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(54) Titre : COMPOSES DESTINES AU TRAITEMENT DE LA DOULEUR
(54) Title: COMPOUNDS FOR THE TREATMENT OF PAIN

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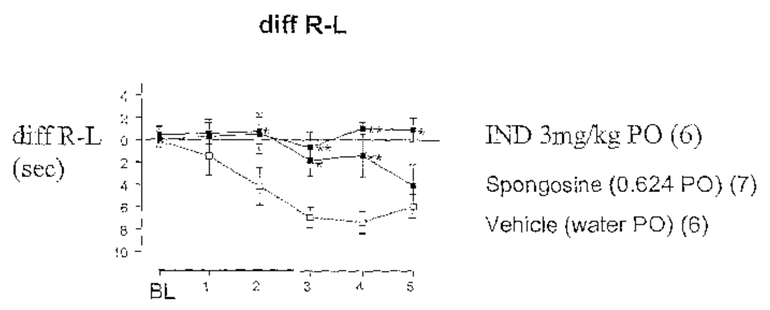

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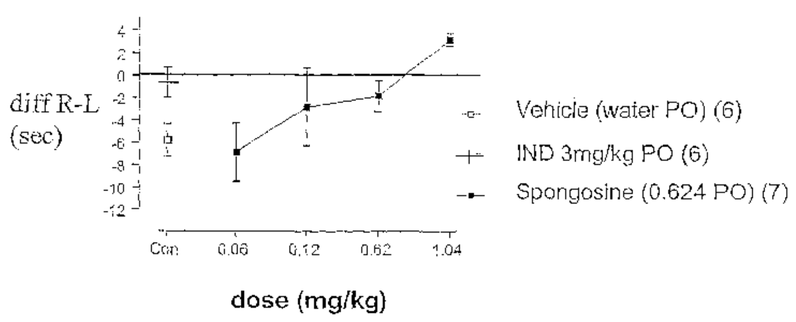

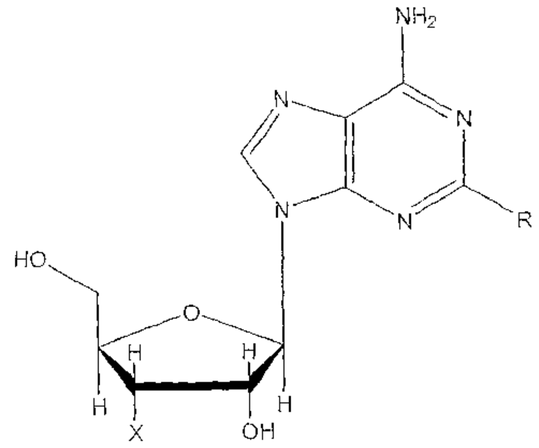

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(57) Abrégé/Abstract:
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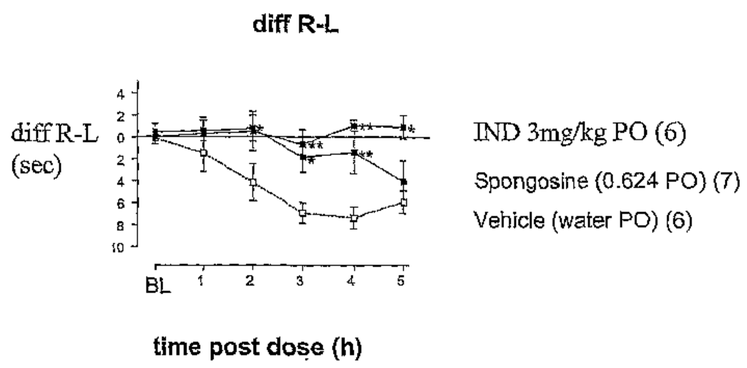

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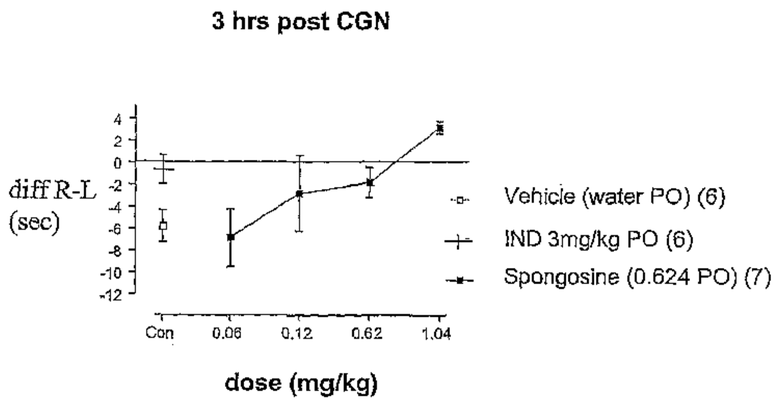
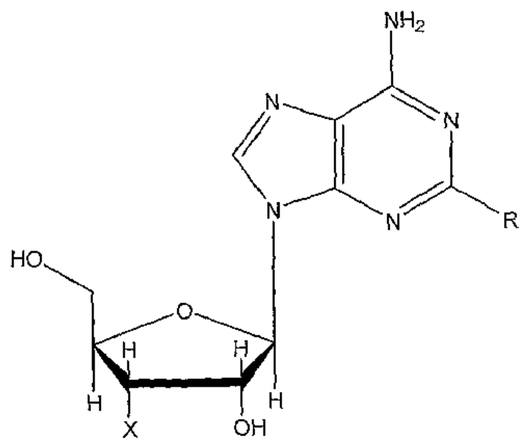


(57) Abstract: Use of compounds of the following formula as analgesics, in particular antihyperalgesics, is described: wherein R is C1-4 alkoxy, and X is H or OH.



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Compounds for the Treatment of Pain

This invention relates to analgesic compounds and to methods of preventing, treating, or ameliorating pain using these compounds.

Pain has two components, each involving activation of sensory neurons. The first component is the early or immediate phase when a sensory neuron is stimulated, for instance as the result of heat or pressure on the skin. The second component is the consequence of an increased sensitivity of the sensory mechanisms innervating tissue which has been previously damaged. This second component is referred to as hyperlagesia, and is involved in all forms of chronic pain arising from tissue damage, but not in the early or immediate phase of pain perception.

Thus, hyperalgesia is a condition of heightened pain perception caused by tissue damage. This condition is a natural response of the nervous system apparently designed to encourage protection of the damaged tissue by an injured individual, to give time for tissue repair to occur. There are two known underlying causes of this condition, an increase in sensory neuron activity, and a change in neuronal processing of nociceptive information which occurs in the spinal cord. Hyperalgesia can be debilitating in conditions of chronic inflammation (e.g. rheumatoid arthritis), and when sensory nerve damage has occurred (i.e. neuropathic pain).

Two major classes of analgesics are known: (i) non steroidal anti-inflammatory drugs (NSAIDs) and the related COX-2 inhibitors; and (ii) opiates based on morphine. Analgesics of both classes are effective in controlling normal, immediate or nociceptive pain. However, they are less effective against some types of hyperalgesic pain, such as neuropathic pain. Many medical practitioners are reluctant to prescribe opiates at the high doses required to affect neuropathic pain because of the side effects caused by administration of these compounds, and the possibility that patients may become addicted to them. NSAIDs are much less potent than opiates, so even higher doses of these compounds are required. However, this is undesirable because these compounds cause irritation of the gastro-intestinal tract.

Adenosine A1 receptor agonists are known to act as powerful analgesics (Sawynok, Eur J Pharmacol. (1998) 347, 1-11), and adenosine A2A receptor agonists are known to act as anti-inflammatory agents. However, development of adenosine-based therapies has generally been precluded because they have unacceptable side effects. Selective A1 receptor agonists cause bradycardia, and A2A receptor agonists cause widespread vasodilation with consequent hypotension and tachycardia.

There is, therefore, a need to provide analgesics, particularly anti-hyperalgesics, which are sufficiently potent to control pain perception in neuropathic and other hyperalgesic syndromes, and which do not have serious side effects or cause patients to become addicted to them.

Spongosine is a compound that was first isolated from the tropical marine sponge, *Cryptotethia crypta* in 1945 (Bergmann and Feeney, J. Org. Chem. (1951) 16, 981, Ibid (1956) 21, 226). Spongosine was the first methoxypurine found in nature, and is also known as 2-methoxyadenosine, or 9H-purin-6-amine, 9-α-D-arabinofuranosyl-2-methoxy.

The first biological activities of spongosine were described by Bartlett *et al.* (J. Med. Chem. (1981) 24, 947-954) who showed that this compound has muscle relaxant, hypothermic, hypotensive, and anti-inflammatory activity in rats.

The affinity of spongosine for the rat adenosine A1 and A2A receptors has been determined. The Kd values obtained (in the rat) were 340nM for the A1 receptor and 1.4μM for the A2A receptor, while the EC50 value for stimulation of the rat A2A receptor was shown to be 3μM (Daly *et al.*, Pharmacol. (1993) 46, 91-100). In the guinea pig, the efficacy of spongosine was tested in the isolated heart preparation and the EC50 values obtained were 10 μM and 0.7 μM for the adenosine A1 and A2A receptors, respectively (Ueeda et al J Med Chem (1991) 34, 1334-1339).

