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Interaction Toxicity Between Ethanol and Narcotics in Mice with Reference to Alpha-l-Acetylmethadol (LAAM)

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HO, A. K. S., R. C. A. CHEN AND C. C. HO. *Interaction toxicity between ethanol and narcotics in mice with reference to alpha-l-acetylmethadol (LAAM).* PHARMAC. BIOCHEM. BEHAV. 9(2) 195–200, 1978.—Interactions between narcotics, especially alpha-l-acetylmethadol (LAAM) and ethanol were studied in mice. Co-administration of LAAM either at 18 or 36 mg/kg significantly potentiated ethanol lethality, the LD_{50} due to ethanol was lowered by 21% and 36%, respectively. At low doses of ethanol (0.5 and 1.0 g/kg), toxicity due to LAAM was decreased; the LD_{50} was increased significantly ($p<0.006$–0.05) to 76 and 64 mg/kg, respectively, compared with 56 mg/kg for LAAM alone. At 4 g/kg of ethanol, the LD_{50} due to LAAM was decreased to 43.9 mg/kg, showing a significant ($p<0.002$) potentiation of interaction toxicity between the two compounds. Chronic pretreatment of LAAM for 7 days produced no significant alteration in ethanol lethality. Treatment with various narcotic agonists (morphine, LAAM, methadone, and levorphanol) and ethanol, the rate of disappearance of ethanol was decreased significantly in the blood and brain whereas naloxone and dextrorphan, an inactive stereoisomer of levorphanol, produced a small but significant increase. Ethanol pretreatment produced no significant alteration on the brain and blood levels of morphine with the exception of 4 g/kg at 150 min after treatment. Increase in toxicity with the combined administration of LAAM and ethanol was attributed in part to the retention of ethanol.

Ethanol-narcotics Interaction toxicity Alpha-l-acetylmethadol Blood-brain ethanol

THERE are many reports in the literature on the widespread use of ethanol and other abused drugs by narcotic addicts when their drugs of choice are not avalable [7]. Addicts maintained on prolonged methadone treatment and who became secondarily dependent on ethanol develop a syndrome with increased mortality rate over those on methadone maintenance alone [10,15]. Recently, alpha-l-acetylmethadol (acetylmethadol, LAAM), a synthetic narcotic analgesic derivative of d-methadone, has been introduced for clinical trials as a possible substitute for heroin dependence. It has the advantage over methadone in that it has a longer duration of action. In view of the similar pharmacological activities between LAAM and methadone, it is reasonable to anticipate that similar interactions may exist between ethanol and LAAM in addicts on LAAM maintenance.

Interactions of various psychoactive drugs with narcotics including LAAM have been reported in rats and mice. Maickel and co-workers [13] reported that on cessation of chronic dosage of both LAAM and methadone, the rats showed a marked decrease in fluid consumption (withdrawal) for over 5 days. They further reported that in chronic LAAM-treated rats given chlordiazepoxide, there were significant increases in open-field and actophotometer activities and an increased rate of rotorod failures in chronic LAAM rats given imipramine. Venho *et al.* [17] reported a marked increase of morphine lethality in mice chronically treated with ethanol. Killam and co-workers [11]studied the effects of various abused drugs including LAAM and alcohol on the self-administration of morphine in morphine-dependent monkeys and observed that methadone and LAAM initially reduced, then increased the morphine intake; combination of ethanol with LAAM produced potentially serious behavioral incapitation due possibly to the marked increase in morphine intake. LAAM is both N-demethylated and deacetylated into its respective metabolites: noracetyl- and dinoracetyl-methadol, methadol and normethadol, all of which are known to possess narcotic activity in animal test systems and thus believed to be responsible for the long duration of drug action [9,16]. Preliminary studies from our laboratory show that a single injection of LAAM, hereafter referred to as acute treatment, like those with morphine and methadone, suppressed the voluntary consumption of ethanol in mice and rats whereas ethanol consumption was found to increase during morphine withdrawal [8]. Our findings showed that ethanol in combination with LAAM produced a biphasic response with respect to lethality due to LAAM depending on the dose of ethanol. In addition, pretreatment with narcotic analgesics including morphine, LAAM, methadone and levorphanol decreased the rate of disappearance of ethanol in the blood and brain whereas naloxone, a narcotic antagonist and dextrorphan, an inactive stereoisomer of levor-

phanol, produced no significant decrease but a small increase in the disappearance of ethanol in both the blood and brain.

