Withdrawal Effect of Codeine and Phenobarbitone on the Brain and Cardiac Function Enzymes and Glucose Metabolism in Adult Albino Rats

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Abstract

This study is to elucidate the withdrawal of codeine and phenobarbiton and their effects on some brain, cardiac activity and glucose-insulin-glucagone relations. This may help to clarify the side effect and metabolic changes which may occur as a result of drug administration. For this aim forty adult albino rats were randomly divided to 5 groups each of eight animals. First group was kept as control. Second and third group received codeine orally in therapeutic and double therapeutic dose. Forth and fifth group were given phenobarbiton intramuscular in therapeutic and double therapeutic dose. Drugs were administered day after day for four consecutive weeks. Alterations in serum Monoamine oxidase (MAO) activities, Cholinesterase (ChE) activities, whereas 5' nucleotidase (5'NT) and creatine kinase (CK) activity lactate dehydrogenase (LDH), Aspartat-aminotransferase (AST), glucose, insulin and glucagon were recorded. Such alterations were discussed in relation to doses and levels of drugs in urine of rats that actually stopped drug and exhibited that the analgesic effects symptoms of the drugs are expression of changes of functioning enzymes

Introduction

Drug abuse is one of the major health problems. It affects health directly from overdose and indirectly from injuries during intoxication.

Routine urine tests for one year (in Alexandria poison treatment center) ituted 12.5-35.0% positive urine for opiates, cannabis, amphetamines, barbiturates benzodiazepines **(Amal and Somaya, 2004).** One hundred and ninety cases of drug abuse were admitted to Menoufyia poison and dependence control center throughout 2 years. The highest number was among age 12 < 25 years. Male represented 97.8% while female showed 2.2%. About sixty five percent of cases were from urban areas and 34.74% from rural areas **(Badawi et al., 2004)**. While majority of the studied psychoactive abusers in Mansoura was found to be between 16-25 years **(Rania, 2004)**. Substance misuse in UK has reported as a factor in over half of homicides and suicide by people with serious mental illness or addictives **(Waheed, 2004)**.

Codeine is one of opioid analgesics **(Walter and Leongway, 1992)**, its effect is due to its conversion to morphine which has greater affinity for opioid receptors **(Jaffe and Martin, 1991).** It modulates release of excitatory neurotransmitters in brain **(Bradley and Nicholson, 1986)**. Barbiturates are used as hypnotic and sedative agent and for treatment of epilepsy and status epileptics. The symptoms of barbiturates toxicity depend on drug, route and rate of administration **(Olson, 1990)**. **Lea et al. (2004)** demonstrated that insulin level and oral glucose tolerance test were normal in addicts, in this respect **Inagawa et al (2004)** stated that cocaine and amphetamines did not affect the pancreatic islets cell types during rat development. Whereas **Knapp et al. (2002)**found that the repeated cocaine administration can cause protracted decreases in basal local cerebral metabolic rate for glucose utilization

Aim of the work : study aims to detect the relation between drugs of abuse in biological samples (urine) and changes of brain and cardiac function.

Materials and Methods

Materials:

Codeine: Codeine anhydrous (Codipront) ® cum expectorants syrup obtained from October Pharma S.A.E. Egypt under license of Heinrich MACK NACHF Germany.

Phenobarbitone: Phenobarbitone sodium (Sominaletta) ® obtained in form of Ampoules from Alexandria Co. for pharmaceuticals Alex.- Egypt.

Experimental design: Forty Albino rats weighting 230-270 gm were used. Rats were kept at a constant environmental and nutritional condition. Water was supplied ad-libitum. Rats were divided into five groups each of eight rats and classified as follows : first group was kept as control. Second and third groups were received codeine at therapeutic (60 mg/kg) and double therapeutic doses orally according to **(Olsen, 1990)** day after day for four consecutive weeks. Forth and fifth groups were received hypnotic dose of phenobarbitone sodium (15 mg/kg) and double hypnotic dose intramuscularly day after day for four consecutive weeks. All doses were calculated for rat according to the formula of **Paget and Barnes (1964)**.

