

Cancer pain, opiodes, and immunosupreession

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Introduction: Anecdotal reports indicated that some on-line users were becoming addicted to the Internet in much the same way, as others became addicted to drugs or alcohol, which resulted in academic, social, and occupational impairment. **Objective:** However, research among sociologists, psychologists, and psychiatrists has not formally identified addictive use of the Internet as a problematic behaviour. This study investigated the existence of Internet addiction among Internet users in the Jordanian Internet cafes. **Method:** This study utilised a simple ratio method to investigate the existence of Internet addiction in the population. A questionnaire, which consisted of 20 statements, was developed to measure Internet addiction amongst the selected sample. There were 300 males and 300 females. **Results:** A statistical analysis suggests significant differences between the two groups related to sex. In addition to this there were significant differences related to the following factors: employment, educational level. Psychological and social implications of pathological Internet use and future directions for research are discussed. **Conclusion:** This study highlights Internet addiction phenomenon in Jordan. This particular field should be given further investigation and study to know about the extant of its existence in Jordan and to try to find a solution for this increasing problem all over the world.



Introduction

All practitioners acting in the field of cancer has approved 2 important clinical observations. The first was that cancer distant metastasis is activated by surgical interference, like biopsy and hence the frozen section was implemented as a safe procedure against widespread metastasis. The second recent observation that patients referred to the pain clinic as soon as their pain is well controlled by opiodes, their health state changes dramatically so as their life span prolongs and the curve for cancer spread dramatically slows. Experimental animal studies proved this fact, and a

change of the concept of management was introduced that defines reduction or block of stress response as much as we can. To understand this new concept, an essential basic scientific data has to be explored.

Immunologic Regulation

Cytokines are polypeptides generated by cells and affect the growth and function of other cells. They have a vital role in the body performance after it is subjected to trauma, infection and stress. Their production comes in sequence of a series of activation, which is totally governed to produce healing and sur-

vival of the individual. The cytokine cascade usually starts by growth cytokines that stimulate inflammatory cells to produce proinflammatory cytokines, which in turn stimulate production of immune cytokines to end by stimulation of haemopoiesis.

Inflammation

Inflammation primarily involves the cytokines IL-1, interleukin-6 (IL-6), and TNF α ^{1,2}[R1]. [R2] The first response to an infectious challenge is the non-specific inflammatory response. The major cell involved in cytokine synthesis in inflammation was thought to be the macrophage; however, recent evidence has shown that the polymorphonuclear neutrophils (PMNs) also may be a source of the cytokines IL-1,^{3,4}[R3] [R4] IL-6,⁵[R5] TNF α ,⁶[R6] ,⁷[R7] and G-CSF⁸[R8]

The inflammatory response begins with an influx of PMNs to the site, followed by an increase in monocyte/macrophages, and then by an influx of lymphocytes. Thus, PMNs (phagocytes) as a source of cytokines in this process must no longer be ignored.

Interaction of these cells by ligand binding to surface receptors or phagocytosis of microbes results in synthesis and release of biologically active molecules, including prostaglandins, complement components, proteolytic enzymes, and cytokines. [R9] 2

IL-1 (a and b), IL-6, and TNF α take part in the activation of T and B lymphocytes and natural killer (NK) cells, monocytes, PMNs, endothelial cells, chondrocytes, osteoclasts, fibroblasts, hepatocytes, and nerve cells.

These cytokines have cytostatic/cytotoxic effects on pancreatic islet cells and take part in vivo in induction of fever, acute-phase protein synthesis, the release of adrenocorticotrophic hormone, leukocytosis, lymphopenia, increased insulin release, hypotension, capillary

leakage, and resistance against infection and irradiation. Many of these functions are necessary to the normal process of activation of phagocytes to remove infectious challenges.

