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(54) Title: OXYCODONE FOR USE IN TREATING PAIN IN A PATIENT UNDERGOING SURGERY

(57) Abstract: The present application is concerned with oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain, preferably post-operative pain, in a cancer patient undergoing cancer surgery or in a patient undergoing surgery, wherein said patient exhibits immunodeficiency.



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Oxycodone for use in treating pain in a patient undergoing surgery

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FIELD OF THE INVENTION

The present invention is concerned with oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient suffering from cancer and undergoing cancer surgery. The present invention is also concerned with oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing surgery, wherein the patient undergoing surgery exhibits immunodeficiency.

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BACKGROUND OF THE INVENTION

There is increasing evidence that opioids including opioid agonists modulate the immune function and that some opioid agonists have a depressant immunomodulatory effect (see e.g. Webster, *British Journal of Anaesthesia*, 1998, Vol. 81, No. 6, 835-836). A depressant immunomodulatory effect has in particular been described for morphine (see e.g. Sacerdote et al., *Curr Pharm Des.*, 2012, 18(37):6034-42) and fentanyl (see e.g. Shavit et al., *Neuroimmunomodulation*, 2004, 11:255-60).

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It is mentioned in the abstract of Sacerdote et al., *supra*, that due to their widespread and expanding use, the immunological effects of opioids are receiving considerable attention because of concerns that opioid-induced changes in the immune system may affect the outcome of surgery or of variety of disease processes, including bacterial and viral infections and cancer. It is further disclosed in Sacerdote et al.,

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supra, that the impact of the opioid-mediated immune effects could be particularly dangerous in selective vulnerable populations, such as the elderly or immunocompromised patients. Cancer patients undergoing cancer surgery are typically also regarded as a vulnerable population.

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Cancer patients undergoing cancer surgery represent a particularly vulnerable population since the handling of the tumour during surgery may result in cancer cells being seeded locally or released into the bloodstream, thus increasing the potential for the formation of metastases. The immune system should thus be as potent as possible to defend the patient against the risk of metastasis formation derived from the cancer surgery.

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Immunocompromised patients may also be referred to as patients exhibiting immunodeficiency. This patient population is particularly vulnerable to e.g. life-threatening infections and sepsis. If a patient exhibiting immunodeficiency undergoes a surgery, the already existing considerable risk for infections and sepsis even further increases. In such a situation, the analgesic, which is administered during surgery for the treatment of in particular post-operative pain, must not have an additional negative impact on the immune system.

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A negative effect on the immune system in surgery has been described in the literature for morphine (see e.g. Sacerdote et al., *supra*) and fentanyl (see e.g. Shavit et al., *supra*). Kaye et al., *The Ochsner Journal* 14:216-228, 2014, discloses such a negative effect also for codeine and points to the use of regional analgesia. Given the observations described in the literature for morphine, fentanyl and codeine, the skilled person is thus rather directed to avoiding opioid agonists and in particular morphine, codeine or fentanyl during surgery.

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It is noted that it is not an option to let the pain during and after surgery untreated since it has been established that pain is also a stressor that impairs the immune

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function, in particular the NK (natural killer) cell activity, see e.g. Vallejo et al., *J Environ Pathol Toxicol Oncol*; 2003; 22:139-46. In view of the findings described above for the mentioned opioid agonists, the skilled person appears to be directed to looking for potent analgesics from a different class than opioids.

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The above forms the framework for the present invention, namely the need to provide a potent analgesic for the treatment of in particular post-operative pain during and after surgery in the particularly vulnerable patient population of patients suffering from cancer and undergoing cancer surgery or of patients exhibiting

10 immunodeficiency and undergoing surgery.

OBJECTS AND SUMMARY OF THE INVENTION

The inventors of the present invention *inter alia* surprisingly found that oxycodone

15 fails to have a negative impact on the immune system, i.e. oxycodone fails to have an immunosuppressive effect, in a specific patient population, namely patients undergoing surgery. The inventors of the present invention furthermore surprisingly found that this positive effect of oxycodone is present in this patient population for at least for two hours after the surgery has started and thus during a time period, where

20 the patient is at most risk for infections and cancer cells seeding in the body. The time point of about two hours seems to be particularly relevant in this respect.

This finding of the inventors is in sharp contrast to the effect of morphine in the patient population referred to above, i.e. in patients undergoing surgery. The

25 inventors found that, contrary to oxycodone, morphine induces an immunosuppression *inter alia* by downregulation of a large number of genes associated with the immune system. The negative effect of morphine on the immune system is particularly pronounced during surgery in the time period of the first two hours after incision into the skin, i.e. after begin of the surgery.

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The aspects and embodiments of the present invention are now described in detail. Initially, embodiments of the indicated use are described in two aspects, followed by embodiments relating to both of these aspects.

5 *Aspects of the present invention relating to the medical use*

In the first aspect, the present invention relates to oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a cancer patient undergoing cancer surgery. This aspect may alternatively be formulated as oxycodone or a
10 pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient suffering from cancer and undergoing cancer surgery or still alternatively as oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing cancer surgery.

15 Preferably, said oxycodone or pharmaceutically acceptable salt thereof is administered at the start of the surgery and/or during the surgery, wherein an administration during the surgery may even be more preferred. The reason for this administration of oxycodone or a pharmaceutically acceptable salt thereof during the ongoing surgery is that the invention aims at covering the treatment of pain at least
20 during the afore-mentioned two hour period after the surgery has started, where the patient is at most risk for infections and cancer cells seeding in the body. The present invention is based on the surprising finding that oxycodone fails to have a negative effect on the immune system in particular during this “two hour window” such that the immune system is capable of fighting infections and cancer cells seeding in the
25 body.

In an embodiment of the first aspect, the cancer patient undergoing cancer surgery exhibits immune responses prior to undergoing surgery, which are equal to or comparable to immune responses in a healthy subject, i.e. the cancer patient is not

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immunosuppressed or immunodeficient. In other words, the cancer patient is not a cancer patient exhibiting immunodeficiency prior to undergoing cancer surgery.

5 It can be preferred that the above cancer patient not exhibiting immunodeficiency prior to undergoing cancer surgery suffers from a cancer selected from the group consisting of breast cancer, prostate cancer, colon cancer, melanoma, ovarian cancer, head and neck cancer, and gastric cancer.

10 In a particularly preferred embodiment, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain at least during the about first two hours in cancer surgery. More preferably, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain during the about first two hours in cancer surgery, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. This particularly preferred
15 embodiment may also be referred to as embodiment, wherein the oxycodone or pharmaceutically acceptable salt thereof is administered such that pain during the about first two hours in cancer surgery is treated, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. The first two hours are defined as starting with the incision into the skin during surgery.

20 In an embodiment relating to the above embodiment of the first aspect, said cancer surgery is a surgery to remove the primary tumour. In an alternative embodiment, said cancer surgery is a surgery to remove at least one metastasis. Still alternatively, said cancer surgery may be a surgery to remove the primary tumour and at least one
25 metastasis (or at least parts thereof).

In another embodiment of the first aspect, said cancer patient exhibits immunodeficiency prior to undergoing cancer surgery.

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The immunodeficiency in the cancer patient is an acquired defect in the immune system and can e.g. be caused by specific cancer types or immunosuppressive therapeutic agents, in particular cancer chemotherapeutic agents. In a particularly preferred embodiment, the first aspect relates to oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing cancer surgery, wherein said patient exhibits immunodeficiency caused by cancer. This particularly preferred embodiment may also be referred to as oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing cancer surgery, wherein said cancer results in immunodeficiency. In another alternative particularly preferred embodiment, the first aspect relates to oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing cancer surgery, wherein said patient exhibits immunodeficiency, and wherein said immunodeficiency is caused by an immunosuppressive therapeutic agent, in particular a cancer chemotherapeutic agent. This particularly preferred embodiment may also be referred to as oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient suffering from cancer and undergoing cancer surgery, wherein an immunosuppressive agent, in particular a cancer chemotherapeutic agent, administered for the treatment of said cancer results in immunodeficiency.

Said immunodeficiency exhibited by said cancer patient may be characterized by a symptom selected from the group consisting of hypogammaglobulinemia; agammaglobulinemia; T-cell deficiency; granulocytopenia including neutropenia; agranulocytosis; asplenia; complement deficiency; and combinations thereof.

Said immunodeficiency in the cancer patient may be caused by a cancer selected from the group consisting of multiple myeloma; leukemia including chronic lymphoid leukemia; and lymphoma.

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As noted above, said immunodeficiency may alternatively be caused by an immunosuppressive agent, preferably a cancer chemotherapeutic agent. This cancer chemotherapeutic agent can be selected from the group consisting of cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, doxorubicin, bleomycin, vinblastine, dacarbazine, bleomycin, etoposide, cisplatin, epirubicin, capecitabine, oxaliplatin and combinations thereof. In this case, the cancer, said patient is suffering from, is a cancer typically treated with a cancer therapeutic agent (or combination) selected from the above group, such as in particular a cancer selected from the group consisting of breast cancer, Hodgkin's disease, non-Hodgkin's disease, stomach cancer, bladder cancer, lung cancer and colorectal cancer. These cancers do not necessarily result in immunodeficiency in the cancer patient. Further cancers may be sarcomas, melanoma, myeloma, skin, bladder and kidney tumours.

Still alternatively, said immunodeficiency in the cancer patient may be caused by a cancer mentioned above and at least one of the cancer chemotherapeutic agents mentioned above.

It is to be noted that the cancer patient exhibiting immunodeficiency already exhibits said immunodeficiency prior to undergoing said surgery. Thus, the immunodeficiency is present at least prior to and during the surgery.

