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M. Bogusz,[1] *M.D.; J. Pach,*[2] *M.D.; and W. Staśko,*[2] *M.D.*

Comparative Studies on the Rate of Ethanol Elimination in Acute Poisoning and in Controlled Conditions

For many years, a view has been established in toxicology that the elimination of ethanol in the blood is by zero-order kinetics, that is, at a constant rate [*1–5*]. A factor which restricts ethanol metabolism is the reoxidation of a reduced form of nicotinamide dinucleotide (NADH) produced during ethanol oxidation to acetaldehyde by an alcohol dehydrogenase (ADH)-NADH system [*6, 7*].

Some workers have expressed the opinion that ethanol metabolism, particularly when it occurs at high concentrations, is subjected to first-order kinetics, specifically, that its rate of oxidation is proportional to the concentration [*8–11*]. This assertion was to some extent supported by the discovery of the microsomal ethanol oxidation system (MEOS). The MEOS has quite different catalytic properties from those of the ADH-NADH system and theoretically may play an important role in the oxidation of high ethanol concentrations [*12, 13*].

The investigations on the rate of ethanol metabolism, carried out on human volunteers, were performed at low ethanol concentrations, usually up to 200 mg/dl [*1, 2, 5, 8, 11*]. Results were generalized along the whole concentration range, including the toxic region.

The purpose of the present paper was to compare the rate of blood ethanol elimination in subjects with a high blood concentration and—in the same persons—after a small dose of ethanol had been administered. Also, the serum antipyrine half-life was studied as an indicator of microsomal enzyme activity.

Experimental Methods

The observations were made in a group of 29 patients, 26 males and 3 females, aged 17 to 60 years, treated in the toxicological department for acute ethanol poisoning. All patients were poisoned by vodka, which is in practice a 40% v/v solution of ethanol in water. The blood ethanol level was determined four times: immediately on admission and after 3, 6, and 12 h of treatment. The treatment regimen was uniform throughout the group and consisted of gastric lavage, bed rest, and intravenous infusion of 5% glucose and Ringer solution in a dose of 40 ml/kg over 6 h. Substances which might have affected the rate of ethanol metabolism (for example, fructose) were not administered. Blood samples for ethanol determination were taken from a cubital vein at the side

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[1] Head, Department of Toxicology, Institute of Forensic Medicine, Academy of Medicine, 31531 Krakow, Grzegorzecka 16, Poland.

[2] Clinical toxicologists, Toxicological Department, Institute of Internal Medicine, Academy of Medicine, Krakow, Poland.

opposite to the infusion. At the same time, blood samples were also collected for determination of hematocrit, acid-base balance, and blood chemistry. The total urine quantity was measured during first day of treatment.

After a two-day treatment bringing complete recovery, in 14 of the 29 patients the rate of ethanol elimination was estimated after oral administration of 0.5 g/kg ethanol. Venous blood samples were taken after 1, 2, and 3 h. No treatment was applied during this experiment.

The blood ethanol level was determined by the classic Widmark dichromate procedure [*14*] and by an enzymatic method [*15*] using complete reagent kits supplied by Fermognost, Dresden, GDR. The precision of both methods, expressed as coefficient of variation, averaged 2.5%.

Three days after treatment the serum antipyrine half-life in 12 of the 14 patients was estimated. The antipyrine was given orally in the dose of 15 mg/kg, and the drug level in the serum was determined according to the method of Brodie et al [*16*].

Results

Twenty patients were comatose on arrival, whereas 9 subjects were excited and aggressive. All of them regained full physical and mental control during the 24 h after admission.

Hematocrit value on admission averaged 44 ± 3 and maintained the same level during observation. The total urine quantity during first 12 h of treatment ranged from 1000 to 2400 ml. The initial concentration of ethanol in the examined group varied from 134 to 488 mg/dl, and in 21 subjects exceeded 300 mg/dl. The elimination rate β_{60} varied from 6 to 36 mg/dl per hour. The mean value amounted 17.9 ± 5.1 mg/dl per hour. In 28 patients the distinct fall of blood ethanol was observed from the beginning, and in one case the ethanol concentration in the second sample was nearly the same as on admission and then decreased. Observed fall of ethanol in the blood was not linear.

