Evaluation of Naloxone as an Antidote for Alcohol Intoxication

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This study evaluates the potential antidotal effect of naloxone on experimentally induced alcohol intoxication in 12 mongrel dogs. Its antidote effects is also evaluated in 20 patients suffering from alcohol intoxication. The clinical findings, blood gases analysis and alcohol levels were suggestive of an antagonistic action of naloxone in alcohol intoxication.

(Egypt.J. Psychiat.,1994, 17: 101-108).

Introduction

Acute alcohol toxicities are mainly due to intake of big amounts of strong alcoholic drinks, i.e. spirits like whisky and brandy, while industrial cases are considered limited (Driesbach, 1983). Mild, moderate and severe toxicities are expressed when blood alcohol levels reach 0.15%, 0.3% and 0.5% respectively (Shoemaker et al., 1984). Alcoholic coma is accompanied with severe respiratory and circulatory depression and subnormal temperature (Arena, 1979).

Naloxone was proved to be a safe drug even in very large doses (Martindale, 1982), that's why we were encouraged to perform this study which aimed to evaluate the potential antidotal effect of naloxone regarding alcohol intoxications.

Subjects and Method

The aim of this work is to study potential counteracting effect of naloxone hydrochloride (Narcan) on respiratory, circulatory and central nervous system changes induced by ethyl alcohol intoxication.

To carry on this goal, this study was done in two aspects:

1- Experimental Part

Twelve dogs were given ethyl alcohol through 5% dextrose infusion in a dose of 4 gm/kgm over 20 minutes period. At the end of the infusion and before starting naloxone treatment, blood samples were withdrawn for determination of alcohol level.

Then, seven dogs received naloxone treatment in the following regimen:

(a) 70 ugm/kgm in one bolus.

(b) 280 ugm/kgm of nolaxone diluted in 100 ml of 5% dextrose and given as continuous intravenous infusion over a period of 30 minutes.

While 5 dogs were kept on the 5% dextrose infusion at the same rate for 30 minutes. Heart rate, blood pressure, respiratory rates, arterial O2 tension, arterial CO2 tension, bicarbonate, and pH were determined after the "Bolus" injection, after 15 minutes of infusion and then after 30 minutes of infusion.

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2- Clinical Part

Twenty patients came to Emergency Room suffering from alcohol intoxication as proved from the clinical manifestations and serum alcohol level; are treated by Naloxone IV and the improvement in their general condition was assessed. The naloxone was administered as:

(a) intravenous bolus of 2 ampoules (0.8 mg).

(b) 280 ugm/kgm of naloxone diluted in 100 ml of 5% dextrose and given as continuous intravenous infusion over a period of 30 minute.

Results

Table (1) shows changes in mean values for pulse rate, blood pressure and respiratory rate in ethanol intoxicated dogs (2 gm/kgm in 10 minutes and 2 gm/kgm in 20 minutes infusion). as compared to control values.

The animals were comatosed and there was a significant decrease of the pulse rate and in the systolic blood pressure, but no significant drop in the diastolic blood pressure. The depression in the respiratory rate was highly significant and respiratory arrest was observed in all the intoxicated dogs after a total dose of 4 gm/kgm given over 20 minutes.

In the naloxone treated animals of this group, naloxone injection in one bolus of 70 ug/kgm, brought a rapid reversal of coma and the animals became responsive to painful stimuli. The effect was clear on respiration regaining a rate comparable to that before intoxication. The cardiovascular response was much less dramatic.

Table (1) also shows the effect of naloxone treatment (15 minutes infusion), on the alcohol- intoxicated dogs. The heart rate increased, blood pressure and respiratory rate all increased.

After 30 minutes treatment of naloxone, all the parameters were comparable to those before administration of ethanol.