Sampling

Urine samples (24h) were collected just after drug administration stopping and at one, two and four weeks from last dose. Urine was collected from each rat using metabolic cage. Blood was collected from the median canthus of eye and left to clot and centrifuged for separation of serum. Urine used for quantitative determination of codeine and phenobarbitone using VIVA apparatus according to **Baselt (1984).** The Sera used for quantitative determination of: monoamineoxidase (MAO) **(McEween, 1969),** cholinesterase (AchE) **(Den Blawen et al. 1983),** 5' nucleotidase (5'-NT) **(Bertrand and Buret 1982)** and creatinkinase (CPK) **(Rosano et al. 1976),** lactatedehydrogenase (LDH) **(Buhl and Jackson, 1978),** aspartat-aminotransferase (AST) **(Belifield and Goldburg 1971).** The serum also used for the quantitative estimation of determinations of glucose **(Barham and Trinder 1972)** and insulin and glucagone according to **Dudley (1985).** Statistical analysis was conducted by "t" test using student program according to **Snedecor, and Cochram (1982).**

Results

Table (1) and fig. (1) revealed that codeine level detected in urine till two weeks after drug holding. While phenobarbitone still detected for four weeks from drug stopping.

Concerning to the effect of codeine table (2) revealed reduction in monoamine oxidase, cholinesterase and 5' nucleotidase at zero and one week from drug holding. Also indicates increased serum level of creatine kinase, lactate dehydrogenase and aspartat-aminotransferase in group taken therapeutic dose in addition to increase in glucose and glucagon in group taken double therapeutic dose at zero and one week of drug holding. Serum insulin level was decreased. Table (3) indicate decrease in serum concentration of MAO, ACHE, 5' NT in group taken therapeutic and double therapeutic doses just after drug holding. Also the table indicates increased level of creatine kinase, lactate dehydrogenase and aspartat-aminotransferase. In addition to high level of glucose and glucagons in group taken double therapeutic dose of phenobarbitone.

Table (2): Mean value of serum enzymes (MAO, ACH, 5' NT) and (CPK, LDH, AST) together with glucose, insulin and glucagon after therapeutic and double therapeutic dose of codeine in comparison to negative control group (Mean ±S.E.).

Animal group / Parameter	Negative control group				Therapeutic dose of codeine				Double therapeutic dose of codeine			
					Weeks after holding therapeutic dose of codeine				Weeks after holding double therapeutic dose of codeine			
	0	1	2	4	0	1	2	4	0	1	2	4
MAO *(U/ml)*	28.30 ±0.71	24.10 ±0.40	25.30 ±0.80	27.30 ±0.80	11.70* ±1.15	10.61* ±0.91	22.75 ±0.95	31.21 ±1.31	8.11* ±0.75	9.97* ±1.21	21.75 ±1.11	28.11 ±2.50
ACHE *(U/ml)*	7.15 ±0.49	7.20 ±0.30	7.14 ±0.40	7.90 ±0.50	3.15* ±0.71	3.59* ±1.01	4.71 ±0.96	9.11 ±0.71	2.71* ±0.79	4.61* ±0.77	5.15 ±0.59	8.71 ±0.97
5' NT *(U/ml)*	5.35 ±0.63	5.50 ±0.40	5.30 ±0.80	5.90 ±1.20	3.05* ±0.11	2.97* ±0.17	3.79 ±0.51	4.59 ±0.76	2.31* ±0.09	2.93* ±0.18	4.19 ±0.21	4.71 ±0.61
CPK *(U/L)*	30.16 ±0.91	35.20 ±0.80	34.10 ±1.20	30.30 ±1.30	59.18* ±1.31	51.31* ±1.71	41.29 ±0.79	41.19 ±0.61	93.15* ±3.10	71.71* ±1.91	47.15 ±0.79	39.11 ±0.91
LDH *(U/L)*	187.00 ±1.84	189.00 ±1.60	195.00 ±1.80	190.00 ±1.20	416.15* ±7.91	391.20 ±6.30	261.00* ±4.15	191.00 ±3.31	459.0* ±7.53	399.10* ±6.21	269.00* ±3.36	219.00 ±3.61
AST *(U/L)*	48.70 ±1.30	47.40 ±1.40	49.30 ±1.30	47.3 ±1.20	119.25* ±2.31	101.35* ±2.60	59.15 ±1.60	43.60 ±1.11	161.36* ±3.51	115.80* ±2.16	92.60* ±1.91	63.51 ±2.00
Glucose *(mg/dl)*	73.80 ±1.96	72.80 ±1.60	70.30 ±1.70	79.2 ±3.10	86.11 ±0.97	105.31* ±1.36	99.71 ±1.31	79.11 ±2.10	117.20* ±2.15	103.75 ±2.00	99.15 ±2.60	69.11 ±2.01
Insulin *(uIU/ml)*	41.71 ±1.10	40.40 ±1.20	45.30 ±1.90	45.30 ±1.20	31.61 ±2.1	30.61 ±1.90	39.81 ±1.01	39.71 ±0.81	19.16* ±1.50	31.71 ±0.91	41.21 ±0.79	43.15 ±1.38
Glucagon *(ng/dl)*	99.75 ±2.20	95.90 ±2.70	99.80 ±2.80	102.3 ±2.30	121.11 ±2.15	112.51 ±1.97	109.11 ±2.06	109.18 ±1.78	131.71* ±2.81	119.71 ±2.51	113.15 ±2.09	100.31 ±2.17

