Endocrine Effects Followed Chronic Use of Morphine in Long–Term Treatment Model

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Abstract: Addiction is a major problem which increasingly developed among the various populations throughout the world, and there are evidences that addiction may affect the hypothalamus-pituitary-gonadal axis and sexual functions. Opioids are the most potent and effective analgesics available and have become accepted as appropriate treatment for acute, cancer and non-cancer chronic pain. In view of the increased use of opioids for chronic pain, it has become increasingly important to recognize and manage their endocrine complications. **Methods:** Forty adult male albino rats of similar weight and age were divided into control groups (8 rats) and experimental groups (32 rats) that were used to evaluate the repeated increasing cumulative dose effect. They were injected intraperitonealy (i.p.) with a single daily dose of 4mg/kg body weight for 7 consecutive days. On day 7, eight rats were sacrificed and the remaining 24 rats were injected (i.p.) with a single daily dose of 8 mg/kg body weight for another 7 consecutive days. On day 14, eight rats were sacrificed and the remaining 8 rats were injected i.p. with a single daily dose of 12 mg/kg body weight for another 7 consecutive days. At the end of this experimental period the last 8 rats were sacrificed .The remaining eight rats carried out to examine the delay effect of the tested dose (withdrawal effect). These rats were kept with no drug treatment over a withdrawal time of 21- days after last given dose. At the end of each experimental period, rats were sacrificed quickly with the least disturbance by fast decapitation. **Results:** There was significant decrease in the levels of serum thyroid stimulating hormone (TSH), serum luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone among all morphine treated rats with elevation in serum triiodothyronine (T_3) and thyroxin (T_4). Moreover, morphine significantly elevated prolactin (PRL) and estradiol (E2) in male rats. Twenty-one days recovery period after last injection, morphine withdrawal groups remained significantly different compared to control values except testosterone. **Conclusion:** The present finding pointed out to the risk of thyroid and sexual dysfunction. Morphine toxic effects should be kept in mind during long-term therapy especially in large doses. These findings suggest that, further investigations are required to determine the need for systematic substitutive therapy in chronic use of opioids in long-term treatment of chronic pain.

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1. Introduction

In spite of the fact that, many research activities are conducted in cases of drug abuse and addiction, yet many problems are still waiting further investigation. Both clinically and in experimental animals, the occasional use of an abusable drug is distinct from repeated drug use and the emergence of chronic drug addiction(Koob and Le Moal 1997). Much of the recent progress in understanding the mechanisms of addiction has derived from the development of animal models of addiction on specific drugs such as opiates and stimulants (Weiss 2010). These animal models have localized the synaptic sites and transductive mechanisms in the nervous system on which drugs of abuse act initially and are beginning to be used to explore how the nervous system adapts to drug abuse (Sandberg and Garris 2010). There are many misunderstandings about the origins and even the definitions of drug abuse and dependence. Although many physicians are concerned about "creating addicts", very few individuals begin their drug addiction problems by misuse of prescription drugs. Confusion exists because the correct use of prescription medications for pain, anxiety, and even hypertension commonly produces tolerance and physical dependence. These are normal physiological adaptations to repeated use of drugs from many different categories (O'Brien, Childress *et al.,* Morphine; opioids are the most potent and effective analgesics available and have become accepted as appropriate treatment for acute, cancer and non-cancer chronic pain(Almakadma and Simpson 2013). Opioids have been used for medicinal and analgesic purposes for millennia and today remain a critical part of the medical use against pain, diarrhea, cough, and other symptoms. In view of the increased use of opioids for chronic pain, it has become increasingly important to recognize and manage their

endocrine complications(Manchikanti, Vallejo et al. 2011). Today, opioids find their widest clinical application in the relief of acute or chronic suffering (Raff, Crosier et al. 2014). Patients may also benefit several of non-analgesic effects engendered by certain opioids. For example, codeine finds widespread use as an antitussive agent and diphenoxylate as an antidiarrheal drug.

