Psychopharmacology (2004) 174:254–259
DOI 10.1007/s00213-003-1739-9

ORIGINAL INVESTIGATION

Magdalena Kwiatkowska · Linda A. Parker · Page Burton · Raphael Mechoulam

A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the *Suncus murinus* (house musk shrew)

Received: 8 August 2003 / Accepted: 25 November 2003 / Published online: 22 January 2004

Abstract *Rationale:* The 5-HT_3 antagonist, ondansetron (OND), and the cannabinoid, Δ^9-tetrahydrocannabinol (Δ^9-THC), have been shown to interfere with emesis; however, their relative and/or combined effectiveness in suppressing vomiting produced by the chemotherapeutic agent, cisplatin, is unknown. *Objectives:* To evaluate the potential of: 1) a broad range of doses of Δ^9-THC and OND to prevent cisplatin-induced vomiting and retching in the *Suncus murinus* (house musk shrew), 2) combined treatment with ineffective individual doses of Δ^9-THC and OND to prevent cisplatin-induced vomiting and retching, 3) the CB_1 receptor antagonist, SR141716, to reverse the antiemetic effects of OND, and 4) cannabidiol (CBD), the principal non-psychoactive component of marijuana, to reverse cisplatin-induced vomiting in the shrew. *Methods:* Shrews were injected with various doses of OND (0.02–6.0 mg/kg), Δ^9-THC (1.25–10 mg/kg) and a combination of ineffective doses of each (0.02 mg/kg OND+1.25 mg/kg Δ^9-THC) prior to being injected with cisplatin (20 mg/kg) which induces vomiting. Shrews were also injected with CBD (5 mg/kg and 40 mg/kg) prior to an injection of cisplatin. *Results:* OND and Δ^9-THC both dose-dependently suppressed cisplatin-induced vomiting and retching. Furthermore, a combined pretreatment of doses of the two drugs that were ineffective alone completely suppressed vomiting and retching. CBD produced a biphasic effect, suppressing vomiting at 5 mg/kg and potentiating it at 40 mg/kg. *Conclusions:* A low dose of the non-intoxicating cannabinoid CBD may be an effective anti-emetic treatment and combined doses of OND and Δ^9-THC that are ineffective alone suppresses cisplatin-induced emetic reactions in shrews.

Keywords Vomiting · Chemotherapy · Serotonin · Retching · Nausea · Anandamide · Δ · -THC · Tetrahydrocannabinol · Cannabidiol · Ondansetron · Cancer

M. Kwiatkowska · L. A. Parker (✉) · P. Burton
Department of Psychology,
Wilfrid Laurier University,
Waterloo, Ontario, N2L 3C5, Canada
e-mail: lparker@wlu.ca
Tel.: +1-519-8840710
Fax: +1-519-7467605

R. Mechoulam
Department of Medicinal Chemistry and Natural Products,
Faculty of Medicine,
The Hebrew University of Jerusalem,
Jerusalem, Israel

Introduction

The pharmacological control of nausea and vomiting produced by chemotherapy treatment, such as cisplatin, is essential to ensure adherence to the therapeutic regime. The most typically employed antiemetic treatments are those that act as antagonists of the serotonin subtype-3 (5-HT_3) receptor. Indeed, 5-HT_3 antagonists also suppress vomiting in a variety of species, including cats (Rudd et al. 2000), ferrets (Ozaki and Sukamoto 1999) and shrews (Torii et al. 1991; Ito et al. 1995; Andrews et al. 1996, 2000; Matsuki et al. 1997; Darmani 1998). In human clinical trials, although 5-HT_3 antagonists are effective in treating the acute phase of chemotherapy-induced emesis, considerable evidence indicates that the 5-HT_3 antagonists are relatively ineffective in attenuating the delayed phase of chemotherapy induced emesis (Fabi et al. 2003) as well as anticipatory nausea and vomiting upon re-exposure to the cues associated with treatment (Tyc et al. 1997; Morrow et al. 1998).