In another particularly preferred embodiment of the first aspect relating to a cancer patient exhibiting immunodeficiency, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain at least during the about first two hours in cancer surgery. More preferably, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain during the about first two hours in cancer surgery, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. This particularly preferred embodiment may also be referred to as embodiment, wherein the oxycodone or pharmaceutically

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acceptable salt thereof is administered such that pain during the about first two hours in cancer surgery is treated, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. The first two hours are defined as starting with the incision into the skin during surgery.

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In an embodiment of the first aspect, said cancer surgery is a surgery to remove the primary tumour. In an alternative embodiment, said cancer surgery is a surgery to remove at least one metastasis. Still alternatively, said cancer surgery may be a surgery to remove the primary tumour and at least one metastasis (or at least parts thereof).

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In the second aspect, the present invention relates to oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing surgery, wherein said patient exhibits immunodeficiency. It is to be noted that the patient already exhibits immunodeficiency prior to undergoing said surgery. Thus, the immunodeficiency is present at least prior to and during the surgery. In other words, the afore-mentioned immunodeficiency is not an effect of the surgery. In still other words, the afore-mentioned immunodeficiency is not derived from the surgery.

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Preferably, said oxycodone or pharmaceutically acceptable salt thereof is administered at the start of the surgery and/or during the surgery, wherein an administration during the surgery may even be more preferred. The reason for this administration of oxycodone or a pharmaceutically acceptable salt thereof during the ongoing surgery is that the invention aims at covering the treatment of pain at least during the afore-mentioned two hour period after the surgery has started, where the patient is at most risk for infections. The present invention is based on the surprising finding that oxycodone fails to have a negative effect on the immune system in particular during this “two hour window” such that the immune system is capable of fighting infections.

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In an embodiment of the second aspect, said immunodeficiency is a primary immunodeficiency. Primary immunodeficiency is always present in a patient suffering therefrom since the patient was already born with the corresponding
5 defect(s) in the immune system. Primary immunodeficiency disorders are hereditary and any underlying disorder commonly known to the skilled person can be the cause for a primary immunodeficiency referred to herein. A primary immunodeficiency disorder is classified by which part of the immune system is affected: i) humoral immunity involving B-cells; ii) cellular immunity involving T-cells; iii) both
10 humoral and cellular immunity; iv) phagocytosis and v) complement proteins.

In another embodiment of the second aspect, said immunodeficiency is a secondary immunodeficiency. Secondary immunodeficiency is/are (an) acquired defect(s) in the immune system and can be caused by specific diseases or therapeutic agents.

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Said secondary immunodeficiency may be caused by a disease selected from the group consisting of cancer; AIDS; marrow including bone marrow transplantation and other cell and/or organ transplantation; chronic granulomatous disease; splenectomy; trauma, sickle-cell anemia; congenital deficiencies; and combinations
20 thereof. Preferably, secondary immunodeficiency may be caused by cancer, wherein said underlying cancer is selected from the group consisting of multiple myeloma; leukemia including chronic lymphoid leukemia; and lymphoma.

Alternatively, said secondary immunodeficiency may be caused by a therapeutic
25 agent suppressing the immune system (such an agent may also be referred to as immunosuppressive agent). Said immunosuppressive agent is preferably selected from the group consisting of a cancer chemotherapeutic agent; a glucocorticoid; a disease-modifying antirheumatic agent and combinations thereof. A cancer chemotherapeutic agent causing secondary immunodeficiency can be selected from
30 the group consisting of cyclophosphamide, methotrexate, 5-fluorouracil,

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doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, doxorubicin, bleomycin, vinblastine, dacarbazine, bleomycin, etoposide, cisplatin, epirubicin, capecitabine, oxaliplatin and combinations thereof. A glucocorticoid causing secondary immunodeficiency can be selected from the group consisting of
5 cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone and combination thereof. A disease-modifying antirheumatic agent causing secondary immunodeficiency can be selected from the group consisting of abatacept, adalimumab, azathioprine, chloroquine,
10 ciclosporin, etanercept, golimumab, infliximab, leflunomide, methotrexate, minocycline, rituximab, sulfasalazine and combinations thereof.

Still alternatively, said secondary immunodeficiency may be caused by at least one of the diseases mentioned above and at least one of the therapeutic mentioned above.
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In yet another embodiment of the second aspect, said patient undergoes a non-cancer surgery. This embodiment is also applicable for a patient exhibiting immunodeficiency caused by cancer or a patient suffering from cancer, wherein the immunodeficiency is caused by an immunosuppressive agent, preferably a
20 chemotherapeutic agent, and not the cancer as such. The findings herein are thus also relevant for the specific patient population of cancer patients exhibiting immunodeficiency undergoing a non-cancer surgery.

In a preferred embodiment, the second aspect relates to oxycodone or a
25 pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing cancer surgery, wherein said patient exhibits immunodeficiency, and wherein said immunodeficiency is a secondary immunodeficiency caused by cancer. This preferred embodiment may also be referred to as oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient
30 suffering from cancer and undergoing cancer surgery, wherein said cancer results in

immunodeficiency. It is to be noted that the patient already exhibits immunodeficiency prior to undergoing said surgery. Thus, the immunodeficiency is present at least prior to and during the surgery.

- 5 Preferably, said cancer causing the immunodeficiency is selected from the group consisting of multiple myeloma; leukemia including chronic lymphoid leukemia; and lymphoma.

10 In a particularly preferred embodiment of the second aspect, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain at least during the about first two hours in cancer surgery. More preferably, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain during the about first two hours in cancer surgery, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. This particularly
15 preferred embodiment may also be referred to as embodiment, wherein the oxycodone or pharmaceutically acceptable salt thereof is administered such that pain during the about first two hours in cancer surgery is treated, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. The first two hours are defined as starting with the incision into the skin during surgery.

20 In an embodiment of the second aspect, said cancer surgery is a surgery to remove the primary tumour. In an alternative embodiment, said cancer surgery is a surgery to remove at least one metastasis. Still alternatively, said cancer surgery may be a surgery to remove the primary tumour and at least one metastasis (or at least parts
25 thereof).

In another particularly preferred embodiment, the second aspect relates to oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing cancer surgery, wherein said patient exhibits immunodeficiency,
30 and wherein said immunodeficiency is a secondary immunodeficiency caused by an

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immunosuppressive agent, preferably a cancer chemotherapeutic agent. This particularly preferred embodiment may also be referred to as oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient suffering from cancer and undergoing cancer surgery, wherein an

5 immunosuppressive agent, preferably a cancer chemotherapeutic agent, administered for the treatment of said cancer results in immunodeficiency. It is to be noted that the patient already exhibits immunodeficiency prior to undergoing said surgery. Thus, the immunodeficiency is present at least prior to and during the surgery.

10 Preferably, said cancer therapeutic agent is selected from the group consisting of cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, doxorubicin, bleomycin, vinblastine, dacarbazine, bleomycin, etoposide, cisplatin, epirubicin, capecitabine, oxaliplatin and combinations thereof. The cancer, said patient is suffering from, is a
15 cancer typically treated with a cancer therapeutic agent (or combination) selected from the above group, such as in particular a cancer selected from the group consisting of breast cancer, Hodgkin's disease, non-Hodgkin's disease, stomach cancer, bladder cancer, lung cancer and colorectal cancer. Further cancers may be sarcomas, melanoma, myeloma, skin, bladder and kidney tumours.

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In a particularly preferred embodiment thereof, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain at least during the about first two hours in cancer surgery. More preferably, the oxycodone or pharmaceutically acceptable salt thereof is for use in the treatment of pain during the about first two
25 hours in cancer surgery, where dissemination of cancer cells into the surrounding tissues and the systemic circulation takes place. This embodiment may also be referred to as embodiment, wherein the oxycodone or pharmaceutically acceptable salt thereof is administered such that pain during the about first two hours in cancer surgery is treated, where dissemination of cancer cells into the surrounding tissues

and the systemic circulation takes place. The first two hours are defined as starting with the incision into the skin during surgery.

5 In one embodiment of this particularly preferred embodiment, said cancer surgery is a surgery to remove the primary tumour. In an alternative embodiment, said cancer surgery is a surgery to remove at least one metastasis. Still alternatively, said cancer surgery may be a surgery to remove the primary tumour and at least one metastasis (or at least parts thereof).

10 In a preferred embodiment, said immunodeficiency exhibited by said patient is characterized by a symptom selected from the group consisting of hypogammaglobulinemia; agammaglobulinemia; T-cell deficiency; granulocytopenia including neutropenia; agranulocytosis; asplenia; complement deficiency; and combinations thereof.

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In yet another preferred embodiment, said patient exhibits said immunodeficiency at least prior to and during the surgery.

The following embodiments relate to the two aspects as outlined above.

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General embodiments

In a preferred embodiment, said pain is post-operative pain. Said pain and post-operative pain, respectively, may further be denoted as moderate to severe pain.

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Said surgery may also be denoted as “major surgery”. Said cancer surgery may also be denoted as “major cancer surgery”.

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Further, it can be preferred that said patient undergoing surgery is fasting for at least about six hours prior to surgery, preferably for about six hours prior to surgery.

Embodiments relating to the administration of the oxycodone or pharmaceutically acceptable salt thereof

- 5 The oxycodone or pharmaceutically acceptable salt thereof is preferably administered shortly before and/or at the beginning of and/or during the surgery (i.e. intra-operatively) and/or shortly after surgery (i.e. post-operatively) with the incision into the skin corresponding to the start of the surgery and the last suture corresponding to the end of the surgery. It can be preferred to administer the
- 10 oxycodone or pharmaceutically acceptable salt thereof shortly before the surgery, intra-operatively and post-operatively.