METHOD

The animals used were adult male Swiss-Webster white mice weighing between 25 to 30 g (supplied by Microbiological Associates, Bethesda, MD). Except when otherwise specified, animals were housed in standard stainless steel wire mesh cages and maintained in humidity and temperature controlled rooms with light-dark cycle of 14–10 hr. The animals had free access to food (Purina Lab Chow) and deionized water.

Interaction Toxicity Between LAAM and Ethanol

To determine the LD_{50} of ethanol and LAAM, either alone or in combination, various doses of each compound were injected into groups (six to eight) of at least eight mice each and observed for seven days. The dosage of ethanol (20% v/v) used for LD_{50} determination was from 5.0 to 11.0 g/kg IP and for LAAM LD_{50} determination, it was from 20 to 100 mg/kg, SC. Controls were given an equivalent volume (up to 1.0 ml) of saline. The data were analyzed by the Litchfield-Wilcoxen procedure [12]. In acute toxicity experiments, when mice were treated with both compounds, ethanol was injected immediately after a subcutaneous injection with LAAM. To determine the effect of ethanol on LAAM lethality, a fixed IP dose of ethanol (0.5, 1.0, 2.0 and 4.0 g/kg) was given in conjunction with various SC doses of LAAM ranging from 20 to 100 mg/kg. To study the effect of LAAM on ethanol toxicity, a fixed dose of either 18 or 36 mg/kg was given in combination with various doses of ethanol ranging from 4.0 to 11.0 g/kg. The LAAM doses were selected from the dose-lethality curve of LAAM alone and both of these doses were below lethality (LD_0) under our conditions. To study the chronic toxicity, one group of mice was pretreated with ethanol for 10 days with a daily dose of 3 g/kg followed by varying single doses of LAAM to determine the LD_{50} due to LAAM. To study the effects of chronic LAAM on ethanol toxicity, mice were pretreated with LAAM (10 mg/kg) daily with incremental increases of 10 mg/kg for 3 days and maintained at 40 mg/kg for another 3 days. The LD_{50} due to ethanol was determined following the last injection of LAAM.

Interaction Between Ethanol and Narcotic Agonists and Naloxone on the Levels of Ethanol in Blood and Brain

The acute effects of varying doses of morphine, methadone, LAAM, and naloxone on the blood and brain levels of ethanol in mice were determined over periods of 20, 50 and 100 min following a prior dose of 2 g/kg (IP) of ethanol. The drugs were supplied as follows: morphine sulfate (Merck Chemical Co.); ℓ-α-acetylmethadol (National Institute on Drug Abuse); methadone hydrochloride (Eli Lilly Co.); levorphanol and dextrorphan hydrochloride (Hoffman LaRoche Co.); naloxone hydrochloride (Endo Laboratory); and ethanol, 95% (Scientific Products Co.). All drugs were administered subcutaneously and within 30 sec prior to ethanol. The concentrations of ethanol in blood and brain were estimated by the enzymatic assay of Bonnichsen [2] using NAD-ADH (obtained from Sigma Chemical Co.), after extraction from 6.0% trichloroacetic acid (TCA) and centrifugation for the blood, and homogenization in four volumes of 6% TCA followed by centrifugation in case of the brain. In chronic toxicity experiments, mice were injected SC with morphine or LAAM daily for eight days with an initial dose of 10 mg/kg and with incremental increases of 10 mg/kg every two days reaching a daily dose of 40 mg/kg. In mice treated with methadone, the initial SC dose was 2 mg/kg with daily incremental increases of 2 mg/kg, and maintained to 10 mg/kg to the 8th day. To study the effect of ethanol on the brain and blood levels of morphine, mice were treated either acutely with a fixed dose of ethanol (0.5, 1.0, 2.0 and 4.0 g/kg, IP) or chronically with 4 g/kg daily for 10 days followed by an initial dose of morphine (20 mg/kg, SC). Morphine was extracted and the levels determined by spectrofluorometry according to the method of Paalzone and Paalzone [14]. The mice were decapitated at 50, 100 and 150 min after the morphine injection and blood and brain samples were obtained.