Table 1
Clinical Manifestations of Ethanol - Intoxicated Dogs

Group	Heart Rate	Blood Pressure		Resp. Rate
		Systolic	Diastolic	
Control	199.6±12.4	190.7±13.6	87.9±115	26.9±3.02
Ethanol-intoxicated (10 min. infusion) II	179.6±15.4	159.9±12.7	75.3±10.4	14.6±2.99
t	2.68	4.36	2.15	7.64
p	<0.05	<0.01	>0.05	<0.01
Ethanol-intoxicated (20 min. infusion) III	143.3±14.02	158.8±8.1	80.17±13.03	0
t	7.7	5.02	1.13	∞
p	<0.01	<0.01	>0.05	>0.01
Naloxone- treat. (70 ug/kg "bolus") IV	1515±23.1	159.7±4.3	74.0±12.7	24.3±8.96
t	0.74	0.22	0.83	∞
p	>0.05	>0.05	<0.05	<0.01
Naloxone (15 min. infusion) V	167.8±25.3	161.17±22.4	75.17±8.3	23.0±4.7
t	2.1	0.24	0.79	∞
p	>0.05	>0.05	>0.05	<0.01
Naloxone (30 min. infusion) VI	182.5±19.7	182.2±12.82	87.5±6.83	22.0±3.35

Table 2
Effect of Ethanol and Naloxone on Arterial O_2 Tension, CO_2 Tension, Bicarbonate and pH in Dogs

Group	Arterial O_2 Tension (mmHg)	Arterial O_2 Tension (mmHg)	Bicarbonate (mmol)	pH
Control	119.6±10.1	31.1±5.1	18.3±2.8	7.339+0.0144
Ethanol-intoxicated (10 min. infusion)	88.2±6.4	47.6±4.9	16.90±2.1	7.278+0.305
t	6.95	6.2	1.1	4.79
p	<0.01	<0.01	>0.05	<0.01
Ethanol-intoxicated (20 min. infusion)	53.8±3.97	50.4±1.4	18.97±1.37	7.220+0.0450
t	14.9	8.9	0.501	6.65
p	<0.01	<0.01	>0.05	<0.01
Naloxone- treat. (70 ug/kg "bolus")	79.02±9.4	38.02±7.7	15.6±4.2	7.236+0.0442
t	9.36	3.87	1.83	0.62
p	<0.01	<0.01	>0.05	>0.05
Naloxone (15 min. infusion)	87.1±15.6	36.3±9.1	17.1±4.4	7.273+0.0255
t	5.07	3.7	1	2.52
p	<0.01	<0.01	>0.05	<0.05
Naloxone (30 min. infusion)	92.5±14.5	41.08±6.5	20.05±3.2	7.297+0.0238
t	6.32	3.43	0.76	3.73
p	<0.01	<0.01	>0.05	<0.01

In the placebo group (Table 3), respiratory depression progressed to complete apnea in 3 dogs. In the two surviving dogs, the pulse rates were 90 and 100 beats/minute, systolic pressures were 100 and 120 mmHg, and the diastolic blood pressures were 58 and 62 mmHg.

The respiratory rates slowed to 2 and 4 cycles / minute to be arrested after 15 and 20 minutes Dextrose infusion. During this period, PO2 dropped to 48.2 and 51.8 mmHg, PCO2 increased to 69.7 and 69.7 and 64.1 mmHg and pH values decreased to 6.837 and 6.963 with bicarbonate values of 9.8 and 11.2 mmol. The blood alcohol level showed non-significant drop from a mean value of 362.±11.6 to 335 and 341 mg.dl.

Table (4) represents a statistical summary of the effect of naloxone treatment bolus 15 minutes and 30 minutes infusion (280 u/kg) on the clinical and analytical parameters in ethanol, intoxicated human patients. The favourable response is clear and the results were significant and highly significant when examined with analysis variant of $P< 0.05$ and $P<0.01$.

Discussion

The results obtained in this study demonstrate that naloxone has effectively produced reversal of deleterious effects of Ethanol intoxication in dogs and human beings. Immediate arousal and recovery of spontaneous breathing occurred after the prime bolus injection. Our results

Table 3
Placebo-Treated Group (Ethanol-Positive Control Group)

Ethanol	5 Dogs Intoxicated (4 gm/kg)	2 Dogs Survived & 5 minutes-Placebo (5% Dextrose)	3 Dogs died before 15-mintes Placebo (5% dextrose)
H.R.	146.0±6.25 (146-155)	110 and 120	90 and 100
S.BP	156.0±6.519 *(150±165)*	125 and 130	100 and 120
D.BP	90.8±4.27 (85-95)	60 and 62	58 and 62
R.R.	0-5	2-4	0-2
PO_2	45.4±3.12 (51.2-60.1)	*50.1 and 52.3*	*48.2 and 51.8*
PCO_2	56.8±6.9 (49.9-65.4)	60.9 and 61.8	69.7 ad 64.1
HCO_3	15.9±1.3 (13.9-17.9)	15.9 and 16.2	9.8 and 11.2
pH	7.234±0.032 (7.19-7.27)	7.18 and 7.19	6.837 and 6.963
Ethanol Blood Level	362.0±11.6	---	335 and 341

clearly showed the statistically highly significant improvement in respiratory parameters within 5 minutes of Naloxone treatment.