*: Significant at (P<0.05) **: highly significant at (P<0.01) ***: Very highly significant at (P<0.001)

Table (3): Mean value of serum enzymes (MAO, ACH, 5' NT) and (CPK, LDH, AST) together with glucose, insulin and glucagon after therapeutic and double therapeutic dose of phenobarbitone in comparison to negative control group (Mean ±S.E.).

Animal group / Parameter	Negative control group				Therapeutic dose of codeine				Double therapeutic dose of codeine			
					Weeks after holding therapeutic dose of phenobarbitone				Weeks after holding double therapeutic dose of phenobarbitone			
	0	1	2	4	0	1	2	4	0	1	2	4
MAO *(U/ml)*	28.30 ±0.71	25.10 ±0.40	25.30 ±0.80	27.30 0.80	9.17* ±0.81	15.50 ±0.73	23.15 ±1.06	28.60 ±1.01	10.33* ±0.91	17.15 ±1.31	17.53 ±1.09	30.21 ±1.21
ACHE *(U/ml)*	7.15 ±0.49	7.20 ±0.30	7.14 ±0.40	7.90 ±0.50	2.95* ±0.09	4.39 ±0.75	6.15 ±0.33	8.33 ±0.61	1.17* ±0.93	3.19* 0.66	6.51 ±0.79	8.08 ±0.97
5' NT *(U/ml)*	5.35 ±0.63	5.50 ±0.40	5.30 ±0.80	5.90 ±1.20	2.19* ±0.05	4.91 ±0.69	5.43 ±0.70	6.91 ±0.39	2.01* ±0.13	2.97* ±0.20	5.61 ±0.15	5.45 ±0.25
CPK *(U/L)*	30.16 ±0.91	35.20 ±0.80	34.10 ±1.20	30.30 ±1.30	67.11* ±2.33	45.80 ±2.91	34.19 ±1.80	31.31 ±1.10	80.15* ±2.11	73.15* ±2.90	59.11 ±1.70	41.19 ±1.07
LDH *(U/L)*	187.00 ±1.81	189.00 ±1.60	195.00 ±1.80	190.00 ±1.20	314.00* ±4.10	251.7* ±3.16	212.00 ±3.01	200.00 ±2.76	405.00* ±6.70	333.61* 6.16	259.15* ±2.77	191.56 ±3.31
AST *(U/L)*	48.70 ±1.30	47.40 ±1.40	49.30 ±1.30	47.30 ±1.20	118.30* ±2.80	100.71* ±1.35	48.10 ±1.60	49.70 ±1.05	136.15* 2.97	121.30* ±2.18	89.30* ±1.97	56.20 ±1.30
Glucose *(mg/dl)*	73.80 ±1.96	72.80 ±1.60	70.30 ±1.70	79.20 ±3.10	83.11 ±2.10	79.71 ±1.70	69.71 ±1.33	79.50 ±3.61	118.11* ±2.91	90.53 ±2.39	68.20 ±1.90	73.11 ±2.10
Insulin *(uIU/ml)*	41.71 ±1.10	40.40 ±1.20	45.30 ±1.90	45.30 ±1.20	33.11 ±0.97	39.61 ±1.10	46.70 ±2.10	45.70 ±1.60	26.16 ±1.30	30.71 ±1.63	43.15 ±0.93	49.61 ±1.01
Glucagon *(ng/dl)*	99.75 ±2.20	95.90 ±2.70	99.80 ±2.80	102.30 ±2.30	111.36 ±3.15	102.00 ±2.91	105.00 ±3.01	112.70 ±2.77	127.30* 3.91	119.71 ±2.51	85.71 ±1.39	89.17 ±2.31