RESULTS

Acute and Chronic Toxic Effects of LAAM and Ethanol

The LD_{50} due to ethanol (20% v/v, IP) over a period of 7 days was 9.2 g/kg (8.9 to 9.4 g/kg, 95% confidence limit, C.L.) and for LAAM it was 56 mg/kg (51 to 62 mg/kg, 95% C.L.). The effects of ethanol in combination with LAAM showed both antagonism and potentiation of lethality as measured by the LD_{50} due to LAAM. At the lower doses of 0.5 and 1.0 g/kg of ethanol, the mean LD_{50} values of LAAM were found to be increased significantly to 76 ($p<0.006$) and 64 mg/kg ($p<0.05$), respectively, showing a significant protection from LAAM toxicity. However, at the higher ethanol dose of 4 g/kg, the LD_{50} due to LAAM was found to be decreased significantly ($p<0.002$) to 43.9 mg/kg, showing a significant potentiation of toxicity. No significant effect was observed with the 2.0 g/kg ethanol dose. In mice treated with acute LAAM at 18 mg/kg and 36 mg/kg, the LD_{50}'s due to ethanol were significantly ($p<0.0005$) decreased to 7.3 and 5.9 g/kg, respectively. In mice chronically pretreated with ethanol, the LD_{50} due to LAAM showed a slight decrease with a LD_{50} of 50 mg/kg, whereas mice chronically pretreated with LAAM, the LD_{50} due to ethanol was not significantly different from the controls (Table 1).

The Effect of Acute and Chronic Treatment with Narcotics on the Blood and Brain Levels of Ethanol

The rate of disappearance of ethanol in the blood and brain was first examined following a single injection of narcotic agonists (morphine, methadone, LAAM, levorphanol), dextrorphan and naloxone. Ethanol (2 g/kg, IP) injected within 30 sec after the test drug, was measured over a period from 20 to 100 min (Table 2). The narcotic agonists (10 mg/kg, SC) given in combination with ethanol, significantly ($p<0.02$) delayed the disappearance of ethanol as indicated by the higher blood and brain concentrations at both 50 and 100 min after treatment. The effect of LAAM was found to be longer lasting than the other narcotic agonists as evident by the blood and brain levels of ethanol at 100 min after treatment. Mean blood ethanol levels (in mg%) were LAAM, 84.5; methadone, 80.0; levorphanol, 75.5; and morphine, 67.5, compared with 56.8 for the controls (N=22). Coadministration of ethanol with naloxone also produced a small but significant increase in the disappearance of ethanol in both the blood and brain. The difference in response between a single injection of levorphanol and dextrorphan (10 mg/kg, SC), with respect to analgesia, was most marked since dextrorphan treatment produced a small increase

TABLE 1

LETHALITY OF LAAM AND ETHANOL INTERACTIONS IN MICE IN 7 DAYS*

	LD_{50}	95% C.L.	Significance†
Ethanol	9.2 g/kg	8.9–9.4	
LAAM	56.0 mg/kg	51.0–61.7	
Ethanol Plus LAAM	LAAM LD_{50}	in mg/kg	
0.5 g/kg Ethanol	76.0	74.0–78.0	$p<0.006$
1.0 g/kg Ethanol	64.0	59.0–70.0	$p<0.05$
2.0 g/kg Ethanol	61.8	56.7–67.4	N.S.
4.0 g/kg Ethanol	43.9	38.0–50.0	$p<0.002$
Chronic Ethanol 3 g/kg daily for 10 days	50.0	45.0–56.0	N.S.
LAAM Plus Ethanol	Ethanol LD_{50}	in g/kg	
18 mg/kg	7.3	6.8–7.8	$p<0.0005$
36 mg/kg LAAM	5.9	5.4–6.5	$p<0.0005$
Chronic LAAM Plus Ethanol	9.0	8.5–9.6	N.S.