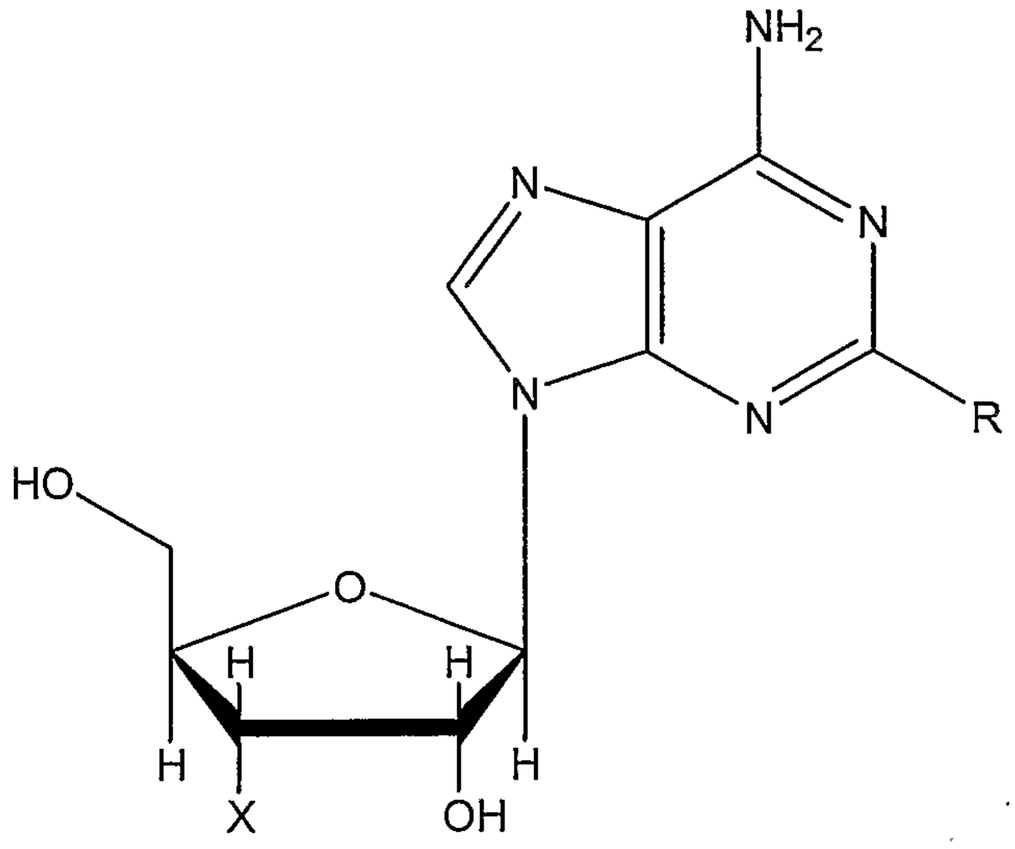
In the early 1990s the other adenosine receptors (the A2B and A3 receptors) were cloned, but the activity of spongosine at these receptors was never investigated. The

low potency and poor receptor selectivity of this compound led to it being largely ignored as more and more potent and receptor selective novel compounds were synthesised.

It has surprisingly been found that spongosine when administered to mammals can give significant pain relief in conditions of increased pain sensitivity (such as neuropathic and inflammatory hyperalgesia), without causing the significant side effects expected from use of purine receptor agonists. The activity of spongosine as an analgesic is the subject of International patent application no. PCT/GB03/05379 (unpublished at the filing date of the present application).

It is believed that other compounds of formula (I) also have analgesic activity and can be administered with reduced probability and severity of side effects compared to other adenosine receptor agonists:

(I)



wherein R is C_{1-4} alkoxy, and X is H or OH. Preferably R is C_{1-4} alkoxy, and X is OH.

According to the invention there is provided use of a compound of formula (I) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, particularly hyperalgesia.

There is also provided according to the invention a method of preventing, treating, or ameliorating pain (particularly hyperalgesia) which comprises administering a compound of formula (I) to a subject in need of such prevention, treatment, or amelioration.

Preferred compounds of formula (I) are 2-methoxyadenosine (although this compound may be excluded in view of PCT/GB03/05379), 2-ethoxyadenosine, and 2-butyloxyadenosine.

Compounds of formula (I) are believed to be effective in inhibiting pain perception in mammals suffering from pain, in particular neuropathic and inflammatory pain, even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. In addition, after administration of spongosine, no effect on normal physiological nociception was observed. Therefore, compounds of formula (I) can treat pain (particularly neuropathic and inflammatory pain) without causing the significant side effects associated with administration of other adenosine receptor agonists, and also without reducing normal sensory perception.

As mentioned above hyperalgesia is a consequence in most instances of tissue damage, either damage directly to a sensory nerve, or damage of the tissue innervated by a given sensory nerve. Consequently, there are many conditions in which pain perception includes a component of hyperalgesia.

According to the invention there is provided use of a compound of formula (I) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of neuropathy, including Diabetic Neuropathy, Polyneuropathy, Cancer Pain, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Pancreatic Pain, Pelvic/Perineal pain, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, HIV pain, Trigeminal Neuralgia, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-operative pain, post physical trauma pain (including gunshot, road traffic

accident, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Renal Colic, Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain (Cancer), Dysmenorhoea/Endometriosis.

According to the invention there is also provided use of a compound of formula (I) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of inflammatory disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage, including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis, bowel pain, cancer pain, back pain, fibromyalgia, post-operative pain.

The amount of a compound of formula (I) that is administered to a subject is preferably an amount which gives rise to a peak plasma concentration that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

It will be appreciated that the EC50 value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest EC50 value of the compound at the different receptors.

Preferably the peak plasma concentration is one thousandth to one fifth, or one fiftieth to one third (more preferably one thousandth to one twentieth, one hundredth or one fiftieth to one fifth, one fiftieth to one tenth, or one tenth to one fifth) of the EC50

value. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour between one thousandth and one fifth, or one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the EC50 value of the compound at adenosine receptors at pH 7.4.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture medium), for example as in (Daly *et al.*, Pharmacol. (1993) 46, 91-100), or preferably as in Tilburg *et al* (J. Med. Chem. (2002) *45*, 91-100). The EC50 could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of formula (I) that is administered may be an amount that results in a peak plasma concentration that is one thousandth to one twentieth, one thousandth to one third, more preferably one hundredth to one fifth, or one fiftieth to one tenth, of the Kd value at adenosine receptors.

It will be appreciated that the Kd value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest Kd value of the compound for the different receptors.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for at least one hour between one thousandth and one fifth, more preferably between one thousandth and one twentieth,

or one hundredth and one fifth, or one fiftieth and one fifth, of the Kd value of the compound at adenosine receptors.

The Kd value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used. Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the Kd of the compound at each receptor.

Alternatively, the amount of a compound of formula (I) that is administered may be an amount that is one thousandth to one fifth, or one fiftieth to one third (preferably one thousandth to one twentieth, or one hundredth or one fiftieth to one fifth) of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount is one tenth to one fifth of the minimum dose that gives rise to the side effects. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth of the minimum dose that gives rise to the side effects.

Alternatively, the amount of a compound of formula (I) that is administered may be an amount that gives rise to plasma concentrations that are one thousandth to one fifth, or one fiftieth to one third (preferably one thousandth to one twentieth, or one hundredth or one fiftieth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount gives rise to plasma concentrations that are one tenth to one fifth of the minimum plasma concentration that causes the side effects. Preferably the amount administered gives rise to a plasma concentration that is maintained for more

than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth, of the minimum plasma concentration that causes the side effects.

It is expected that the amount of a compound of formula (I) that is administered should be 0.01 to 15 mg/kg, for example 0.01 to 5 or 10 mg/kg. Preferably the amount is less than 6 mg/kg, for example 0.01 to 2 mg/kg. Preferably the amount is at least 0.01 or 0.1 mg/kg, for example 0.1 to 2 mg/kg, or 0.2 to 1 mg/kg. A typical amount is 0.2 or 0.6 to 1.2 mg/kg.

Preferred doses for a 70kg human subject are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7 to 70mg, or 14 to 70mg.

The dosage amounts specified above are significantly lower (up to approximately 100 times lower) than would be expected (based on the EC50 value of spongosine at the adenosine A2A receptor) to be required for the compounds of formula (I) to have any beneficial therapeutic effect.

The appropriate dosage of a compound of formula (I) will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

A compound of formula (I) may be administered with or without other therapeutic agents, for example analgesics or anti-inflammatories (such as opiates, steroids, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants).

It has been found that additive analgesic effects can be obtained if spongosine is administered with another analgesic agent. Thus, spongosine and the other analgesic agent can be administered to obtain a desired level of analgesic effect, each at a lower

dose than would be required to achieve that level if either agent was administered alone. Because lower doses of each agent can be administered, side effects associated with administration of higher doses of the agents are reduced. Alternatively, an increased level of analgesic effect can be obtained by administering spongosine and the other analgesic agent at higher doses. It is believed that this will also be the case with the other compounds of formula (I).

The preferred dosage of a compound of formula (I) when administered with another analgesic agent is lower than a preferred dosage specified above for administration of the compound alone.