Recently, however, it has become obvious that a systemic response to these cytokines results in the syndrome known as septic shock, which can eventually lead to multiple organ failure and

APCs take in and process antigens, presenting the processed antigen to the T cells and B cells in the presence of cytokines and products of the major histocompatibility complex

death⁹[R10]. Considering this response, it would seem beneficial to the host to intervene in this process and stop the production of these molecules. In the normal response to infection, the body regulates the synthesis of these products via glucocorticoids and the products of the arachidonic acid metabolic pathway -e.g. the prostaglandins. Complete down-regulation of these molecules, however, may be deleterious to the host because they are necessary to the normal processes of phagocytosis and the killing of invading organisms and to other physiologic responses to infection. For example, the administration of anti-TNF has been shown to ameliorate the septic shock syndrome¹⁰[R11] . In at least two different murine models,¹¹[R12],¹² [R13] however, this administration also resulted in decreased response to infectious challenge, resulting in high mortality. Thus, a major therapeutic goal must be to "educate the phagocyte".¹³[R14]

Interleukin-8 (IL-8) and interferon gamma (IFN γ) also are involved in the inflammatory process. Ik-8 is chemotactic for phagocytes, and IFN γ , along with IL-1 and TNF, induces respiratory burst in these cells, activates eosinophils to kill parasites, and activates NK cells that may take part in removing bacterial and viral infection.

Immunity

The immune response to infection involves antigen-presenting cells (APCs), T cells, and B cells. The response is antigen-specific but the cytokines involved are not. APCs take in and process antigens, presenting the processed antigen to the T cells and B cells in the presence of cytokines and products of the major histocompatibility complex. IL-1 α and IL-1 β are both active in promoting IL-2 production by T cells, and IL-6 also may have a role in activating T cells in this process¹⁴[R15] . On activation, the T cells produce IL-2, IL-4, IL-5, IL-6, IFN γ , and TNF β . The cytokines resulting from T-cell activation take part in the differentiation of B cells from the resting state to plasma cells and drive the secretion of immunoglobulin.

In cloned murine T cells have been divided into subsets called T-helper (Th 1 and Th 2) based on cytokine secretion. Th1 cells make and secrete IL-2, IFN γ , and TNF, whereas Th2 cells secrete the B-cell stimulatory molecules IL-4, IL-5, and IL-6. Evidence suggests that successful resolution of infections such as leishmaniasis depends on the activity of Th1 cells and is prevented by Th2 cells,¹⁵[R16] indicating that there may be a role for differential activation of these subsets in infection therapy. Deficiency in IL-2 production has been shown in several diseases and syndromes associated with infection, such as thermal injury and AIDS¹⁶[R17] ,¹⁷[R18] . Although the immune response is normal early after thermal injury, IL-2 production by splenocytes is deficient from 4 to 14 days following the

injury, and then eventually returns to normal. During the time that IL-2 is suppressed, the animals succumb to an infectious challenge, but when IL-2 is not suppressed, the animals survive¹⁸[R19]. Deficiency in IL-2 production has been shown to be associated

Local inflammatory reactions specifically alterations in immune competence

with the product of the activation of the arachidonic acid cascade, prostaglandin E₂ (PGE₂). In this model, survival may be restored by therapy with recombinant IL-2, especially when combined with an inhibitor of PGE₂ synthesis¹⁹[R20],²⁰[R21].

Hemopoiesis

Myelocytes take part in the nonspecific killing of bacteria and viruses, the inflammatory response, and the immune response to infection. The response to infection involves a significant increase in the circulating pool of granulocytes, resulting in a need to stimulate myelopoiesis. The cytokines IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, GM-CSF, G-CSF, and TNF affect myeloid cell proliferation and differentiation². They act at varying stages of differentiation of the cells, from stem cells to fully differentiated monocytes and granulocytes. Although the myelocytes may secrete some of these cytokines as autocrine growth factors, many of them are secreted by T cells, so that T-cell functional deficiency also may affect myelopoiesis. Cytokines also are reported to be involved in erythropoiesis.