*Each LD_{50} Value was obtained from 8–10 groups of at least eight adult Swiss Webster mice (20–25 g). Data were estimated by the Litchfield-Wilcoxin procedure.

†Significantly different from either LAAM or alcohol alone, $p \leq 0.05$.

TABLE 2

EFFECTS OF ACUTE NARCOTICS AND NARCOTIC ANTAGONIST TREATMENT ON BLOOD AND BRAIN LEVELS OF ETHANOL AT DIFFERENT TIME AFTER ETHANOL LOADING IN SWISS-WEBSTER WHITE MICE

Treatment‡ Ethanol (2.0 g/kg, IP) in combination with various drugs	Time in Minutes after Ethanol Injection (IP) 20		50		100	
	Brain mg/g Mean ± SD	Blood mg% Mean ± SD	Brain mg/g Mean ± SD	Blood mg% Mean ± SD	Brain mg/g Mean ± SD	Blood mg% Mean ± SD
Saline control (N=8)	3.74 ± 0.08	176.18 ± 1.40	2.54 ± 0.08	125.48 ± 3.39	1.51 ± 0.02	55.97 ± 4.59
Morphine (10 mg/kg) (N=6)	3.73 ± 0.09	180.20 ± 5.70	2.89 ± 0.09*	141.19 ± 2.01*	1.60 ± 0.10†	67.51 ± 6.54*
Methadone (10 mg/kg) (N=6)	3.64 ± 0.09†	176.97 ± 3.01	2.74 ± 0.09*	136.85 ± 7.37*	1.78 ± 0.09*	79.99 ± 7.14*
Saline control (N=8)	3.72 ± 0.12	175.63 ± 4.78	2.56 ± 0.10	127.18 ± 4.72	1.53 ± 0.09	57.58 ± 4.68
ℓ-α-Acetylmethadol (10 mg/kg) (N=6)	3.74 ± 0.05	174.78 ± 5.42	2.76 ± 0.04*	142.40 ± 5.07*	2.15 ± 0.20*	84.48 ± 4.02*
Levorphanol (10 mg/kg) (N=6)	3.74 ± 0.08	177.60 ± 1.75	2.90 ± 0.08*	137.27 ± 3.53*	1.88 ± 0.14*	75.54 ± 6.47*
Saline control (N=6)	3.68 ± 0.14	176.00 ± 7.50	2.56 ± 0.09	126.58 ± 3.90	1.50 ± 0.12	60.41 ± 4.90
Naloxone	3.65 ± 0.12	174.50 ± 3.20	2.29 ± 0.09*	117.98 ± 6.70*	1.20 ± 0.09*	46.10 ± 5.20*

