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(54) Titre : UTILISATION DE SPONGOSINE (2-METHOXYADENOSEINE) POUR LE TRAITEMENT DE LA DOULEUR, EN PARTICULIER DE L'HYPERALGIE

(54) Title: USE OF SPONGOSINE (2-METHOXYADENOSEIN) FOR THE TREATMENT OF PAIN, IN PARTICULAR HYPERALGESIA

(57) Abrégé/Abstract:
Use of spongosine (2-methoxyadenosine) as an analgesic, in particular for the treatment of hyperalgesia, is described.

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(54) Title: USE OF SPONGOSINE (2-METHOXYADENOSEIN) FOR THE TREATMENT OF PAIN, IN PARTICULAR HYPERALGESIA

(57) Abstract: Use of spongosine (2-methoxyadenosine) as an analgesic, in particular for the treatment of hyperalgesia, is described.

USE OF SPONGOSINE (2-METHOXYADENOSEIN) FOR THE TREATMENT OF PAIN, IN PARTICULAR HYPERALGESIA

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

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 which are sufficiently potent to control pain perception in neuropathic, inflammatory, 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 (anti-inflammatory activity was assessed by inhibition of carrageenan-induced oedema in a rat paw).

The affinity of spongosine for the rat adenosine A1 and A2A receptors has been determined. The Kd values obtained were 340nM for the A1 receptor and 1.4μM for the A2A receptor (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 gives 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.

According to the invention there is provided use of spongosine in the manufacture of a medicament for the prevention, treatment, or amelioration of pain.

The term "spongosine" is used herein to include spongosine free base, or a pharmaceutically acceptable salt of spongosine.

Use of spongosine according to the invention is particularly concerned with the prevention, treatment, or amelioration of pain other than the early or immediate phase of pain as described above, and is especially concerned with the prevention, treatment, or amelioration of hyperalgesia.

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

Spongosine has surprisingly been found to be 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. Thus, spongosine can treat neuropathic and inflammatory pain without causing the significant side effects associated with administration of other adenosine receptor agonists.

No analgesic effect on normal physiological nociception was observed after administration of spongosine.

Because hyperalgesia is a consequence of tissue damage, either directly to a sensory nerve, or to tissue innervated by a sensory nerve, there are many diseases or conditions in which pain perception includes a component of hyperalgesia.

Spongosine can be used as an anti-hyperalgesic for the prevention, treatment, or amelioration of hyperalgesia caused as a result of neuropathy, including bowel pain, back pain, cancer pain, HIV pain, phantom limb pain, post-operative pain, diabetic neuropathy, polyneuropathy, post-herpes neuralgia, and trigeminal neuralgia.

Other diseases or conditions involving damage to sensory nerves which contain a component of neuropathic pain include, pancreatic pain, pelvic/perineal pain, lower back pain, chest pain, cardiac pain, pelvic pain/PID, joint pain (for example, associated with tendonitis, bursitis, acute arthritis), neck pain, obstetric pain (labour or Caesarean-Section), chronic neuropathic pain, failed back surgery pain, post physical trauma pain (including pain caused by a gunshot wound, a road traffic accident, or a burn), scar tissue pain, 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, fibromyalgia, myofascial pain syndrome, osteoarthritis, rheumatoid arthritis, sciatica or lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, renal colic, dysmenorrhoea/endometriosis.

Spongosine can be used as an anti-hyperalgesic for the prevention, treatment, or amelioration of hyperalgesia caused as a result of inflammatory disease, including bowel pain, back pain, cancer pain, fibromyalgia, post-operative pain, osteoarthritis, and rheumatoid arthritis.

Other diseases or conditions in which hyperalgesia plays a prominent role in pain perception because they are associated with chronic inflammation include other arthritic conditions such as rheumatoid spondylitis, gouty arthritis, or asthma, chronic obstructive pulmonary disease, fibrosis, multiple sclerosis, sepsis, septic shock, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, cerebral malaria, organ transplant rejection, pain secondary to cancer, HIV, chronic pulmonary inflammatory disease, silicosis,

pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, multiple sclerosis, myasthenia gravis, 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, bacterial meningitis, or adverse effects from amphotericin B treatment, interleukin-2 treatment, OKT3 treatment, or GM-CSF treatment.

The pain associated with many of the above diseases or conditions are relatively resistant to NSAIDs and opiates.

It will be appreciated that spongosine may be administered together with a pharmaceutically acceptable carrier, excipient, or diluent.

The appropriate dosage of spongosine will vary with the age, sex, and weight of the subject being treated, and the route of administration.

Preferably spongosine is administered at a dose that gives rise to plasma concentrations one fifth to one thousandth, preferably one fifth to one hundredth, of the minimum plasma concentration of spongosine 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.

