Naloxone as an Antidote for Benzodiazepine: An Experimental and Clinical Study

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This study evaluates the potential antidote action of naloxone on experimentally induced diazepam and flunitrazepam (benzodiazepines) intoxication in dogs. Its antidote effects is also evaluated in a clinical sample of 8 patients suffering from flunitrazepam intoxication. The clinical findings were suggestive of an antagonistic action of naloxone in flunitrazepam intoxication. It was also found that flunitrazepam exhibits a different pharmacological profile from other members of the benzodiazepine group. Our findings of a selective naloxane-flunitrazepam reversal need to be explained in relation to the mechanism of action of this benzodiazepine, as well as to the equated naloxane-opiates reversal.

(Egypt.J. Psychiat.,1992,15: 53-65).

Introduction

The intoxication with benzodiazpine is less as a problem since serious complications are rare with pure benzodiazepines. Severe manifestations are unexpected and indicate synergy with other central nervous depressants. (Greenblatt and Allen, 1978; and Harvey, 1980)

The typical syndrome of overdosage is characterized by muscular hypotonic with hyporeflexia and oesteotendinous areflexia, coma with reactive pupils, hypotension, and hypothermia. Muscular tone is a characteristic element constituting a specific diagnostic value (Marrubini et al., 1987). In massive doses, there is an initial phase of hypotonic, ataxia, and somnolence, but the patient is still reactive to auditory stimuli and / or intensively painful stimuli, with the respiration only slightly affected, this is commonly followed by coma (Cerchiari et al., 1983).

Severe respiratory depression is not a characteristic feature of diazepam overdose even in comatosed patients, and cheyne-stokes breathing is rare (Korczyn, 1980). Diazepam overdosage can induce depression of alveolar ventilation and mild respiratory acidosis which occur in response to hypoxic rather that hypercapneic drive (Clarke and Lyons, 1977). In diazepam overdoses, the level of coma rarely deepens than grade II or III and rarely exceeds 24 hour duration (Korczyn, 1980). There are very few documented cases of coma lasting more that 24 hours to diazepam overdose (Greenblatt et al., 1977). However, Marrubini et al., 1987. reported a case of a 48-years-old woman who sustained 10-day coma from diazepam overdosage.

In the absence of predisposing elements (old age or pre-existing heart disease), cardiovascular manifestations of benzodiazepines overdosages are minor presentation as hypotension accompanied by a reflex increase in the heart rate (Harvey, 1980). Mixed drug intake can transform the benign intoxication of benzodiazepines into a grave intoxication (Finkle et al., 1979).

Flunitrazepam in overdoses produces the same pattern of poisoning of benzodiazepines in general. However, while benzodiazepines are known as relatively

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safe drug, a high incidence of deaths amounting to 35% has been reported after massive flunitrazepam intoxications, indicating its potentially fatal toxicity (Langendijk and Van Heijest, 1985). The more severe symptoms of deep coma, respiratory insufficiency and hypotension are reported more commonly with flunitrazepam comato, are seen after minimal doses of 20 mg in adults & 0.3 mg / kg in children, and in some isolated cases 0.12 - 0.22 mg / kg (Gossweiler, 1985). In massive ingestions, the progression of central depression is very fast and in one to two hours, the patient may develop grade IV coma with severe respiratory depression (Mahieu et al., 1985).

The differentiating features of flunitrazepam intoxications are explained by the drug characteristics, i.e, potency, absorption rate, and specially the intensity of its action and lipophilicity (Dundee et al., 1976). In overdoses, gastrointestinal absorption of flunitrazepam is lengthened and the half-life of the drug is prolonged (Mahieu et al., 1985). Occasionally, acute flunitrazepam toxicity may be presented by muscular hypertonia, hyperreflexia, or even grand mal seizures (Harvey, 1980). The cardiovascular depression in flunitrazepam overdosages is more serious than in other benzodiazepines toxicity and is characterised by hypotension with evident bradycardia as the drug decreases the cardiac work by direct myocardial depression (Langendijk and Van Hei Jest, 1985).

Aim of the Work

Our attention was drawn to the potential efficacy of naloxone to eliminate the toxic effects of benzodiazepines through some clinical trials. Naloxone administration resulted in lightening of coma due to diazepam overdose in two case and reversal in only one case (Poison Information Service, 1986)

This study aims to evaluate the potential antidotal effects of naloxone on induced acute intoxication in dogs by diazepam and flunitrazepam (benzodiazepines). Assessment is affected by clinical observations together with analytical investigations. Parameters include: degree of central nervous system depression, variations in pulse rate, blood pressure, and respiratory rate, as well as arterial oxygen tension (pOz) and arterial carbon dioxide tension (pCOz) bicarbonate, and PH values.

Material and Method

Study of the potential counteracting effect of naloxone hydrochloride (Narcane) on respiratory, circulatory, and central nervous system changes was undertaken in dogs intoxicated by two benzodiazepine drugs (diazepam and flunitrazepam).