The results of clinical trials also demonstrated that cannabinoids, including Δ^9-tetrahydrocannabinol (Δ^9-THC), can prevent not only acute nausea and vomiting in chemotherapy patients (for recent review, see Tramer et al. 2001), but also the delayed phase (Abrahamov et al. 1995). Experimental evidence with animals confirms the anti-emetic potential of cannabinoids in cats (McCarthy and Borison 1981), ferrets (Simoneau et al. 2001; Van Sickle et al. 2001), pigeons (Feigenbaum et al. 1989), and shrews (Darmani, 1998, 2001a, 2001b, 2001c; Parker et

al. 2004). The anti-emetic effect of cannabinoids may be mediated by action at specific cannabinoid (CB_1 and CB_2) receptors (Darmani 2001b, 2001c; van Sickle et al. 2001). Cannabinoids have also been reported to be more effective than other antiemetics in suppressing anticipatory nausea and vomiting associated with chemotherapy (Weddington et al. 1982; Gurley et al. 1998). In an animal model of anticipatory nausea and vomiting, Parker and Kemp (2001) reported that Δ^9-THC suppressed the expression of conditioned retching in the *Suncus murinus* (house musk shrew) elicited by an environment that had previously been associated with lithium-induced vomiting. This suppressed retching was apparent at doses that did not suppress general activity level.

The cannabinoid and serotonin systems have been shown to interact in the emetic systems of the brain (Himmi et al. 1996) and the gut (Fan 1995). In the brainstem, both CB_1 and 5-HT_3 receptors have been found in the solitary tract nucleus, an important structure in the emetic pathway (Himmi et al. 1996, 1998). Furthermore, most Δ^9-THC-sensitive neurons in this structure showed opposite responses to Δ^9-THC and the 5-HT_3 receptor agonist, 1-phenylbiguanide, which induces vomiting in ferrets (Higgins et al. 1989). Using the patch-clamp technique, Fan (1995) reported that cannabinoid receptor agonists inhibit the inward current induced by 5-HT_3 receptors in the cell bodies of vagal afferent neurons. It has also been shown that the pharmacological activity of the endocannabinoid, anandamide, may be partially mediated through serotonin receptors (Kimura et al. 1998). Finally, Hermann et al. (2002) reported extensive CB_1 coexpression with 5-HT_3 receptors in several cortical regions.

Since serotonin and cannabinoid systems have been shown to interact in the brain and the gut, it is possible that Δ^9-THC and ondansetron (5-HT_3 receptor antagonist, OND) may have a synergistic or additive effect on the control of vomiting and retching. Recently, Soderpalm et al. (2001) report that ondansetron may be more effective than smoked marijuana in the control of nausea, but they are both effective in the control of vomiting produced by syrup of ipecac in humans; however, only limited doses were evaluated. There are no experimental studies that directly compare the potential of cannabinoids and 5-HT_3 antagonists to suppress vomiting produced by cisplatin. Furthermore, the effect of co-administration of a cannabinoid and a 5-HT_3 receptor antagonist on emesis has not been investigated. Therefore, the following experiments were designed to evaluate the relative efficacy of Δ^9-THC and OND as well as their combined efficacy in preventing cisplatin-induced vomiting and retching in the *Suncus murinus*. Additionally, the potential of the CB_1 receptor antagonist, SR141716, to reverse OND-induced inhibition of vomiting was evaluated. Although SR has been reported to produce vomiting in shrews on its own at doses of 5 mg/kg or greater (Darmani 2001a), it did not produce vomiting at the 2.5 mg/kg dose used here (Darmani 2001a; Parker et al. 2004). Finally, the potential of cannabidiol (CBD), the principal non-intoxicating cannabinoid found in marijuana, to prevent cisplatin-induced emesis was evaluated. Parker et al. (in press) observed a suppression of lithium chloride-induced vomiting in the *Suncus murinus* (house musk shrew) not only by Δ^9-THC pretreatment, but also by pretreatment with CBD. CBD produced a biphasic effect: Lower doses (5 and 10 mg/kg) suppressed lithium-induced vomiting while higher doses (24 and 40 mg/kg) potentiated lithium-induced vomiting. The CB_1 receptor antagonist, SR-141617A (SR), reversed the effect of Δ^9-THC, but not the effect of CBD on lithium-induced vomiting, suggesting that the effect of CBD was not CB_1 receptor mediated.