Alternatively, it is preferred that spongosine is administered at a dose that is one fifth to one fiftieth, preferably one fifth to one tenth, of the minimum dose of spongosine 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.

Preferably spongosine is administered at a dose of less than 6mg/kg, and preferably at least 0.01mg/kg, more preferably at least 0.05mg/kg, most preferably at least 0.1mg/kg. More preferably spongosine is administered at a dose of 0.1 to 1mg/kg, or 0.2 to 1mg/kg.

Thus, 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.

Spongosine may be administered by any suitable route, preferably orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally.

Preferably spongosine is administered at a frequency of 2 or 3 times per day.

It has also 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.

The preferred dosage of spongosine when administered with another analgesic agent is lower than a preferred dosage specified above for administration of spongosine alone.

It is believed that an additive analgesic effect is achieved if the other analgesic agent does not act in the same way as spongosine. Suitable other analgesic agents that may be administered with spongosine 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 4 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 5 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 spongosine. Such agents include topamax, pregabalin, ziconitide, and cannabinoid derivatives.

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 (*$p<0.05$, **$p<0.01$ versus vehicle (Sidak's), $p>0.05$ versus BL over 5 hrs for Spongosine and IND (Dunnett's)); 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 (*$p<0.05$, **$p<0.01$ vs veh (ANOVA Sidak's);
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 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 5 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.

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

Figure 4: 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 5

Figure 5: 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.

Spongosine can therefore be used as an anti-hyperalgesic which can be administered orally for the treatment of hyperalgesia caused as a result of neuropathy or inflammatory disease, including bowel pain, back pain, cancer pain, fibromyalgia, HIV pain, phantom limb pain, osteoarthritis, rheumatoid arthritis, post-herpes neuralgia, trigeminal neuralgia, polyneuropathy, diabetic neuropathy and post-operative pain.

Claims

1. Use of spongosine in the manufacture of a medicament for the prevention, treatment, or amelioration of pain.

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 bowel pain, pancreatic pain, pelvic/perineal pain, back pain, lower back pain, chest pain, cardiac pain, pelvic pain/PID, joint pain (for example, associated with tendonitis, bursitis, acute arthritis), neck pain, obstetric pain (labour or Caesarean-Section), cancer pain, HIV pain, phantom limb pain, post-operative pain, chronic neuropathic pain, failed back surgery pain, post physical trauma pain (including pain caused by a gunshot wound, a road traffic accident, or a burn), scar tissue pain, acute herpes Zoster pain, acute pancreatitis breakthrough pain (cancer), post-herpes neuralgia, or trigeminal neuralgia, 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, rheumatoid arthritis, sciatica or lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, renal colic, dysmenorrhoea/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.

8. Use according to claim 1, 2, 6, or 7 for the prevention, treatment, or amelioration of bowel pain, back pain, cancer pain, fibromyalgia, post-operative pain,

or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with arthritic conditions such as osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, or asthma, chronic obstructive pulmonary disease, fibrosis, multiple sclerosis, sepsis, septic shock, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, cerebral malaria, organ transplant rejection, pain secondary to cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, multiple sclerosis, myasthenia gravis, 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, bacterial meningitis, or adverse effects from amphotericin B treatment, interleukin-2 treatment, OKT3 treatment, or GM-CSF treatment.

9. Use according to any preceding claim, wherein spongosine is used with another analgesic agent.

10. Use according to claim 9, wherein the other analgesic agent is an opioid receptor agonist or partial agonist, a cyclooxygenase inhibitor, a sodium or calcium channel modulator, a Selective Serotonin Reuptake Inhibitor (SSRI), or an agent that treats neuropathic pain.

11. A method of preventing, treating, or ameliorating pain which comprises administering spongosine to a subject in need of such prevention, treatment, or amelioration.

12. A method according to claim 11, wherein the pain is hyperalgesia.

13. A method according to claim 12, wherein the hyperalgesia is neuropathic pain.

14. A method according to any of claims 11 to 13, wherein the pain is caused by or associated with a disease that causes damage to sensory neurones.

15. A method according to any of claims 11 to 14 for the prevention, treatment, or amelioration of bowel pain, pancreatic pain, pelvic/perineal pain, back pain, lower back pain, chest pain, cardiac pain, pelvic pain/PID, joint pain (for example, associated with tendonitis, bursitis, acute arthritis), neck pain, obstetric pain (labour or Caesarean-Section), cancer pain, HIV pain, phantom limb pain, post-operative pain, chronic neuropathic pain, failed back surgery pain, post physical trauma pain (including pain caused by a gunshot wound, a road traffic accident, or a burn), scar tissue pain, acute herpes Zoster pain, acute pancreatitis breakthrough pain (cancer), post-herpes neuralgia, or trigeminal neuralgia, 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, rheumatoid arthritis, sciatica or lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, renal colic, dysmenorrhoea/endometriosis.