Although opioids are being widely used since very long time, their long-term effects especially at hypothalamic-pituitary-gonadal axis are not clearly investigated. This system is modulated by a complex series of outside influences. Opioids are one of a number of such influences(Font, Lujan et al. 2013). The term opioid refers broadly to all compounds related to opium and derived directly from the opium poppy (colorful flowering plant). The drug being extracted from the poppy plant (*Papaver somniferum*), which contains powerful medicinal alkaloids such as morphine and has been used since ancient times as analgesic and narcoticmedicinal and recreationaldrugs(Pasternak 1993). Opiates are drugs derived from opium, and include the natural products morphine& codeine. Many semisynthetic opioid, such as heroin and oxycodone, may be created by the modification of an opiate. Alternatively synthetic opioids are newly synthesized chemical compounds that are capable of producing opioid effects experimentally or clinically. The term referred to any drug that induced sleep, but then it became associated with opioids(Pasternak 1993). It is now well know that opioids such as heroin and morphine exert their effects by mimicking naturally occurring substances, termed endogenous opioid peptides or endorphins (Pang, Liu et al. 2013).Morphine is available for oral use, but it is two-to six folds less potent orally than parenterally.This important to remember when converting the patient from parenteral to oral medication and the dose should be titrated to the patients' need. Opium was used as a drug by the Arabian physicians and introduced by the Arabian traders to the orient about the 10th century where it was used mainly for the treatment of dysenteries. By the middle of the 16th century, opium began to be widely used in Europe, and then it becomes widely used also in India and China(Hough, Nalwalk et al. 2000).

Endocrine hormones are the class of the regulatory biochemical produced by specific glands to control the organisms' physiological and behavioral activities. Changes in the sexual activity are commonly found in addicted subjects. The effects of drug abuse on sexual functions and sex hormones are one of the major scopes of investigations throughout the world.

In view of the increased use of opioids for the treatment of acute pain such as post-operative pain, as well as degenerative conditions such as rheumatoid arthritis. It has become increasingly important to recognize and manage their endocrine complications. Under such condition of limited information about the drug abuse and the drug toxicity, it seemed necessary to add further information to our knowledge about the endocrine complication and biochemical changes towards chronic toxicity of abuse of the given drug, morphine. The current investigation focuses on the long-term effects of morphine on pituitary-gonadal axis and pituitary-thyroid axis accompanying the toxicity resulting from the misuse of this drug in mammalian experimental model. Also throws some light on the influence of the withdrawal period on the drug toxicity, hopeful to solve such problem.

2. Materials and Methods

Rats:

Forty male adult albino rats (*Rattus norvegics*) were used in the current study. They were obtained from Breeding Unit of the Egyptian Organization for Vaccine and Biological Preparations, with initial body weight ranging from 160-180 gm. All rats were kept under the same environmental conditions for two weeks before study. The animals were fed *ad Libitum* with a standard diet and allowed free access of water. Male rats were used to avoid hormonal interference during different stages of estrous cycle.

Drug:

Morphine was purchased from Misr Co. (For Pharma S.A.R.) and wasused at the doseof the therapeutic level for the drug. The use of therapeutic dose enables us to follow drugs at an average used dose that is commonly taken by most abusers. Subsequently it was upgraded to other levels to follow up the dangerous effect of drug. The adopted experimental dose level has been calculated as equivalent of human therapeutic dose.

Experimental protocol:

After two weeks of acclimatization to the laboratory environment, forty (40) selected animals of nearly a similar weight and age were divided into the five groups; Control groups (8 rats) has been always kept in parallel with the experimental groups and subjected to simultaneous investigation. Thirty two rats carried out to evaluate the repeated increasing cumulative dose effect. They were injected intraperitonealy (i.p.) with a single daily dose of 4mg/kg body weight for 7 consecutive days. On day 7, eight rats were sacrificed and the remaining 24 rats were injected (i.p.) with a single daily dose of 8 mg/kg body weight for another 7 consecutive days. On day 14, eight rats were sacrificed and the remaining 8 rats were injected (i.p.) with a single daily dose of 12 mg/kg body weight for another 7 consecutive days.

At the end of this experimental period the last 8 rats were sacrificed .The remaining eight; carried out the delay effect of the tested dose (withdrawal effect). These rats were kept with no drug treatment over a withdrawal time of 30 days after last given dose. At the end of each experiment, rats were sacrificed quickly with the least disturbance by fast decapitation. In case of controlgroup, the blood was withdrawn from tail region.

