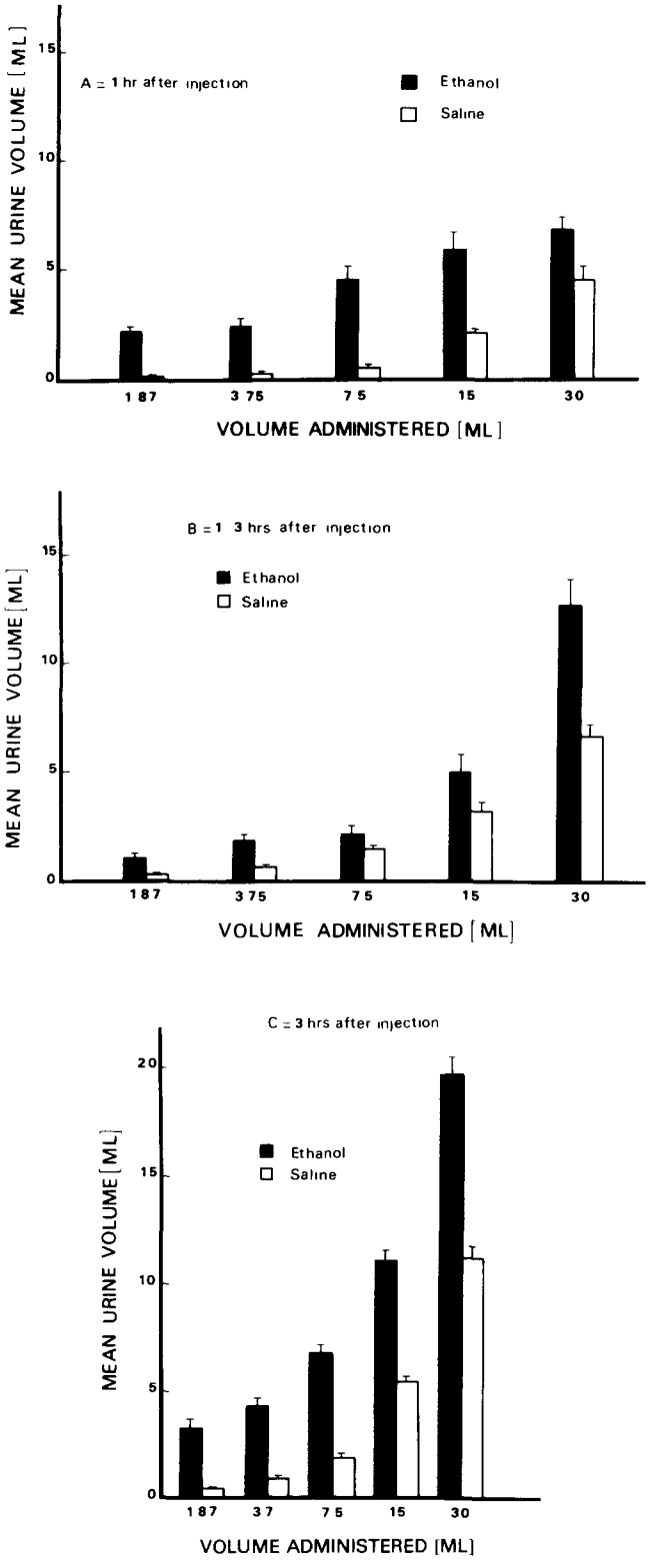

FIG 2 Mean urine volume as a function of ethanol concentration in 0 9% saline and volume of solution administered Results are expressed as mean±SEM (N=10)

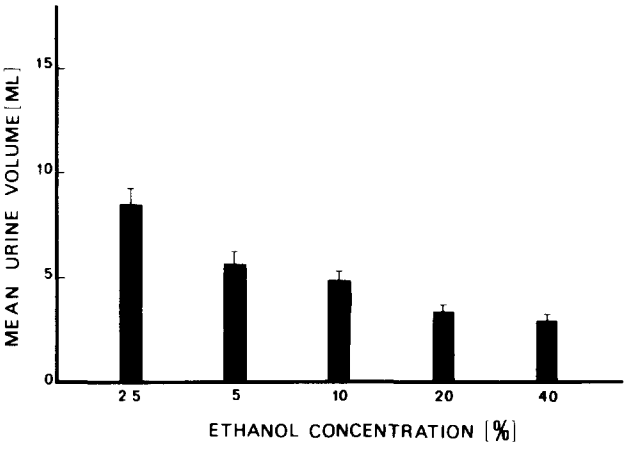

FIG 3 Specific diuretic effect of 3 g/kg BW ethanol in 0 9% saline administered intragastrically Results are expressed as mean±SEM of the differences in the urine volumes between ethanol and saline shown in Fig 2