It is believed that an additive analgesic effect is achieved if the other analgesic agent does not act in the same way as the compound of formula (I). Suitable other analgesic agents that may be administered with the compound include opioid receptor agonists and partial agonists (such as morphine, diamorphine, fentanyl, buprenorphine, codeine, or derivatives thereof), cyclooxygenase inhibitors (such as aspirin, paracetamol, ibuprofen, diclofenac, or derivatives thereof), sodium or calcium channel modulators (such as lignocaine, or gabapentin), or Selective Serotonin Reuptake Inhibitors (SSRI's) (such as paxil).

Example 5 below shows that the anti-hyperalgesic properties of spongosine are unaffected by co-administration of the opioid receptor antagonist naloxone indicating that spongosine does not act via an opioid receptor. Example 6 below demonstrates the additive analgesic effects of co-administration of spongosine and gabapentin. Gabapentin is effective against neuropathic pain. It is expected that other analgesic agents that are designed to treat neuropathic pain may have additive analgesic effects with compounds of formula (I). Such agents include topamax, pregabalin, ziconitide, and cannabinoid derivatives.

In general, a compound of formula (I) may be administered by known means, in any suitable formulation, by any suitable route. A compound of the invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular,

subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

It will be appreciated that a compound of formula (I) may be administered together with a physiologically acceptable carrier, excipient, or diluent.

Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention typically comprises up to 500 mg (for example 1 to 500 mg, preferably 5 to 500 mg) of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1 to 2, e.g. 0.5 to 1, typically about 0.2 or 0.6, mg of the active agent per kg of the (human) subject. At these levels, effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

Preferably a compound of formula (I) is administered at a frequency of 2 or 3 times per day.

Embodiments of the invention may exclude 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine and 3' deoxy 2 ethoxyadenosine.

Embodiments of the invention are described in the following examples with reference to the accompanying drawings in which:

Figure 1 shows the anti-hyperalgesic actions of spongosine (0.6 mg/kg p.o.) on carrageenan induced hyperalgesia. A: time course; B: dose dependency of the anti-hyperalgesic effect;

Figure 2 shows the anti-hyperalgesic actions of spongosine (0.6 mg/kg p.o.) in the chronic constriction injury model of neuropathic pain;

Figure 3 shows the effect of spongosine (0.6 mg/kg p.o.) on A: blood pressure in normal rats; B: heart rate;

Figure 4 shows the change in plasma concentration over time after administration of spongosine;

Figure 5 shows the effect of spongosine (0.6 mg/kg p.o.) in the presence and absence of naloxone in the chronic constriction injury model of neuropathic pain; and

Figure 6 shows the additive effect of spongosine and gabapentin in the chronic constriction injury model of neuropathic pain.

Examples

Example 1

Figure 1: A. Spongosine (0.624mg/kg p.o.) inhibits carrageenan (CGN) induced thermal hyperalgesia (CITH) with comparable efficacy to indomethacin (3mg/kg, po). B. Concentration-response relationship for Spongosine at 3 hrs post dosing. Carrageenan (2%, 10 microlitres) was administered into the right hind paw. A heat source was placed close to the treated and untreated hind paws, and the difference in the paw withdrawal latencies is shown. Spongosine was administered at the same time as carrageenan. Spongosine was as effective as indomethacin (Indo, 3 mg/kg p.o.).

Example 2

Figure 2: Spongosine (0.624mg/kg p.o.) inhibits thermal hyperalgesia caused by chronic constriction injury of the rat sciatic nerve. Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed thermal hyperalgesia in the operated leg as judged by the difference in paw withdrawal latencies of the right and left paws. Administration of spongosine reduced the hyperalgesia as shown by the

reduction in the difference between the withdrawal latencies. Spongosine was as, or more, effective than carbamazepine (CBZ, 100mg/kg s.c.)

Example 3

Figure 3: Spongosine (0.624 mg/kg p.o.) has no significant effect on blood pressure or heart rate. An implantable radiotelemetry device was placed in the abdominal cavity of 6 rats per group. The pressure catheter of the device was inserted in the abdominal aorta and two electrodes tunnelised under the skin in a lead II position (left side of abdominal cavity/right shoulder). Individual rats were placed in their own cage on a radioreceptor (DSI) for data acquisition. A: blood pressure; B: heart rate.

Example 4

The EC50 value of spongosine at adenosine receptors (measured at pH7.4) is 900ng/ml (3 μM). Figure 4 shows the change in plasma concentration over time after administration of spongosine at 0.6 mg/kg to a rat. It can be seen that the plasma concentration remains above 2% of the EC50 value for more than 3 hours. Anti-hyperalgesic effects have been observed (without blood pressure changes) when the peak plasma concentration is between 1% and 30% of the EC50 value determined in vitro. If the peak plasma concentration reaches the EC50 value profound reductions in blood pressure occur that last for hours.

Example 5

Figure 5: Spongosine (1.2 mg/kg p.o.) inhibits static allodynia caused by chronic constriction injury of the rat sciatic nerve, both in the presence and absence of naloxone (1 mg/kg s.c.). Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed static allodynia in the operated leg as judged by the difference in paw withdrawal thresholds of the right and left paws. Administration of spongosine reduced the hyperalgesia as shown by the increased paw withdrawal threshold (PWT) in the presence and absence of naloxone. Veh: vehicle.

Example 6

Figure 6: Spongosine and gabapentin inhibit static allodynia caused by chronic constriction injury of the rat sciatic nerve. Spongosine and gabapentin were administered (p.o.) in different proportions as indicated in the drawing. The total dose administered is shown on the horizontal axis, and the paw withdrawal threshold (PWT) on the vertical axis. The predicted anti-hyperalgesic effect (derived from the dose response curves obtained with each agent alone) if the effects of the two compounds are additive is shown (•). The observed effects are indicated by (■). It is apparent that the observed effects are not significantly different from those predicted by additivity.

Spongosine is effective in inhibiting pain perception in mammals suffering from neuropathic and inflammatory pain even when administered at doses expected to give concentrations well below those known to activate adenosine receptors. At these doses it can be seen that neither the heart A1 receptors nor the vascular A2A receptors are sufficiently stimulated to cause a change in the cardiovascular status of the animals.

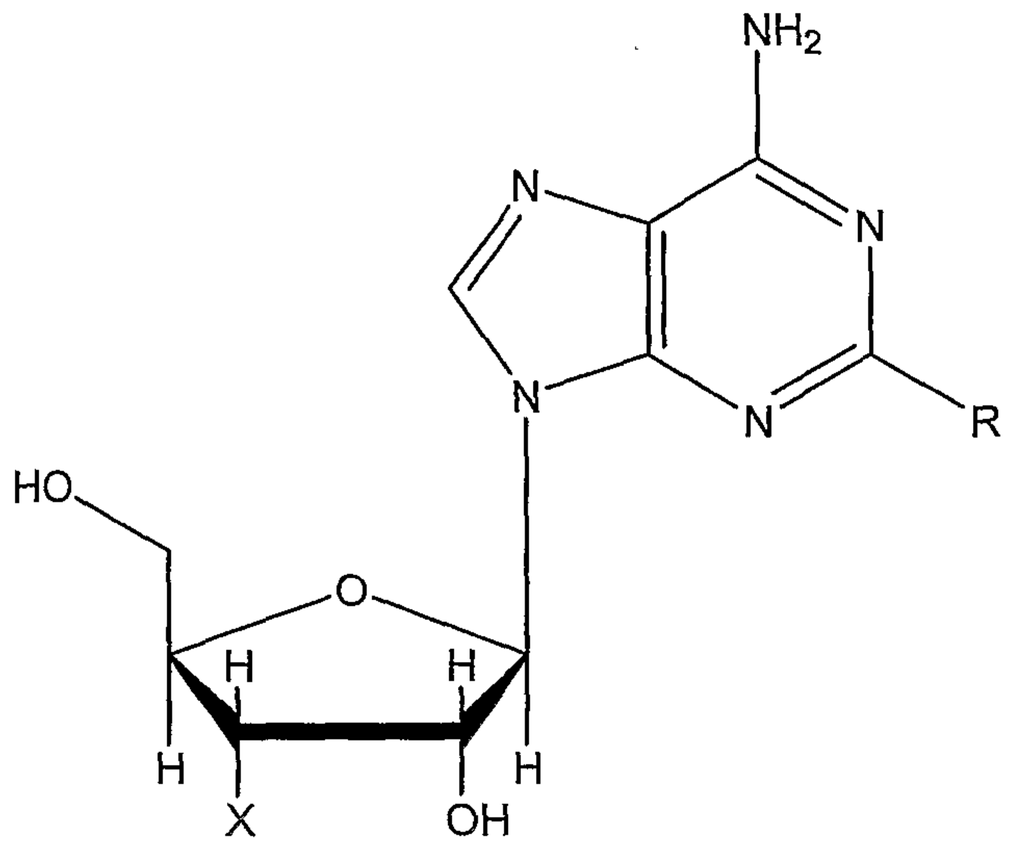
Compounds of formula (I) can be used as analgesics (particularly anti-hyperalgesics) which can be administered orally for the treatment of pain (particularly hyperalgesia) caused as a result of neuropathy and/or inflammatory disease, including Diabetic Neuropathy, polyneuropathy,Cancer Pain, Fibromyalgia, Myofascial Pain Syndrome, Pancreatic Pain, Pelvic/Perineal pain, back pain, Post Herpetic Neuralgia, Rhematoid Arthritis, Sciatica / Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, HIV pain, Trigeminal Neuralgia, Chronic Neuropathic Pain, Lower Back/ pain, Failed Back Surgery pain, post operative pain, post physical trauma pain (including gunshot, RTA, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel pain, Phantom limb pain, Obstetric Pain (labour/C-Section), Renal Colic, Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain, Cancer pain, Dysmenorhoea/Endometriosis, rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g.

myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.

