Effect of Tramadol Dependence on The Immune System In A Sample Of Egyptian Male Patients

Thesis

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List of Abbreviations

Abbr.	Full term
ACMD	Advisory Council on Misuse of Drugs
AIS	adaptive immune system
AUC	area under the concentration-time curve
BMI	body mass index
CNS	central nervous system
GLC	gas-liquid chromatography
GPCR	G-protein coupled receptor
HPLC	high-performance liquid chromatography
IFN	Interferon
IIS	innate immune system
IL	Interleukin
IR	Immediate-release
MBL	mannose-binding protein
MHC	major histocompatibility complex
MMT	methadone maintenance treatment
MOR	μ opioid receptor
MS	multiple sclerosis
NK	natural killer cells
NO	nitric oxide
NRAP	National Research Addiction Program
PAMP	pathogen-associated molecular pattern
PRR	pattern recognition receptor
REMS	Risk Evaluation and Mitigation Strategy
SR	sustained-release
Th	T-helper
TIR	Toll/interleukin-1 receptor
TLC	thin-layer chromatography
TLR	Toll-like receptor

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INTRODUCTION

The nonmedical use of prescription opioid analgesics is an ongoing challenge. Its overall burden to society has been difficult to quantify, though it manifests itself in several ways, including the physical and psychological consequences of addiction and the effect of illicit use on physicians' prescribing habits. The financial burden associated with such misuse and abuse is significant, especially when such factors as associated health care and workplace costs and the cost of treatment for patients with opioid addiction are considered. ***(Aaron and Paul, 2009)***

In USA, for example, the increase in abuse of marketed medications in recent years has highlighted the need for abuse-liability assessment. The numbers of new nonmedical users of four major classes of prescription-type drugs (pain relievers, tranquilizers, stimulants, and sedatives) increased between 1991 and 2001, with the largest increase in pain relievers. The number of primary treatment admissions for narcotic-analgesic abuse increased 76 percent between 1997 and 2000. ***(Zacny et al., 2003)***

Tramadol [(±)-Trans-2-(dimethylaminomethyl)-1-(m-methoxyphenyl)-cyclohexanol hydrochloride] was introduced as a non-scheduled drug on the market in the UK in 1994 and in the USA in 1995 for treatment of moderate to moderately severe pain. It was first synthesized in 1962 and has been available in Germany since 1977. As a centrally acting analgesic, tramadol is atypical because it produces analgesia through both mu opioid and monoamine actions. The pharmacology of tramadol is further complicated by the fact that it is administered as a racemic mixture with two active enantiomers, each of which is biotransformed to an active metabolite: (+)-O-desmethyltramadol or (−)-O-desmethyltramadol. These metabolites are believed to be responsible for most of tramadol's mu-agonist properties. Clinically, the recommended dose of tramadol for mild to moderate pain is 50–100 mg every 6 hours p.o. or parenterally. Based on analgesic studies, tramadol is thought to be approximately one-tenth as potent as morphine when each is administered parenterally and approximately one-third as potent when each is administered orally. Tramadol has a low incidence of adverse effects, particularly of

respiratory depression, constipation and abuse potential. ***(David et al., 2006)***

An increasingly alarming phenomenon of Tramadol (Tramal, Amadol, Tramax, Contramal, Trama SR, Ultradol, Tramundin) abuse has been heavily demonstrated in the Egyptian community in the last four years. Though the issue of drug abuse is not new to Egyptian society, tramadol is associated with a wide range of abuse and illegal transactions that made it easily accessible and readily provided at cheap cost despite of it being scheduled. The alleged usages of tramadol contributed greatly to its popularity and massive use especially among youth and middle- aged groups as a remedy for premature ejaculation and for extended orgasm and to increase sexual pleasure as promoted in many online drug stores and media. ***(Fawzi, 2011)***

The idea that opioids suppress the immune system and lower resistance to infections is not new. There is evidence that opioids modulate both innate and acquired immune responses, altering resistance to a variety of infectious agents. Acute and chronic administration of opioids is known to have inhibitory effect on humoral and cellular immune responses

including antibody production, natural killer lymphocyte activity, cytokine expression and phagocytic activity. Not all opioids induce the same degree of immunomodulatory effects. From reviewing the literature, it is evident that the majority of studies investigating the effects of opioids on the immune system have been conducted in animals. From these animal studies conclusions have been drawn that opioids can be divided into those that are immunosuppressive, such as codeine, methadone, morphine and remifentanil. And those that are less immunosuppressive, including buprenorphine, hydromorphone, oxycodone and tramadol. ***(Paola Sacerdote, 2006)***

Rationale of the study:

An increasingly alarming phenomenon of tramadol drug abuse has been demonstrated in the Egyptian community in the last few years (Fawzi, 2011). Few studies had examined the effect of tramadol abuse on the immune system and to our knowledge no Egyptian studies are conducted in this field , and whether the treatment from tramadol dependence restore the normal function of the immune system or not is not well understood .

Hypothesis:

The study hypotheses are:

1. Immune function is suppressed in Tramadol dependent male patients as compared to healthy controls.
2. Immune function will improve after 6 months of abstinence in Tramadol dependent patients.
3. Immune function will improve more in patients on naltrexone as compared to those not receiving naltrexone.

AIM OF THE WORK

1- To determine the effect of tramadol dependence on the immune system function.

2- To determine the effect of abstinence from tramadol dependence on the immune system.

3- To determine the effect of the opioid antagonist naltrexone on the immune system

Chapter (1)

Epidemiology of Tramadol Dependence

Epidemiological data:

Half of the US population aged twelve and above were current alcohol users (58.1 % were males). 22.7% had binge drinking (defined as five or more drinks on one occasion) at least once in the previous month, and 6.6 % reported being heavy drinkers. Illicit drug use was observed in (8.1%) of the total population above twelve years of age, the majority (54.5%) of whom used marijuana only, in the past month. Use of cocaine (1%), crack (0.3%), hallusinogens (0.4%) and heroin (0.1 were relatively lower) ***(Lutterman et al., 2006).***

When compared to other regions, Europe had the highest alcohol consumption in the world. In 38 countries, the average alcohol consumption per person in 1998 was 7.3 liters; ranging from 0.9 liters (Azerbaijan) to 1303 liters per person (Luxembourg) ***(Woelfer et al., 2001)***.

The European National population surveys have shown that cannabis is the most commonly used substance in the European adult population (aged 15-64 years) ranging