- It is preferred to administer the oxycodone or pharmaceutically acceptable salt thereof such that it provides effective analgesia for at least the first two hours after
- 15 incision into the skin. It is most preferred to administer the oxycodone or pharmaceutically acceptable salt thereof such that it provides effective analgesia for the first two hours after incision into the skin. It is noted that the first two hours after incision into the skin correspond to the time period where the patient is at most risk for infections and/or development of metastases.

- 20 Importantly, said effective analgesia (or said treatment of pain, preferably post-operative pain) is achieved while concurrently not worsening the immune system of said patient (at least during the afore-mentioned two hour window). In other words, said treatment of pain, preferably post-operative pain, is achieved while concurrently
- 25 failing to induce a negative impact on the immune system of said patient (at least during the afore-mentioned two hour window). In still other words, said treatment of pain, preferably post-operative pain, is achieved while concurrently not negatively modulating the immune function of said patient (at least during the afore-mentioned two hour window). In yet other words, said treatment of pain, preferably post-

operative pain, is achieved while oxycodone is concurrently not exhibiting an immunosuppressive effect (at least during the afore-mentioned two hour window). It is furthermore most preferred to administer the oxycodone or pharmaceutically acceptable salt thereof as the sole analgesic for the treatment of pain, preferably post-operative pain, i.e. not in combination with a further analgesic. This in particular applies to the time period of the at least about two hours after incision into the skin during surgery, more particularly to the time period of the about two hours after incision into the skin during surgery.

- 10 It is furthermore most preferred to administer the oxycodone or pharmaceutically acceptable salt thereof as the sole opioid agonist for the treatment of pain, i.e. not in combination with a further opioid agonist. Most importantly, the oxycodone or a pharmaceutically acceptable salt thereof is not administered with morphine, codeine or fentanyl or pharmaceutically acceptable salts thereof for use in treating pain in a
- 15 patient as defined above, i.e. a patient undergoing surgery, wherein the patient suffers from cancer and undergoes cancer surgery or wherein the patient exhibits immunodeficiency. Thus, morphine, codeine or fentanyl or pharmaceutically acceptable salts thereof are not administered for the treatment of pain as described herein, preferably post-operative pain, in combination with the oxycodone or
- 20 pharmaceutically acceptable salt thereof.

- It is further preferred to administer the oxycodone or pharmaceutically acceptable salt thereof in combination with an anesthetic agent, wherein said anesthetic agent is for use in providing general anesthesia and wherein said anesthetic agent is
- 25 administered intravenously. In this respect, it is particularly preferred to administer the oxycodone or pharmaceutically acceptable salt thereof in combination with intravenous propofol, wherein said propofol is for use in providing general anesthesia. It is also preferred to not administer the oxycodone or pharmaceutically acceptable salt thereof in combination with an anesthetic agent, wherein said
- 30 anesthetic agent is for use in providing general anesthesia and wherein said

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anesthetic agent is administered by inhalation. It is also preferred to not administer the oxycodone or pharmaceutically acceptable salt thereof in combination with a volatile anesthetic agent, wherein said anesthetic agent is for use in providing general anesthesia.

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The oxycodone or pharmaceutically acceptable salt thereof can most suitably be administered subcutaneously as injection or infusion or intravenously as injection or infusion. It is preferred to administer the oxycodone or pharmaceutically acceptable salt thereof intravenously as injection or infusion.

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Amounts of oxycodone to be administered

The amounts given herein are all stated as amounts of the HCl salt of oxycodone. If the oxycodone base should be used or a different salt than the HCl salt should be used, the skilled person can easily calculate the corresponding amount on the basis of the molecular weight of the HCl salt of oxycodone. By way of example, it is noted that an amount of 10 mg oxycodone HCl corresponds to an amount of 9 mg oxycodone base.

20 Generally, if oxycodone or a pharmaceutically acceptable salt thereof is administered intravenously, the oxycodone or pharmaceutically acceptable salt thereof is provided in the form of a concentrate, which is typically to be diluted to a concentration of corresponding to about 1 mg oxycodone HCl/ml. Dilutions are usually carried out in 0.9% saline, 5% dextrose or water for injections. Typical concentrated solutions of oxycodone or a pharmaceutically acceptable salt thereof (i.e. the concentrate prior to the dilution) comprise the oxycodone or pharmaceutically acceptable salt in a concentration corresponding to about 50 mg oxycodone HCl/ml, about 40 mg oxycodone HCl/ml, about 30 mg oxycodone HCl/ml, about 20 mg oxycodone HCl/ml, about 10 mg oxycodone HCl/ml, or about 5 mg oxycodone HCl/ml.

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If the oxycodone or pharmaceutically acceptable salt thereof is administered subcutaneously, a corresponding amount may be administered from a liquid dosage form comprising the oxycodone or pharmaceutically acceptable salt in a concentration corresponding to about 10 mg oxycodone HCl/ml, about 7.5 mg
5 oxycodone HCl/ml or about 5 mg oxycodone HCl/ml. For the subcutaneous administration, it might not be necessary to prepare a dilution.

The following amounts are typically administered for use in the treatment of pain. Of course, the amount actually administered may vary depending on the patient and it is
10 noted that there is no defined upper limit since some patients may require rather large total dosages, albeit administered in frequent boluses. Generally, the amount is of course titrated to the individual patient's need. Furthermore, the different administration routes may be combined.

15 For intravenous bolus administration, a bolus dose of corresponding to oxycodone HCl of about 1 mg to about 10 mg is usually administered, usually slowly over one to two minutes.

For intravenous infusion administration, a typical starting dose corresponding to
20 oxycodone HCl of about 2 mg/hour is administered. An alternative resides in the use of a dose corresponding to from about 0.03 mg to about 0.5 mg oxycodone HCl/kg body weight, preferably 0.1 mg oxycodone HCl/kg body weight.

For subcutaneous bolus administration, a bolus dose of corresponding to oxycodone
25 HCl of about 5 mg is typically administered.

For subcutaneous infusion administration, a typical starting dose corresponding to oxycodone HCl of about 7.5 mg/day is recommended in opioid naive patients. This dose should be adapted according to the patient's needs.

Pharmaceutically acceptable salts of oxycodone

The pharmaceutically acceptable salt of oxycodone is preferably selected from the group consisting of the hydrochloride, the sulphate, the bisulphate, the tartrate, the
5 nitrate, the citrate, the bitartrate, the phosphate, the malate, the maleate, the hydrobromide, the hydroiodide, the fumarate and the succinate salt.

A particularly preferred salt is the hydrochloride salt.

10 *Further features of the dosage form of the present invention*

The dosage form for use of the present invention is preferably a liquid dosage form and may comprise further pharmaceutically acceptable excipients and/or adjuvants.

15 Typical excipients are citric acid monohydrate, sodium citrate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water.

Most preferred dosage form according to the present invention

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A most preferred dosage form for use according to the present invention is an oxycodone HCl solution for injection or infusion, wherein the solution may have a concentration of e.g. about 50 mg/ml or about 10 mg/ml.

25 Particularly preferred dosage forms for use according to the present invention are Oxygesic® infusio 50 mg/ml, Oxygesic® inject, and OxyNorm® 10 mg/ml.

DESCRIPTION OF THE FIGURES

Figure 1 outlines the setup and the number of participants of the study.

- 5 Figure 2 shows the surface expression of CD107a on NK cells from patients treated with morphine (left bar at all time points), oxycodone (middle bar in all time points) or epidural analgesia (right bar at all time points). NK cells were either not stimulated (1st and 3rd row of bars) or stimulated (2nd and 4th row of bars) at the indicated time points.

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Figure 3 shows the RNA Integrity Number (RIN) for morphine, oxycodone and epidural groups, wherein the data were combined for all time points.

DETAILED DESCRIPTION OF THE INVENTION

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The inventors of the present invention *inter alia* succeeded in unraveling that the administration of oxycodone when treating pain in a cancer patient undergoing cancer surgery or in an immunodeficient patient undergoing surgery is surprisingly beneficial since oxycodone fails to have a negative effect on the immune system of the patient undergoing surgery.

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These findings are in sharp contrast to the results obtained for morphine, which go into the opposite direction, namely that morphine exhibits a pronounced negative effect on the immune system in the specific patient populations outlined above.

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This comparison shows that it is not possible to transfer results obtained for a single opioid agonist to another opioid agonist but rather that each opioid agonist is unique with respect to its effect on the immune system in the very specific setup or patient population, in which it is used.

30

1. Definitions

As used in the specification and the claims, the singular forms of “a” and “an” also include the corresponding plurals unless the context clearly dictates otherwise.

5

The terms “about” and “approximately” in the context of the present invention denotes an interval of accuracy that a person skilled in the art will understand to still ensure the technical effect of the feature in question. The term typically indicates a deviation from the indicated numerical value of $\pm 10\%$ and preferably $\pm 5\%$.

10

It needs to be understood that the term “comprising” is not limiting. For the purposes of the present invention, the term “consisting of” is considered to be a preferred embodiment of the term “comprising of”. If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also meant to encompass a group which preferably consists of these embodiments only.

15

If reference is made herein to “oxycodone”, this always includes the reference to a pharmaceutically acceptable salt of the free base of this pharmaceutically active agent unless it is specifically indicated that the reference to the pharmaceutically active agent should only refer to the free base.

20

“Pharmaceutically acceptable salts” include, but are not limited to, inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, malate, maleate, tartrate, bitartrate, fumarate, succinate, citrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparagine, glutamate and the like, and metal salts such as sodium salt, potassium salt, caesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine

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salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like.

5 “Treatment of pain” is to be understood as referring to an improvement or even complete cure of the patient’s pain or to the alleviation of pain. Such an improvement/ cure or alleviation can either be detected by the patient’s subjective feeling and/or by external observations, preferably by suitable indices such as e.g. a Numerical Analog Scale (NAS) using a range of 0-100 (0 = no pain, 100 = worst imaginable pain).