Claims

1. Use of a compound of formula (I) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain:

(I)



wherein R is C_{1-4} alkoxy, and X is H or OH, excluding 2-methoxyadenosine.

2. Use according to claim 1, wherein the pain is hyperalgesia.

3. Use according to claim 2, wherein the hyperalgesia is neuropathic pain.

4. Use according to any preceding claim, wherein the pain is caused by or associated with a disease that causes damage to sensory neurones.

5. Use according to any preceding claim for the prevention, treatment, or amelioration of

Cancer Pain, Pancreatic Pain, Pelvic/Perineal pain, HIV pain, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-operative pain, post physical trauma pain (including gunshot, RTA, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Acute Herpes Zoster

Pain, Acute Pancreatitis Breakthrough Pain (Cancer), or for the prevention, treatment, or amelioration of neuropathic or other pain caused by, or associated with Diabetic Neuropathy, Polyneuropathy, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, Trigeminal Neuralgia, Renal Colic, Dysmenorhoea/Endometriosis.

6. Use according to claim 2, wherein the hyperalgesia is inflammatory pain.

7. Use according to any of claims 1, 2, or 6, wherein the pain is caused by or associated with an inflammatory or immune disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage.

8. Use according to claim 1, 2, 6, or 7 for the prevention, treatment, or amelioration of bowel pain, cancer pain, back pain, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, fibromyalgia, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.

9. Use according to any preceding claim at a dosage which, after administration to a subject, gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

10. Use according to any preceding claim at a dosage that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia,

hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

11. Use according to claim 10, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects.

12. Use according to any preceding claim at a dosage which, after administration to a subject, gives rise to a plasma concentration of the compound that is maintained for more than one hour between one thousandth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

13. Use according to any preceding claim, at a dosage of less than 6mg/kg.

14. Use according to any preceding claim at a dosage of at least 0.01mg/kg.

15. Use according to any preceding claim at a dosage of 0.2 to 1mg/kg.

16. A method of preventing, treating, or ameliorating pain which comprises administering a compound of formula (I) to a subject in need of such prevention, treatment, or amelioration.

17. Use according to claim 16, wherein the pain is hyperalgesia.

18. Use according to claim 17, wherein the hyperalgesia is neuropathic pain.

19. Use according to any of claims 16 to 18, wherein the pain is caused by or associated with a disease that causes damage to sensory neurones.

20. Use according to any of claims 16 to 19 for the prevention, treatment, or amelioration of Cancer Pain, Pancreatic Pain, Pelvic/Perineal pain, HIV pain, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-

operative pain, post physical trauma pain (including gunshot, road traffic accident, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain (Cancer), or for the prevention, treatment, or amelioration of neuropathic or other pain caused by, or associated with Diabetic Neuropathy, Polyneuropathy, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, Trigeminal Neuralgia, Renal Colic, Dysmenorhoea/Endometriosis.

21. Use according to claim 17, wherein the hyperalgesia is inflammatory pain.

22. Use according to any of claims 16, 17, or 21, wherein the pain is caused by or associated with an inflammatory or immune disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage.

23. Use according to claim 16, 17, 21, or 22 for the prevention, treatment, or amelioration of bowel pain, cancer pain, back pain, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, fibromyalgia, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.

24. A method according to any of claims 16 to 23, wherein the compound is administered at a dose that gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

25. A method according to any of claims 16 to 24, wherein the compound is administered at a dose that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the dose is to be administered.

26. A method according to claim 25, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects

27. A method according to any of claims 16 to 26, wherein the compound is administered at a dose that results in a plasma concentration of the compound that is maintained for more than one hour between one hundredth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

28. A method according to any of claims 16 to 27, wherein the compound is administered at a dose of less than 6mg/kg.

29. A method according to any of claims 16 to 28, wherein the compound is administered at a dose of at least 0.01mg/kg.

30. A method according to any of claims 16 to 29, wherein the compound is administered at a dose of 0.2 to 1mg/kg.

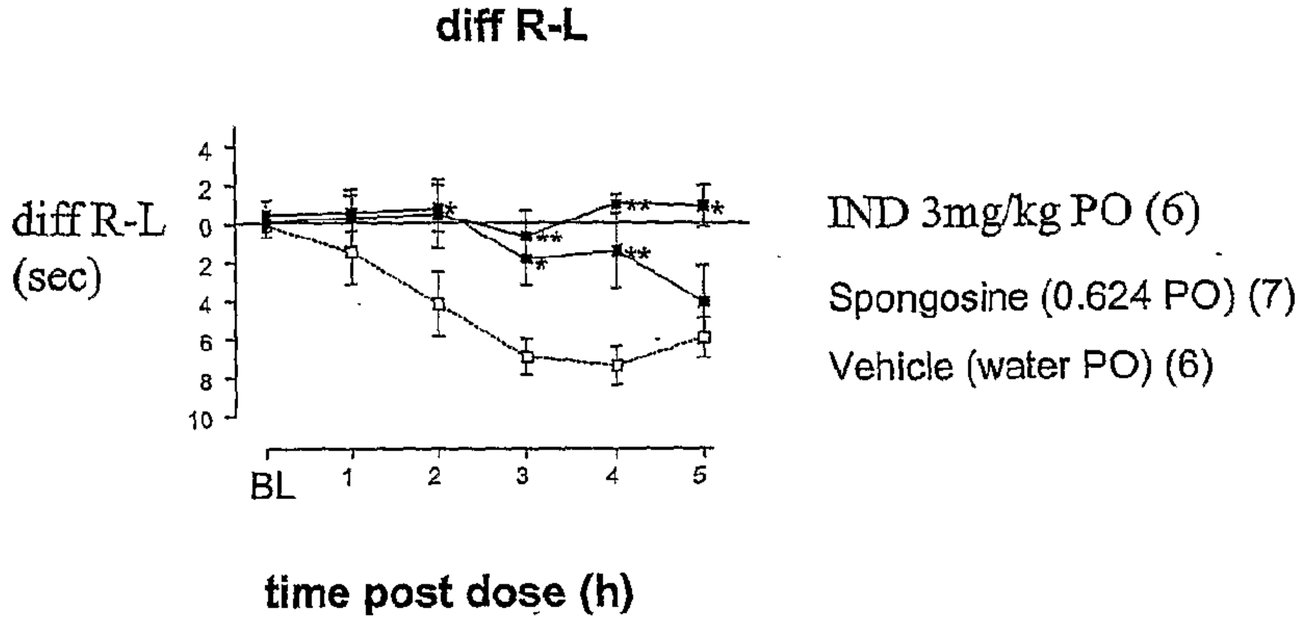
31. A method according to any of claims 16 to 30, wherein the compound is administered orally, parenterally, sublingually, transdermally, intrathecally, transmucosally, intravenously, intramuscularly, subcutaneously, topically, or by inhaling.

32. A method according to any of claims 16 to 31, wherein the compound is administered at a frequency of 2 or 3 times per day.

33. A method according to any of claims 16 to 32, wherein the subject is a human subject.

Figure 1

A)



*p<0.05, **p<0.01 versus vehicle (Sidak's)

B)