Values expressed as Mean ± SD, significantly different from control

*$p<0.0025$

†$p<0.025$

‡Ethanol was administered within 30 sec after subcutaneous injection of drug

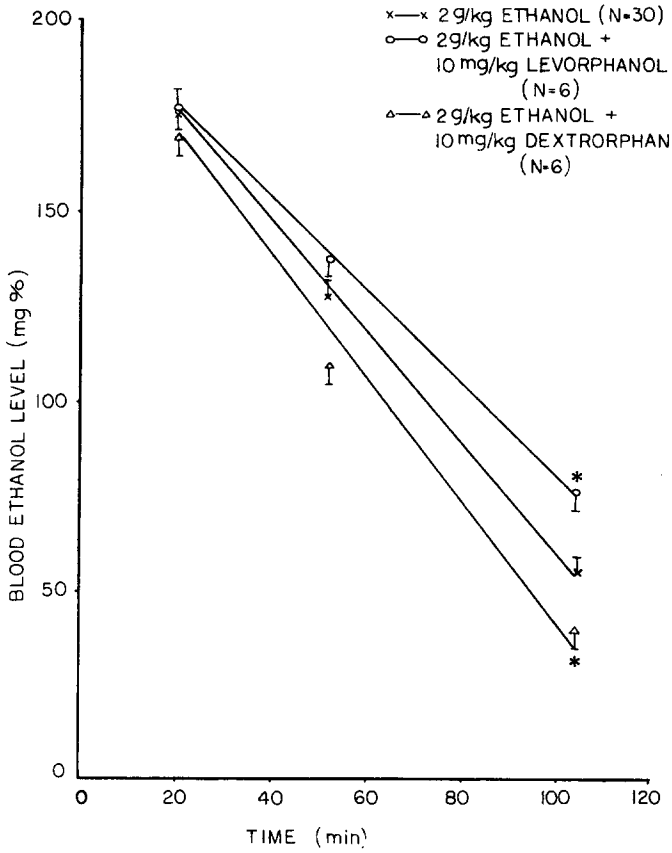

FIG. 1. Effects of acute levorphanol and dextrorphan on the ethanol level of blood after a loading dose (2 g/kg, IP) in Swiss-Webster mice. Drugs were injected (SC) 30 sec prior to ethanol administration. Data expressed as mean ± SD. *Significance $p<0.002$.

($p<0.002$) in the rate of disappearance of ethanol instead of a significant decrease ($p<0.002$) as found with levorphanol (Fig. 1). It was also evident that the response to both narcotics and naloxone were dose-dependent. Data obtained on the acute effects of various doses of morphine (2.5 to 30 mg/kg, SC), LAAM (2.0 to 30 mg/kg, SC), and naloxone (1 to 30 mg/kg, SC) on a single dose of ethanol (2.0 g/kg, IP) at 50 min after treatment are summarized in Table 3. Except for the lowest dose (2.5 mg/kg, SC), morphine treatment resulted in a small but significant increase of ethanol in both the brain and blood. Similarly, retention of ethanol was observed in mice treated with a LAAM-ethanol combination. However, dextrorphan (Fig. 1) and naloxone treatment resulted in a small but significant decrease in the blood and brain ethanol concentrations.

Pretreatment with narcotics for 8 days produced a small increase in blood and brain ethanol levels at 50 min after an ethanol (2.0 g/kg, IP) injection (given simultaneously with the test drug). Mean brain levels of ethanol in mg/g wet weight (mean ± SD) were morphine, 2.68 ± 0.09; methadone, 2.65 ± 0.05; LAAM, 2.63 ± 0.03, and controls, 2.54 ± 0.08. Mean values obtained for blood in mg% (mean ± SD) were morphine, 129.6 ± 1.8; methadone, 133.1 ± 3.1; LAAM, 128.5 ± 5.6; and controls, 125.5 ± 3.9. With the exception of the blood ethanol value for LAAM treatment, the remaining values were small but significantly different from controls ($p<0.05$).

TABLE 3

ACUTE EFFECTS OF VARYING DOSES OF NARCOTICS AND NARCOTIC ANTAGONIST ON THE BRAIN AND BLOOD LEVEL OF ETHANOL 50 MINUTES AFTER A LOADING DOSE IN SWISS-WEBSTER WHITE MICE