*: Significant at (P<0.05) **: highly significant at (P<0.01) ***: Very highly significant at (P<0.001)

Discussion

Nowadays uses of drugs are much more than any time before. Such extensive varied use must result in the occurrence of numerous cases of poisoning. Drug abuse is more than a health problem. It is a moral, social and economic challenge with pandemic dimensions. Substance abuse is showing an increasing trend. The mode of use is shifting from oral use and inhalation to the injecting route, which is more harmful **(Mohit and Srinivasa, 2004).**

The obtained data revealed that detection of codeine and phenobarbitone sodium in urine of rats after stopped drug taking are clear in Table (1) and Fig. (1). Regular urine analysis were performed at 0, 1, 2 and 4 weeks to detect for how long urine still having the drug. Codeine still persistent for 2 weeks while barbiturate still in urine even after 4 weeks from drug holding.

Results of urine codeine levels were disagree with **(Vargas et al. 2004)**; while urine barbiturate levels were agree with same author. Such author detected that codeine persist for 7 days while barbiturate remains in urine for 21-28 days. Also, agree with **(Elsohy et al., 1990)** who detected that the highest concentration of opiates in urine were found 3-8 h after ingestion or in first void samples. Also partially agree with **Needham et al. (1981)** who mentioned that 18% of codeine is excreted in urine. These results may be explained as the elimination half life of codeine is 3 h and 80 -120 h for Phenobarbital **(Olsen, 1990).** The activity of neurotransmitters system may be better understood as a reflection of a relative failure in their regulation rather than a simple increase or decrease in their activity. MAO is a membrane bound mitochondrial enzyme plays a role in the intraneuronal inactivation of neurotransmitters in catecholaminergic and serotonergic neurons **(Young et al., 1989).** AchE is a membrane-bound enzyme present in all cholinergic neurons and plays essential role in the regulation of physiological events **(Bekpimar et al., 1994).**

The recorded data of Table (2) showed that their were significant decrease in MAO and AchE in the codeine administered groups at 0 and 1 weeks from holding of drug use in comparison with the mean values of the control group. These results partially agreed with **(Kitabayashi et al., 2000)** who recorded a case of cough suppressant tablet dependence contain dihydrocodeine showed psychomotor excitement, hyperactivity and irreversible brain damage based on abnormal change in neural system. Also, partially agree with **Kamei et al. (2003)** who mentioned that dihydrocodeine stimulate the central dopaminergic system via dopamine receptors. The noticed decrease in serum MAO and ACHE might be related to the gradual loss of effectiveness due to tolerance and characteristic withdrawal or abstinences syndrome. The chronic exposure and tolerance to opoids is associated with an elevation of intracellular Ca^{2+} content unlike acute exposure, which often causes decrease. Also, in tolerance change in receptors ability to associate with G-coupling proteins were occurred leading to increased level of G-proteins and up regulated cAMP system. In addition the number of receptors affected by codeine may be reduced by internalization **(Walter and Leongway, 1992).** Also, results are in accordance with the hypothesis of **Loghin et al. (2004)** who revealed that the abstinences and chronic codeine administration express increased activity of neuronal adenyl cylase and cAMP-dependant kinase, which unlike the pharmacologic action.

5'NT is a microsomal and membrane associated enzyme found in a wide variety of tissue most specifically liver tissue **(Anderson and Cockayne, 1994).** The decreased value of 5'-Nt due to codeine withdrawal may be reflecting cholestatic injury of the liver **(Hayes, 1989).** These explanations confirm the results of **James et al. (1982)** who reported that opioid analgesics cause liver dysfunction.