The cytokine response to infection is a complicated cascade of events that may lead to the efficient removal of the infectious challenge and immunity to a sec-

ond insult. Lack of proper regulation of normal cytokine function, however, may lead to immune deficiency, and uncontrolled inflammatory cytokine secretion may result in processes leading to multiple organ failure and death. Our goal must be to continue to identify these mechanisms and learn how to modify the outcome.

Pain and Anaesthesia

Painful experiences, including those associated with surgery, result in a perturbation of the neuroendocrine system, leading to immune suppression and the promotion of pathological processes that are normally resisted by the immune system, such as infection and cancer.

Evidence that natural killer (NK) cells control the development of metastasis provides a link between immune function and health outcomes. Using an NK-sensitive tumor model in rats, it was recently shown that the pre- and post-operative administration of an analgesic dose of morphine attenuated the observed surgery induced increase in metastasis, suggesting that pain relief enabled the host to resist this life-threatening consequence of surgery. Further, other studies have shown that whereas rats become rapidly tolerant to the immune-suppressive and tumor-enhancing effects of morphine, without developing tolerance to daily exposure to painful foot shock stress. Taken together, these findings affirm both the benefits and relative safety of morphine contrasted with the pathogenic nature of pain in this context, thus suggesting that the adequate management of pain must become a vital aspect of health care.

The Impact of Neuroendocrine and immune responses to surgery

Surgical procedures is associated with neuroendocrine and metabolic responses:²¹[R22] the hypothalamic-pituitary-adrenal axis is activated, lead-

ing to increase in corticosterone, catecholamines, enkephalins, and norepinephrine is released by sympathetic nerve endings. Hypothalamic activity, including the secretion of releasing factors to the median eminence, initiates a pituitary release of opioids, growth hormone, prolactin, and arginine vasopressin.

Major metabolic changes include an increase in glucagon secretion and a decrease in insulin levels resulting in a hypermetabolic state characterized by fat and protein catabolism and hyperglycemia coupled with poor glucose utilization.

Local inflammatory reactions specifically alterations in immune competence. Lymphoid organs are known to be innervated by the sympathetic nervous system, and lymphocytes and monocytes possess catecholamine receptors. Glucocorticoid receptors are found in the thymus, spleen, and lymph nodes and are prevalent in the intracytoplasm of immune cells. Glucocorticoids have been shown to suppress various immune functions²²[R23].

Tissue damage from the surgical procedure results in the local release of factors initiating an inflammatory response and a cascade of cellular and biochemical events leading to immune and central nervous system activation. These factors include substance P, histamine, serotonin, calcitonin gene-related peptide, bradykinin, prostaglandins, and various cytokines released from activated leukocytes migrating to the site of injury. The local response includes arterial dilation, increased capillary permeability, and the sensitization of peripheral afferent nerve fibers resulting in allodynia and hyperalgesia²³[R24],²⁴[R25].

Prostaglandin E has been shown to participate in local neurosensitization²⁵[R26] and in the suppression of NK cell activity²⁶[R27],²⁷[R28]. Interleukin-1, produced by activated macrophages, has been shown to induce systemic activation of several

immune functions²⁸ as well as local hyperalgesia²⁹ and a systemic state and illness symptoms such as fever and malaise via activating the hepatic vagus or the CNS^{30,31}. Thus, locally released factors affect immunity and the peripheral systems and CNS.

Surgery has been shown to cause the suppression of immune function in both humans³² and animals³³, with a magnitude and duration related to the invasiveness of the surgery³⁴. Particularly, individuals with cancer appear to be more vulnerable to these immune suppression³⁵ suggesting a mechanism for metastatic-enhancing consequences.³⁶

1. A decrease in numbers of T lymphocyte sub-populations³⁴ and lymphocyte function.³⁷
2. A suppression of blood and splenic NK cell activity has been reported^{38,39}.