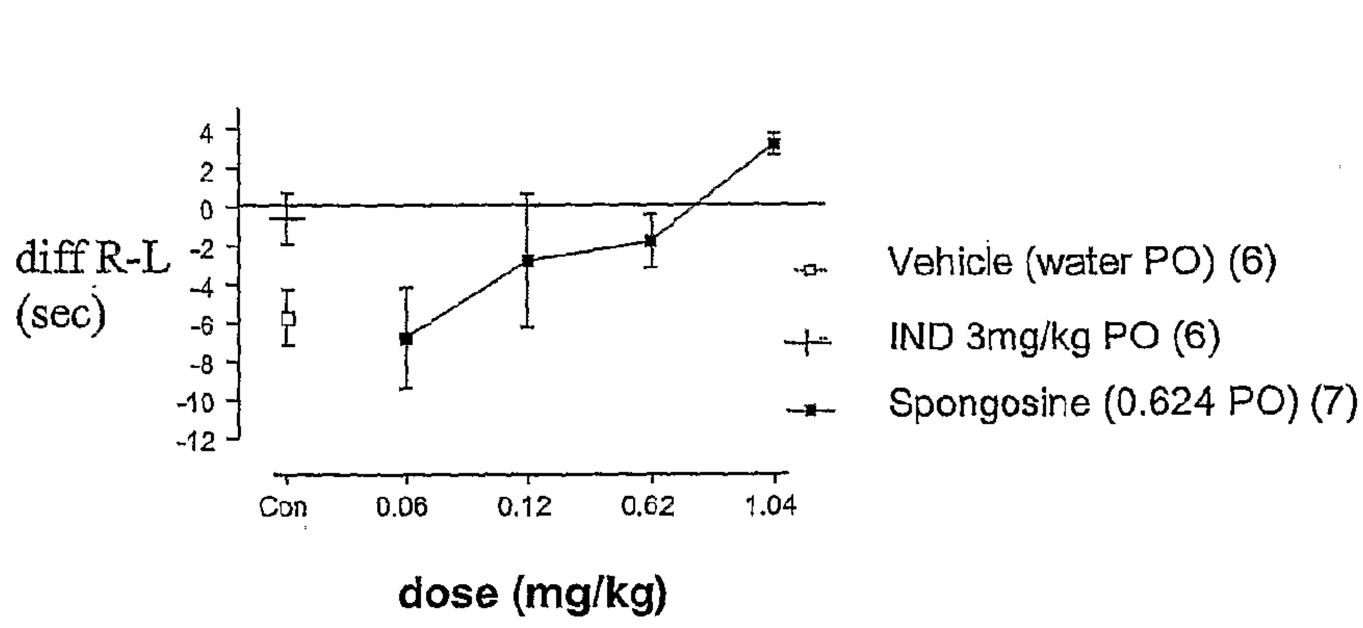


Figure 2

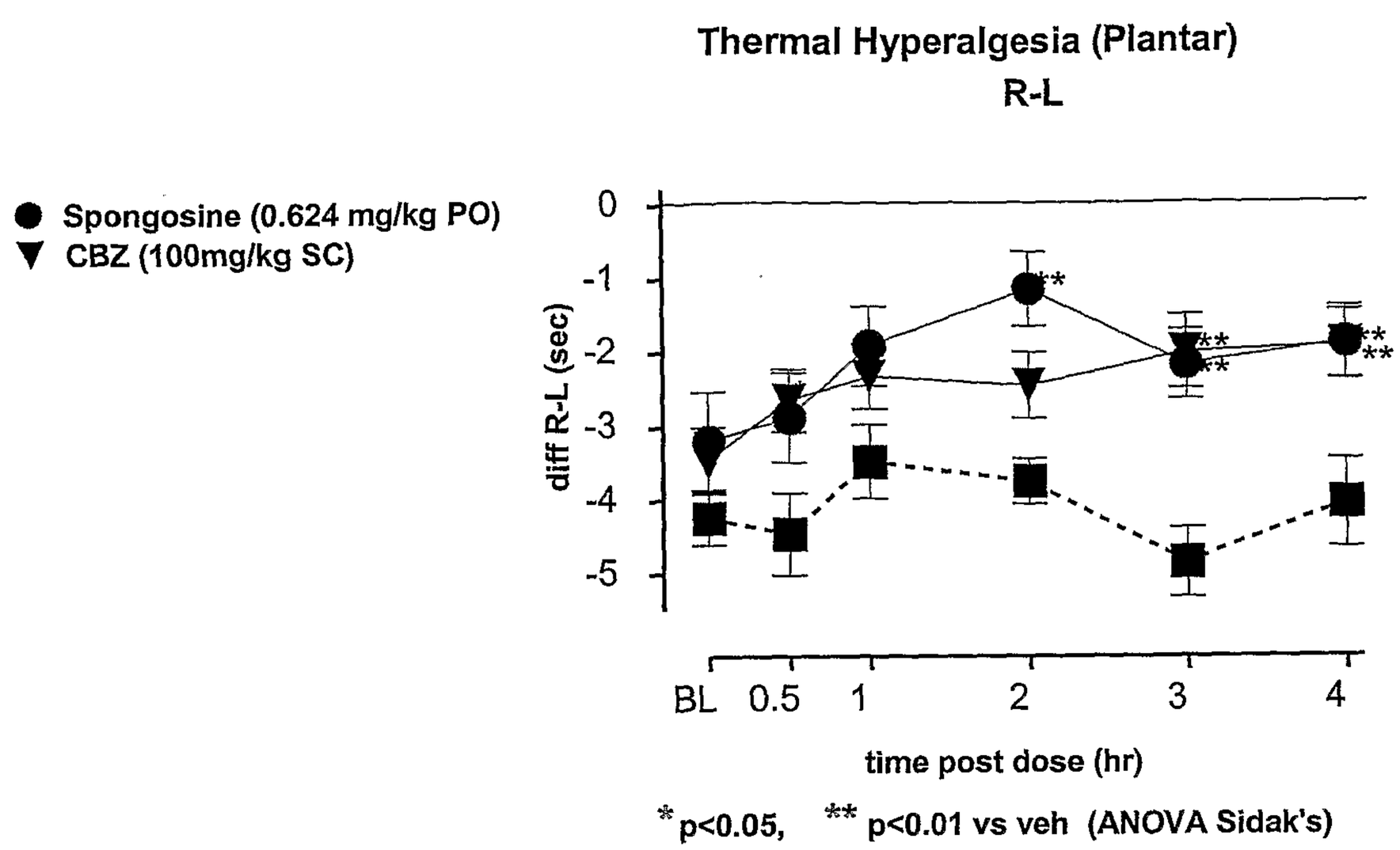
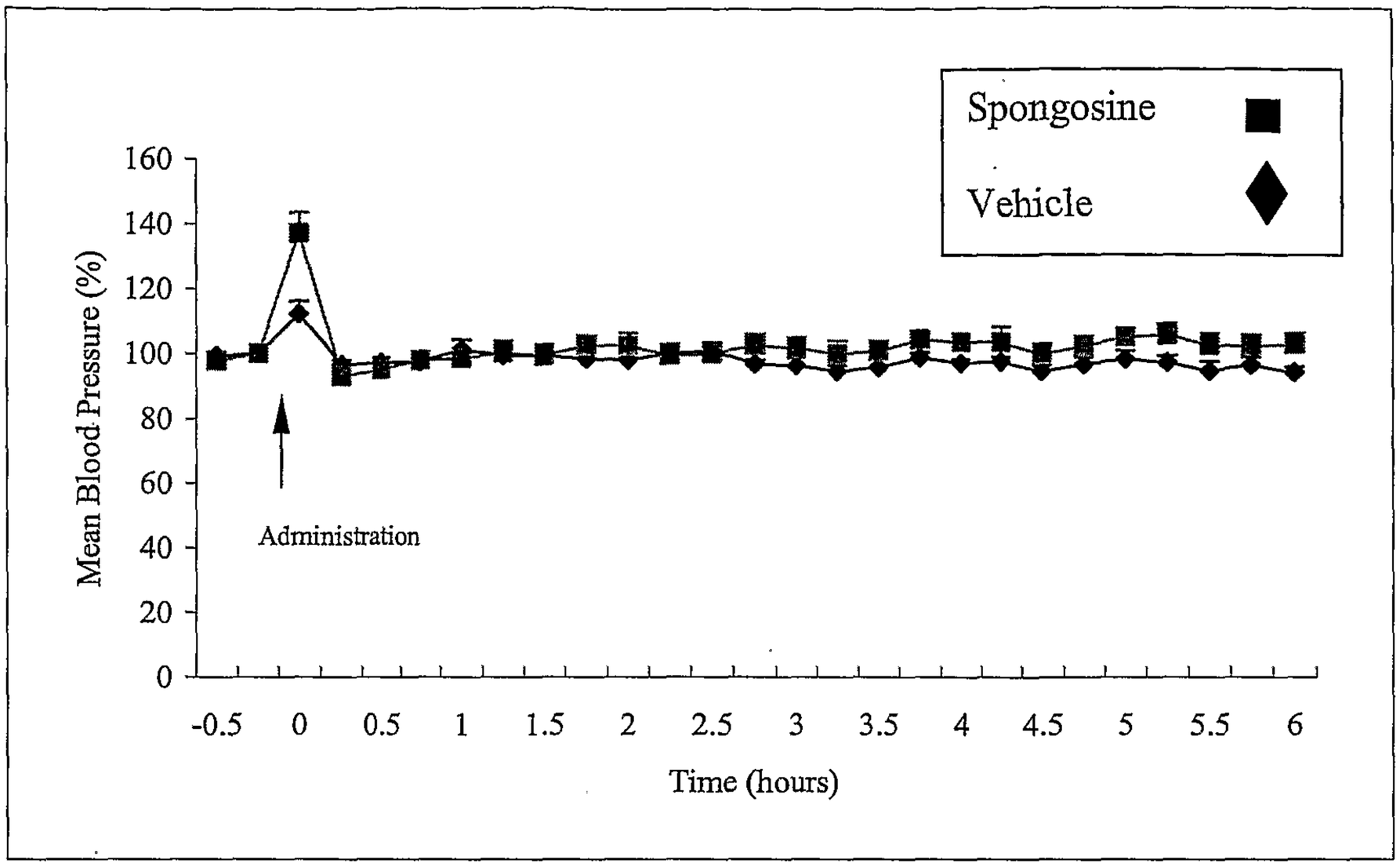