16. A method according to claim 12, wherein the hyperalgesia is inflammatory pain.

17. A method according to claim 11, 12, or 16, wherein the pain is caused by or associated with an inflammatory or immune disease.

18. A method according to claim 11, 12, 16, or 17 for the prevention, treatment, or amelioration of bowel pain, back pain, cancer pain, fibromyalgia, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with arthritic conditions such as osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, or asthma, chronic obstructive pulmonary disease, fibrosis, multiple sclerosis, sepsis, septic shock, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, cerebral malaria, organ transplant rejection, pain secondary to cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, multiple sclerosis, myasthenia gravis, 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, bacterial meningitis,

or adverse effects from amphotericin B treatment, interleukin-2 treatment, OKT3 treatment, or GM-CSF treatment.

19. A method according to any of claims 11 to 18, wherein spongosine is administered at a dose that gives rise to plasma concentrations one fifth to one thousandth of the minimum plasma concentration of spongosine 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.

20. A method according to claim 19, wherein the dose is one fifth to one hundredth of the minimum does that gives rise to the side effects.

21. A method according to any of claims 11 to 18, wherein spongosine is administered at a dose that is one fifth to one fiftieth of the minimum dose of spongosine 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.

22. A method according to claim 21, wherein the dose is one fifth to one tenth of the minimum dose that gives rise to the side effects.

23. A method according to any of claims 11 to 18, wherein spongosine is administered at a dose of less than 6mg/kg.

24. A method according to any of claims 11 to 18, or 23, wherein spongosine is administered at a dose of at least 0.01mg/kg, preferably at least 0.05mg/kg.

25. A method according to any of claims 11 to 18, or 23, wherein spongosine is administered at a dose of at least 0.1mg/kg.

26. A method according to claim 25, wherein spongosine is administered at a dose of 0.1 to 1mg/kg, or 0.2 to 1mg/kg.

27. A method according to any of claims 11 to 18, wherein the subject is administered with spongosine and another analgesic agent.

28. A method according to claim 27, wherein the other analgesic agent is an opioid receptor agonist or partial agonist, a cyclooxygenase inhibitor, a sodium or calcium channel modulator, a Selective Serotonin Reuptake Inhibitor (SSRI), or an agent that treats neuropathic pain.

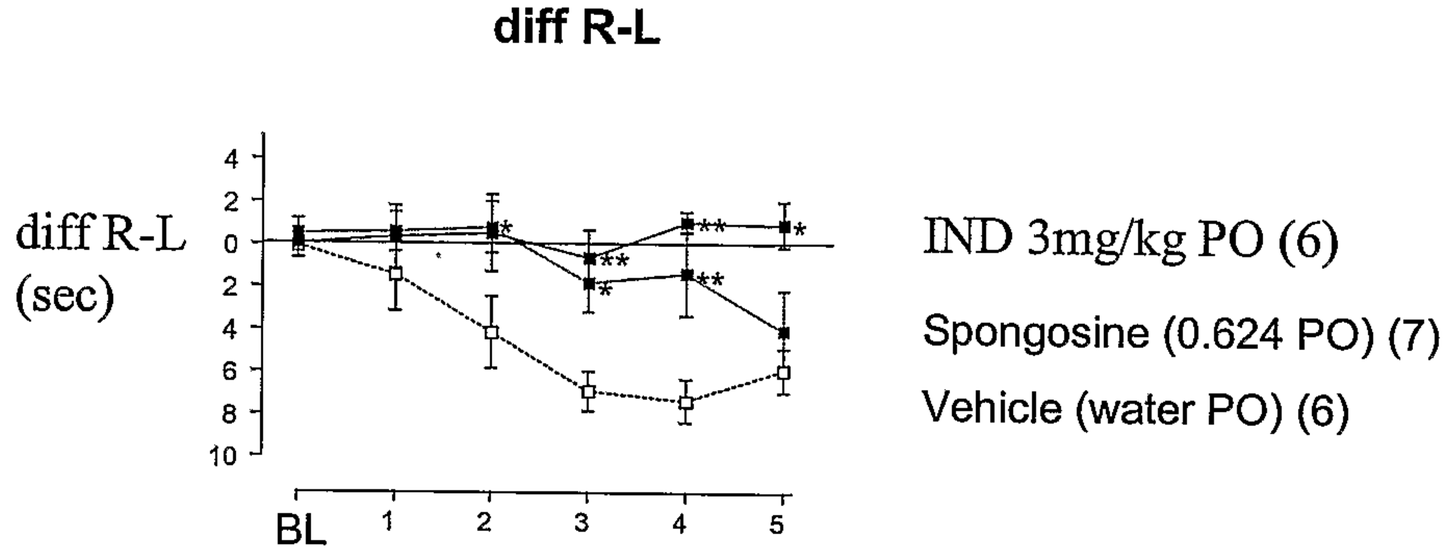
29. A method according to any of claims 11 to 28, wherein spongosine is administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally.