All the agents used for implementation of the experiments were obtained in the proper pharmaceutical forms. The doses were initially estimated according to Puget and Barnes (1964) calculations, and thereafter, the administrations were adjusted in respect to the vital functions parameters in each agent-treated animal. Eight intoxicated patients with flunitrazopane were also handled by naloxane and results recorded. Narcane was available in the form of 1 ml ampoules, each containing 0.4 mg naloxone hydrochloride. The total dose of naloxone administered to the intoxicated dogs was 280 of 70 ug / kg, and the rest of the dose was diluted in 100 ml of 5% dextrose and given as continuous intravenous infusion over a period of 30 minutes. Diazepine was available in the form of 2 ml ampoules, each containing 10 mg diazepam. Flunitrazepam (Rohypnol) was obtained as 1 ml ampoules, each containing 2 mg flunitrazepam. The dogs were given 0.9 mg / kg as one intravenous injection over 5 min.

Group I: (Diazepam-naloxone)

Twelve dogs received 10.7 mg / kg diazepam slowly intravenously until they developed signs of intoxications. Seven dogs were given naloxone and the remaining 5 animals given placebo (5% dextrose) over the same period).

Group II: (Flunitrazepam-naloxone) These second group of 12 animals, were given 0.9 mg / kg flunitrazepam by intravenous injection. The animals rapidly became analgesic, lost consciousness and showed marked respiratory and circulatory depression. Naloxone was administered to seven dogs while 5 dogs received the dextrose vehicles.

Correlation of the clinical and analytical parameters provide a very useful interpretative aid, specially in treatment of acute intoxications.

Results (Tables 1-10)

Group I

The dogs were intoxicated by diazepam (10.7 mg / kg). The animals were comatosed, flaccid with areflexia. The cardiovascular findings (Table 1) indicated slight changes. The heart rate increased to 195.71 ± 7.32 beats / minute, systolic blood pressure decreased to 192.86 ± 7.32 beats / minute, systolic blood pressure decreased to 192.86 ± 6.99 mmHg and the diastolic blood pressure was 102.71 ± 9.3 mmHg. The mean respiratory rate was slowed to 26.86 ± 2.12 / minute. During this period the p02 mean value decreased from 120.84 ± 5.34 mmHg to 104.54 ± 11.26 mmHg, pCO2 showed slight increased from the mean value of 37.3 ± 2.52 mmHg to 40.56 ± 2.99 mmHg, and a slight decrease in the bicarbonate level (from 20.85 ± 1.61 to 19.79 ± 1.36 mmol), and ph value showed no variation (7.347 ± 0.0109) (table 2).

Table (1 & 2) show the effect of 280 (mg / kg) naloxone on clinical manifestations in diazepam intoxicated dogs. No difference in the manifestations of poisoning has resulted as judged on clinical ground or by blood gases analysis.

Tables (1) shows the mean values to be: pulse rate 197.14 ± 6.99 beats / minute, systolic blood pressure of 193.53 ± 6.9 mmHg, diastolic pressure of 104.29 ± 6.73 mmHg, and a respiratory rate of 29.14 ± 3.49 / minute.

Table (2) represents the corresponding results of blood gases analysis where the mean values for P02 was 108.56 ± 10.99 mmHg, for pc02 was 39.76 ± 1.69 mmHg, for hc03 was 20.37 ± 1.65, and ph values was 7.364 ± 0.0294.

The same clinical and analytical parameters of the positive control dogs are given in Table (3), showing non significant changes of the toxic manifestations till the end of a 30 minutes period of 5% dextrose infusion.

Group II: The flunitrazepam intoxicated dogs (0.9 mg / kg) manifested deep coma (grade III and IV) with hypertonia & hyperreflexia and cardiovascular and respiratory depression. The early toxic effects occuring 10 minuted after flunitrazepam infusion, (Tables 4 & 5), while indicating higly significant changes were not augmented by further infusiong to 20 minutes The mean values for the heart rate and systolic and diastolic blood pressures decreased (from 196.14 ± 5.4 to 173.57 ± 8.02 beat / minute, 202.0 ± 11.18 to 155 ± 7.83 mmHg, and from 110.29 ± 9.12 to 88.0 ± 11.43 mmHg, respectively). Respiration was more markedly affected and respiratory rate dropped from a range of (26 - 34) and with a mean value of 29.29 ± 2.87 / minute to a rate ranging between (12 - 16) with a mean value of 13.86 ± 1.35 / minute (Table 4). At this stage, results of blood gases analysis indicated mixed respiratory and metabolic acidosis (Table 5). P02 dropped from control values in the range of (118.9 - 136.2) with a mean value of 127.86 ± 6.51 mmHg to a range of (73.1 - 90.1) and a mean value of 79.97 ± 7.09 mmHg. Pc02 increases from a mean value of 39.27 ± 3.58 mmHg (34.3 - 44.3 mmHg). Highly signly significant decreases were also recorded in bicarbonate levels (Table 5), changing from control range of (19.8 - 23.0) and mean value of 21.1 ± 1.24 mmol, to a range of (13.1 - 16.9) &

Table 1

Clinical Manifestations In Diazepam-Intoxicated Dogs (10.7 mg / kg) and Naloxone (280 ug / kg).