Hormones measurement:

Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin (PRL), Testosterone (Tes), Estradiol (E2), total Thyroxin (T_4), Triiodothronine (T_3) and thyroid stimulating hormone (TSH) were determined using enzyme linked immunosorbant assay (ELISA) kits according to manufacture structure.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data was expressed using median, minimum and maximum.For normally distributed data, comparisons between different groups were analyzed using F-test (ANOVA) and Post Hoc test (LSD) for pair wise comparison. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

3. Results:

Effect of morphine administration on body weight and pituitary–thyroid axis at different intervals

General Toxic Observations after Morphine Administration: The action of the drug under investigation; morphine at the different tested doses and intraperitoneal injection was investigated.

Treating rats with daily morphine administrations over 7, 14 and 21- days at different dose levels induced weight loss with percentage decreases 3.6, 9.6 and 16.1 respectively. As regards, the withdrawal group showed percentage of decrease 2.8 compared to control value (Table 1). In addition, at the higher tested doses, some of the injected animals displayed noticeable behavioral neurotoxicological changes as excitation and disturbances of the locomotors activity. Moreover, reduction in testicular size has been observed. In addition, there were remarkable developments of gynecomastia at the higher tested doses.

The effect of morphine at different dose levels and selected time periods 7, 14, 21- days and 21-days' withdrawal period on thyroid hormone levels in male albino rats.

As regards the cumulative effect of increasing morphine doses, the data recorded for the daily intraperitoneal injection of 4, 8 and 12 mg/kg body weight for 7, 14 and 21- days and their withdrawal period on TSH, T_3, and T_4 are given in table 1. Concerning, TSH levels the data recorded showed significant decrease in TSH levels at the tested dose levels 4,8mg/kg with percentage decrease of 24.9, and 54.6 respectively as compared to control value. On the other hand, at the dose level 12mg/kg on day 21^{st,} there was insignificant relation (P>0.05) when comparing its level on the 21st day with that on the 7th day. There was, a significant relation (P<0.001) with a percentage decrease 24.3 when comparing the level of TSH on the 21st day with control value. Similarly, the morphine withdrawal group showed a significant percentage decrease of 26.6 (P<0.001) as compared with control value. Moreover, insignificant relation (P>0 .05) was detected in the TSH level when comparing its level in withdrawal group with that on the 21st day of drug administration.

Within morphine- treated groups , significant increases were detected when comparing the T_3 andT_4 levels on the 7th day , 14th day and the 21st groups of daily drug injection as compared to the control value (P<0.001)with a percentage increases 18.6,58.1, 20.9;26.7, 55.6 and 28.5 respectively .(In case of T4 and T3 there were insignificant relation between 21st and 7th day(P>0.05) , whereas there were significant relation between 21st and 7th days compared to 14th day of injection).On the other hand, there was insignificant relation (P>0.05) when comparing their levels on the 21st day with that on the 7th day. Moreover, there was a significant relation (P<0.001) when comparing the concentrations of these hormones on the 21st day and withdrawal group with that on the 14th day. Similarly, a significant relation (P<0.001) was detected in the T_3 andT_4 when comparing their levels in withdrawal group with that on the 21st day of drug injection.

Effect of morphine administration on gonadal activities at different intervals

The cumulative increasing morphine doses 4, 8, 12 mg/kg as illustrated in table 2 on LH, FSH, testosterone, estradiol and prolactin showed closely similar pattern as thyroid hormones. After 21 days recovery period, the measuring parameters did not reach their normal values except testosterone (P>0.05) when comparing their values with controls. The data recorded in Table 2 showed that, morphine significantly elevated prolactin (PRL) and estradiol (E2) in male rats. 21 days recovery period after last injection, morphine withdrawal groups remained significantly different compared to control values except testosterone.