10

“Post-operative pain” as referred to herein designates pain occurring at a certain point in time, namely after surgery. As such, post-operative pain can be caused by incision of skin, fascia and muscles (somatic pain), attributed to nerve damage (neuropathic pain) and/or caused by visceral distortion or ischemia (visceral pain).

15

The term “surgery” is used herein equivalent to the term “major surgery”. A “major surgery” is any surgery, in which the patient must be put under general anesthesia and given respiratory assistance. A “cancer surgery” as referred to herein refers to a major surgery where at least part of the primary tumour and/or at least part of at least one metastasis is/are removed.

20

The term “intra-operatively” refers to a state during the surgery, whereas the term “post-operatively” refers to a state shortly after surgery. The incision into the skin corresponds to the start of the surgery and the last suture corresponds to the end of the surgery.

25

The term “undergoing surgery” or “undergoing a surgery” is to be understood as referring to ongoing surgery. The condition of undergoing a surgery and a major surgery, respectively, means for the patient that this patient is characterized by the unique and specific setup of a major surgery, namely most importantly by the

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presence of general anesthesia and respiratory assistance, wherein the patient is usually unconscious and wherein an incision into the skin is part of the surgery. The patient's condition is thus *inter alia* characterized by the presence of anesthetics as well as damages to the patient's body at least in the form of an incision into the skin.

- 5 The term "undergoing surgery" therefore denotes a well-characterized, clearly defined and clearly confined patient population to the skilled person. As outlined below, the skilled person is e.g. clearly aware that the surgery itself has an immunosuppressive effect on the patient undergoing surgery such that this *inter alia* confines the patient undergoing surgery from a patient not undergoing surgery but
10 exhibiting pain, such as e.g. cancer pain. In other words, the patients undergoing surgery are a distinct patient population. It is important to note that the surgery itself is not part of the present invention.

- The term "immunodeficiency" is used herein interchangeably with the terms
15 "immunocompromised" and "compromised immune system" and refers to a state, in which the immune system's ability to fight infectious diseases is compromised or even entirely absent. Such a state may also decrease cancer surveillance of the immune system. Immunodeficiency is usually classified into two groups: primary immunodeficiency, where an individual is born with defects in the immune system,
20 and secondary immunodeficiency, where the deficiency is acquired (in particular via certain diseases or because of side effects of specific therapeutic agents as discussed herein).

- Typical symptoms of immunodeficiency are *inter alia* hypogammaglobulinemia;
25 agammaglobulinemia; T-cell deficiency; granulocytopenia including neutropenia; agranulocytosis; asplenia; and complement deficiency.

- Immunodeficiencies may be grouped by the affected component and thus into i) humoral immune deficiency (B-cells, plasma cells or antibodies affected); ii) T-cell
30 deficiency (T-cells affected); iii) neutropenia (neutrophil granulocytes affected); iv)

asplenia (spleen affected); and v) complement deficiency (complement system affected).

5 The term “excipient” or “pharmaceutically acceptable excipient” as used herein refers to compounds commonly comprised in pharmaceutical compositions, which are known to the skilled person. A pharmaceutically acceptable excipient is pharmaceutically inactive.

2. Description of the patient populations addressed herein

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2.1. Cancer patients undergoing cancer surgery

A specific population addressed herein is a cancer patient undergoing cancer surgery. This patient population is *inter alia* exposed to the risks as outlined in the following.

15

Cancer surgery

As described in the review by Angele and Faist, *Critical Care*, August 2002, Vol. 6, No. 4, several studies suggest that organ failure is the leading cause of death in
20 surgical patients, wherein there appears to exist a causal relationship between the surgical injury and the predisposition of such patients to develop septic/infectious complications and/or multiple organ failure. It is further disclosed in the review by Angele and Faist that the excessive inflammatory response, together with a dramatic paralysis of cell-mediated immunity following surgery, appears to be responsible for
25 the increased susceptibility to subsequent sepsis.

On a more general level, surgery leads to surgical stress by the activation of the HPA axis and the sympathetic nervous system, resulting in an alteration of immune responses. Furthermore, several immune functions are suppressed, such as e.g. the
30 NK cell activity, cytokine production and lymphoproliferation.

The above of course also applies to cancer surgery, see in particular Snyder and Greenberg, *British Journal of Anaesthesia* 105(2):106-115 (2010).

- 5 The first two hours after incision into the skin usually correspond to the time period where the patient is at most risk for infections. Thus, it is known that surgery itself has an immunosuppressive effect (entitled “immunodepression” in the review by Angele and Faist) and that a patient undergoing surgery is at an increased risk for infections due to surgical stress. This also applies to cancer surgery and this risk must
10 be kept to a minimum. Furthermore, due to the surgical stress, several immune functions appear to be suppressed and might act via mediators causing an upregulation of major promalignant pathways promoting local and distant metastasis.

- Importantly, there is the problem of spreading of cancer cells during cancer surgery
15 because of the surgical (mechanical) procedures, which increases the risk for the development of metastases, see e.g. Kaye et al., *supra*, and Snyder and Greenberg, *supra*. Thus, it is generally accepted that surgery for removing primary cancer or metastases inadvertently disseminates tumour cells into both surrounding tissues and the systemic circulation (e.g. by being spread by the surgical gloves either locally or
20 into the bloodstream) such that there is a higher risk for the development of metastases, in particular at the time of surgical handling of the tumour and the early period after that, which is about 2 hours (see Yamaguchi et al., *Annals of Surgery*, Vol. 232, No.1, 58-65). The immune system must therefore be as potent as possible during the cancer surgery, particularly during the first two hours of the surgery, in
25 order to identify these disseminated cancer cells and to destroy them. The first two hours after incision into the skin usually correspond to the time period where the patient is at most risk for the development of metastases.

- 25 -

In view of the above, the cancer patient undergoing cancer surgery has an increased risk for infections and the development of cancer metastases arising from cancer surgery.

- 5 Therefore, there is the strong need to not even further increase this risk for infections and development of metastases during cancer surgery of a patient. It has been established that the administration of morphine has a negative impact on the immune system of the afore-mentioned patient population, see Kaye et al., *supra*. This has been confirmed by the results gained herein. Thus, by using morphine as analgesic
10 during the surgery in the patient population addressed herein, the risk for infections and the development of metastases is further increased.

- The present inventors have surprisingly found that the administration of oxycodone for the specific patient population of cancer patients undergoing cancer surgery fails
15 to have a negative impact on the immune system.

2.2. Patients exhibiting immunodeficiency undergoing surgery

- Another patient population addressed herein is a patient undergoing surgery, wherein
20 said patient exhibits immunodeficiency. This will be discussed in more detail in the following.

Immunodeficiency

- 25 Independent from the surgery, the patient is characterized by exhibiting immunodeficiency. This may be a primary or secondary immunodeficiency, which may be caused by the underlying diseases or treatments discussed herein or by further diseases known to the skilled person.

- 26 -

As a result of the immunodeficiency, the patient is at an increased risk for infections, which might be life-threatening depending on the patient's condition. This risk must be kept to a minimum. The patient may furthermore be at an increased risk of developing cancer due to the decreased cancer immunosurveillance of the immune
5 system. Again, this risk must be kept to a minimum.

Surgery

It has been established above that the surgery itself has a negative effect on the
10 immune system. In other words, surgical stress is induced that negatively affects the immune system (see the review by Angele and Faist, *supra*). Examples in this respect are the suppression of the NK cell activity, cytokine production and lymphoproliferation.

15 Therefore, a patient undergoing surgery is at an increased risk for infections. This risk must of course be kept to a minimum. A patient undergoing surgery may furthermore be at an increased risk of developing cancer due to the decreased cancer immunosurveillance of the immune system. Again, this risk must be kept to a
20 minimum.

Immunodeficiency in combination with surgery

In view of the above, the patient described in the present section has two factors potentiating the risk for infections: i) the first risk arises from the immunodeficiency,
25 which exists independent from the surgery, and ii) the second risk arises from the immunosuppressive effect of the surgery, the patient is undergoing.

Therefore, there is the strong need to not even further increase the potentiated risk for infections during the surgery of such a patient. As found herein, morphine has a
30 negative effect on the immune system in a patient undergoing surgery, in particular

- 27 -

during the first two hours after incision into the skin. Thus, by using morphine as analgesic during the surgery in the patient population addressed herein, the risk for infections is further increased. The present inventors have surprisingly found that the administration of oxycodone for this specific patient population fails to have a
5 negative impact on the immune system.

The specific sub-population of cancer patients exhibiting immunodeficiency

A specific sub-population addressed herein is a cancer patient undergoing a surgery,
10 wherein said patient exhibits immunodeficiency, wherein said immunodeficiency is a secondary immunodeficiency caused by cancer and/or an immunosuppressive agent, in particular a cancer chemotherapeutic agent, and wherein said patient undergoes cancer surgery. This will be discussed in more detail in the following.

15 Immunodeficiency as a result of cancer

Independent from the surgery, the patient is characterized by exhibiting immunodeficiency, which is caused by cancer and/or an immunosuppressive agent, in particular a cancer chemotherapeutic agent (usually described as a secondary
20 immunodeficiency).

As a result of the immunodeficiency, the patient is at an increased risk for infections, which can be life-threatening given the patient's condition. This risk must of course be kept to a minimum. The patient is furthermore at an increased risk of developing
25 metastases due to the decreased cancer immunosurveillance of the immune system. Again, this risk must be kept to a minimum.

Non-cancer surgery

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Surgery has already been described above and it has been established that surgery leads to surgical stress and has a negative effect on the immune system, see in particular Angele and Faist, *supra*. Thus, a patient undergoing non-cancer surgery is at an increased risk for infections, which must of course be kept to a minimum. A
5 cancer patient undergoing non-cancer surgery may furthermore be at an increased risk of developing metastases due to the decreased cancer immunosurveillance of the immune system.