Group	Heart Rate (beats / min)	Blood Pressure Systolic	Blood Pressure Diastolic	Res. Rate (cycle / min)
Control				
Mean ± SD	192.86 (± 6.36)	198.57±7.93	106.57 ± 902	29.57 ± 1.99
Rang	(185 - 200)	(185 - 210)	(90 - 115)	(27 - 32)
Diazepam - Intoxicated				
Mean (± SD)	195.71 ± 7.32	192.86±6.99	102.71±9.3	26.86±2.12
Range	(190 - 210)	(185-200)	(90-114)	(25-30)
t	0.7795	1.43	0.788	2.474
p	> 0.05	> 0.05	> 0.05	< 0.05
Naloxane - Treat				
Mean ± SD	197.14 ± 6.99	193.57 ± 69	104.29 ± 6.73	29.14 ± 3.49
Range	(190 - 210)	(190 - 205)	(95 - 115)	(25 - 35)
t	0.374	0.184	0.35	1.11
p	>0.05	> 0.05	> 0.05	> 0.05

p > 0.05 non - significant, p< 0.05 significant, p< 0.01 highly significant

Table 2

Effect of Diazepam on Arterial 02 Tension, Co2 Tension, Bicarbonate and PH In Dogs & Effect of Intravenous Naloxone (280 mg / kg).

Group	Arterial O^2 Tension (mmHg)	Arterial CO^2 Tension (mmHg)	Bicarbonate	pH
Control				
Mean ± SD	120.74 ± 5.34	37.3 ± 2.52	20.85 ± 1.61	7.32 ± 0.0093
Range	(110.6 - 128.1)	(33.4 - 41.1	(18.9 - 23.4)	(7.341 - 7.36)
Diazepan - Intoxicated				
Mean ± SD	104.54 ± 11.26	40.56 ± 2.99	19.79 ± 1.36	7.347 ± 0.00109
Range	(89.7 - 120.9)	(36.9 - 45.7)	(18.3 - 22.4)	(7.330 - 7.362)
t	3.46	2.205	1.334	1.0008
p	<0.05	<0.05	> 0.05	> 0.05
Naloxone - Treat.				
Mean (±) SD	108.56 ± 10.99	39.76 ± 1.60	20.37 ± 1.65	7.364 ± 0.0294
Range	(96.7 - 124.1)	(37.5 - 42.1)	(18.7 - 23.4)	(7.346 - 7.43)
t	0.688	0.62	0.746	2.35
p	>0.05	>0.05	>0.05	<0.05

p >0.05 non - significant, p <0.05 significant, p <0.01 highly significant

Table 3

Placebo-Treated Group (Diazepam-Positive Control Grop)

	Diazepam Intoxicated (10.7 mg / kg)	10-Minutes place-bo (5% Dextrose)	20-Minutes Place-bo (5% Dextrose)	30-Minutes Placebo (5% Dextrose)
H.R.	198.0 ± 7.58 (190-210)	200.0 ±7.9 (190-210)	192.0 ± 5.7 (185-200)	187.0 ± 5.7 (185-195)
S.BP	188.4±5.94 (180-195)	189.0 ± 4.18 (185-195)	181.0 ± 6.52 (175-190)	182.0 ± 5.7 (180-190)
D.BP	100.0 ± 791 (90-110)	95.0 ± 7.91 (85-105)	88.0 ± 5.7 (80-95)	86.0 ± 6.52 (80-95)
R.R.	28.0 ±1.58 (26-30)	26.0 ± 1.6 (24-28)	24.8 ± 1.92 (22-27)	25.0 ± 1.58 (23-27)
P02	79.9 ± 4.12 (921-102.1)	96.56±6.95 (89.5-105.3)	90.1±5.02 (821-98.1)	85.46±4.56 (79.9-90.2)
P002	38.82±2.34 (36.3-41.7)	42.54±1.89 (40.9-45.6)	42.53±2.44 (39.1-452)	43.16±2.1 (39.9-45.3)
H003	19.48 ± 4.79 (18.4-202)	20.68 ± 1.07 (19.6-22.1)	19.28 ± 1.38 (18.9-22.3)	18.82 ± 0.89 (17.9-202)
PH	7.344 ± 0.061 (7.337-7.351)	7.351 ± 0.087 (7.338-7.380)	7.315 ± 0.0147 (7.299-7.331)	7.137 ± 0.0866 (7.798-7.334)

Table 4

Clinical Manifestations In Flunitrazepam-Intoxicated Dogs (10 Minutes and 20 Minutes After Injection)