Surgery-induced enhancement of metastasis and its mediation by the immune system

There is debate among health care professionals that some individuals undergoing operations for cancer seem to fall upon a "downward" course after surgery, including an increased rate of cancer

immunity and promotes metastasis:

1. Spontaneous metastasis to the lungs from a remote primary tumor was increased in animals undergoing surgery³⁹.
2. Survival time was decreased in animals receiving subcutaneous³⁹ or intravenous tumor inoculation after surgery⁴⁰.
3. Surgery-induced increases in the metastatic efficiency of i.v. injected tumor cells were also shown by assessing tumor cell seeding or colonization in the lungs^{36,40}.

Several studies have provided evidence for the role played by the immune system, particularly NK cells, in controlling tumor development:

1. Rodents given an NK antiserum in order to eliminate NK activity or given drugs that reduce NK cell activity (e.g., cyclophosphamide) exhibited markedly greater numbers of lung metastases after i.v. tumor injection^{41,42}.
2. These effects were reversed by the i.v. injection of splenocytes or purified large granular lymphocyte LGL/ NK cells (adoptive transfer/replacement therapy)^{41,42}.
3. A selective depletion of LGL / NK cells that was shown not to affect other immune functions caused a large (greater than 100-fold) increase in the lung metastasis of a mammary adenocarcinoma in rats^{46,43}.
4. Stimulation of the immune system decreased the number of metastases of this tumor⁴³.
5. Several manipulations that were shown to suppress NK activity (e.g., exposure to swim stress, ethanol, or estradiol^{44,45}) were also shown to increase the metastasis of NK-sensitive tumors.

Various approaches have been used to suggest a causal relationship between the immune suppression effects of surgery and increased tumor development. Using different surgical procedures, three groups of investigators found that surgery suppressed NK cell activity and

increased metastasis, using tumor cell lines that were sensitive to NK cell activity^{36,38,46}.

Morphine attenuating effects on surgery-induced increases in metastasis

Analgesic and anesthetic interventions may decrease some neuroendocrine and immune consequences of surgery^{35,47} as well as postoperative pain.⁴⁸

- a High-dose narcotic anesthesia has been shown to suppress the hormonal response to surgery.⁴⁹
- b Regional blockade has been shown to be effective against both the hormonal and immune responses to surgery^{29,50} as well as postoperative infections⁵¹.
- c The addition of nonsteroidal anti-inflammatory drugs to postoperative treatment was reported to ameliorate surgery-induced immune suppression⁵², and pain intensity and opiate requirements⁵³.

NK-sensitive tumor cell line was used to explore whether the pre- and postoperative administration of an analgesic dose of morphine would decrease the metastatic-enhancing effects of surgery. It was found that whereas surgery resulted in a two- to fourfold increase in metastasis in unmedicated animals, this increase was significantly attenuated in animals receiving morphine.

This pattern of results was replicated on seven different occasions. Thus, because morphine exerted its beneficial effects only in the context of surgery and its associated postoperative pain, it could be suggested that pain alleviation underlies these effects of morphine. Additionally, preliminary results have indicated lower postoperative serum corticosterone levels in rats treated with morphine compared to untreated rats at 5 hours after surgery, suggesting that medicated animals were experiencing less stress⁵⁴.

Various approaches have been used to suggest a causal relationship between the immune suppression effects of surgery and increased tumor development

progression, infectious disease, and general health problems³⁸. This observation is consistent with the following animal studies showing that surgery suppresses

Findings reported by Yeager and Colacchio⁵⁵ support the beneficial effects of morphine administration on the metastatic process associated with surgery. They found that pre- and postoperative morphine administration resulted in a decreased hepatic tumor burden following the portal venous injection of colon adenocarcinoma cells.

In a very different study, Herzberg et al.⁵⁶ reached similar conclusions. They reported that unilateral peripheral mononeuropathy, induced by sciatic nerve constriction, resulted in chronic nociception and caused changes in cell-mediated immunity recorded weeks later. When the local anesthetic bupivacaine was administered before assessing cell-mediated immunity, the observed changes in the immune response in the constricted animals was blocked, suggesting the involvement of pain in these immune changes.