Table (1): Effect of morphine administration on body weight and pituitary –thyroid axis at different intervals, 7, 14, 21-days and 21 days withdrawal recovery period after cessation of the drug

	Control (n = 8)	7 days (n = 8)	14 days (n = 8)	21 days (n = 8)	Withdrawal (n = 8)	F	*P*
Body Weight	160.29±8.13	154.56±7.99	144.96±5.17	134.41±5.06	155.78±7.97	17.446*	<0.001*
p_1		0.111	<0.001*	<0.001*	0.206		
p_2			0.010*	<0.001*	0.731		
p_3				0.005*	0.004*		
p_4				<0.001*			
% chg.$_1$		Dec.-3.6%	Dec.-9.6%	Dec.-16.1%	Dec.-2.8%		
% chg.$_2$			Dec.-6.2%	Dec.-13.0%	Inc. 0.8%		
% chg.$_3$				Dec. -7.3%	Inc. 7.5%		
% chg.$_4$				Inc. 15.9%			
TSH	10.08±0.77	7.57±0.75	4.58±0.77	7.63±0.74	7.40±0.73	54.137*	<0.001*
p_1		<0.001*	<0.001*	<0.001*	<0.001*		
p_2			<0.001*	0.879	0.658		
p_3				<0.001*	<0.001*		
p_4				0.552			
% chg.$_1$		Dec. -24.9%	Dec. -54.6%	Dec. -24.3%	Dec. -26.6%		
% chg.$_2$			Dec. -39.5%	Inc. 0.8%	Inc. -2.2%		
% chg.$_3$				Inc. 66.6%	Inc. 61.6		
% chg.$_4$				Dec. -3.0%			
T3	0.43±0.57	0.51±0.060	0.68±0.06	0.52±0.06	0.48±0.07	19.606*	<0.001
p_1		0.014*	<0.001*	0.004*	0.128		
p_2			<0.001*	0.654	0.312		
p_3				<0.001*	<0.001*		
p_4				0.148			
% chg.$_1$		Inc. 18.6%	Inc. 58.1%	Inc. 20.9%	Inc. 11.6%		
% chg.$_2$			Inc. 33.3%	Inc. 2.0%	Dec. -5.9%		
% chg.$_3$				Dec. -23.5%	Dec. -29.4%		
% chg.$_4$				Dec. -7.7%			
T4	2.88±0.64	3.65±0.42	4.48±0.56	3.70±0.39	3.43±0.38	11.140*	<0.001*
p_1		0.003*	<0.001*	0.002*	0.031*		
p_2			0.002*	0.839	0.364		
p_3				0.003*	<0.001*		
p_4				0.268			
% chg.$_1$		Inc. 26.7%	Inc. 55.6%	Inc. 28.5%	Inc. 19.1%		
% chg.$_2$			Inc. 22.7%	Inc. 1.4%	Dec. -6.0%		
% chg.$_3$				Dec. -17.4%	Dec. -23.4%		
% chg.$_4$				Dec. -7.3%			

F: F test (ANOVA)
p_1 : p value for Post Hoc test (LSD) for comparing between control and each other group
p_2 : p value for Post Hoc test (LSD) for comparing between 7 days and each other group
p_3 : p value for Post Hoc test (LSD) for comparing between 14 days and each other group
p_4 : p value for Post Hoc test (LSD) for comparing between 21 days and withdrawal
*: Statistically significant at $p \leq 0.05$
Inc.: Increase
Dec.: Decrease
% chg $_1$: between control and each other group
% chg $_2$: between 7 days and each other group
% chg $_3$: between 14 days and each other group
% chg $_4$: between 21 days and withdrawal

Table (2): Effect of morphine administration on gonadal activities at different intervals, 7, 14, 21-days and 21 days withdrawal recovery period after cessation of the drug