Group	Heart Rate (beats / min)	Blood Pressure Systolic	Blood Pressure Diastolic	Respiratory Rate (Gycle / min.)
Control				
Mean (± SD)	196.14 ± 5.4	202.0 ± 11.18	110.29 ± 9.12	29.29 ±2.87
Range	(185-200)	(185-216)	(95-120)	(26-34)
Flunitrazepam-Intoxicated (10 Min.)			90.57 ± 9.81	14.14 ± 1.35
Mean (± SD)	172.14 ± 7.56	156.71 ± 5.25	(72-101)	(12-16)
Range	(160-180)	(148-165)		
t	6.835	9.485	3.894	12.975
p	<0.01	<0.01	<0.01	<0.01
Flunitrazepam-Intoxicated (20 Min.)				
Mean (± SD)	173.57 ± 8.02	155.0 ± 7.83	88.0 ± 11.43	13.86 ± 1.35
Range	(160-185)	(145-170)	(79-105)	(12-16)
t	6.179	9.11	4.032	12.88
p	<0.01	<0.01	<0.01	<0.01

p >0.05 non-significant, p <0.05 significant, p <0.01 highly significant

Table 5

Effect of Flunitrazepam (10 Minutes and 20 Minutes After Injection) On Arterial O_2, Tension, C02 Tension, Bicarbonate and PH In Dogs.

Group	Arterial O_2 Tension (mmHg)	Arterial CO_2 Tension (mmHg)	Bicarbonate (mmol)	PH
Control				
Mean (± SD)	127.86 ± 6.51	38.27 ± 3.58	21.1 ± 1.24	7.34 ± 0.0168
Range	(118.9-136.2)	(34.3-44.3)	(19.8-2.3)	(7.327-7.371)
Flunitrazepam - Intoxicated (10 Min.)				
Mean (± SD)	81.91 ± 5.8	49.99 ± 10.3	15.63 ± 12.3	7.243 ± 0.0152
Range	(73.6-89.6)	(35.6-62.1)	(1.36-17.2)	(7.22 ± 7.261)
t	13.906	2.6	8.264	11.938
p	<0.01	<0.05	<0.01	<0.01
Flunitrazepam-Intoxicated (10 Mins.)				
Mean (± SD)	79.97 ± 7.09	49.7 ± 13.45	14.59 ± 1.25	7.236 ± 0.03
Range	(73.1-90.1)	(30.1-64.6)	(13.1-16.9)	(7.203-7.291)
t	13.153	1.982	9.781	8.365
p	<0.01	>0.05	<0.01	<0.01

p >0.05 non-significant, p <0.05 significant, p <0.01 highly significant

Table 6

Effect of Intravenous Naloxone (70 mg / kg & 280 ug / kg) on Clinical Manifestations In Flunitrazepam-Intoxicated Dogs.

Group	Heart Rate (beats / min.)	Blood Pressure Systolic	Blood Pressure Diastolic	Respiratory Rate (Cycle / min)
Flunitrazepam-Intoxicated				
Mean (± SD)	173.57 ± 8.02	155.0 ± 7.83	88.0 ± 11.43	13.86 ± 1.35
Range	(160-185)	(145-170)	(79-105)	(12-16)
Naloxone-Treat. (70 ug/ kg)				
Mean (± SD)	192.43 ± 4.79	179.29 ± 9.76	101.71 ± 4.65	24.43 ± 1.99
Range	(185-200)	(165-190)	(96-110)	(22-28)
t	3.497	5.136	2.941	11.654
p	<0.01	<0.01	<0.05	<0.01
Naloxone-Treat. 280 ug / kg				
Mean (± SD)	192.43 ± 4.79	179.29 ± 9.76	101.71 ± 4.65	24-25 ± 1.99
Range	(185-200)	(165-190)	(96-110)	(22-28)
t	3.497	5.136	2.941	11.654
		<0.01	<0.05	<0.01

p >0.05 non-significant, p <0.05 significant, p <0.01 highly significant

Table 7

Effect of Intravenaus Naloxone (70 ug / kg & 280 ug / kg) On Arterial 02 Tension, CO_2 Tensions, Bicarbonate and ph In Flunitrazepam Intoxicated Dogs.

Group	Arterial O_2 Tension (mmHg)	Arterial CO_2 Tension (mmHg)	Bicarbonate	PH
Flunitrazepam Intoxicated				
Mean (± SD)	79.97 ± 7.09	49.7 ± 13.45	14.58 ± 1.25	7.236 ± 0.03
Range	(73.1-90.1)	(30.1-64.1)	(13.1-16.9)	(7.206-7.291)
Naloxone-Treat.				
Mean (± SD)	104.49 ± 11.89	37.99 ± 5.75	16.83 ± 2.21	7.324 ± 0.0064
Range	(91.1-124-6)	(27.8-46.2)	(13.6-19.3)	(7.317-7.332)
t	4.686	2.168	2.34	7.563
p	<0.01	>0.05	<0.05	<0.01
Naloxone-Treat. (280 ug / kg)				
Mean (± SD)	103.21 ± 9.51	36.89 ± 3.56	18.26 ± 1.22	7.327 ± 0.00785
Range	(86-1182)	(32.9-41.9)	(162-19.6)	(7.32-7.342)
t	5.184	2.479	5.571	7.738
p	<0.01	<0.05	<0.01	<0.01

p >0.05 non-significant, p <0.05 significant, p <0.01 highly significant

Table 8

Statistical Summary of the Effect of Naloxane On Cardiovascular and Respiratory Parameters In Flunitrazepam Intoxicated Dogs.