Treatment§ Ethanol Interaction With Various Doses of Drugs		50 Minutes After Ethanol (2 g/kg) Injection (IP) Ethanol Level in mg/g—Brain Wet Weight Mean ± SD	Ethanol Level in mg%—Blood Mean ± SD
Ethanol control	(N=8)	2.54 ± 0.08	125.41 ± 3.60
Morphine			
2.5 mg/kg	(N=6)	2.53 ± 0.01	126.94 ± 1.98
7.5 mg/kg	(N=6)	2.66 ± 0.03*	129.89 ± 1.83‡
10 mg/kg	(N=6)	2.89 ± 0.09*	141.19 ± 2.01*
30 mg/kg	(N=6)	2.83 ± 0.09*	139.65 ± 6.65*
Ethanol control	(N=8)	2.56 ± 0.10	127.18 ± 4.74
ℓ-α-acetylmethadol			
2.0 mg/kg	(N=6)	2.61 ± 0.07	132.99 ± 2.70‡
10 mg/kg	(N=6)	2.76 ± 0.04*	142.40 ± 5.07*
30 mg/kg	(N=6)	2.91 ± 0.09*	145.27 ± 6.37*
Ethanol control	(N=6)	2.57 ± 0.09	126.58 ± 3.90
Naloxone			
1.0 mg/kg	(N=6)	2.54 ± 0.06	125.35 ± 3.00
2.5 mg/kg	(N=6)	2.44 ± 0.09†	120.49 ± 2.65‡
5.0 mg/kg	(N=6)	2.37 ± 0.08*	118.41 ± 3.90*
10 mg/kg	(N=6)	2.29 ± 0.09*	117.98 ± 6.70*
30 mg/kg	(N=6)	2.30 ± 0.08*	117.41 ± 3.60*

Values ar expressed as Mean ± Standard Deviation, significantly different from controls
*$p<0.002$
†$p<0.01$
‡$p<0.02$
§Drugs and ethanol were administered within 30 sec

The data obtained on the effects of acute and chronic ethanol treatment in combination with morphine (20 mg/kg, SC) on the blood and brain morphine levels in mice over a period of 50 to 150 min after morphine injection are summarized in Table 4. With the exception of a single ethanol dose of 4 g/kg, no significant effect of ethanol was observed on morphine concentrations in both brain and blood. The 4 g/kg dose of ethanol was the only dose that was found to produce a small but significant ($p<0.05$) increase in both blood and brain morphine levels at 150 min after morphine loading.

DISCUSSION

The results of this study clearly demonstrated interactions between ethanol and various narcotic agonists and antagonists with respect to toxicity, and disappearance of ethanol in blood and brain. The marked potentiation of ethanol toxicity in mice by a single dose of LAAM at 18 or 36 mg/kg with a reduction in the values of LD_{50} by 21 and 36%, respectively, showed the effect was dose-dependent. It should be noted that both doses of LAAM used in this study are many times greater than the equivalent therapeutic dose and yet below the toxic dose. These doses were selected since 36 mg/kg was at the threshold of toxicity and 18 mg/kg

TABLE 4

EFFECTS OF ACUTE AND CHRONIC ETHANOL ON BLOOD AND BRAIN LEVEL OF MORPHINE AT DIFFERENT TIME AFTER MORPHINE LOADING IN SWISS-WEBSTER MICE

	Time in Minutes After Morphine Sulfate Injection (IP)					
	50		100		150	
Morphine Sulfate (20 mg/kg)† Interaction with Ethanol	Brain ng/g Wet Weight Mean ± SD	Blood μg/ml Mean ± SD	Brain ng/g Wet Weight Mean ± SD	Blood μg/ml Mean ± SD	Brain ng/g Wet Weight Mean ± SD	Blood μg/ml Mean ± SD
Morphine control (N=12)	244.97 ± 8.74	2.00 ± 0.07	86.36 ± 6.32	1.74 ± 0.09	45.83 ± 7.19	1.27 ± 0.10
Acute Ethanol						
Ethanol (4 g/kg) (N=6)	249.75 ± 11.96	2.05 ± 0.21	88.72 ± 6.57	1.75 ± 0.08	55.67 ± 5.50 ($p<0.0125$)*	1.34 ± 0.08 ($p<0.05$)*
Ethanol (2 g/kg) (N=6)	246.63 ± 7.54	1.96 ± 0.20	86.65 ± 4.42	1.74 ± 0.12	43.50 ± 9.73	1.26 ± 0.06
Ethanol (1 g/kg) (N=6)	244.37 ± 6.99	1.94 ± 0.17	86.91 ± 4.23	1.77 ± 0.07	43.67 ± 6.77	1.24 ± 0.08
Ethanol (0.5 g/kg) (N=6)	245.99 ± 11.73	1.96 ± 0.10	86.68 ± 5.16	1.78 ± 0.11	42.16 ± 5.87	1.29 ± 0.11
Chronic Ethanol						
Last Dose (4 g/kg) (N=6)	245.59 ± 11.44	1.97 ± 0.08	88.67 ± 4.82	1.74 ± 0.09	47.83 ± 8.90	1.24 ± 0.09