CPK is higher in skeletal muscle, brain and heart tissue. CPK is elevated in diseases of myocardiac and nervous tissue **(Hassanein et al. 2003).** Data in Table (2) indicated that codeine had increased level of serum creatine phosphokinase of rat. CPK were increased in second and third group at 0 and 1 week from drug holding. These results may be explained as codeine caused damage

to brain and heart tissue as mentioned by **Young (1989).**

Codeine administered to rat by therapeutic and double therapeutic dose caused increase in serum lactate dehydrogenase at 0, 1 and 2 weeks from holding of drug. These results agree with **Ellington and Rosen (1987)** who stated that codeine mediates leakage of lactate dehydrogenase from cells and this lead to decrease in cell viability. This result explained as codeine caused reduction of glutathione level. This effect leads to increase of cellular damage, where glutathione is responsible for cellular integrity leading to escape of the enzymes into the blood.

The present study reported that codeine administration by therapeutic or double therapeutic dose induced significant increase in serum AST levels, at 0 and 1 week in group taken therapeutic dose of codeine and, at 0, 1 and 2 weeks in group taken the double therapeutic dose. These results confirm the results of **James et al. (1982),** and **Abeir (1999)** who reported that opoid analgesics cause liver dysfunction due to the intermediate of codeine (norcodeine and morphine) generated by cytochrome P-450. These results confirmed by detection of codeine in urine of rats for two weeks.

Table (2) illustrated glucose, insulin and glucagon level in serum of rats administered therapeutic and double therapeutic dose of codeine. Glucose, insulin and glucagon in rats administered therapeutic dose of codeine (table 2) showed non significant variation after 0, 1, 2 and 4 weeks from stopped drug administration. Only an increase in glucose and glucagon level after one week was detected and increase in ucose level and decrease in insulin level in taken double therapeutic dose were ected just after stopped drug taken week). Increase in glucose level agrees th **O'byrne and Feely (1990)** and **Abeir 999).** They recorded that codeine inistration for 30 days induced significant rease in serum glucose level. Also reased in insulin level agree with **(Reid et 1984).** Increase in glucagon agrees with **ampe a nd H arvey (1994).** This effect is tral and is abolished after section of splancnic nerve or removal of suprarenal gland **(Klepper et al., 2002).** Also, opoids have a hyperglycemic effect, where the endogenous opoid peptide metenkephalin has been found in endocrine pancreas and have an inhibitory effect on insulin secretion **(O'byne and Feely, 1990).** Morphine and related compounds had stimulatory effect on glucagon release which stimulates gluconeogenesis **(Reid et al., 1984).** Non significant variation of glucose, insulin and glucogon at 1, 2 and 4 weeks from drug stopping augmented by the level of codeine in urine as clear in Table (1).

Barbiturates are used as hypnotic and sedative agents. Serum MAO and AchE levels were decreased in serum of rats administered different doses of barbiturate in sample taken just after drug stopping. These results agree with, **Tominaga et al. (2001)** and partially agree with **Singh and Sanyal (2003)** who recorded that morphine analgesia and pentabarbitone sodium hypnosis caused changes in brain serotonin level of rats. Reduction of MAO and AchE levels may occur as a result of chronic toxicity and gradual loss of drug effectiveness or due to tolerance which associated with insomnia, anxiety and irritability which unlike acute toxic symptoms, where receptors become less effective to phenarbitone **(Olsen, 1990)** who mentioned that chronic users or abusers may have striking tolerance to barbiturate depressant effect.

Moreover the recorded decreased levels of MAO could be related to the direct effect of drugs as confirmed by **(Singh et al. 2004)** who stated that Phenobarbital induce different suppressions of brain MAO, decrease lipid antioxidant enzymes and antioxidant vitamins. These changes due to the reduction of intracellular cAMP concentration by inhibition of adenyle cyclase activity and inhibition of neural firing by modulating membrane channels

The data of Table (3) indicated that phenobarbiton sodium had decreased serum 5' NT which is a plasma membrane marker. These results indicated chronic toxicity and gradual loss of drug effectiveness or due to tolerance.