30. A method according to any of claims 11 to 29, wherein spongosine is administered at a frequency of 2 or 3 times per day.

31. A method according to any of claims 11 to 30, wherein the subject is a human subject.

Figure 1

A)


diff R-L
diff R-L (sec)
4
2
0
2
4
6
8
10
BL
1
2
3
4
5
IND 3mg/kg PO (6)
Spongosine (0.624 PO) (7)
Vehicle (water PO) (6)
time post dose (h)

B)

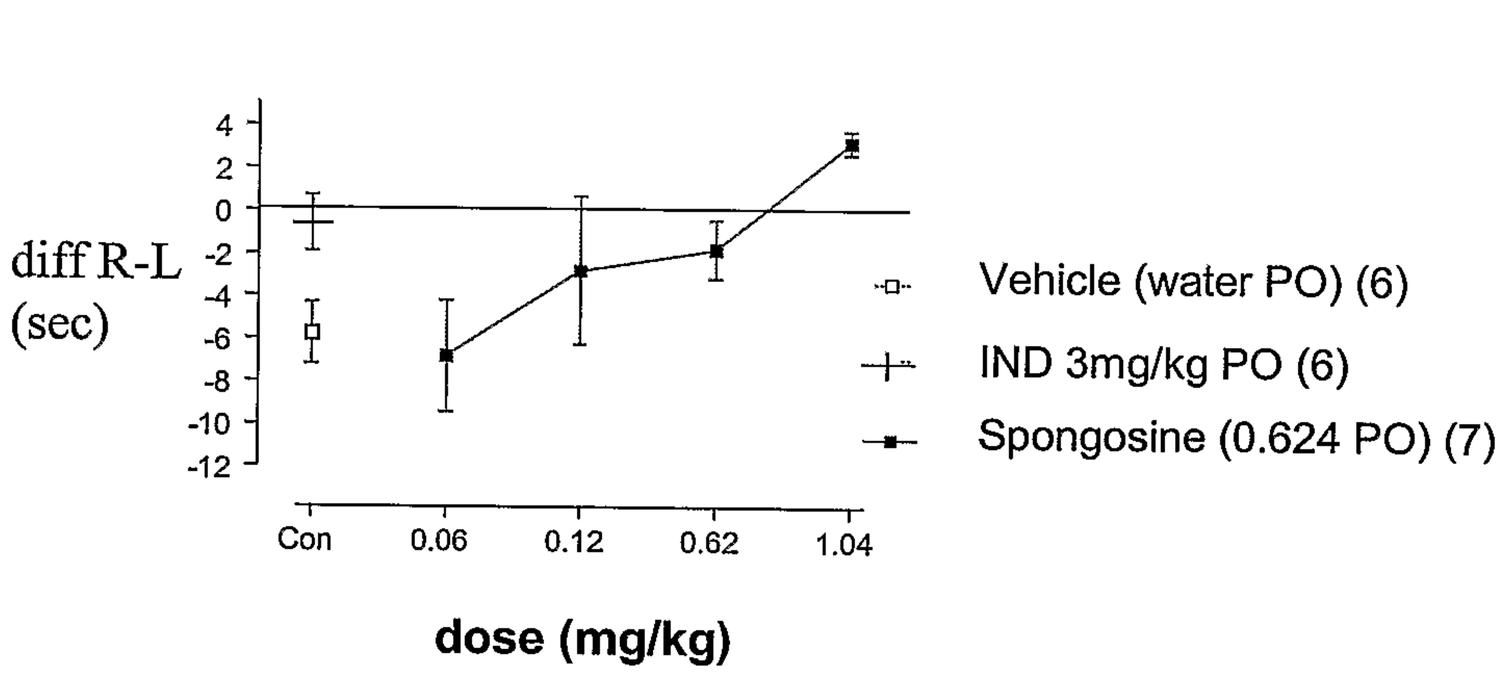
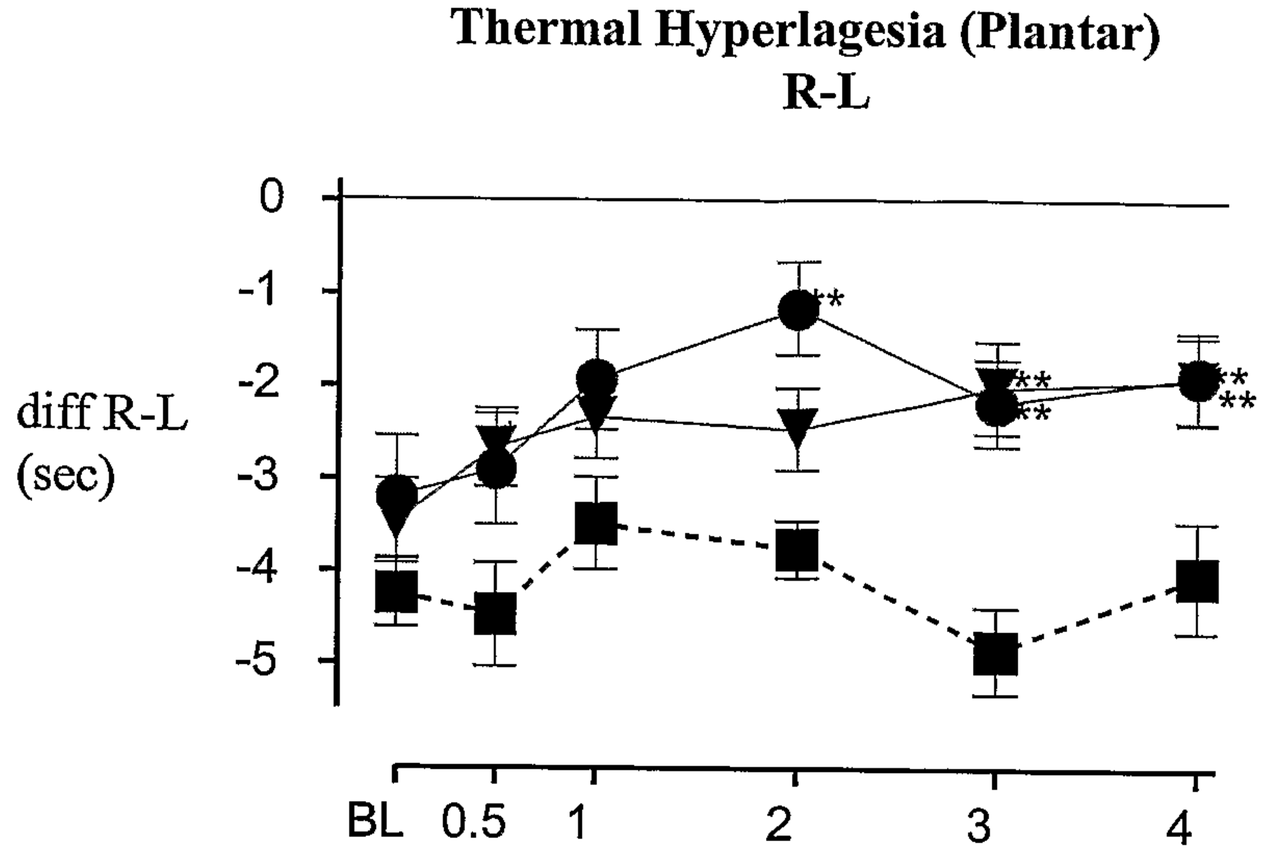