In view of the above, the cancer patient undergoing non-cancer surgery has in
10 particular an increased risk for infections and the immune system must therefore be as potent as possible during the surgery.

Cancer surgery

15 Cancer surgery has already been described above and it has been established that cancer surgery leads to surgical stress, see in particular Snyder and Greenberg, *supra*. Moreover, it is generally accepted that cancer surgery inadvertently disseminates tumour cells into both surrounding tissues and the systemic circulation such that there is a higher risk for the development of metastases.

20 In view of the above, the cancer patient undergoing cancer surgery has an increased risk for infections and the development of cancer metastases arising from cancer surgery and the immune system must therefore be as potent as possible during the cancer surgery.

25

Immunodeficiency in combination with non-cancer surgery

In view of the above, the patient defined in this sub-section has at least the following factors potentiating the risk for infections and the development of cancer metastases:
30 i) the first risk arising from the existing immunodeficiency as a result of cancer

- 29 -

and/or cancer treatment, ii) the second risk arising from the surgery, the patient is undergoing, and iii) the third risk for the development of metastases of said cancer since the cancer immunosurveillance is decreased.

- 5 Therefore, there is the strong need to not even further increase the potentiated risk for infections and development of metastases during the non-cancer surgery of a patient suffering from cancer. The present inventors have surprisingly found that the administration of oxycodone for the specific patient population of cancer patients undergoing surgery fails to have a negative impact on the immune system.

10

Immunodeficiency in combination with cancer surgery

In view of the above, the patient defined in this sub-section has at least the following factors potentiating the risk for infections and the development of cancer metastases:

- 15 i) the first risk arising from the existing immunodeficiency as a result of cancer and/or cancer treatment, ii) the second risk arising from the surgery, the patient is undergoing, and iii) the third risk for the development of metastases of said cancer since the cancer immunosurveillance is decreased and at least some of the cancer cells are furthermore disseminated in the body due to the surgery procedures during
20 the cancer surgery.

- Therefore, there is the strong need to not even further increase the potentiated risk for infections and development of metastases during the cancer surgery of a patient suffering from cancer. The present inventors have surprisingly found that the
25 administration of oxycodone for the specific patient population of cancer patients undergoing cancer surgery fails to have a negative impact on the immune system.

3. Alternative formulations

The present application including the claims is written in the further medical use-language according to the EPC. Of course, this language may be adapted to specific
5 local patent practice.

In the USA, for example, an independent claim may refer to a method of treating pain in a patient undergoing cancer surgery, wherein the method comprises administering an effective amount of oxycodone or a pharmaceutically acceptable
10 salt thereof to said patient in need thereof. As regards the second population, an independent claim may refer to a method of treating pain in a patient undergoing surgery, wherein the method comprises administering an effective amount of oxycodone or a pharmaceutically acceptable salt thereof to said patient in need thereof, and wherein said patient exhibits immunodeficiency.

15

In Japan, an independent claim may refer to oxycodone or a pharmaceutically acceptable salt thereof for treating pain in a cancer patient undergoing cancer surgery. As regards the second population, a claim may refer to oxycodone or a pharmaceutically acceptable salt thereof for treating pain in a patient undergoing
20 surgery, wherein said patient exhibits immunodeficiency.

An alternative wording is the so-called Swiss-type language for further medical use claims. According to this language, an independent claim may refer to the use of oxycodone or a pharmaceutically acceptable salt thereof for the manufacture of a
25 medicament to treat pain, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered to a cancer patient undergoing cancer surgery. As regards the second population, an independent claim may refer to the use of oxycodone or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to treat pain, wherein said oxycodone or pharmaceutically acceptable salt thereof is

administered to a patient undergoing surgery, and wherein said patient exhibits immunodeficiency.

In the following, examples of embodiments of the present invention are outlined.

5 Said examples should not be construed as limiting the scope of the present invention.

4. Examples

4.1. Methods

10

Study design and patients

The study underlying the present invention was conducted as randomised, parallel group, pilot study. Included in the study were female patients aged 18 years and over
15 who were undergoing an elective gynaecological surgical procedure under general anaesthesia with a Pfannenstiel incision. All participants had an American Society of Anesthesiologists classification 1 to 3. Exclusion criteria included: an allergy to morphine, oxycodone or bupivacaine; history of an anaesthetic complications; substance abuse or long-term opioid use; the use of opioids within one month of the
20 start of the study; and patients undergoing surgery for cancer (as the present study was a pilot study, it was essential to have a homogeneous starting population. By including patients undergoing surgery for cancer, there would have been a higher variability between the patients, which might have had an impact on the evaluation of the results. The conclusions from the present pilot study nevertheless apply for
25 patients undergoing surgery for cancer). Patients were randomised into three analgesic groups: morphine, oxycodone or epidural bupivacaine.

Procedures

General anaesthesia was induced and maintained with propofol (no other
30 anaesthetics were used). Propofol was given intravenously as continuous infusion. Morphine sulphate or oxycodone hydrochloride were given as 0.1 mg/kg iv

intraoperatively and then 1 mg bolus iv as required both intraoperatively and postoperatively. Bupivacaine was given as 0.25% strength plain bupivacaine (2.5 mg/ml) administered as 10 ml bolus via the epidural route prior to surgery, with extra bolus doses as required, followed by a 0.125% epidural infusion postoperatively.

- 5 Postoperative morphine and oxycodone bolus doses were delivered via a patient-controlled analgesia (PCA) with previously established standard PCA pump settings implemented as follows: demand dose of 1 mg morphine or oxycodone followed by a 5 minute lockout. Morphine or oxycodone consumption during 24 h post-surgery was recorded.

10

Cell assays

Venous peripheral blood (40 ml) was obtained from patients at four time points: Baseline, 2, 6, and 24 h and stored at 4°C prior to processing. Peripheral blood mononuclear cells were separated using ficoll-hypaque density gradient

- 15 centrifugation (1500 RPM, RT, 25 min). CD4+, CD8+ and NK cells were separated via manual magnetic cell separation (Miltenyi Biotec).

RNA isolation and integrity

- 20 RNA was extracted from sorted cells for later gene expression analysis using Qiagen Rneasy kits and stored at -80°C. An Agilent 2100 bioanalyser was used to measure quality of RNA post-extraction, post-defrosting prior to amplification, and during the later hybridisation process to confirm fragmentation had occurred. The RNA integrity number (RIN) was calculated using the bioanalyser and ranged from 1–10
- 25 using the total area under the curve for the entire electropherogram, where 1 was completely degraded RNA and 10 was completely undegraded/intact RNA.

Gene expression assay

- For gene expression profiling the Affymetrix GeneScan 3000 7G scanner was used
- 30 in conjunction with Affymetrix GeneChip 3' IVT Express Kit; U133+2.0 GeneChips

were used in the hybridisation experiments. Microarrays were scanned for fluorescence using a GeneScan 3000 7G scanner and files imported to Partek Suite 6.6, where data were corrected and normalized. Gene lists were generated using a fold-change of at least 2-fold up or down, and a p value cut-off of 0.05. Gene lists
5 were created for each treatment (morphine, oxycodone and bupivacaine) individually, to find differentially-expressed genes at 2 h, 6 h and 24 h, each compared to baseline.

Analysis of differentially expressed genes

10 Genes selected were analysed through DAVID v6.7 (The database for Annotation, Visualisation and Integrated Discovery) to identify biological pathways and functions that were affected by the differential expression.

NK cell degranulation assay

15 The NK cells were examined using a degranulation method adapted from Betts et al. (Betts et al., *J Immunol Methods*, 2003 Oct 1; 281(1-2):65-78) with lysosomal associated membrane protein 1 (LAMP 1 or CD107a) as a functional marker. Briefly, samples were divided in two and to one-half the stimulant Staphylococcal enterotoxin B (SEB Sigma) was added. Anti-human CD107a antibody (eBioscience)
20 was added to each sample (with and without SEB) and incubated for 1 h at 37°C. Momensin was added, then following a 4 h incubation at 37°C, cells were harvested into FACS tubes, centrifuged and then washed with FACS buffer and recentrifuged. Surface antibodies Acd3 and Acd56 (eBioscience) were added and cells incubated at 4°C for 30 min. Samples were then analysed on a flow cytometer.

25

Cytometric bead array

A cytometric bead array (CBA) was used to measure the serum concentration of seven major cytokines expressed by Th1, Th2 and Th17 cells (interleukin [IL]-2, IL-4, IL-6, IL-10, IL-17a, TNF and IFN- γ). Baseline and 6 h samples were compared
30 across all three treatment groups using a BD Biosciences kit as per standard protocol.

Standard curves were prepared in FACSDiva using the mean fluorescing intensities of known concentrations of each cytokine, and unknown sample concentrations interpolated from this.

5 *Statistical analysis*

Data were produced as CEL files from the Affymetrix software. These were imported to a software package (Partek suite 6.6) designed to analyse gene expression data and extract biological signals from noisy data, with intensity values normalized, logged to base 2, and analysed with an ANOVA. As well as raw
10 intensity values, the values for treatment, time-point, RIN and batch date were imported and used in the ANOVA as they are known to influence intensity values. False Discovery Rate (FDR) correction was used in microarray analysis to correct for false positives produced as a result of multiple tests. An ANOVA using a p value of 0.05 would expect to generate 5% false positive results simply as a result of multiple
15 testing. The numbers of genes identified indicate the numbers of genes for each treatment group and included any that were also differentially expressed in other treatment groups. Genes were identified at 2, 6 and 24 h post-induction that were differentially expressed at a ≥ 2 -fold increase or decrease from baseline in group, with an FDR-adjusted and un-adjusted p value ≤ 0.05 . Dependent samples t tests were
20 performed in each treatment group with baseline and 6 h cytokine concentration values paired per subject. One-way ANOVAs were performed between treatment groups at baseline and 6 h, for each cytokine.