	Flunitrazepam-Intoxicated	I.V. Naloxane Treated	
		70 ug / kg	280 ug / kg
H.R	173.57 ± 8.02	192.43 ± 4.79 H.S.	192.43 ± 4.79 H.S.
S.BP	155.0 ± 7.83	179.29 ± 9.76 H.S.	179.29 ± 9.76 H.S.
D.BP	88.0 ± 11.43	101.71 ± 4.65 H.S.	101.71 ± 4.65 H.S.
R.R	13.86 ± 1.35	24.43 ± 1.99 H.S.	24.25 ± 1.99 H.S.
P02	79.97 ± 7.09	104.49 ± 11.89 H.S.	103.21 ± 9.51 H.S.
P002	49.7 ± 13.45	37.99 ± 5.75 N.S.	36.89 ± 3.56 S.
H003	14.59 ± 1.25	16.83 ± 2.21 S.	18.26 ± 1.22 H.S.
PH	7.236 ± 0.03	7.324 ± 0.0064 H.S.	7.327 ± 0.00785 H.S.

N.S.: Non significant, S.: Significant, H.S.: Highly significant

Table 9

Placebo-Treated Group (Flunitrazepam-Positive Control Group)

	Flunitrazepam Intoxicated (0.9 mg / kg)	10 Minute-placebo (5% Dextrose)	20 Minute-placebo (5% Dextrose)	30 Minute-placebo (5% Dextrose)
H.R.	173.6 ± 8.02 (160-185)	156.0 ± 3.81 (150-160)	146.2 ± 4.44 (140-151)	139.5 ± 4.64 (135-145)
S.BP	150.0 ± 7.91 (140-160)	143.0 ± 6.71 (135-150)	141.0 ± 2.5 (130-151)	130.0 ± 3.81 (125-135)
D.BP	85.0 ± 7.9 (72-95)	77.0 ± 8.59 (70-85)	71.2 ± 2.29 (69-75)	62.0 ± 2.12 (60-65)
R.R	14.6 ± 3.42 (12-17)	10.8 ± 1.92 (8-13)	9.2 ± 1.3 (8-11)	8.4 ± 1.14 (7-10)
P002	79.8 ± 4.79 (72.8-85.6)	69.06 ± 2.04 (65.9-71.3)	68.94 ± 1.34 (67.3-70.9)	65.45 ± 3.61 (60.5-69.1)
P002	47.5 ± 6.47 (39.1-55.1)	52.8 ± 4.19 (48.1-55.4)	52.8 ± 2.03 (50.1-55.7)	60.78 ± 3.24 (57.5-65.2)
H003	15.0 ± 3.25 (10.4-18)	14.06 ± 1.89 (12.8-15.3)	13.62 ± 1.76 (11.9-16.2)	10.28 ± 1.01 (92-11.9)
PH	7.264 ± 0.079 (7.223-7.301)	7.221 ± 0.0604 (7.213-7.23)	7.215 ± 1.0078 (7.17-7.22)	7.203 ± 0.845 (7.199-7.211)

Table 10

Salient Feature of 8 Patients Intoxicated By Flunitrazepam (Admitted To Pcc)

No.	Age	Sex	Dose	Time	Temp.	Pulse	Bp	Resp.	Coma	Pupils	Reflexes	Blood	Gases
1	18/12	M	6mg	3 hrs.	35.5°c	130	90/70	25 / min. deep Stridor, pulmonary oedema & Cyanosis (Acute respiratory failure)	III	Sluggish Constricted	Hypertonia exaggerated reflexes	Po_2 Pco_2 ph Hco_3	52.9 65.9 7.19 24.5
2	41 yrs.	M	unknown	2 hrs.	36.0°c	115	110/70	6/minute coarse crepitation	III	constricted reactive	hypertonia Hyperreflexia	Po_2 Pco_2 ph Hco_3	46.5 63.4 7.21 24.7
3	26 yrs.	M	unknown	6 hrs.	37°c	100	80/50	40/ minute - creperation - cyanosis	III	constricted reactice	hyper-reflexia	Po_2 Pco_2 Hco_3	32.2 43.6 27.1
4	42 yrs.	M	unknown	-----	36°c	105	100/70	45/ minute, coarse creptations	II	constricreative	hyper-refle	Po_2 Pco_2 ph Hco_3	48.2 62.3 7.23 26.1

mean of 14.59 ± 1.25 mmol, while ph values dropped from 7.345 ± 0.0168 (7.327 - 7.371 to 7.236 ± 0.03 (7.203 - 7.291).

The effect of naloxone treatment on the flunitrazepaminduced intoxication are demonstrated in Tables (6 through 8) Naloxone bolus (70 ug / kg) injection produced prompt arousal and recovery of all vital function.