Surgery is often necessary in individuals bearing a tumor with metastatic potential or one that is already metastasized. Given that surgery may result in the embolization of cancer cells and that NK activity is suppressed following surgery, surgery itself becomes a risk factor for metastasis. Thus, prophylactic measures against such a life-threatening consequence of surgery, especially measures as simple as adequate pain relief, become a vital aspect of surgical care.

Opioids : a double-edged sword

Moderate to high doses of morphine have been shown to be NK suppressive⁵⁷ and tumor enhancing⁵⁸ in rats. It is important to recognize that these negative effects of morphine were demonstrated in normal animals not exposed to surgery and post-surgical experiences. Further, elevated corticosterone levels have been reported in animals receiving a high dose of morphine^{57,59}, indicating its stressful nature. Thus, whereas morphine can suppress NK cell activity and promote tumor development in a pain-

free recipient, it is important to look to these same outcomes when administered in an analgesic dose to a host experiencing pain.

Confirming the safety of long-term morphine administration is evidence showing that rats become rapidly tolerant to the NK-suppressive and tumor-enhancing effects of high doses of morphine^{58,60}. Further, the analgesic effects of morphine administration show little to no tolerance when given to rats experiencing pain⁶¹. Thus, the short- or long-term use of analgesic doses of mor-

There is rapid development of tolerance to the NK suppressive and tumor-enhancing effects of high doses of morphine

phine for pain relief would not be expected to have negative immune and metastatic consequences. On the other hand, the opioid form of painful foot shock suppresses NK cell activity⁶² and accelerates tumor growth, and no lessening of these NK-suppressive and tumor-enhancing effects of this painful stressor was evident even after 2 weeks of daily foot-shock sessions⁶³. Thus, even as pain relief with opiates is confirmed safe by these studies, pain itself is seen to be significantly and permanently pathogenic.

The general argument is has led to:

- 1 Pain elicits endocrine and autonomic changes.
- 2 These endocrine and autonomic alterations interfere with various aspects of immune function.
- 3 This interference with immunity promotes diseases that are normally regulated by immune processes.

Under-treated and over-treated Pain

There is a price that is paid in the form of increased tumor incidence, infectious disease, and suffering due to the under use of opioid analgesics in post-surgical trauma. Altered immune function, increased tumor metastasis, hyperalgesia, and illness symptoms such as fever and malaise following surgery. Decreased incidence of these surgical sequelae with appropriate use of opioid analgesics to provide adequate pain management is strongly argued position.

Many experiments demonstrating metastatic processes and increases in cancer were shown in animal models of disease and therefore cannot be easily studied in a clinical setting. Although reliance on pre-clinical data may not be viewed a major strength of her argument, it should not be regarded as a weakness, considering the many examples of increased morbidity and mortality due to the reluctance of physicians to prescribe opioid analgesics for pain⁶⁴ despite the absence of addiction and drug abuse seen in patients⁶⁵.

There is rapid development of tolerance to the NK suppressive and tumor-enhancing effects of high doses of morphine. The short-term use of morphine for pain relief may not have negative immune consequence. There are, however, certain clinical situations where the administration of morphine might be inadvisable, such as burn victims and exposure to infectious agents.

Opioids: Immune suppression and Infection

The effects of opioids on immune function is an intensely studied area and has focused on elucidating the central nervous system (CNS) and peripherally mediated mechanisms through which exogenous and endogenous opioids suppress and modulate immune function⁶⁵.

Review of the extensive literature describing the immunosuppressive effects of opioids would logically lead to a prediction that these drugs would have detrimental effects on the capacity of immune cells to clear viral, bacterial, and fungal infections. Clinical observations first suggested that opiate addicts have increased susceptibility to infections⁶⁶, findings subsequently shown to be related to deficits in immune function⁶⁷.