25 4.2. Results

A total of 60 patients consented to take part in the study and of these 57 were enrolled and randomly assigned to analgesia with morphine, oxycodone or epidural (see figure 1). Of those, 15 patients were subsequently withdrawn and a total of 42 patients completed the study with 40 having satisfactory RNA hybridization to gene
30 chips: morphine (n=16), oxycodone (n=16) or bupivacaine (n=8). No statistically

significant differences were found between treatment groups comparing age, Body Mass Index or duration of surgery. The mean (SD) total opioid doses used in the morphine or oxycodone groups were 48.1 (21.9) and 42.5 (25.1) mg, respectively (not significant).

5

Surface expression of CD107a remained unchanged 6 h after surgery in the morphine group even after stimulation (see figure 2). In contrast, expression was increased at 6 h compared with baseline (baseline: 1251.0 vs. stimulated: 3094.7) in the stimulated oxycodone group but not in the unstimulated oxycodone group. Surface expression
10 of CD107A was increased after surgery in the epidural group in both the stimulated (baseline: 1780.5 vs. stimulated: 3631.5) and unstimulated groups (baseline: 1483.0 vs. unstimulated 3591.0).

Of the seven cytokines, IL-2, IL-4 and IFN- γ in all samples were below the
15 theoretical level of detection given by the kit manufacturer. TNF and IL-17a were below the level of detection for almost all samples. Baseline levels of IL-6 and IL-10 were similar between treatment groups, with no statistically significant difference found using a one-way ANOVA. Statistically significant differences in mean [SD] values of IL-6 were found at 6 h between the morphine and oxycodone groups
20 (morphine: 52.9 [40.0] vs. oxycodone: 19.4 [11.2]; $p=0.034$) and between the morphine and the epidural groups (morphine: 52.9 [40.0] vs. epidural: 23.0 [13.1]; $p=0.048$). Differences between groups were noted for IL-10 at 6 h, but these were not significant.

25 No statistically significant difference in RIN was found between the treatment groups (see figure 3) or at different time points (data not shown) indicating that RNA was not disproportionately degraded in any one treatment group or time point. The median RIN numbers were: morphine 4.2, oxycodone 3.7 and epidural 3.5.

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The number of genes that were significantly up- or down-regulated by at least 2-fold according to treatment group and time point are shown in Table 1:

Time / treatment	Number of genes FDR-unadjusted			Number of genes FDR-adjusted		
	Up	Down	Total	Up	Down	Total
Morphine 2 h	55	1699	1754	101	482	583
Morphine 6 h	17	10	27	156	2	158
Morphine 24 h	2	119	121	1	0	1
Oxycodone 2 h	90	0	93	3	0	3
Oxycodone 6 h	730	12	742	790	20	810
Oxycodone 24 h	5	213	218	1	0	1
Epidural bupivacaine 2 h	178	142	320	0	0	0
Epidural bupivacaine 6 h	320	143	463	21	30	51
Epidural bupivacaine 24 h	200	120	320	0	0	0

Table 1. Gene expression: up and down-regulation of genes by a factor of ≥ 2 fold (p-value ≤ 0.05) following analgesia with morphine, oxycodone or epidural bupivacaine.

Overall, when numbers were FDR-adjusted, the number of genes identified was reduced considerably. Notably, the results showed a greater number of down-regulated genes at 2 h in the morphine group as compared to the epidural group and no downregulated genes in the oxycodone group.

Analysis using DAVID v6.7 (The database for Annotation, Visualisation and Integrated Discovery) showed that numerous key immune system pathways were

affected by the differential regulation, in particular the down-regulation, at 2 hours in the morphine group. These included MAPK, JAK-STAT and regulation of actin cytoskeleton, which influence cell differentiation and proliferation, survival, cytoskeleton formation and vesicle trafficking.

5

4.3. Interpretation of the results

Suppression of the immune response in the immediate postoperative period can impact on infection rates and healing, and affect the spread of tumour metastases following surgery for tumour removal.

10

NK cells are a subset of lymphocytes that play a central role in the innate immune response to tumours and infections. LAMP-1 or CD107a can be used as marker of NK cell functional activity as it lines the membranes of the cytolytic granules contained within the NK cells, which are rapidly released inducing death of a target cell. In the current study, no increase in the expression of CD107a was reported at 6 h after surgery in the morphine group even in stimulated cell samples, in contrast to the increase in the oxycodone samples that were stimulated and the epidural samples with or without stimulation. These results suggest that NK function was reduced in the morphine group at 6 h (not degranulating properly) while it was maintained in the oxycodone and epidural groups (normal degranulation).

15

20

Comparable baseline levels in the three analgesic groups were observed for the cytokines IL-6 and IL-10. The level of IL-6 increased significantly at 6 h in the morphine group as compared with both the oxycodone and the epidural groups. Cytokines have an important role in modulation of the immune system. IL-6 is secreted by T cells and macrophages to stimulate the immune response and this increase of IL-6 levels and hence the inflammatory response in the morphine group might result in increased morbidity. It is noted that TNF levels were below detection

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limit (see above) such that an important component for a pro-inflammatory response appears to be missing.

The gene expression profiling conducted using FDR unadjusted data suggest that by
5 2 h, morphine had exerted a greater downregulation of gene expression than either of
the two other groups. In the epidural group, the number of genes whose expression
was increased or decreased was comparable, while a greater number of genes had
increased than decreased expression in the oxycodone group. At 24 h the pattern of
upregulation and down regulation was similar in the morphine and oxycodone groups
10 pointing to the importance of the 2 h window and the effect that morphine has at this
critical time. At 24 h more genes were upregulated than down regulated in the
epidural group.

The critical time period for distinguishing the effects of morphine to oxycodone or
15 epidural analgesia was identified as 2 h. In surgical patients, this potentially
immunosuppressive period coincides with the intraoperative period where they are
known to be particularly vulnerable.

5. Further preferred embodiments

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In the following, further preferred embodiments are given.

1A. Oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment
of pain in a cancer patient undergoing cancer surgery.

25

2A. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
embodiment 1A, wherein wherein said pain is treated at least during the about first
two hours in surgery.

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3A. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 1A or 2A, wherein the oxycodone or pharmaceutically acceptable salt thereof is the sole analgesic administered for the treatment of pain.

- 5 4A. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1A, 2A and 3A, wherein the oxycodone or pharmaceutically acceptable salt thereof is administered intravenously.

- 10 5A. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1A, 2A, 3A and 4A, wherein the oxycodone or pharmaceutically acceptable salt thereof is administered in combination with intravenous propofol, wherein said propofol is for use in providing general anesthesia.

- 15 6A. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 1A, wherein said pain is treated at least during the about first two hours in surgery; wherein the oxycodone or pharmaceutically acceptable salt thereof is the sole analgesic administered for the treatment of pain, and wherein the oxycodone or pharmaceutically acceptable salt thereof is administered intravenously.

20

- 7A. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 1A, wherein said pain is treated at least during the about first two hours in surgery; wherein the oxycodone or pharmaceutically acceptable salt thereof is the sole analgesic administered for the treatment of pain; wherein the oxycodone or pharmaceutically acceptable salt thereof is administered intravenously; and wherein the oxycodone or pharmaceutically acceptable salt thereof is administered in combination with intravenous propofol, wherein said propofol is for use in providing general anesthesia.
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1B. Oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing surgery, wherein said patient exhibits immunodeficiency.

- 5 2B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 1B, wherein said immunodeficiency is a secondary immunodeficiency.

- 3B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 2B, wherein said immunodeficiency is a secondary immunodeficiency
10 caused by cancer and said patient undergoes cancer surgery or wherein said immunodeficiency is a secondary immunodeficiency caused by a cancer chemotherapeutic agent and said patient undergoes cancer surgery.

- 4B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
15 any one of embodiments 1B, 2B, and 3B, wherein said pain is treated at least during the about first two hours in surgery.

- 5B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1B, 2B, 3B, and 4B, wherein the oxycodone or
20 pharmaceutically acceptable salt thereof is the sole analgesic administered for the treatment of pain.

- 6B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1B, 2B, 3B, 4B, and 5B, wherein the oxycodone or
25 pharmaceutically acceptable salt thereof is administered in combination with intravenous propofol, wherein said propofol is for use in providing general anesthesia.

- 7B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
30 embodiment 1B, wherein said immunodeficiency is a secondary immunodeficiency;

wherein said pain is treated at least during the about first two hours in surgery;
wherein the oxycodone or pharmaceutically acceptable salt thereof is administered
intravenously; and wherein the oxycodone or pharmaceutically acceptable salt
thereof is the sole analgesic administered for the treatment of pain.

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8B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
embodiment 1B, wherein said immunodeficiency is a secondary immunodeficiency;
wherein said pain is treated at least during the about first two hours in surgery;
wherein the oxycodone or pharmaceutically acceptable salt thereof is administered
intravenously; wherein the oxycodone or pharmaceutically acceptable salt thereof is
the sole analgesic administered for the treatment of pain; and wherein the oxycodone
or pharmaceutically acceptable salt thereof is administered in combination with
intravenous propofol, wherein said propofol is for use in providing general
anesthesia.

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9B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
embodiment 1B, wherein said immunodeficiency is a secondary immunodeficiency caused
by cancer and said patient undergoes cancer surgery or wherein said immunodeficiency is
a secondary immunodeficiency caused by a cancer chemotherapeutic agent and said
patient undergoes cancer surgery; wherein said pain is treated at least during the about first
two hours in surgery; wherein the oxycodone or pharmaceutically acceptable salt thereof is
administered intravenously; and wherein the oxycodone or pharmaceutically acceptable
salt thereof is the sole analgesic administered for the treatment of pain.