	Control (n = 8)	7 days (n = 8)	14 days (n = 8)	21 days (n = 8)	Withdrawal (n = 8)	F	*P*
LH	2.89±0.70	2.08±0.42	1.44±0.35	2.07±0.41	2.02±0.39	9.491*	<0.001*
p_1		0.002*	<0.001*	0.001*	0.001*		
p_2			0.010*	0.912	0.805		
p_3				0.014*	0.019*		
p_4				0.891			
% chg.$_1$		Dec. -28.0%	Dec. -50.2%	Dec. 28.4%	Dec. -30.1		
% chg.$_2$			Dec. -30.8	Dec -0.5%	Dec. -2.9%		
% chg.$_3$				Inc. 43.8%	Inc. 40.3%		
% chg.$_4$				Dec. -2.4%			
FSH	2.49±0.766	1.54±0.38	1.05±0.43	1.48±0.41	1.44±0.40	9.227*	<0.001*
p_1		0.001*	<0.001*	<0.001*	<0.001*		
p_2			0.054	0.802	0.678		
p_3				0.091	0.124		
p_4				0.869			
% chg.$_1$		Dec. -38.2%	Dec. -57.8%	Dec. -40.6%	Dec. -42.2%		
% chg.$_2$			Dec. -31.8%	Dec. -3.9%	Dec. -6.5%		
% chg.$_3$				Inc. 41.0%	Inc. 37.1		
% chg.$_4$				Dec. -2.7%			
Testosterone	4.27 ± 0.58	2.98 ± 0.72	2.09 ± 0.26	2.94 ± 0.71	4.28 ± 0.31	8.641*	<0.001*
p_1		0.007*	<0.001*	0.006*	1.000		
p_2			0.061	0.935	0.007*		
p_3				0.072	<0.001*		
p_4				0.006*			
% chg.$_1$		Dec. -30.2%	Dec. -51.1%	Dec. -31.1%	Inc. 0.2%		
% chg.$_2$			Dec. -29.9%	Dec. -1.3%	Inc. 43.6%		
% chg.$_3$				Inc. 40.7%	Inc. 104.8%		
% chg.$_4$				Inc. 45.6%			
E2	41.76±10.17	55.61±6.18	65.49±8.83	56.46±6.40	56.25±6.40	9.599*	<0.001*
p_1		0.001*	<0.001*	0.001*	0.001*		
p_2			0.016*	0.828	0.870		
p_3				0.026*	0.023*		
p_4				0.957			
% chg.$_1$		Inc. 33.2%	Inc. 56.8%	Inc. 35.2%	Inc. 34.7%		
% chg.$_2$			Inc. 17.8%	Inc. 1.5%	Inc. 1.2%		
% chg.$_3$				Dec. -13.8%	Dec. -14.1%		
% chg.$_4$				Dec. -0.4%			
PRL	7.84±1.13	9.65±1.23	11.73±1.56	10.0±1.20	9.76±1.25	9.259*	<0.001*
p_1		0.008*	<0.001*	0.002*	0.005*		
p_2			0.003*	0.589	0.862		
p_3				0.011*	0.004*		
p_4				0.713			
% chg.$_1$		Inc. 23.1%	Inc. 49.6%	Inc. 27.6	Inc. 24.5		
% chg.$_2$			Inc. 21.6%	Inc. 3.6%	Inc. 1.1%		
% chg.$_3$				Dec. -14.7%	Dec. -16.8		
% chg.$_4$				Dec. -2.4%			

F: F test (ANOVA)
p_1 : p value for Post Hoc test (LSD) for comparing between control and each other group
p_2 : p value for Post Hoc test (LSD) for comparing between 7 days and each other group
p_3 : p value for Post Hoc test (LSD) for comparing between 14 days and each other group
p_4 : p value for Post Hoc test (LSD) for comparing between 21 days and withdrawal
*: Statistically significant at $p \leq 0.05$
Inc.: Increase Dec.: Decrease
% chg $_1$: between control and each other group % chg $_2$: between 7 days and each other group
% chg $_3$: between 14 days and each other group % chg $_4$: between 21 days and withdrawal

4. Discussion

Addiction is a problem which increasingly developed among the various populations throughout the world, and there are evidences that addiction may affect the hypothalamus-pituitary-gonadal axis and sexual functions(Moshtaghi-Kashanian, Esmaeeli et al. 2005). Nowadays, opioids are increasingly consumed as drug of abuse problems that affecting almost all classes of mankind and societies. These problems are triggering steadily increasing attention of the concerned international, regional and national authorities. It is regrettable to watch drug addiction spreading particularly among teenagers from both sexes particularly among those who have been exposed to psychoneurosis, social or financial problems. The pharmacological effects of chronic use of opium on serum level of pituitary-thyroid and gonadal axes hormone are not studied extensively. This study was conducted to investigate the changes followed in a long- term use of morphine in an experimental model.