Highly significant increases were demonstrated in heart rate reaching a mean value of 192.43 ± 4.79 beats / minute (185 - 200) and in the systolic blood pressure to a mean of 179.29 ± 9.76 mmHg (165 - 190) (Table 6). The diastolic blood pressure was raised to 101.71 ± 4.65 mmHg (96 - 110) and respiratory rate to 24.43 ± 1.99 (22 - 28 / minute) (Table 6). Corresponding measurements in blood gases analysis (Table 7) showed marked amelioration of hypoxaemia to P02 mean value of 104.49 ± 11.89 mmHg (91.1 - 124.6), and moderate correction of hyper capnea to 37.99 ± 5.75 mmHg (27.8 - 46.2) and increase in bicarbonate to a mean value of 16.83 ± 2.21 mmol (13.6 - 19.3) and in ph with a mean value of 7.324 ± 0.0064 (7.317 - 7.332).

Comparing these results obtained in Table (6 and 7) clearly indicates that normalisation or optimum reversal of the studied parameters were achieved after 5 - minuts from naloxone injection (70 ug / kg bolus) and a further increase to a 30 - minute dosing (280 ug / kg) did not add to the improvement (Tables 6 & 7).

Table (8) summarises the findings in the flunitrazepam intoxicated dogs and the effect of naloxone treatment on the changes in heart rate, blood pressure, respiratory rate and blood gases analysis results.

Table (9) shows the changes in cardiovascular and respiratory parameters i the flunitrazepam-intoxicated dogs during 30-minutes 5% dextrose infusion. The heart rate continued to decrease from 173.6 ± 8.02 to 156.0 ± 3.81, 146.2 ± 4.44 and 139.5-4.64 beat / minute after 10, 20 & 30 minutes respectively. This was accompanied by a progressive decrease in systolic blood pressure from 150.0 ± 7.91 to 143.0 ± 6.71, 141.0 ± 2.5 and 130.0 ± 3.81 mmHg, and of diastolic blood pressure from 85 ± 7.9 to 77.0 ± 8.59, 71.2 ± 2.39 and 62.0 ± 2.12 mmHg. The respiratory rate showed further marked reduction from 14.6 ± 3.42 to 10.8 ± 1.92, 9.2 ± 1.3 & 8.4 ± 1.14 / minute. The blood gases reflected a rapidly progressing hypoxaemia, hypercapnea with metabolic and r espiratory acidosis. P02 mean values decreased from 79.8 ± 4.79 to 69.06 ± 2.04, 68.94 ± 1.34 and 65.54 ± 3.6 mmHg, Pc02 from 47.5 ± 6.47 to 52.8 ± 4.19, 52.8 ± 2.03 and 60.78 ± 3.24 mmHg denoting rapidly occuring acute ventilatory failure. ph values showed further acidic deviation from 7.264 ± 0.079, 7.221 ± 0.0604, 7.215 ± 0.0078 to 7.203 ± 0.0845 with bicarbonate decrease from 15.0 ± 3.25, 14.06 ± 1.89, 13.62 ± 1.76 to 10.28 ± 1.01 mmol.

Clinical Cases

Naloxone was administered to eight case of flunitrazepam (Rohypnol) intoxications that were admitted to the Poison Control Center of Ain Shams. The age of the patiets (7 males and one female) ranged widely between 18 months and 42 years, with a mean value of 32 ± 7.79 for the adults. The dose of flunitrazepam was identified in 4 cases and varied between 6 - 60 mg, taken as Rohypnol tablets.

Poisoning episode was due to abusive ingestion by addicts in 6 patients, attempted suicide in one case, and to accidental ingestion by an infant. The cases were admitted after a time lag varying from 3 hours to 24 hours. All the patients were comatosed (Grade II and III) with cyanosis, pupillary arefelxia, and respiratory disturbances in the form hypoventilation, laboured breathing, stridor, and pulmonary oedema. Arterial blood pressure was or lowered. All patients received the routine resuscitative

and supportive measures for correction of acidosis, hypothermia, and pulmonary oedema. Naloxone was administered as intravenous bolus of 2 ampoules (0.8 mg) resulting in prompt arousal and return of cough reflex in all the cases. Improvement of respiratory manifestations occured with administration of 80 ug doses, half-hourly, repeated as indicated. All patients were discharged after a period of hospitalisation rangig between 1 and 15 days. Table (10) provides a summary of the salient clinical features of those naloxone treated intoxicated cases *.

Discussion

This specific opiate antagonist, naloxone, when given to 8 patients intoxicated by flunitrazepam, has markedly reduced the coma state, and resulted in improvement of vital functions. The patients became awakened, responsive and respired normally within 10-15 minutes from intravenous administration of naloxone in doses varying from 0.1-2.4 mg.

The clinical findings thus while suggestive of an antagonistic action of naloxone in flunitrazepam intoxication they do not confirm the agreement considering naloxone produced an effect which was a selective as that produced in opiate toxicity. Some isolated case reports and some animal studies suggested that naloxone may be useful in reversing benzodiazepines-induced coma and respiratory depression. Moss (1973) was the first to report naloxone reversal of apnea occurring after a combined ingestion of barbiturate, alcohol and diazepam. Ho and Ho (1979) suggested that high doses of naloxone may antogonise diazepam acute intoxication. Bell (1980) reported successful reversal of a confirmed acute diazepam intoxication in 27-month-old child by naloxone. Malizia et al., (1980) supported the suggestion of naloxone being useful in treating diazepam-induced coma. Jefferys and Volans (1983) reported successful use of naloxone in reversing coma induced by Benzodiazepines overdoses in two patients out of 31 patients.