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10B. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
embodiment 1B, wherein said immunodeficiency is a secondary immunodeficiency caused
by cancer and said patient undergoes cancer surgery or wherein said immunodeficiency is
a secondary immunodeficiency caused by a cancer chemotherapeutic agent and said
patient undergoes cancer surgery; wherein said pain is treated at least during the about first
two hours in surgery; wherein the oxycodone or pharmaceutically acceptable salt thereof is

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administered intravenously; wherein the oxycodone or pharmaceutically acceptable salt thereof is the sole analgesic administered for the treatment of pain; and wherein the oxycodone or pharmaceutically acceptable salt thereof is administered in combination with intravenous propofol, wherein said propofol is for use in providing general anesthesia.

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1C. Oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a cancer patient undergoing cancer surgery.

2C. Oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment
10 of pain in a patient undergoing surgery, wherein said patient exhibits immunodeficiency.

3C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 2C, wherein said immunodeficiency is a secondary immunodeficiency.

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4C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 3C, wherein said secondary immunodeficiency is caused by a disease selected from the group consisting of cancer; AIDS; marrow including bone marrow transplantation and other cell and/or organ transplantation; chronic granulomatous
20 disease; splenectomy; trauma, sickle-cell anemia; congenital deficiencies; and combinations thereof.

5C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 3C, wherein said secondary immunodeficiency is caused by a
25 therapeutic agent selected from the group consisting of a cancer chemotherapeutic agent; a glucocorticoid; a disease-modifying antirheumatic agent and combinations thereof.

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6C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 2C, wherein said immunodeficiency is a secondary immunodeficiency caused by cancer and said patient undergoes cancer surgery.

- 5 7C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to embodiment 2C, wherein said immunodeficiency is a secondary immunodeficiency caused by a cancer chemotherapeutic agent and said patient undergoes cancer surgery.

- 10 8C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1C to 7C, wherein said pain is treated at least during the about first two hours in surgery.

- 9C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
15 any one of embodiments 1C to 8C, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered at the start of the surgery and intra-operatively.

- 10C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
20 any one of embodiments 1C to 9C, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered subcutaneously or intravenously.

- 11C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1C to 10C, wherein said oxycodone or pharmaceutically
25 acceptable salt thereof is administered subcutaneously via a bolus administration of corresponding to about 5 mg oxycodone HCl.

12C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of embodiments 1C to 10 C, wherein said oxycodone or pharmaceutically

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acceptable salt thereof is administered intravenously via a bolus administration of corresponding to about 1 mg to about 10 mg oxycodone HCl.

13C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
5 any one of embodiments 1C to 12C, wherein said oxycodone or pharmaceutically acceptable salt thereof is the sole analgesic administered for the treatment of pain.

14C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
any one of embodiments 1C to 12 C, wherein morphine, codeine or fentanyl or
10 pharmaceutically acceptable salts thereof are not administered for the treatment of pain.

15C. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
any one of embodiments 1C to 14C, wherein said oxycodone or pharmaceutically
15 acceptable salt thereof is administered in combination with intravenous propofol,
wherein said propofol is for use in providing general anesthesia.

CLAIMS

1. Oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a cancer patient undergoing cancer surgery, wherein said
5 oxycodone or pharmaceutically acceptable salt thereof is administered at the start of the surgery and/or during the surgery.
2. Oxycodone or a pharmaceutically acceptable salt thereof for use according to claim 1, wherein said oxycodone or pharmaceutically acceptable salt thereof is
10 administered during the surgery.
3. Oxycodone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in a patient undergoing surgery, wherein said patient exhibits immunodeficiency, wherein said immunodeficiency is exhibited by said patient prior
15 to undergoing surgery.
4. Oxycodone or a pharmaceutically acceptable salt thereof for use according to claim 3, wherein said immunodeficiency is a secondary immunodeficiency.
- 20 5. Oxycodone or a pharmaceutically acceptable salt thereof for use according to claim 4, wherein said secondary immunodeficiency is caused by a disease selected from the group consisting of cancer; AIDS; marrow including bone marrow transplantation and other cell and/or organ transplantation; chronic granulomatous disease; splenectomy; trauma, sickle-cell anemia; congenital deficiencies; and
25 combinations thereof.
6. Oxycodone or a pharmaceutically acceptable salt thereof for use according to claim 4, wherein said secondary immunodeficiency is caused by a therapeutic agent selected from the group consisting of a cancer chemotherapeutic agent; a
30 glucocorticoid; a disease-modifying antirheumatic agent and combinations thereof.

7. Oxycodone or a pharmaceutically acceptable salt thereof for use according to claim 3, wherein said immunodeficiency is a secondary immunodeficiency caused by cancer and said patient undergoes cancer surgery.

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8. Oxycodone or a pharmaceutically acceptable salt thereof for use according to claim 3, wherein said immunodeficiency is a secondary immunodeficiency caused by a cancer chemotherapeutic agent and said patient undergoes cancer surgery.

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9. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of the preceding claims, wherein said pain is treated at least during the about first two hours in surgery.

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10. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of claims 3 to 9, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered at the start of the surgery and/or during the surgery.

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11. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of claims 3 to 9, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered during the surgery.

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12. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of the preceding claims, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered subcutaneously or intravenously.

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13. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 12, wherein said oxycodone or pharmaceutically acceptable salt thereof is administered subcutaneously via a bolus administration of corresponding to about 5 mg oxycodone HCl.

14. Oxycodone or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 12, wherein said oxycodone or pharmaceutically acceptable

salt thereof is administered intravenously via a bolus administration of corresponding to about 1 mg to about 10 mg oxycodone HCl.

15. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
5 any one of the preceding claims, wherein said treatment of pain is achieved in said patient while concurrently not worsening the immune system of said patient.

16. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
any one of claims 1 to 15, wherein said oxycodone or pharmaceutically acceptable
10 salt thereof is the sole analgesic administered for the treatment of pain.

17. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
any one of claims 1 to 15, wherein morphine, codeine or fentanyl or
pharmaceutically acceptable salts thereof are not administered for the treatment of
15 pain.

18. Oxycodone or a pharmaceutically acceptable salt thereof for use according to
any one of the preceding claims, wherein said oxycodone or pharmaceutically
acceptable salt thereof is administered in combination with intravenous propofol,
20 wherein said propofol is for use in providing general anesthesia.