Hypercapnea was nearly normalized shortly after the bolus of Naloxone was injected, then was less significantly affected with further administration. Whereas reversal of hypoxaemia continued to be enhanced by the Naloxone infusion.

In comparison to the dramatic and almost spontaneous improvement of the respiratory functions, the better amelioration of the cardiovascular depression was attained after 30 minutes of Naloxone treatment.

Many factors are involved in such alcohol-induced effect on the cardiovascular system. The main element is the central vasomotor and respiratory depression (Wallgren and Barry. 1970). A direct action on myocardial contractibility and working efficiency has been attributed to Ethanol in a blood level as low as 100 mg/dl (Zoster and Sellers, 1977).

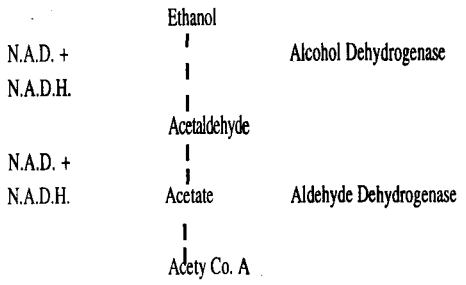
Associated causes are the acidosis and metabolic derangements (Ritchie, 1980). However, the evaluation of the manifestation in this experiment, and the dissociation of the response to Naloxone is the favour of a direct effect of alcohol on myocardium. This is substantiated by the mean alcohol blood level remaining relatively high, 258.33±12.17 mg/dl (Table 1), inspite of its significant decrease by naloxone.

Table 4
Statistical Summary of the Effects of Naloxone on Cardiovascular and Respiratory Parameters in Ethanol Intoxicated Patients

	Ethanol-Intoxicated 362.3+8.9 mg%	**I.V. Naloxone** 0.8 mg Bolus	**Naloxone Infusion** 15 - minutes infusion	**(280 ugm/kgm)** 30 minutes infusion
H.R.	51.3±4.02	53.5±3.1 N.S.	58.8±5.3 N.S.	82.5±9.7 N.S.
S.BP	75.8±8.1	79.7±4.3 N.S.	81.17±22.4 N.S.	112.2±12.8 H.S.
D.BP	50.17±13.03	54.0±12.7 N.S.	55.17±8.3 N.S.	71.5±6.83 N.S.
R.R.	10	24.3±8.96 H.S.	23.0±4.7 H.S.	22.0±3.55 H.S.
PO_2	53.8±3.97	79.02±99.4 H.S.	87.1±15.6 H.S.	92.5±14.5 H.S.
PCO_2	50.4±1.4	38.2±7.7 H.S.	36.39±9.1 H.S.	41.08±6.5 H.S.
HCO_3	18.97±1.37	15.6±4.2 N.S.	17.1±4.4 N.S.	20.05±3.2 N.S.
pH	7.22±0.0450	7.236±0.0442 N.S.	7.273±0.0255 S.	7.297±0.0238 H.S.

Such outstanding results of the Ethanol-Naloxone experiment, appears to confirm the ability of naloxone to reduce alcohol blood levels. The marked drop (29%) in the mean alcohol blood level took place within the 30 minutes - infusion of naloxone in a dose of 280 ug/kg. Similar results were obtained by Badawy and Evans (1981), in rate recording a drop of 31% of the blood alcohol level. They, however, use a much higher dose on naloxone (1 mg/kg). Also, Rae (1986), treated sixteen patients with impaired sensorium as result of Ethanol overdose and they showed clinical improvement in sensorium following high dose of naloxone administration. On the other hand, the administration of naloxone in a single dose intoxicated by ethanol (4 mg/kg) (Lignain et al., 1983). It is thus concluded that the recommended therapeutic doses of naloxone are not always adequate. In our study and in other reports, where naloxone was successfully effective, high doses of the drug were necessary.