3 hrs post CGN
diff R-L
diff R-L (sec)
4
2
0
-2
-4
-6
-8
-10
-12
Con
0.06
0.12
0.62
1.04
Vehicle (water PO) (6)
IND 3mg/kg PO (6)
Spongosine (0.624 PO) (7)
dose (mg/kg)

Figure 2

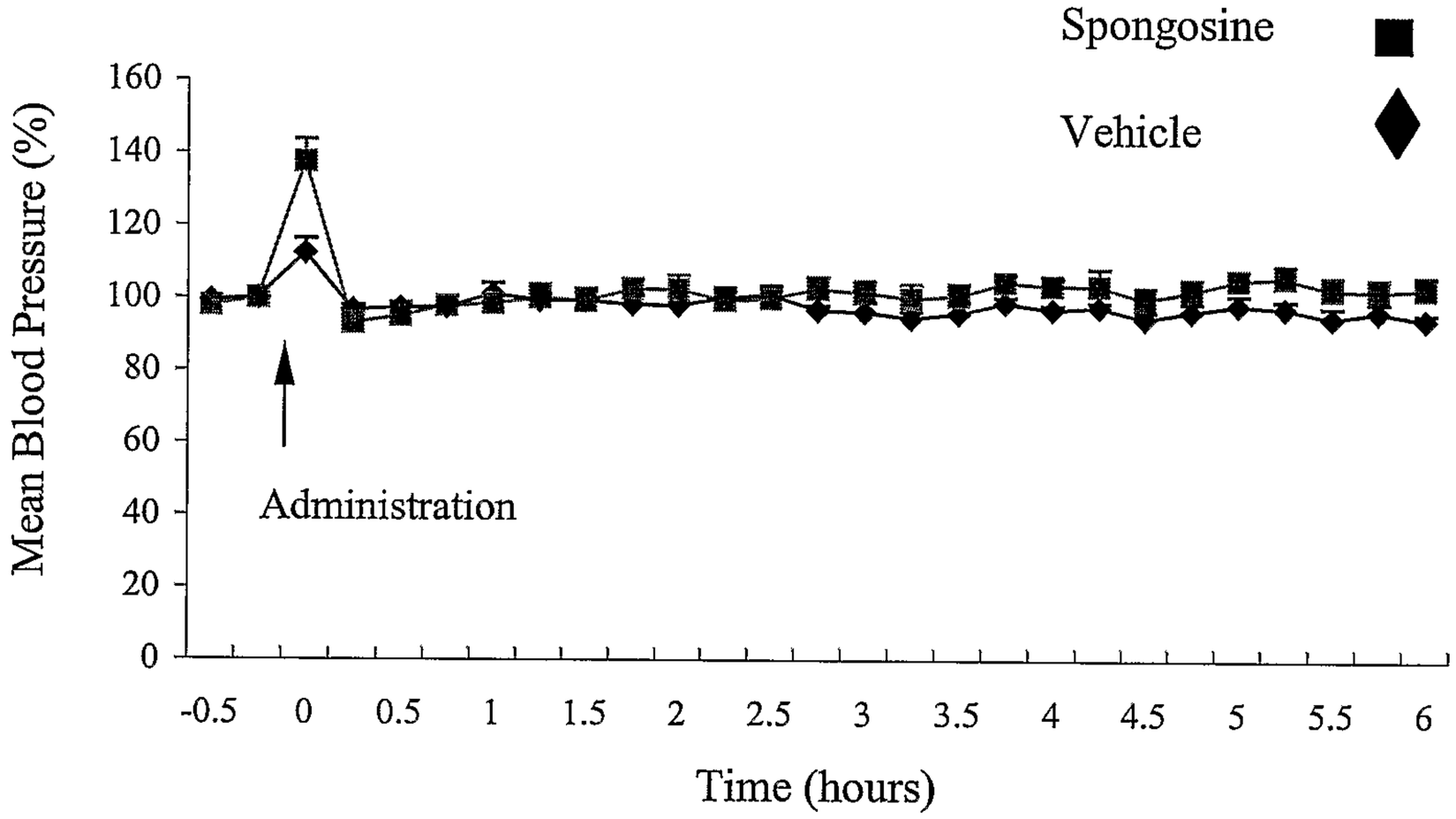


● Spongosine (0.624 mg/kg PO)

▼ CBZ (100mg/kg SC)

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)