*Values are expressed as Mean ± SD, significantly different from controls
†Morphine Sulfate was administered within 30 sec after ethanol
Chronic treatment=3 g/kg of 20% ethanol was given orally for 10 days to mice

was a dose equivalent to 50% below the threshold and thus any increase in toxicity could be easily observed. Nevertheless, these findings may be significant in terms of acute intoxication of LAAM in the presence of ethanol. Furthermore, LAAM and its various active metabolites are known to have a long duration of action and may accumulate in tissues. In this regard, Maickel and co-workers [13] have noted that the values for the acute toxicity, as measured by LD_{50}, decreased over five-fold from 2 to 24 hr. In this study, the mean LD_{50} value for LAAM was 56 mg/kg, SC, for an observation period of 7 days; whereas, a mean LD_{50} value of 111 mg/kg was reported by Maickel *et al.* for a 24 hr period. Another possible source of discrepancy may be that our mice were kept in groups of four or five whereas Maickel *et al.* reported their mice were kept in isolation. On the other hand, the effects of a single injection of ethanol on LAAM toxicity appeared to be biphasic. For example, at the lower doses of ethanol (0.5 to 1.0 g/kg, IP), toxicity due to LAAM was significantly antagonized whereas at the high dose of ethanol (4.0 g/kg, IP) toxicity due to LAAM was potentiated. Mice given a low dose of ethanol (0.5 g/kg) in combination with LAAM, produced an initial stimulation on respiration and motor activity whereas at the high dose (4.0 g/kg), a severe depression of both parameters was observed. It is not known to what extent has LAAM and its various active metabolites contributed to the lethality during the 7-day period. It would be interesting to study the metabolism of LAAM under the influence of ethanol.

The fact that narcotic agonists, given in conjunction with ethanol significantly delayed the disappearance of ethanol in both brain and blood may offer some explanation for the increase in toxicity of narcotics taken with ethanol, as observed in previous clinical and animal studies [7, 10, 15, 17] as well as in this study. Of interest were the relative mild effects of chronic methadone, LAAM, and morphine on the rate of disappearance of ethanol in the blood and brain. These findings suggest that tolerance has developed to the effects of narcotics on the rate of disappearance of ethanol. The difference between levorphanol and dextrorphan, a stereoisomer of levorphanol, on blood and brain ethanol levels is also suggestive of some stereospecific action in the effects of narcotics on tissue ethanol concentrations.

The finding that naloxone, a narcotic antagonist, produced opposite effects to those of the active narcotic agonists on blood and brain ethanol distributions would further suggest that the interaction between ethanol and narcotics is relatively specific. The fact that either acute or chronic ethanol treatment has little effect on the morphine contents in the blood and brain, except at the high single dose of ethanol (4 g/kg) suggests that the increase in ethanol levels in the brain may be a more important factor explaining the combined toxicity of these two compounds.

The mechanisms for ethanol-narcotic interaction is at present unknown, although several studies have appeared postulating a common chemical basis. Studies by Davis and Walsh [6] and Cohen and Collins [5] independently postulated that a tetrahydropaperoline (THP) alkaloid formed from a condensation product of acetaldehyde and dopamine is responsible for ethanol dependence. Blum and co-workers further showed that naloxone inhibits ethanol dependence and blocks narcosis produced by ethanol in mice [3,4]. Amit and Levitan [1] reviewed the literature and suggested a possible differential involvement of catecholamines as a common basis for ethanol and morphine self-administration. Recently, Blum *et al.* reviewed the literature and stressed the increasing evidence for a common biochemical and behavioral basis of action of ethanol and opiates [3].

In conclusion, the increase in blood and brain ethanol

levels and toxicity of LAAM and other narcotics may be of clinical significance in view of the fact that ethanol, either by acute or chronic intoxication, has a relatively narrow safety margin.

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