Materials and methods

Subjects

The subjects were 63 male (30–52 g) and 64 female (21–31 g) *Suncus murinus* bred and raised at the Wilfrid Laurier University colony. Each group consisted of approximately half males and half females. Because of the toxicity of cisplatin, the animals were euthanized immediately following each trial. The animals were housed individually in polyethylene cages (25×16×12 cm) with pine wood shavings and shredded paper towels for nesting material. The colony room was maintained at 22±1°C at 14:10 h light-dark schedule (light on at 0700 hours). The shrews had free access to dry cat food plus mink diet and tap water. Normal HCl (1 ml/l) was added to the drinking water to maintain a pH of 5.5 in order to reduce the risk of gastrointestinal disease. All procedures were approved by the Wilfrid Laurier University Animal Care Committee, in accordance with the regulations of the Canadian Council on Animal Care.

Drugs

All pretreatment drugs were prepared in a solution of 1 ml ethanol/1 ml emulsifier (Sigma)/18 ml saline. Δ^9-THC was prepared as a 1 mg/ml solution of the vehicle, and was administered in volumes of 1.25, 2.5, 5 and 10 ml/kg. OND was prepared as a 1 mg/ml solution and was administered in volumes of 0.6, 1.5, 3 and 6 ml/kg. For lower doses, OND was prepared as 0.02 mg/ml and 0.2 mg/ml solutions and administered at a volume of 1 ml/kg. SR141716 was prepared as a 1 mg/ml solution and administered in a volume of 2.5 ml/kg. CBD was prepared as a 1 mg/ml solution and was administered at volumes of 5 ml/kg and 40 ml/kg. Vehicle was administered at volumes of 10 ml/kg when compared with THC and OND and at a volume of 40 ml/kg when compared with CBD. The treatment drug was cisplatin prepared as a 1 mg/ml solution of saline and administered in a volume of 20 ml/kg. All drugs were injected intraperitoneally.

Apparatus

The clear Plexiglas observation chambers (22.5×26×20 cm) were illuminated by four 60 W lights suspended from the chamber's floor. A mirror was mounted at a 45° angle beneath the chamber floor, which allowed for the observation of the ventral surface for the recording of activity and behaviours of the animal.

Procedure

Each animal was offered four mealworms (*Tenebrio* sp.) in its home cage 15 min prior to pretreatment injections. The shrews received two pretreatment injections 30 min prior to receiving an

injection of cisplatin (20 mg/kg) or saline (20 ml/kg), and 15 min later were placed in the observation chamber for 60 min. The test chambers were thoroughly cleaned between trials.

The groups differed on the basis of the pretreatment injections. The Δ^9-THC groups received an injection of 1.25 (n=6), 2.5 (n=4), 5.0 (n=4), or 10.0 (n=4) mg/kg Δ^9-THC immediately prior to receiving an injection of vehicle (5 ml/kg). The OND groups received an injection of 0.02 (n=6), 0.2 (n=6), 0.6 (n=8), 1.5 (n=8), 3.0 (n=4), or 6.0 (n=4) mg/kg of OND immediately prior to receiving an injection of vehicle (5 ml/kg). The vehicle group (n=8) received two injections of vehicle (5 ml/kg each). The OND+Δ^9-THC group (n=7) received an injection of 1.25 mg/kg Δ^9-THC immediately prior to receiving an injection of 0.02 mg/kg OND. The SR-OND groups received an injection of 2.5 mg/kg SR141716 immediately prior to an injection of vehicle (5 ml/kg; n=4), 0.2 mg/kg (n=6), 0.6 mg/kg (n=4) or 1.5 mg/kg (n=4) OND.

Additionally, the potential of CBD to suppress cisplatin-induced vomiting was evaluated. The CBD groups were treated as the Δ^9-THC and OND groups except that they received a single pretreatment injection 30 min prior to receiving an injection of 20 mg/kg cisplatin or 20 ml/kg saline. The groups included: vehicle (40 ml/kg)-saline (n=7), 40 mg/kg CBD-saline (n=7), vehicle (40 ml/kg)-cisplatin (n=8), 5 mg/kg CBD-cisplatin (n=6), 40 mg/kg CBD-cisplatin (n=6).

During the 60-min observation period, an observer recorded the frequency of retching and vomiting as well as the latency to the first episode of retching or vomiting. Retching was characterized by abdominal contractions and wide opening of the mouth, without the expulsion of gastrointestinal material. Vomiting was defined as abdominal contractions and expulsion of gastrointestinal substance.