This study also examined the question of whether there is any interrelation between the blood ethanol concentration and the rate of ethanol elimination. For this purpose, in a group of 28 patients in the postabsorptive phase from the beginning of treatment, mean β_{60} was calculated from the period between the first and second blood sampling (0 to 3 h) and between the third and fourth sampling (6 to 12 h). Fifty-six elimination coefficients obtained in this manner were plotted against corresponding ethanol concentrations C (Fig. 1). Statistical analysis showed a strong positive correlation between the ethanol concentration and its rate of decrease in the observed range of concentrations. The correlation coefficient r of 0.6426 was significant at the level $P = 0.001$ and was nearly five times greater than the standard error of coefficient of 0.135. The linear regression equation for elimination rate, calculated according to the formula $y = a + bx$, was $\beta_{60} = (0.064)(C - 0.9)$ mg/dl per hour.

According to these findings, the course of the elimination curve is related to the apparent ethanol concentration. This relation seems to be more and more distinct at higher levels of ethanol. Dubowski [*11*] found the coefficient value $r = 0.305$ at a mean ethanol concentration of 123.9 ± 21.8 mg/dl, whereas in the present study the mean concentration was more than 2.5 times Dubowski's value and the r value was 2.1 times greater. Table 1 shows the comparison of the elimination rates, calculated according to Dubowski's data and the present observations. In Fig. 2 the theoretical course of the elimination is shown, calculated according to the regression equation. It must be pointed out here that these findings refer only to the toxic range and cannot be adapted to lower ethanol concentrations.

In the group of 14 of the total 29 patients the elimination rate was determined after

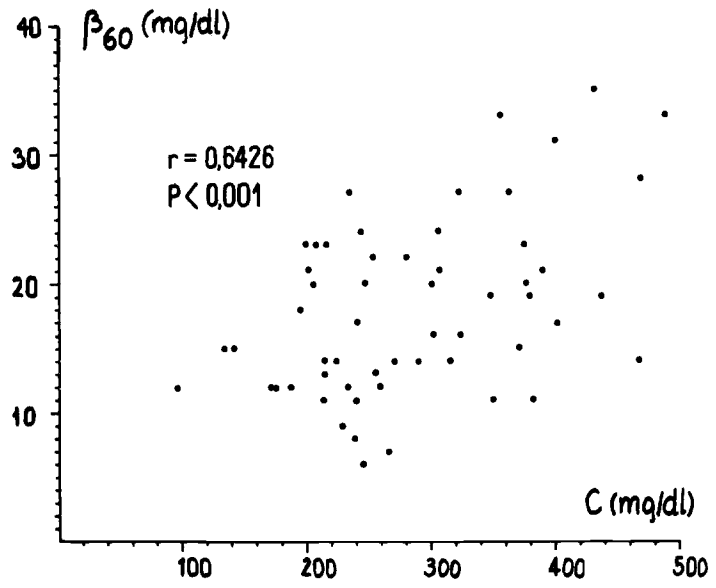

Fig. 1—*The correlation between the ethanol level in acute poisoning and its rate of elimination.*

TABLE 1—*Comparison of β_{60} values calculated according to corresponding regression equations.*

Blood Alcohol Concentration, mg/dl	Dubowski's Study [11] $y = 0.032x + 12.2$	Present Study $y = 0.064x - 0.9$
100	15.4	...
150	17.0	...
200	18.6	...
300	21.8	18.3
400	25.0	24.7
500	...	31.1

the oral administration of 0.5 g/kg ethanol. The highest value in each case was observed in the first sample, taken 1 h after the ethanol was administered, and the subsequent fall of ethanol level was linear. The mean elimination rate estimated for the small-dose condition was significantly lower than the mean rate found during the first 12 h of poisoning (Student's t distribution = 3.0544 and $P = 0.01$). Table 2 shows the blood ethanol concentrations and corresponding elimination coefficients in poisoning and after the 0.5 g/kg dose in comparison with data presented by some other authors. Complete data are presented in Table 3. In 2 patients blood ethanol decrease was independent of concentration, whereas in the 12 remaining subjects with high blood concentrations the rate of elimination was distinctly higher than after a small dose of ethanol.

No correlation was found between the rate of ethanol elimination and that of antipyrine metabolism. The serum antipyrine probably does not reflect the potential for ethanol metabolism at a toxic level.

Discussion

Blood ethanol decrease at high concentrations (about 300 mg/dl) is faster than at