Thermal Hyperalgesia (Plantar)
R-L
Spongosine (0.624 mg/kg PO)
CBZ (100mg/kg SC)
diff R-L (sec)
0
-1
-2
-3
-4
-5
BL
0.5
1
2
3
4
time post dose (hr)
* p<0.05, ** p<0.01 vs veh (ANOVA Sidak's)

Figure 3

A)


Spongosine
Vehicle
Mean Blood Pressure (%)
160
140
120
100
80
60
40
20
0
Administration
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (hours)

B)

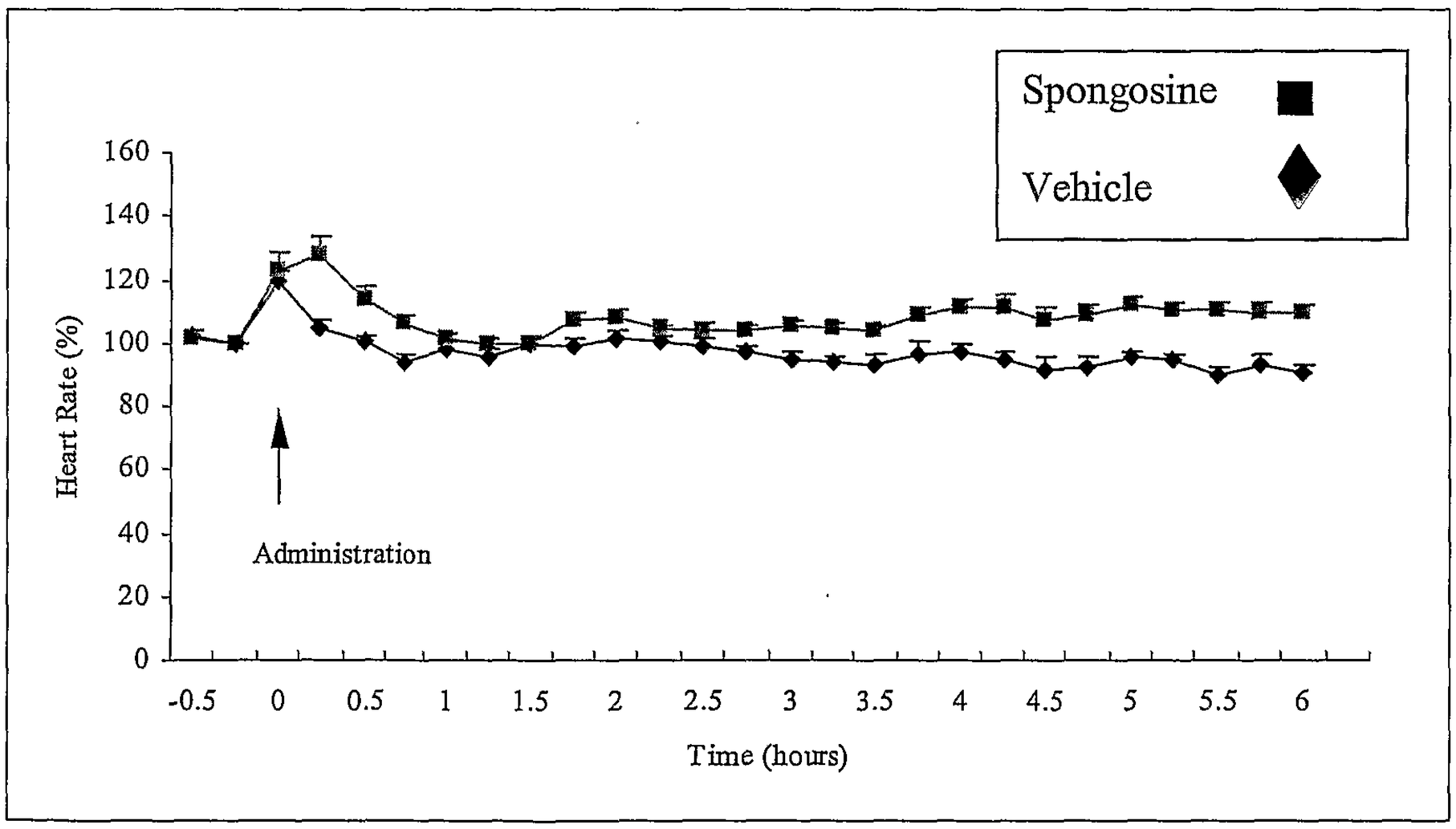

Spongosine
Vehicle
Heart Rate (%)
160
140
120
100
80
60
40
20
0
Administration
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (hours)

Figure 4

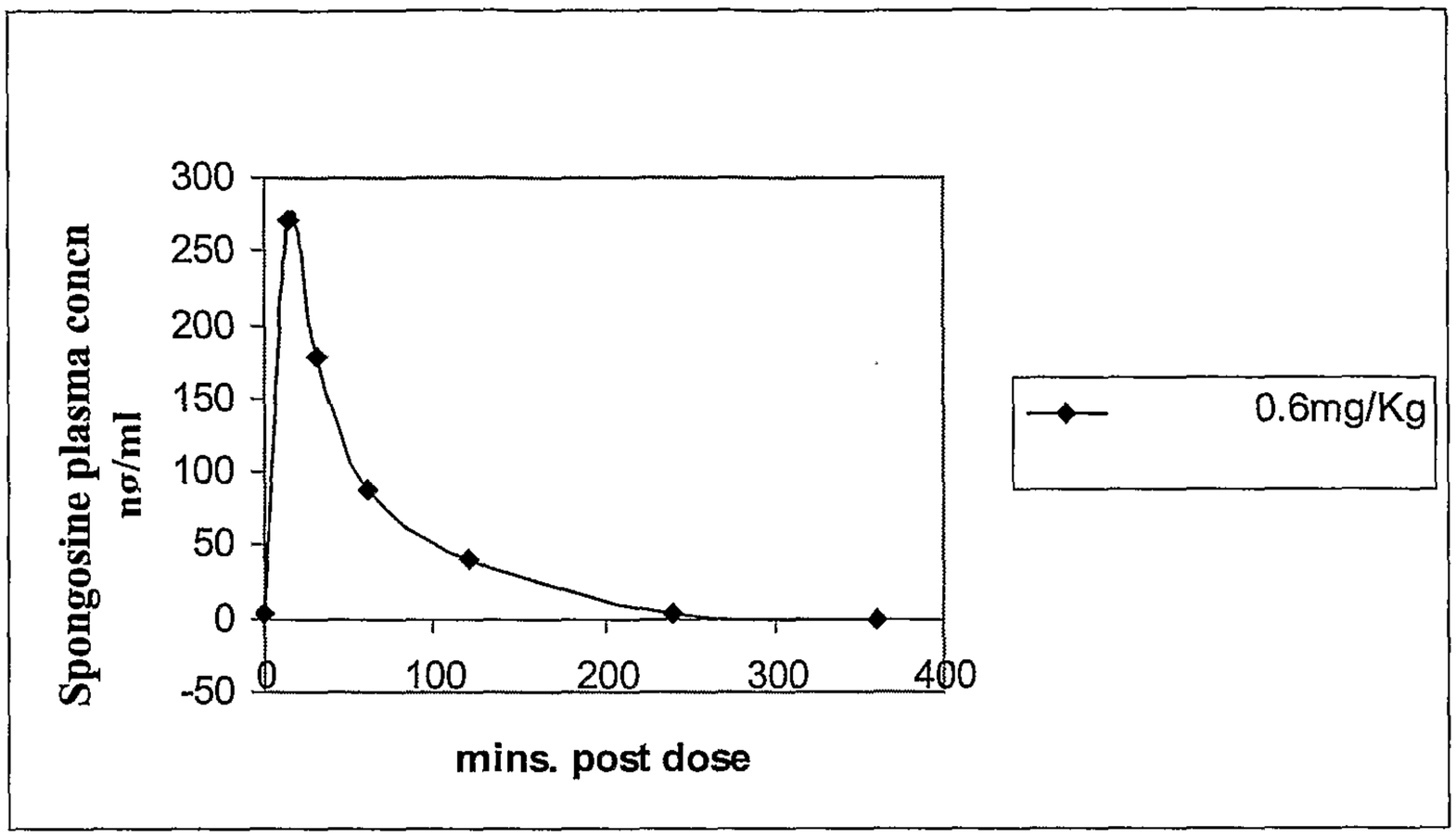

Spongosine plasma concn
ng/ml
300
250
200
150
100
50
0
-50
0
100
200
300
400
mins. post dose
0.6mg/Kg