significant for all five volumes, $t(18)=4\ 85$ (1 87 ml), 5 34 (3 75 ml), 6 48 (7 5 ml), 4 56 (15 ml), 2 39 (30 ml), $p<0\ 05$ In contrast during the three hours following the IG administration, the difference between urine volume after ethanol or saline increased from the smallest to the highest volumes This difference, at a minimum of 2 9 ml after administration of 1 87 ml (40%) solution, reached a maximal level of 8 5 ml after administration of the 30 ml of the 2 5% solution (Fig 3) Here again this difference between diuresis after ethanol or saline was statistically significant at all five concentrations, $t(18)=8\ 5$ (2 5%), 10 4 (5%), 10 7 (10%), 8 25 (20%), 7 03 (40%), $p<0\ 01$

As a result of the additive effects of volemic and ethanol-induced diuresis, the total three-hour urine excretion increased from 3 3 ml after the small volume of concentrated ethanol solution to 19 7 ml after the most diluted solution This difference was statistically significant, $t(18)=18\ 3$, $p<0\ 001$

Experiment 3

Table 2 shows that the ethanol content of urine was approximately constant from 30 to 300 min after administration of 30 ml (2 5%) and 7 5 ml (10%) of ethanol solution However, the ethanol concentration in urine was significantly lower 30 and 60 min after administration of the most concentrated ethanol solution compared to either less concentrated solution This difference was statistically significant at 30 min after administration, $t(16)=8\ 49$ (2 5% vs 40%), 5 37 (10% vs 40%) and at 60 min, $t(16)=4\ 02$ (2 5% vs 40%), 3 54 (10% vs 40%), $p<0\ 01$ Ethanol content was not different with the three solutions after 120 min

Data from experiment 1 allow us to establish the urine to blood ethanol ratio from 30 to 300 min after ethanol administration (Table 3) These ratios decreased over time after the 30 ml (2 5%) administration from 1 5 during the first hour to 1 1 during the fifth hour The inverse evolution was observed after the 1 87 ml (40%) administration In this case the ratio of urine to blood ethanol concentration increased overtime from 0 8 during the first hour to 1 5 during the fifth hour

TABLE 2

MEAN URINARY ETHANOL CONCENTRATION AFTER THE ADMINISTRATION OF 3 g/kg BODY WT ETHANOL IN 0 9% SALINE

Ethanol concentration (%)	Time (min) 30	60	120	180	300
2 5	2 9 ± 0 1	3 2 ± 0 1	3 1 ± 0 1	2 8 ± 0 1	2 0 ± 0 1
10	2 9 ± 0 2	3 3 ± 0 2	3 3 ± 0 1	3 1 ± 0 1	2 4 ± 0 1
40	1 7 ± 0 1	2 3 ± 0 2	3 1 ± 0 1	3 1 ± 0 1	2 6 ± 0 1

Results are mean ± SEM (N=9)

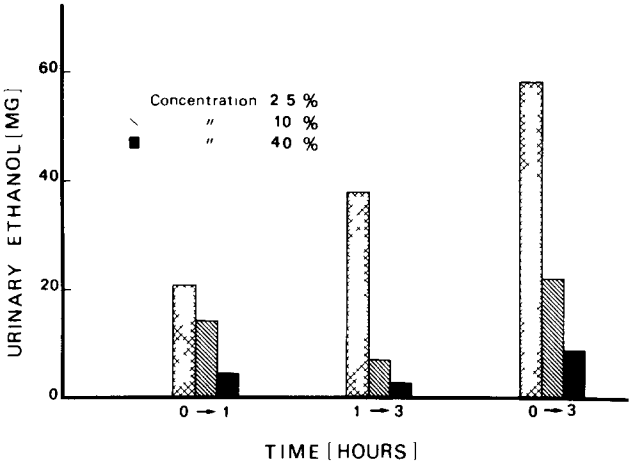

FIG 4 Urinary ethanol excretion as a function of ethanol concentration and time after the intragastric administration of 3 g/kg BW ethanol in 0 9% saline (N=9)