Data analysis

The dose-response data for OND and THC alone and were each evaluated by a one-way analysis of variance (ANOVA) and subsequent least significant difference (LSD) pairwise comparison tests. The vehicle group (10 ml/kg) was the same for both analyses. Subthreshold doses of OND and THC were then combined and the data were compared with that for each of the doses separately in a one-way ANOVA and subsequent LSD pairwise comparison tests. The ability of SR 141716 to reverse the effects of OND was evaluated in a 2 (pretreatment-vehicle or SR) by 4 (dose of OND [0.0, 0.2, 0.6, 1.5 mg/kg]) ANOVA. Finally, the ability of CBD to suppress cisplatin induced vomiting and retching was evaluated as a one-way ANOVA with LSD pairwise comparison tests.

Results

Ondansetron

The dose-response data revealed that OND pretreatment suppressed cisplatin-induced vomiting and retching. The upper section of Fig. 1 depicts the mean number (±SEM) of vomiting episodes among groups pretreated with various doses of OND. The ANOVA revealed that the groups significantly differed [$F(6,37)=7.5$; $P<0.01$]. Least significant difference (LSD) pairwise comparison tests revealed group vehicle (0.0 mg/kg OND) and 0.02 mg/kg OND vomited more than any other OND pretreated group ($P<0.05$). The middle section of Fig. 1 presents the mean (±SEM) latency (s) of first vomiting episode the groups pretreated with OND; there was a significant dose effect [$F(6,37)=12.7$; $P<0.01$]. As was evident with vomiting frequency, pairwise comparisons tests showed that groups vehicle and 0.02 mg/kg OND displayed shorter vomiting latency then any other OND group ($P<0.05$). The bottom portion of Fig. 1 shows the mean number of retches displayed by the OND groups. There was a significant dose effect in the number of retches displayed during the observation session [$F(6,37)=5.7$; $P<0.01$]. LSD pairwise comparison tests indicated that groups vehicle and 0.02 mg/kg displayed more retching than all groups except group 6.0 mg/kg ($P<0.05$). Furthermore, group 6.0 mg/kg displayed more retching than groups 0.2 and 1.5 mg/kg ($P<0.05$). Therefore, as measured by retching, OND produced a bell shaped dose-response curve, with the high dose (6.0 mg/kg) no longer reversing the cisplatin-induced retching.

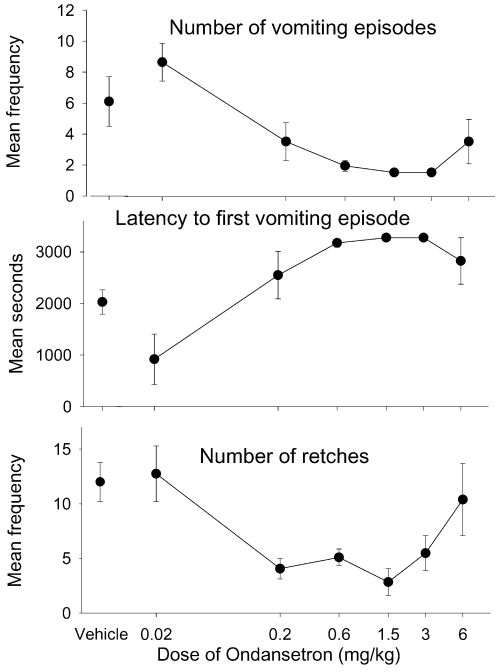

Fig. 1 Effect of OND on cisplatin-induced vomiting and retching. Mean (±SEM) number of vomiting episodes (*top section*), latency to the first vomiting episode (*middle section*) and number of retches (*bottom section*) displayed by shrews pretreated with various doses of OND, 30 min prior to an injection of cisplatin (20 mg/kg)

Δ^9-THC

Δ^9-THC inhibited cisplatin-induced vomiting and retching in a dose-dependent manner. The upper section of Fig. 2 presents the mean (±SEM) number of vomiting episodes displayed by the groups pretreated with Δ^9-THC. The single factor ANOVA revealed a significant effect [$F(4,21)=3.3$; $P<0.05$]. LSD pairwise comparisons tests revealed that the vehicle group vomited more frequently than any other group ($P<0.05$), except group 1.25 Δ^9-THC. Furthermore, 1.25 mg/kg Δ^9-THC group vomited more frequently than group 10 Δ^9-THC ($P<0.05$) and marginally differed from groups 2.5 and 5 Δ^9-THC ($P=0.061$). The middle section of Fig. 2 shows the mean latency (s) to the first vomiting episode for the Δ^9-THC