Figure 5

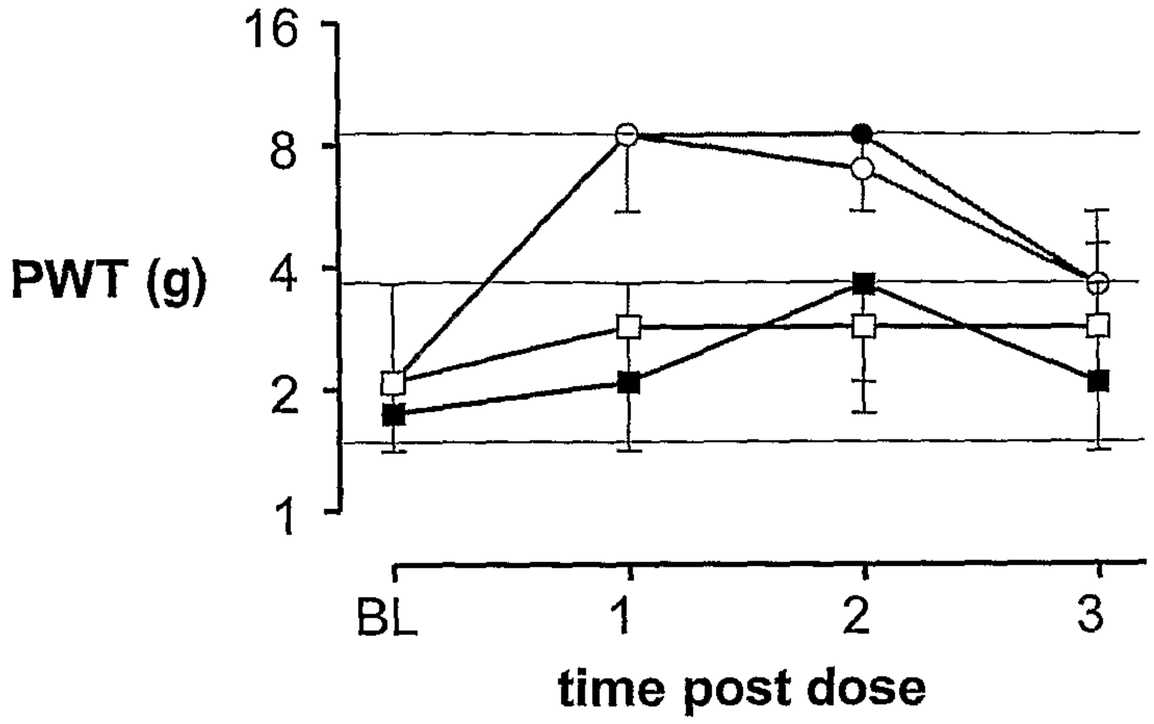
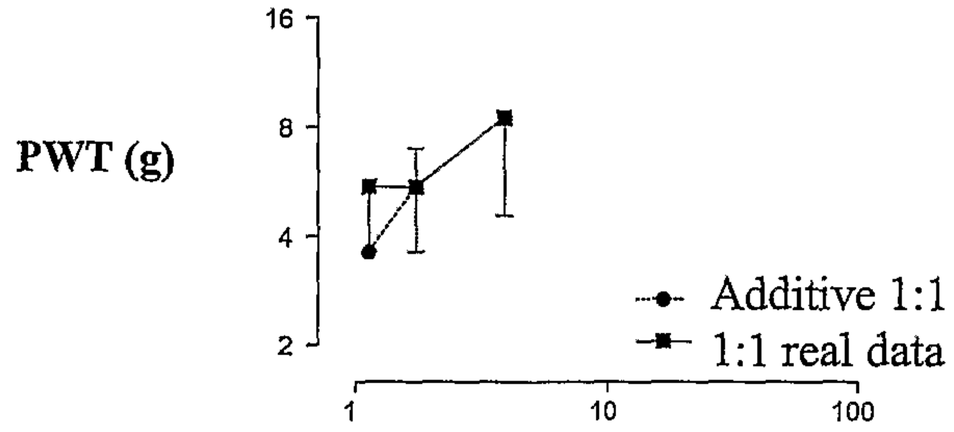
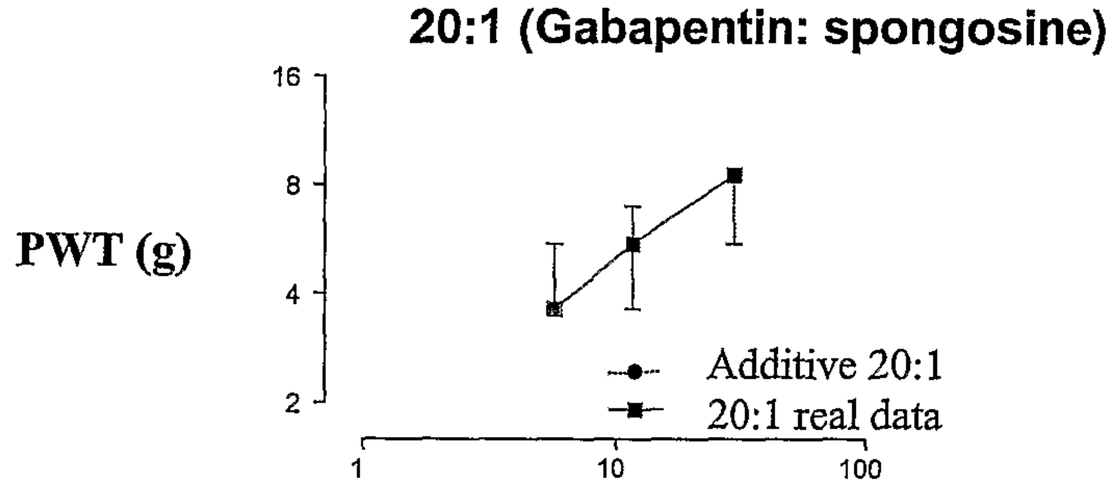

16
8
4
2
1
PWT (g)
BL
1
2
3
time post dose
Vehicle + Vehicle
Vehicle + spongosine (1.2 p.o.)
Nalox (1 s.c.) + Vehicle
Nalox (1 s.c.) + spongosine (1.2 p.o.)

Figure 6

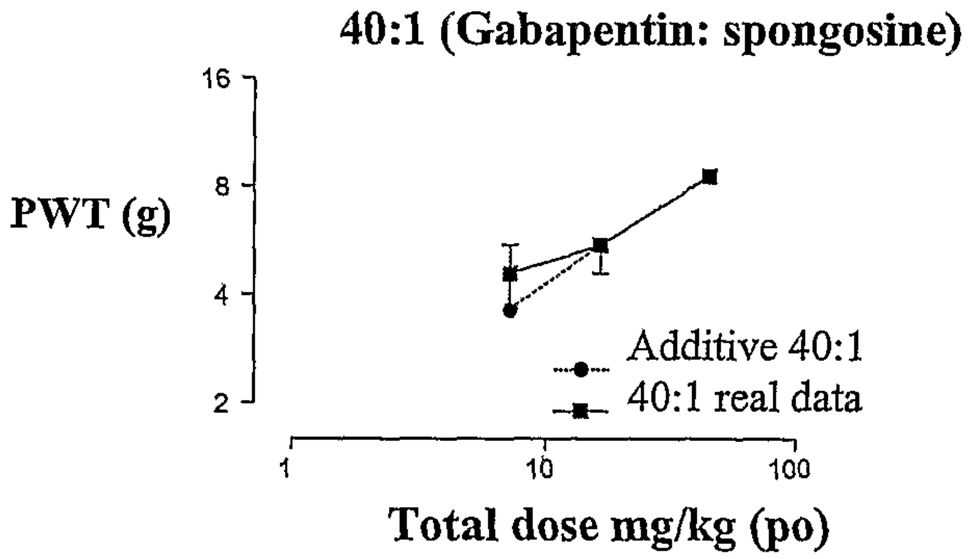
A)


1:1 (Gabapentin: spongosine)
PWT (g)
16
8
4
2
Additive 1:1
1:1 real data
1
10
100
Total dose mg/kg (po)

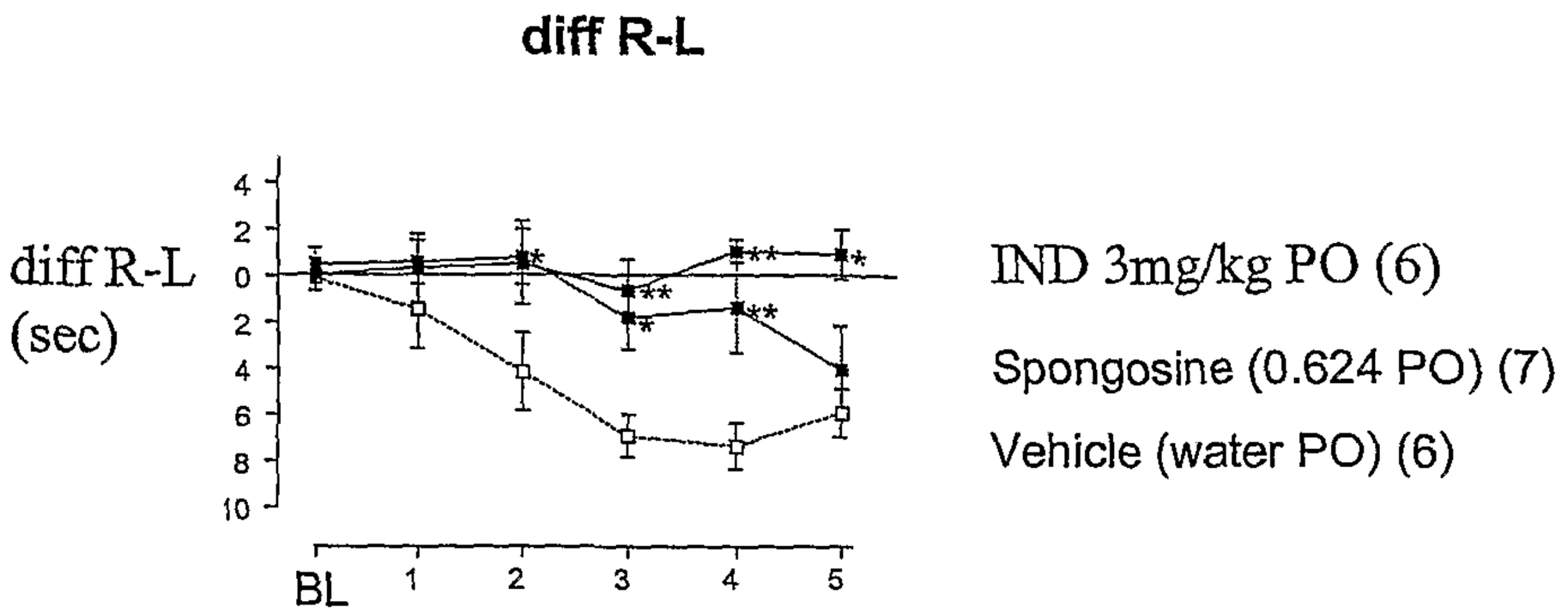
B)