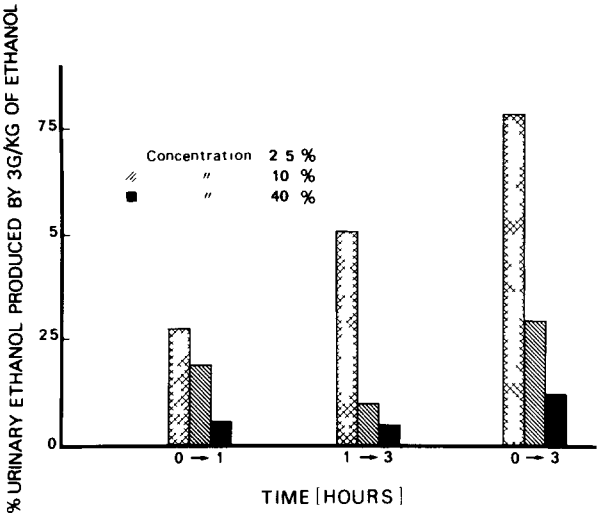

FIG 5 Percentage of administered ethanol excreted in the urine as a function of volume and concentration of 3 g/kg BW ethanol in 0 9% saline (N=9)

Experiments 2 and 3 Combined

From the results of experiments 2 and 3, the amount of ethanol eliminated through renal excretion and the difference of this excretion as a function of volumes and concentrations of the administered solution were determined Figure 4 shows that during the first hour the amounts of ethanol excreted were 20 7, 14 and 4 4 mg after administration of 30 ml (2 5%), 7 5 ml (10%) and 1 87 ml (40%) solutions respectively During the two subsequent hours these amounts were 37 9, 7 3 and 3 4 mg respectively During the three hours the total amounts excreted were 58 6, 21 3 and 7 8 mg Since the urinary flow from the third to the fifth hour was not observed, it was not possible to calculate the amount of ethanol excreted at this time during which, as was seen in experiment 3, ethanol content of urine is still relatively high Thus, the total amounts computed are likely to underestimate total ethanol extraction during the five hours following intragastric administration of ethanol solutions However, it appears that during the first three hours the amount of ethanol through urine was seven fold greater after administration of the 3 g/kg dose as a 30 ml (2 5%) solution than it was as a 1 87 ml (40%) solution Considering only the first three hours, the proportions of the net dose of ethanol administered which was excreted by the kidneys were 7 9%, 3 7% and 1 2% for the more diluted to the more concentrated solutions, respectively (Fig 5)

TABLE 3

RATIO OF URINARY AND BLOOD ETHANOL CONCENTRATIONS AFTER ADMINISTRATION OF 3 g/kg BODY WT ETHANOL IN 0 9% SALINE

Ethanol concentration (%)	Time (min) 30	60	180	300
2 5	1 5	1 2	1 0	1 1
10	1 4	1 3	1 4	1 7
40	0 8	0 8	1 2	1 5

Data are means (N=9)

DISCUSSION

In experiment 1 it was shown that after an intragastric administration of 3 g/kg ethanol in rats, the rate of increase of blood ethanol level was slower, longer and reached a maximal level when this dose was administered as 30 ml (2 5%) solution compared to smaller volumes of more concentrated solutions

Contradictory results have been published about the role of ethanol concentration in the increasing phase of blood alcohol level, generally taken as an indication of the rate of intestinal absorption According to several reports [3, 8, 9, 18, 20] ethanol would be more rapidly absorbed when administered in solutions from 15 to 30% than in solutions lower than 10% and higher than 30%

Haggard *et al* [9], in agreement with our present results, showed that complete absorption of a dose of ethanol was shorter for concentrated than for diluted solutions However, in man, Briard [2] claimed, contrary to our results in rats, that the peak in blood-ethanol level is lower after the ingestion of ethanol in a diluted solution

Three factors or mechanisms may contribute to the slower rate and longer increase of blood ethanol level with a high volume of diluted ethanol solution observed in the present study first, a slower rate of intestinal absorption, second a more rapid elimination concomitant with the absorption and third, the larger space of diffusion due to the hypervolemia induced by the 30 ml of aqueous solution

In the absence of a determination of the first factor, the rate of intestinal absorption, it is difficult to evaluate the respective contribution of these three different factors combined The more rapid elimination of the most diluted solution is apparent during the removal phase of blood alcohol level The hypervolemia after a 30 ml IG administration (more than 10% body-weight) is considerable, and leads necessarily to a more diluted ethanol in the extended space of ethanol diffusion