Chronic administration of morphine prior to development of tolerance causes suppression of the early phase of the primary antibody response but not the secondary response to antigenic challenge. This effect on the immune response is dependent on T cells or macrophages because no effect is seen on an antibody production to a T-independent antigen⁶⁸. Other examples of suppression of cell-mediated immunity following chronic morphine administration have been demonstrated. Morphine administration suppresses leukocyte mitogenic responses⁶⁹ and decreases delayed hypersensitivity responses and graft-versus-host reactions in rodents⁷⁰. Marked cellular atrophy of spleen and thymus was observed in morphine-pelleted mice⁷⁰. Bryant et al.⁷² demonstrated the adrenal cortical involvement of chronic morphine-induced immunosuppression in mice.

A single injection of morphine (300 mg/kg) given to the Friend murine leukemia virus-infected mice caused mortality (100%), whereas a chronic dosing regimen (10-100 mg/kg) for 10 days (inducing a state of tolerance) prior to virus infection had no effect on mortality⁷³. Opioids (i.e., morphine) have also been shown to sensitize mice to lipopolysaccharide-induced endotoxic shock, suggesting that morphine may act as a cofactor in Gram-negative sepsis⁷⁴. Clearly, preclinical studies strongly suggest that the use of opioids should be carefully considered in certain clinical situations where the potential for bacterial and viral infection exists.

Although addiction heroin abuse is known to cause immuno-suppression in non-infected drug users. It has been hypothesized that suppression of immune function in HIV-positive heroin users early in the disease could result in decreased viral replication in virally infected cells and delay progression to AIDS⁷⁵. Clearly, opioid administration in an immunodeficient subject with advanced disease would be contraindicated.

Although substantial information exists on the effects of morphine and other opioids on immune function in the normal subject, little data are available on the therapeutic value of these drugs in immunocompromised subjects, or patients with immunologic disorders. There may be potential clinical uses of immunosuppressive regimens of opioid analgesics to treat chronic pain and inflammation in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and diseases of unknown etiology, such as fibromyalgia. Studies on the efficacy of opioid analgesics in these diseases could provide important information about the etiology of pain in these syndromes.

Opioids without Immunosuppression

Certain opioid analgesics, such as buprenorphine and mirfentanil, do not suppress parameters of immune function in rodents. Buprenorphine does not suppress NK activity when administered at a dose equal to or five times the analgesic equivalent compared to morphine⁷⁵. Further development of immunotherapeutic opioids could be useful in the treatment of pain in clinical situations described above as well as cancer, infectious diseases, such as herpes zoster and immuno-deficiency disorders, such as AIDS.

Opioid Immunopotentiators

Although many immunosuppressive effects of opioids are CNS-mediated,

certain direct effects of opioids are immuno-stimulatory. Treatment of lymphocytes with novel selective opioid agonists enhances T-cell proliferation. It has also been shown that endogenous opioids and their effector systems are involved in T-lymphocyte development⁷⁶ and immune modulation^{77,78}. Conceivably, development of opioids with these unique pharmacological properties could provide new agents for the stimulation of immune function in patients with cancer, immuno-deficiency disorders, and infectious diseases, including AIDS.

The effects of opioids on immune function are determined by physiological and behavioral variables, including disease state. Certain variables that alter the effects of drugs include the baseline rate of responding, the distinctiveness of the environment in which the drug is administered, and the physiological, behavioral, and drug history of the subject. Some of the effects that have been altered by these variables include the development of tolerance and/or sensitization, alteration in reinforcing effects, differences in the neurotransmitter turnover in discrete brain regions⁷⁹ and possibly effects on immune function. These variables should be taken into consideration when attempting to predict the consequences of opioid administration.

Balancing the Risks of Pain versus Pain-relieving Drugs

Clearly, the findings most directly illustrating the immune and metastatic benefits of morphine administration are preliminary at best. If we are to view the management of pain as a medical necessity, we must have substantially more information to balance the physiologic risks of pharmacologic interventions with the physiologic risks of inadequately managed pain.

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