On the contrary, Christensen and Huttel (1979) performed a double-blind placebo controlled study in 46 subjects to investigate naloxone potential to reverse diazepam-induced sedation. They obtained non-significant difference between naloxone and placebo.

In this work, flunitrazepam administration to dogs resulted in coma and severe respiratory and cardiovascular depression. These effects were evidenced by development of hypoxaemia, hypercapnea, acidosis, as well as hypotension and bradycardia. Naloxone administration produced reversal of coma and improved respiratory and circulatory functions within 5 minutes. Such effects of naloxone efficiently antagonising the severe toxic manifestations of flunitrazepam, was no reproducible in the diazepam-induced intoxication in dogs. In the latter, non-significant differences were found between the naloxone-treated and the placebo infused groups.

It has been found that flunitrazepam exhibits important differences from other members of the benzodiazepines (Marrubini et al., 1987). These are reflected on its toxic manifestations suggesting different mechanisms of actions, probably mediated through specific receptors. It was found that in diazepam-induced intoxication, respiratory depression was rarely seriously affected, even in severe overdoses, the drug produced depression of alveolar ventilation and some acidosis. The cardiovascular changes were those of moderate hypotension with some increase in heart rate. On the other hand, flunitrazepam produced deeper grades of coma, severe respiratory depression hypotension and bradycardia. An important clinical observation was the hypertonia and hypereflexia, which are known to occur in severe intoxication by flunitrazepam. The mechanism

* Toxicological screening tests of all hospitalisation were negative to opiates.

of the hypertonic effect is thought to be mediated by inhibition of GABA synthesis and release at the post synaptic membranes (Harvey, 1980).

Our findings of a selective naloxone-flunitrazepam reversal need to be brought into meaningful relation to mechanism of action of this benzodiazepine, as well as to the equated naloxone-opiate reversal. Both opiates and benzodiazepines bind stereospecifically to membrane lipids of the brain (Muller, 1981). Also similar to opiates, the existence of multiple forms of benzodiazepine receptors has been confirmed. Separate distinguishable binding sites for benzodiazepines have been demonstrated and found to be very selective and stereospecific for only pharmacologically active benzodiazepines (Mohler and Okada, 1978; Muller 1981, and Ehlert et al., 1981).

The binding sites are saturable, i.e. dependent on drug concentration similar to that found for neurotransmitter receptors and opiate receptors in the central nervous system (Braestrup and Squires, 1978). Muller (1981) and Ehlert et al., (1981) classified the sites containing benzodiazepines receptors into 3 types according to the degree of affinity. 3 types and was found to bind specially to the L-receptor or Bz2 receptors which are more abundant in the cerebellum, pars reticulata of the substantia nigra and spinal cord (Ehlert et al., 1981;

Samson et al., 1985; and Tietz et al., 1986). Other sites of benzodiazepine receptors are the hippocampal formation, the cerebral cortex, occipital cortex, superior colliculus, the dorsal geniculate nucleus, lateral amygdala and lateral hypothalamus These sites of benzodiazepine receptors showed greater affinity towards diazepam rather than to flunitrazepam (Tietz et al., 1986). Ehlert et al., (1981) studied the affinity of flunitrazepam for the benzodiazepine receptors and proved its competitive nature.

Our results, therefore, suggest that the specific opiate antagonist "naloxone" exerts its antidotal effects toward flunitrazepam through an influence or interaction on specific flunitrazepam receptor sites. An objective critical judgement of such important finding would compare favourable to the recent trials of the benzodiazepine-antagonist-Ro-1788 (Samson et al., 1985). Both findings present 15 potentiality for additional possibilities regarding the mechanism of action of benzodiazepines.

References

Bell, E.F (1980): Naloxone reversal of diazepam effects. *Anaesthesilogy*, **53**: 264.

Braestrup, C: and Squires, R.F: Specific benzepine receptors in rat brain characterized by high - affinity3 (H) diazepam finding. *Proc. Natn. Acad. Sci, USA*, **74**: 3805 - 3809, 1877.

Cerchiari, E.: Carugo, D: Ravizza, A: and Morrubini, M (1983): Pupillary and ocular reflexes in toxic coma. *Human Toxicology*, Vol 2: No. 2.

Christensen, K. N: and Huttel, M (1979): Naloxone does not antagonise diazepam-induced sedation. *Anaesthesiology*, **51**: 187.

Clarke, R.S.J. : and Lyons, S.M (1977) : Diazepam and flunitrazepam as induction agents for cardiac surgical operations. *Acta. Anaesthesiol. Scand*, **21**: 282-292.

Ehlert, F.J.: Roeske, W.R. and Yamamura, H.I. (1981) : Multiple benzodiazepine receptors and their regulation by y-aminobutyric acid. *Life Sciences*, **29**: 235 - 248.