20:1 (Gabapentin: spongosine)
PWT (g)
16
8
4
2
Additive 20:1
20:1 real data
1
10
100
Total dose mg/kg (po)

C)

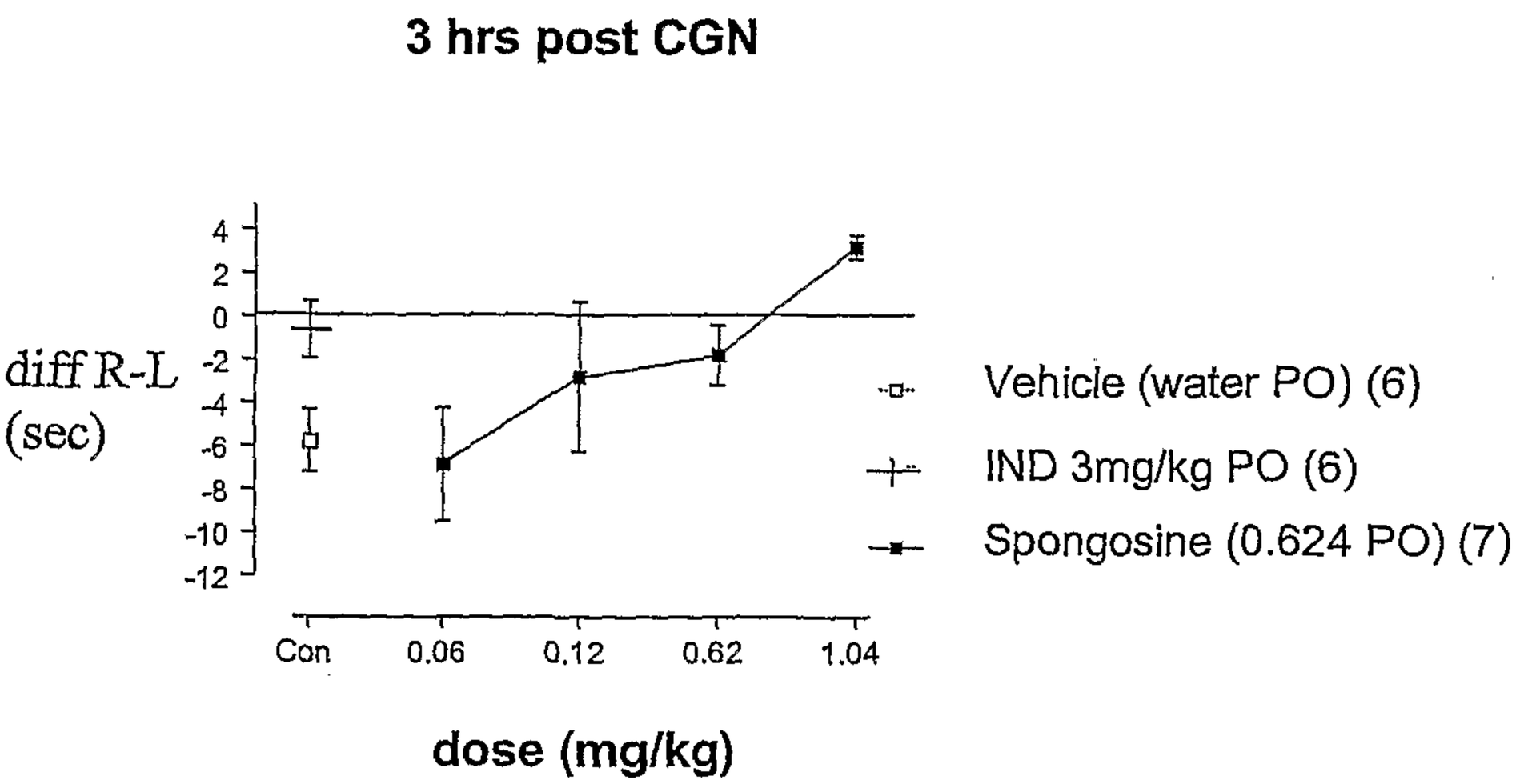

40:1 (Gabapentin: spongosine)
PWT (g)
16
8
4
2
Additive 40:1
40:1 real data
1
10
100
Total dose mg/kg (po)

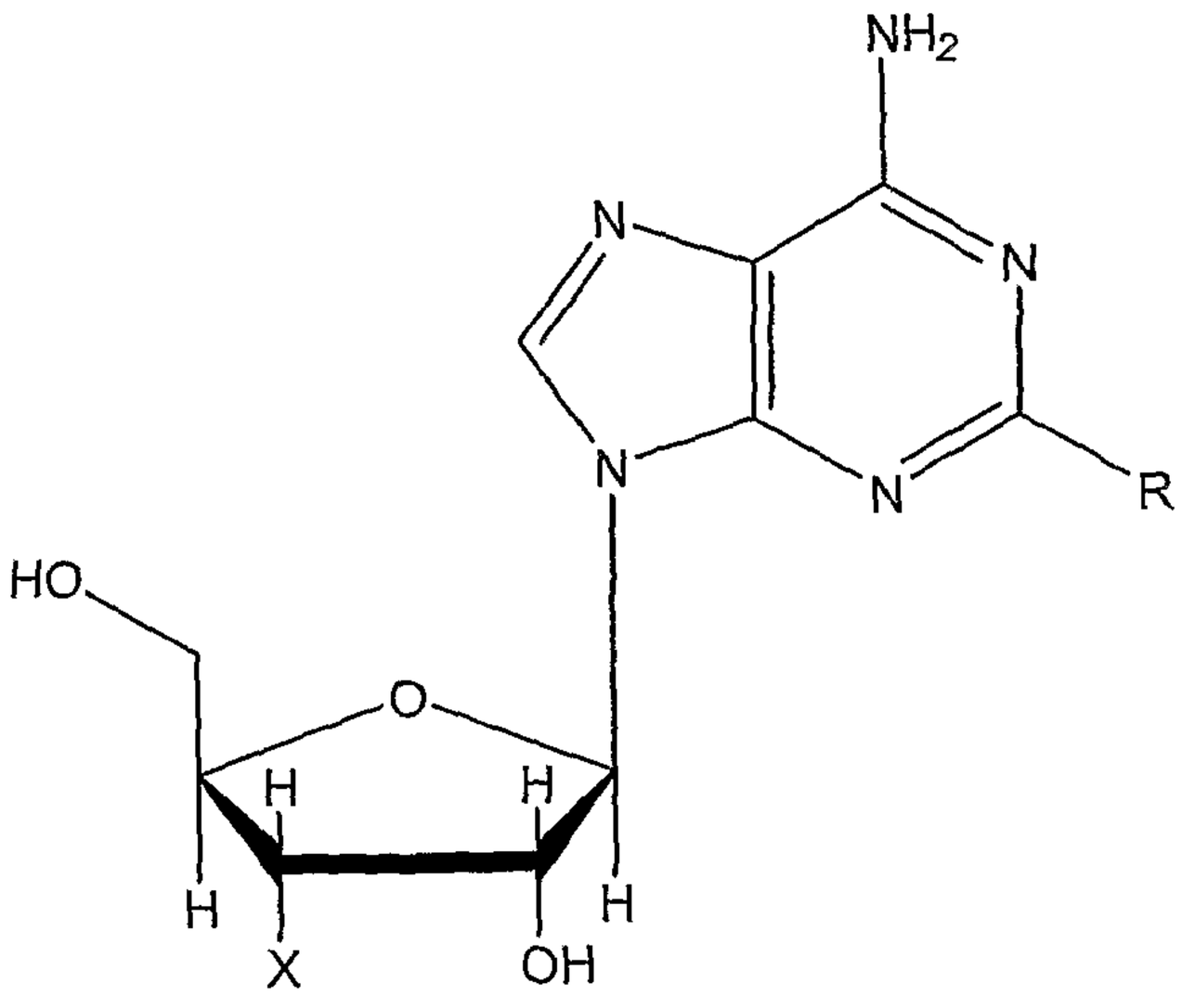
A)



*p<0.05, **p<0.01 versus vehicle (Sidak's)

B)





(I)