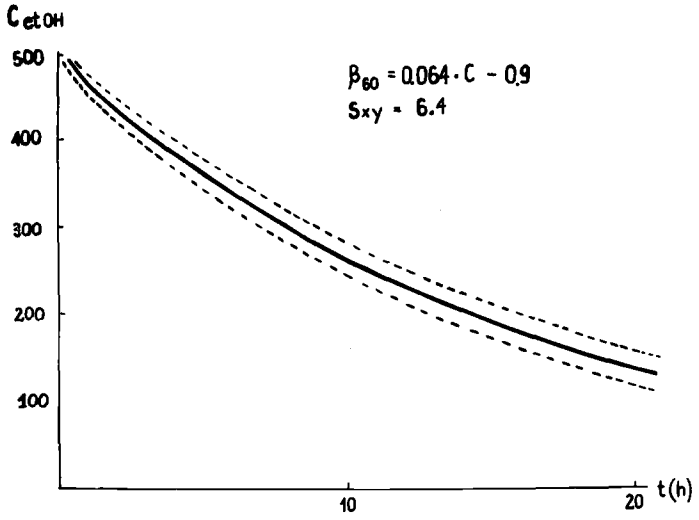

FIG. 2—*The course of ethanol elimination in acute poisoning, plotted according to the present findings* (solid line *represents the theoretical course,* dotted lines *show the scatter*).

TABLE 2—*Comparison of the rate of ethanol metabolism on the various levels of ethanol in blood* (*mean* ± *SD*).

Author	*n*	C_{max}, mg/dl	β_{60}, mg/dl per hour	B_{60}, mg/kg per hour
Present study	14[a]	336 ± 114	21.9 ± 7.2	...
	14[b]	42 ± 11	14.6 ± 4.8	...
Brown et al 1972 [*17*]	10[a]	239 ± 92	22.5 ± 5.9	...
Nasilowski 1965 [*18*]	33[c]	112 ± 19.4	13.7 ± 4.0	10.1 ± 3.0
	3[d]	209 ± 25	19.0 ± 7.8	15.2 ± 2.2
Abele 1955 [*8*]	14	173 ± 35	15.4 ± 1.9	...
Dubowski 1975 [*11*]	41	124 ± 22	16.1 ± 3.6	10.7 ± 1.7

[a] Intoxication.
[b] Dose, 0.5 g/kg.
[c] Dose, 1 g/kg.
[d] Dose, 2 g/kg.

low concentrations. There are several possible explanations of this phenomenon. The rate of ethanol disappearance from the blood and from the entire organism is a sum of hepatic oxidation and excretion with breath and urine [*3,4*]. It is possible that at high concentrations excretion of unchanged ethanol distinctly increases [*2*]. It should be added that the β_{60} value does not reflect the rate of ethanol metabolism. Metabolism also depends on Widmark's *r* factor, which is reciprocally related to β [*1–4*]. Acute ethanol poisoning may modify the distribution of water in the body and subsequently affect the *r* value and the rate of ethanol disappearance from the blood.

It is also possible, however, that the observed differences were caused by metabolic factors. It is known from experimental studies that the microsomal system plays an essential role in ethanol oxidation of high concentrations [*12,13,19*]. Experiments performed by Lundquist et al [*20*] confirm this hypothesis. He showed that at a 4-m*M* concentration about 80% of the ethanol is oxidized by ADH; at 40 m*M*, 50%; and at 80

TABLE 3—*Blood ethanol level and its elimination rate in acute poisoning and after a dose of 0.5 g/kg body weight.*[a]

Subject	C_{tox}	β_{60tox}	C_c	β_{60c}	$\Delta\beta_{60}$	$T_{½}$
1	399	25	28	10	15	13
2	271	14	21	12	2	15
3	468	20	28	20	0	11
4	302	17	55	9	12	15
5	134	20	60	12	8	20
6	488	27	31	20	7	8
7	225	36	42	20	16	12
8	215	16	36	9	7	...
9	406	27	40	22	5	14
10	467	16	53	10	6	15
11	279	13	38	11	2	9
12	401	17	44	17	0	...
13	219	23	45	17	6	15
14	431	35	63	16	19	11

[a] Abbreviations:
C_{tox} = initial concentration of ethanol during poisoning.
β_{60tox} = elimination rate during poisoning.
C_c = peak concentration of ethanol after a dose of 0.5 g/kg.
β_{60c} = elimination rate after a dose of 0.5 g/kg.
$\Delta\beta_{60}$ = the difference between β_{60tox} and β_{60c}.
$T_{½}$ = antipyrine half-life in hours.

m*M* or 370 mg/dl, only 24%. Lieber [*13*] demonstrated that the Michaelis constant K_m for the ADH-NADH system is about one order of magnitude lower than K_m for the MEOS system. Therefore it is possible that the MEOS system takes part in the oxidation of high amounts of ethanol and forms the exponential or biphasic shape of the elimination curve.

The nonlinear course of the ethanol decrease at high concentrations and the great individual variability in the rate of elimination suggest that extreme caution in the use of speculative retrograde calculations in medicolegal practice should be exercised.

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Dr. med. Maciej Bogusz
Institute of Forensic Medicine
31531 Krakow, Grzegorzecka 16
Poland