The activity of thyroid gland is predominantly regulated by the concentration of thyroid stimulating hormone (TSH), and thyrotropin that controls the sensitivity of the body to other hormones. Besides, they participates in these process by producing thyroid hormones, the principal ones being triiodothyronine (T_3) and thyroxin; tetraiodothyronine (T_4). These hormones regulate the rate of function of many other systems in the body. The thyroid gland produces thyroid hormones, when it functions properly; it considers part of a feedback loop with the pituitary gland that senses the level of thyroid hormone to release into the bloodstream. The role of TSH is to stimulate the thyroid to release more thyroid hormone. In the current study the significant decrease in the TSH level, suggests that such decrease caused overactive of the thyroid gland to exert more effort on the pituitary to return the system to normalize thyroid function. This assumption is supported by the work of Tale *et al.* (1984) who reported that morphine may exert a short-term stimulatory effect on the thyroid gland with a concomitant inhibitory action on the hypothalamus-pituitary TSH system which explain the reduction in TSH.

Concerning results about testosterone showed that chronic morphine treatment in incremental doses, 4, 8 and 12 mg/kg for 7, 14, and 21-days represented significant reduction in testosterone levels. The reduced levels of testosterone throughout incremental dose of morphine treatments may be explained probably through acting directly on peripheral glands. The current results are in agreement with(Aloisi, Aurilio et al. 2009) who reported that morphine reduces hormones like testosterone and cortisol in both male and female subjects in just a few hours. In addition, the increased dose levels did not induce significant changes in most of the studied parameters on day 21st compared to day 7th. This can be attributed to the fact that, the long-term use of opioids can, however, result in tolerance and dependence. There are number of studies linking acute receptor desensitization to tolerance and dependence(Ueda, Inoue et al. 2001, Bohn, Lefkowitz et al. 2002, Freye and Latasch 2003, Whistler 2012). Furthermore the results of the present investigation come in accordance with (Dang and Williams 2004) who reported that tolerance and dependence result from long-term exposure to opioids, and there is growing evidence linking acute receptor desensitization to this more long-term process. Receptor desensitization encompasses series of events leading to loss of receptors function.

Most commonly prescribed drugs can have adverse effects on male reproduction such as sedatives, tranquilizers, hypnotics, narcotics and cannabis, antihypertensive, antipsychotics and antidepressants. (Devinsky 2005) stated that opiate use is known to decrease the levels of sex hormones in both sexes and this lowered hormonal level is thought to be responsible for the diminished fertility of both male and female opiate users. In addition, along the same line, the present findings indicate that there were significant decrease in the levels of LH, FSH, and testosterone and this reduction, was positively co-related with the duration of morphine consumption. These findings are in accordance with the(Estienne, Harper et al. 2002, Daoud, Bataineh et al. 2004) who reported significant reduction in serum testosterone and FSH levels in antiepileptic treated patients and in rats respectively. Moreover, the significant effect of chronic morphine administration at different dose levels on prolactin release is consistent with (Moshtaghi-Kashanian, Esmaeeli et al. 2005) who indicated that there is a positive co-relation between the dose of opium and the plasma prolactin level as an inhibitor of gonadotropinreleasing hormone (GnRH) in opium dependents , thus the suppression of gonadotropin secretion by adenohypophysis may be due to suppression of GnRH release from the hypothalamus .Furthermore, there are some reports suggesting the direct effects of opium on pituitary gonadotropin releasing cells via kappa(Zhang and Gallo 2003) and mu opioid receptors(Sokolowska-Mikolajczyk, Socha et al. 2005).

The recovery groups showed that most of the tested parameters remained significantly different compared to control group. This may explain that morphine has toxic effects induced by long-term treatment. Moreover, it is known that opiate abuse exerts extensive adaptive changes in brain function, including many aspects of neurotransmission, such as

transmitter release during morphine withdrawal. The results of the withdrawal group suggest that the maintenance of elevations of; T3, T4, PRL, E2 and the reductions in FSH, LH, and TSH levels could be the expression of new adjustments in central nervous system neurotransmission after discontinuation of the chronic morphine treatment.

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