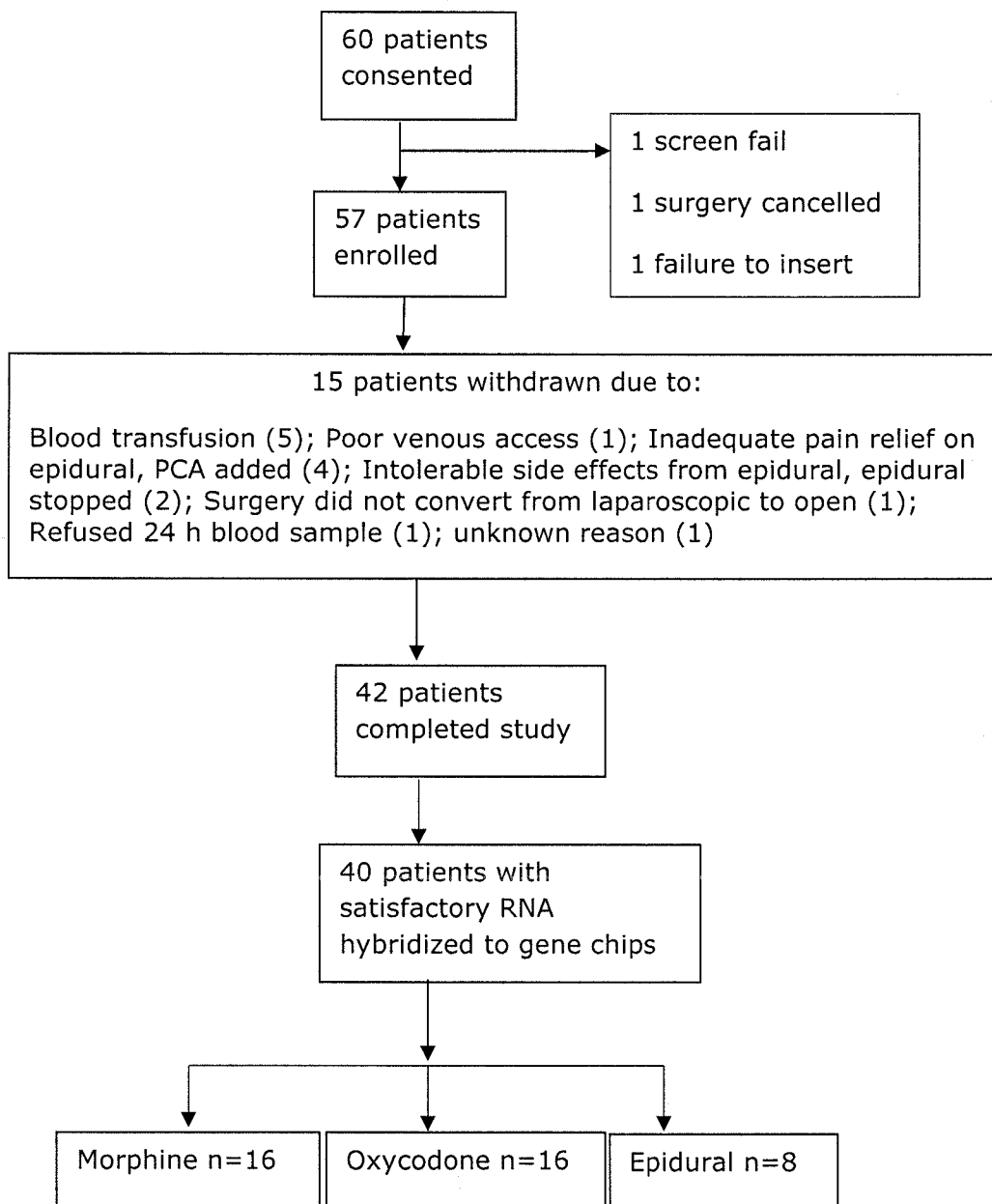
Fig. 1

Fig. 2

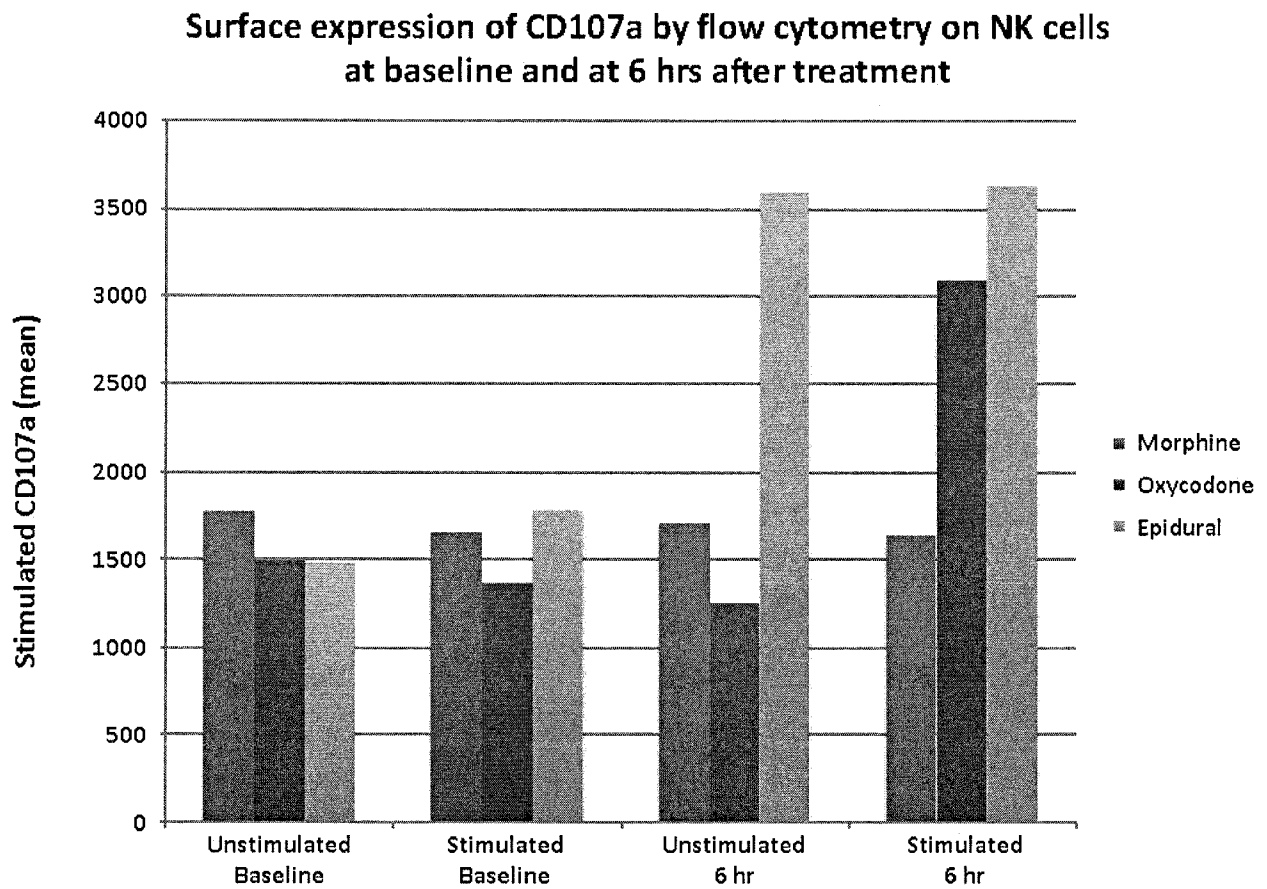
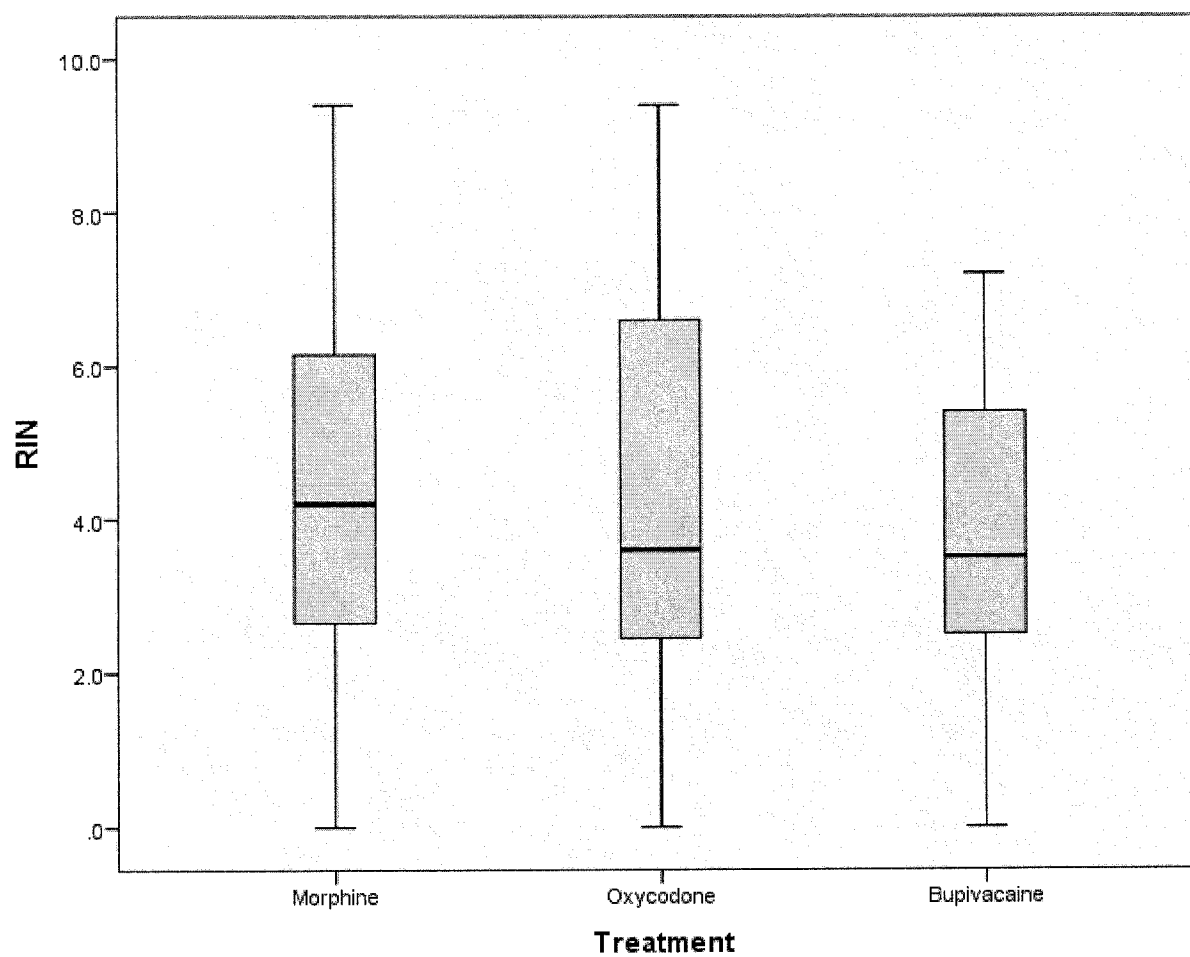


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/061068

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/485 A61P43/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/105205 A1 (UNIV KENTUCKY RES FOUND [US]; CROOKS PETER [US]; AL-GHANANEEM ABEER [U] 5 October 2006 (2006-10-05) page 7, column 11 - page 8, column 15 page 14, line 7 - line 11 -----	1-18
X	US 2016/095830 A1 (PAVLIV LEO [US] ET AL) 7 April 2016 (2016-04-07) paragraph [0069] ----- -/-	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 June 2017

Date of mailing of the international search report

19/07/2017

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/061068

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Paola Sacerdote ET AL: "Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study 1", British Journal of Pharmacology, 1 January 1997 (1997-01-01), pages 834-840, XP055382979, Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1564723/pdf/121-0701138a.pdf [retrieved on 2017-06-20] the whole document	1-18
X	----- YANG PAO-PAO ET AL: "Effects of dextromethorphan and oxycodone on treatment of neuropathic pain in mice", JOURNAL OF BIOMEDICAL SCIENCE, vol. 22, September 2015 (2015-09), XP009194772, the whole document	1-18
A	----- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; December 2012 (2012-12), SACERDOTE PAOLA ET AL: "Non-Analgesic Effects of Opioids: Mechanisms and Potential Clinical Relevance of Opioid-Induced Immunodepression", XP009192158, Database accession no. PREV201200766772 cited in the application abstract & CURRENT PHARMACEUTICAL DESIGN, vol. 18, no. 37, December 2012 (2012-12), pages 6034-6042, ISSN: 1381-6128(print) -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/061068

Patent document cited in search report			Publication date		Patent family member(s)			Publication date	
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			WO	2006105205	A1		05-10-2006		

US 2016095830	A1	07-04-2016	CA	2963916	A1		14-04-2016		
			US	2016095830	A1		07-04-2016		
			WO	2016057389	A1		14-04-2016		