Our results on urinary flow confirm classical data on the ethanol and hypervolemic-induced water diuresis Their combined effect is shown to be inversely proportional to concentration and thus proportional to the volume of administered solution However, this is true for the three-hour urine excretion only Limited to the first hour, this additive effect is maximal with the 15 and 7 5 ml solutions and lower after the most diluted 30 ml solution This fact is consistent with the observed slow rate of increase of blood alcohol level during the first hour after the administration of the more diluted solution It is consistent also with reported data on the stimulation of ethanol diuresis as a function of blood ethanol level The ethanol inhibition of pituitary ADH release and, therefore, the stimulation of ethanol diuresis vary as a function not of the absolute level but of the slope of increasing blood-ethanol level [5] Since the slope is steeper during the first 40 min after administering 15 and 7 5 ml than after administration of the 30 ml of 2 5% solution this leads, as it was effectively observed, to a smaller urine excretion during the first hour (Fig 2) The maximal ethanol diuresis observed during the three hours after the most diluted solution likely results from the longer rise of blood ethanol level This diluted solution provides a less intense but 30% more lasting stimulus of ethanol diuresis This interpretation is confirmed by the fact that beyond one hour ethanol enhancement of diuresis became practically nil with the 15 ml (5%) and 7 5 ml (10%) solutions and, on the contrary, persisted and even was increasing after the 30 ml (2 5%) solution

The main finding of the three experiments combined is that the proportion of a dose of 3 g/kg of ethanol administered to rats eliminated by the kidneys is seven fold higher when this dose is contained in 30 ml than in 1 87 ml of solution and in concentrations of 2 5 and 40% respectively This proportion of the total elimination reaches and presumably exceeds 8% when the two conditions of a maximal ethanol diuresis were achieved These conditions are a high volume of aqueous ethanol solution above the threshold of onset of water diuresis, and a weak concentration of ethanol in the solution

What are the consequences of these different elimination rates of ethanol as a function of volume and concentration on the acute and chronic toxicity of ethanol on the central nervous system? It is possible to assume that the ingestion of ethanol in a volume of solution above the threshold of water diuresis and at a low concentration of ethanol may reduce its neurotoxicity In these two conditions, we have observed that the initial rate of increase of blood ethanol level was reduced It has been shown that this rate, more than the absolute value of blood ethanol level, is the dominant variable, not only for the inhibition of pituitary release of ADH, but also for the general toxicity of ethanol on the CNS [5] Thus the lethal effect of ethanol on respiratory centers may be related to the slope of increase more than to the absolute value of blood ethanol level The dose used in this study (3 g/kg) rapidly injected intravenously, i e a square wave increase of blood ethanol level, would be lethal In addition to this effect of the rate of increase of blood ethanol, the acute toxic effect of ethanol and possibly the chronic induction of tolerance and dependence are likely related to the duration of elimination of ethanol The observation of a 20% shorter time for elimination supports the suggestion of a lower toxicity of dilute ethanol solutions

This conclusion is consistent with data reported by Kulkosky [15] on voluntary consumption of ethanol in rats It is well known that rats offered a diluted aqueous solution of ethanol spontaneously limit their daily intake to an amount of the order of 4 to 5 g/kg It has been demonstrated by Lester *et al* [17] that the limiting factor was the acute toxicity of ethanol acting as an unconditioned stimulus in a conditioned taste aversion In the Kulkosky experiment, rats were offered a mixture of a 30% glucose and 0 125% saccharine solution As shown previously by Valenstein *et al* [25], rats drink up to 150 ml per day of such a highly palatable solution When 2 5% of ethanol was added to this solution, rats reduced their daily intake but it was nevertheless maintained at the high level of 100 ml Thereby rats ingested more than 9 g/kg ethanol per day This high intake of ethanol under these conditions may be interpreted as an effect of the high volume and low concentration of the solution consumed which probably elevated the threshold of a conditioned oral aversion through a post-ingestive reduced toxicity

It is not entirely speculative to extend these results to human alcohol drinking The equivalent conditions to those utilized with rats in this study would be the comparison of the acute effects in humans of the consumption of 500 ml of wine at 10% concentration of ethanol to those of the consumption of 125 ml of 40% concentrated spirits By extrapolating data obtained in rats, it is possible to assume that 500 ml of wine produce a volume and ethanol induced diuresis higher than the same dose drunk as spirits Thus wine would be less toxic, due to a combined effect of a maximal amount of ethanol elimination by the kidneys and the associated features of ethanol blood removal

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