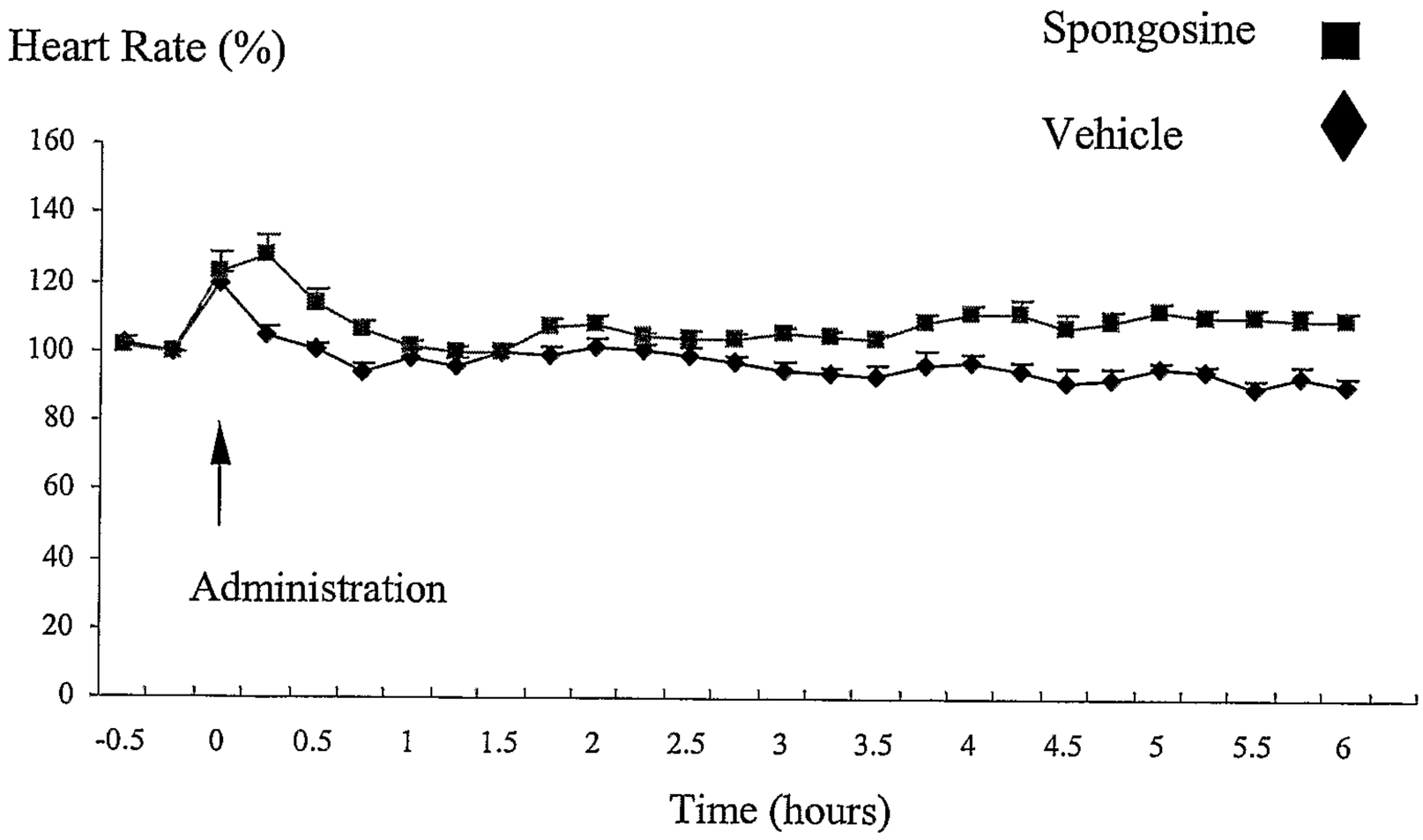
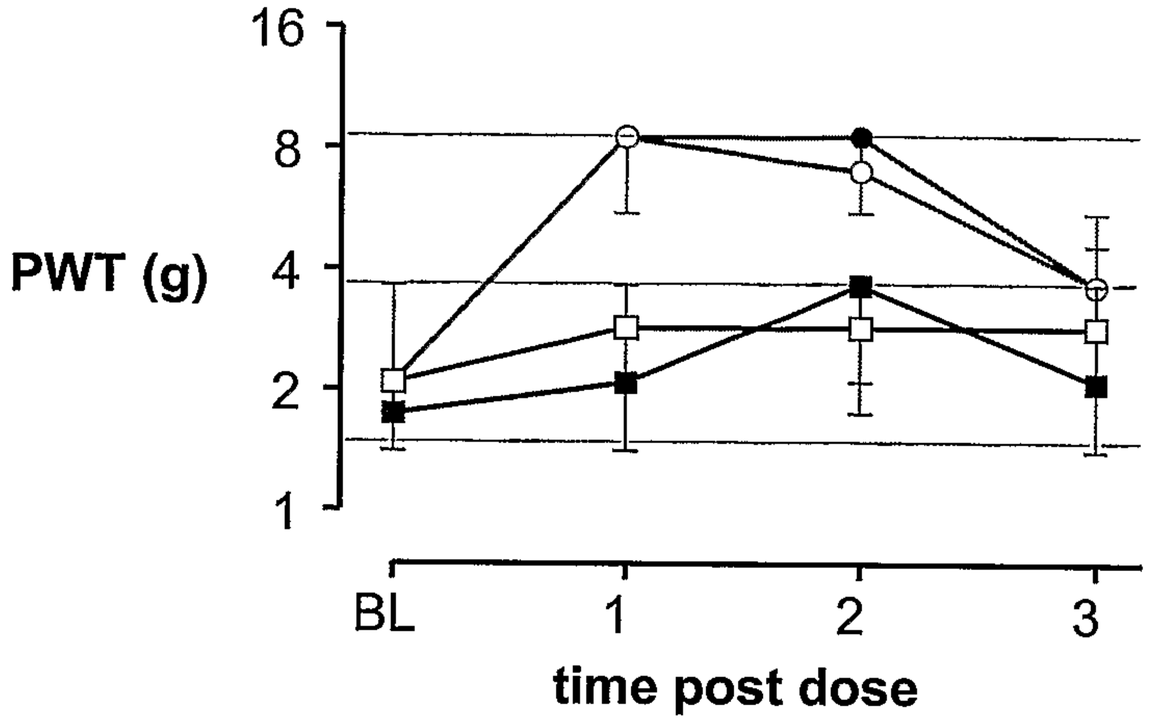

Heart Rate (%)
Spongosine
Vehicle
160
140
120
100
80
60
40
20
0
Administration
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (hours)