The effect of naloxone upon alcohol blood level is brought about by increasing ethanol metabolism. The postulation that naloxone can correct the redox ratio disturbance in ethanol intoxications has been investigated by Badawy et al. (1981), Badawy and Evans (1981) and Ryle et al. (1985). Naloxone administration to ethanol-pretreated rats reversed not only the drug - induced narcosis but also the markedly increased redox ratio, together with the reduction in ethanol



levels (Badawy and Evans, 1981). Recently, Ryle et al. (1985) treated rats with Naloxone (2 mg/kg) intraperitoneally one hour after ethanol (2 gm/kg). They found that naloxone presented ethanol-induced redox state changes. Badawy and Evans (1981) also suggested that naloxone possible activated transdehydrogenase reaction in the microsomes with resultant nicotine - amide dinucleotide (NAD) regeneration. The authors measured restoration of NAD and NADH after naloxone administration in acute alcohol intoxicated rats. Ethanol caused a 59% decrease in liver NAD and 106% increase in NADH with a consequent 80% increase in NADH/NAD, then naloxone produced a 37% decreased in the NADH/NAD.

The decreased in the coenzyme NAD is known to act as limiting factor for further ethanol metabolism (Ritchie, 1980).

Such action of naloxone denote specific pharmacokinetic antagonism to ethanol. The antidotal effects of naloxone, the most specific opiate antagonist, in acute alcohol intoxications supports the hypothesis of an endorphin and enkephalin effect of alcohol. This was first suggested by Davis and Walsh (1970) and Cohen and Collins (1970). In 1980, Schwartz et al., demonstrated an increase of enkephalin in the striatum of B-endorphin in the hypothalamus of rats after acute administration of alcohol. Moreover, specific inhibition of u-receptors was estabilised (Hiller et al., 1981).

Jefferys et al. (1980) reported a series of 100 cases of ethylic coma where naloxone was effective in reversing coma in 12 patients in which toxicological investigations identified ethanol as the sole cause of come. Ten of these alcohol intoxicated cases exhibited a flush on chlorpropamide - alcohol challenge. The existence of an "enkephalin - sensitive" population, therefore postulated by Jefferys et al. (1980) and this was further explained by Ritchie (1980) to be due to the appearence of flushing and sensation of hotness when the hypoglycaemia chlorpropamide is given together with alcohol. The symptoms are due to accumulation of acetaldehyde with marked release of catecholamines. This could account for the lack of effect of naloxone in the study of Catley et al. (1981), who administered naloxone at doses as high as 10 mg intravenous and could not reverse sensory or motor impairment by ethanol in man as none of their cases showed a positive alcohol flusher test.

The before mentioned date, strongly suggest a specific antidotal effect of naloxone in alcohol intoxications. The production of rapid reversal of coma and respiratory depression and cardiovascular changes indicated a competitive antagonistic effect while the drop of alcohol blood level denotes as well a pharmacokinetic antagonistic action. Thus, the uses of naloxone can successfully be extended to include specific therapy of alcohol intoxication.

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L'évaluation du Naloxone comme Antidote pour l'intoxication d'alcohol.

Cette étude évalu l'antidote potential du naloxone dans l'intoxication d'alcohol expérimentallement influeucé sur 12 chiens mongrels. Leurs autidote effects est aussi évalué sur 20 patients souffrauts de l'intoxicatcon d'alcohol. Les decouverts clinicals, l'analyse des gazes du sang, les niveaux de l'alcohol étaient suggestifs et avaient une action antagonistique du naloxone dans l'intoxication d'alcohol.

تقييم النالوكسان كمضاد للتسمم الكحولى

تقيم هذه الدراسة إمكانية إستخدام عقار النالوكسان كعقار مضاد للتسمم الكحولى التجريبى فى إثنى عشر كلباً من حيوانات التجارب - وتم تقييم فعالية العقار أيضاً فى عشرين مريضاً بالتسمم الكحولى، وتشير النتائج الإكلينيكية وتحاليل الغازات فى الدم ومستويات الكحول فى الدم إلى دور عقار النالوكسان كمضاد فى حالات التسمم الكحولى.