Serum CPK, LDH and AST were increased in rat administered low and high dose of phenoharbitone sodium just after drug holding and after one weak (high dose) from drug stopping as shown in Table (3). These data agree with **Allende et al. (2004)** where they observed increase in total serum CPK and AST due to barbiturates administration. The recorded increased value could be related to cerebral and cardiovascular disorder resulted from exposure to barbiturates which are lipid-soluble and rapidly penetrate the brain then are quickly redistributed to other tissue **(Olson, 1990),** which lead to decrease in cell viability and cellular damage leading to escape of these enzymes into the blood.

The recorded increased values of serum glucose and glucagon level in groups administered high doses of barbiturate only just after drug holding was in contrary to **Olsen (1990)** and partially agree with **Klepper et al. (2003)** who mentioned that barbiturate help in relive of defect glucose transport to brain.

From the present study it could be concluded that the analgesic and anesthetic effects of used drugs and the exhibited symptoms are expression of changes of brain and cardiac functioning enzymes. We should pay attention to the trend of drugs abuse and may need to regulate the market by law more severly.

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تأثير انسحاب الكوديين والفينوباربيتون على بعض إنزيمات وظائف المخ و القلب و كذلك الأيض فى الفئران

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تستخدم الأدوية المخدرة خاصة المخدرة منها على نطاق واسع فى الإنسان والحيوان. قد يكون لأغراض علاجية كما فى مرض السرطان أو للتخفيف من الآلام أو فى خيول السباق. كما قد تتعرض الكلاب البوليسية لجرعات من تلك المواد أثناء التدريب على كيفية اكتشافها والتعرف على أماكن تواجدها. يضاف إلى ذلك انتشار ظاهرة تعاطى المخدرات بجميع أنواعها بين النشء. وتكمن الخطورة فى أن تأثير سوء استعمال الأدوية يظهر على المدى الطويل من تدمير للجهاز العصبى خاصة وباقى أجهزة الجسم عامة. لذلك يهدف البحث إلى إظهار الآثار الجانبية الناشئة عن طول فترة التعرض وما يحدث خلال فترات انسحابها من تأثير على وظائف المخ والقلب ومستوى الجلوكوز والأنسولين و الجلوكاجون .

تم استخدام ٤٠ فأر أبيض بالغ من الجنسين قسمت إلى خمسة مجموعات متساوية (ثمانية فئران فى كل مجموعة) واستخدمت المجموعة الأولى كمجموعة سالبة بينما أعطت المجموعة الثانية والثالثة ٦٠ مجم/كجم، ١٢٠ مجم/كجم من الكوديين على التوالى. وأعطيت المجموعة الرابعة والخامسة ١٥ مجم، ٣٠مجم/كجم من فينوباربيتون الصوديوم لمدة أربعة أسابيع متتالية. تم تجميع عينات البول والمصل بعد توقف الحقن مباشرة وبعد أسبوع وأسبوعان وأربعة أسابيع من توقف الحقن. تم قياس مستوى كل من دواء الكوديين والصوديوم فينوباربيتون فى بول الفئران. بالإضافة لقياس مستوى كل من خميرة أحادى أمين أوكسيديز وكولين استيريز والنيكلوستيديز والكريتين فسفوكينيز واللاكتيت دى هيدروجينيز والاسبرتيت أمينوترانس فيريز والجلوكوز والانسولين والجليكوجون فى مصل الدم . وقد أظهرت النتائج نقص فى مستوى خميرة أحادى أمين أوكسيديز وكولين إستيريز والنيكلوتيديز فى كل المجموعات بعد توقف الحقن وكذلك حدث زيادة فى مستوى الكريتين فسفوكينيز واللاكتيت دى هيدروجينيز والاسبرتيت أمينوترانس فيريز وكذلك الجلوكوز و بعد مناقشة النتائج التى تم التوصل إليها لوحظ أن التأثير المخدر لهذه العقاقير مبنى على تأثيرها على إنزيمات المخ و القلب والجلوكوز الذى هو مصدر الطاقة الأساسي فى الجسم .