Figure 4



Vehicle + Vehicle

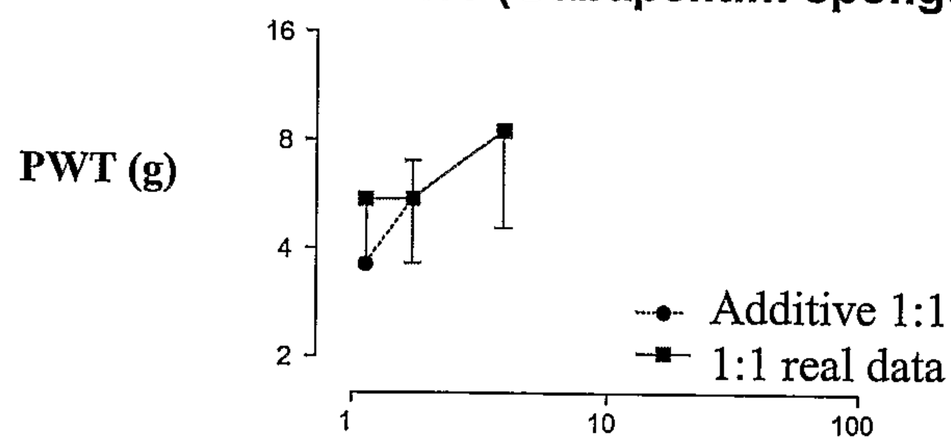
Vehicle + spongosine (1.2 p.o.)

Nalox (1 s.c.) + Vehicle

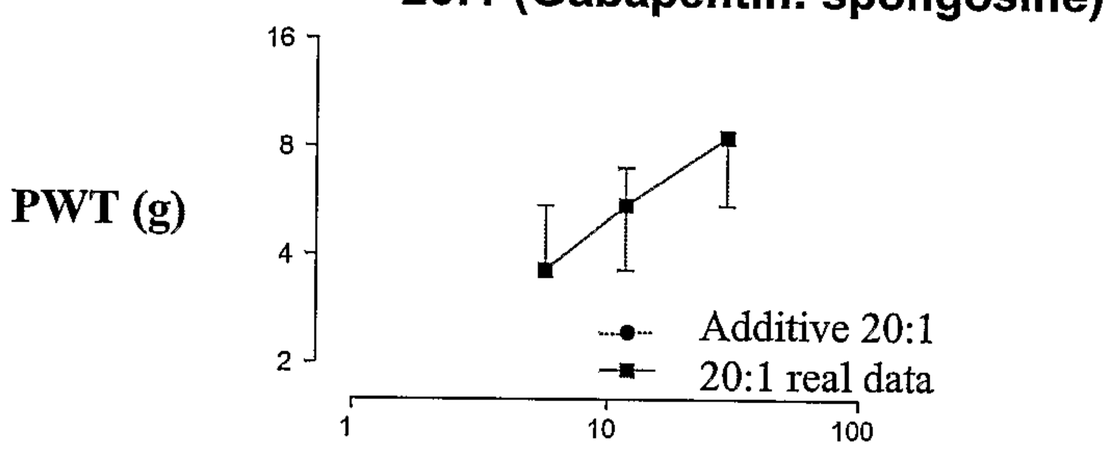
Nalox (1 s.c.) + spongosine (1.2 p.o.)

Figure 5

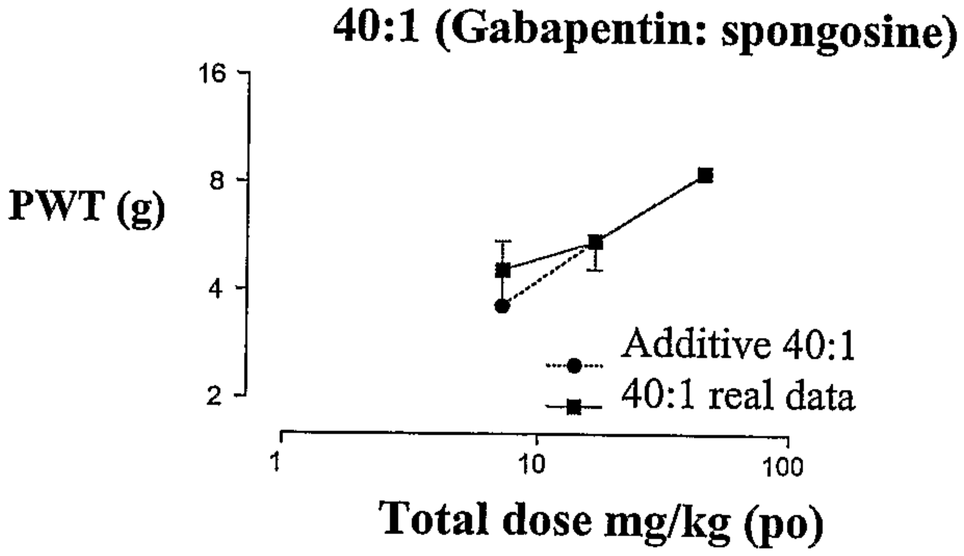
A)


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)