Finkle, B.S.: Mccloskey, K.L.; Goodman, L.S (1979): Diazepam and drug associated deaths., *J.A.M.A.*, 292, 429 - 434, 1979.

Gossweiler, B.; Flunitrazepam (1985): Toxicity and therapy. Experiences with the benzodiazepine antagonist Ro 15-1788; European Association of Poisons Control Centres, 1985.

Greenblatt, D.J: Allen, M.D.; Noel, B.J.; and Shader, R.I (1977).: Acute overdos-

age with benzodiazepine derivatives. *clin. Pharmacol. Ther.*, **4**: 497-514.

---------- and ---------- (1978) Rapid recovery from massive diazepam overdose. *J.A.M.A.*, **240**: 1874.

Harvey, S.C (1980) *Hypnotics and Sedatives*, In: Goodman and Gillman, Macmillan Publishing Co., Inc., New York.

Ho, A.K.S.; and Ho, C.C. (1979) Toxin interaction of ethanol with other central depressants antagonism by naloxone to narcosis and lethality. Pharmol. *Biochem. and Behav.* **11**: 11-114.

Jefferys, D.B.; and Volans, G.N. (1983) An investigation of the role of the specific opioid antagonist naloxone in clinial toxicology. *Human Toxicol.*, **2**: 227.

Langendijk, P.N.J.; and Vanheijst, A.N.P. (1985) Intoxications with flunitrazepam and other benzodiazepine hypnotics: European Association of Poison Control Centres, *New Letters*, p. 18-19, September.

Malizia, E.; Cerbo, R.; and Andreucci, G. (1980) Use of naloxone in toxicological emergencies. In *Toxicological* Aspects, ed. A. kovatsis, Thessaloniki, P.P. 394-414.

Marrubini, M.L.; Laurenzi, R.C.; and Uccelli P. (1987) Intossicazioni Acute: 2nd Ed. Organizzazione Editoriale Medico Farmaceutic Via Edolo, 42 milano.

Mohler, H.; and Okada, T. (1978) The benzodiazepine receptors in normal and pathological human brain. *Brit. J. Psychiat*, **133**: 261 - 268.

Moss, L.M.; Naloxone reversal of non-narcotic induced apnea. J. Amer. Coll. *Emerg. Physicians*, 46-48, 1973 (Jan / Feb.).

Muller, W.E. (1981) The benzodiazepine receptro., *Pharmacology*, **22**: 153-161.

Paget, G.E.; and Barnes, J.M. (1964) *Evaluation of drug activities. Pharmacometrics*, (ed, Leurence, D.R.; and Bacharach, A.L.). Academic Press, London and New York, **1**: 135.

Poison Information Service (1986) In Poison Control Centre of Ain Shams University.

Samson, Y.; Hantraye, P.; and Baron, J.C.(1985) Kinetics and displacement of 11C) Ro 15-1788, a benzodiazepine antagonist, studied in human brain in vivo by position tomography. *Eur. J. Pharmacol.*, **110**: 2, 247-251.

Tietz, E.L.; Rosenberg, H.C.; and Chiu, T.H. (1986) Autoradiographic localization of benzodiazepine receptor down-regulation. *J. Pharmacol. Exp. Ther.*, 236 / **1**: 292.

Naloxone Comme Antidote aux Benzodiazépines: Une Etude Expérimentale et Clinique

Cette étude évalue la possibilité d'utiliser le naloxone comme antidote aux benzodiazepines. Une étude expérimentale de cet effet antidote dans l'intoxication par diazepame et flunitrazépame chez les chiens a été menée. Une autre étude a observé l'effet du naloxone dans l'intoxication par flunitrazépame dans un groupe clinique de 8 patients.

Les résultats de l'étude clinique suggèrent une action neutralisante du naloxone dans l'intoxication par flunitrazépame. Il est fort probable que le flunitrazépame possède un profil pharmacologique distinct des autres benzodiazépines. La neutralisation sélective naloxone-flunitrazépame nécessite une comprehension du mechanisme d'action de cette benzodiazepine ainsi qu'une mise en parallèlle avec la neutralisation naloxone-opiacés.

النالكسون كعقار مضاد للبنزوديازبين.
دراسة تجريبية و اكلينيكية

تقيم هذه الدراسة تقيم فاعلية النالكسون كعقار مضاد للتسمم بالبنزوديازبين من خلال دراسة معملية على الكلاب ودراسة إكلينيكية على ٨ حالات تسمم بالفلونترازيبام. تشير نتائج الدراسة الأكلينيكية إلى فاعلية النالكسون كمضاد للتسمم بالفلونترازيبام، كما تشير أيضا الى وجود اختلاف فى الخواص الفارماكولوجية للفلونترازيبام عن بقية مجموعة البنزوديازبين.

وقد انتهت الدراسة إلى أن فاعلية النالكسون تستدعى ضرورة فهم طبيعة التفاعل التعادلى من واقع خصائص عمل وكيفية تأثير الفلونترازيبام مع مقارنتها مع خصائص التفاعل بين النالكسون و مجموعة الأفيونيات.