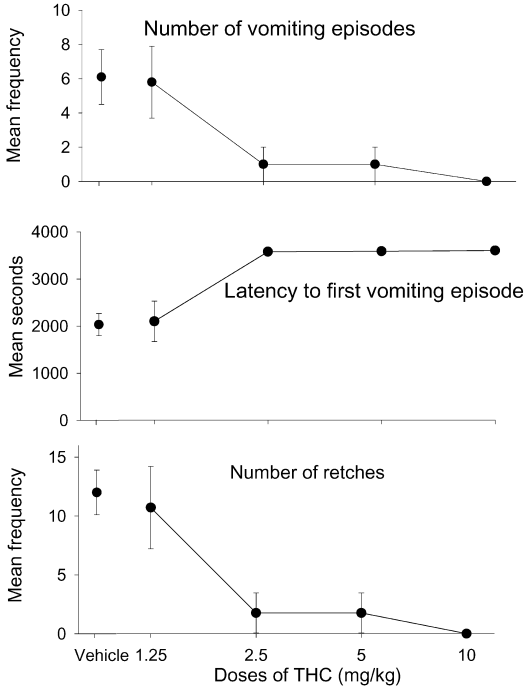

Fig. 2 Effect of Δ^9-THC on cisplatin-induced vomiting and retching. Mean (±SEM) number of vomiting episodes (*top section*), latency to the first vomiting episode (*middle section*) and number of retches (*bottom section*) displayed by shrews pretreated with various doses of Δ^9-THC, 30 min prior to an injection of cisplatin (20 mg/kg)

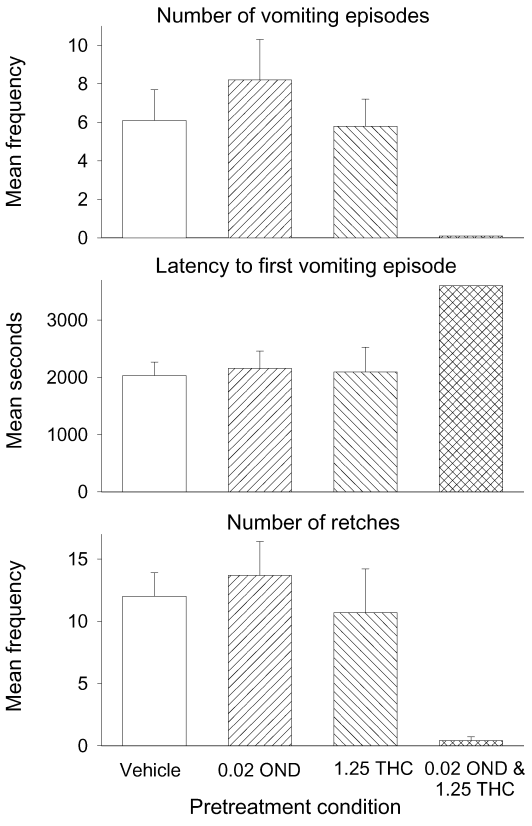

Fig. 3 Effect of a combination of OND+Δ^9-THC on cisplatin-induced vomiting and retching. Mean (±SEM) number of vomiting episodes (*top section*), latency to the first vomiting episode (*middle section*) and number of retches (*bottom section*) displayed by shrews pretreated with ineffective doses of OND (0.02 mg/kg) and Δ^9-THC (1.25 mg/kg) and an effective combined dose of 0.02 mg/kg OND and 1.25 mg/kg Δ^9-THC, 30 min prior to an injection of cisplatin (20 mg/kg)

groups. There was a significant dose effect for latency to first emetic episode [$F(4,21)=9.1$; $P<0.01$]. LSD post hoc comparison tests show that vehicle and 1.25 mg/kg groups showed a shorter latency to the first vomiting episode than all other groups ($P<0.05$). The bottom section of Fig. 2 displays the mean number of retches during the observation session for the Δ^9-THC groups. The groups differed significantly [$F(4,21)=5.8$; $P<0.01$]. Post hoc comparison tests showed that both vehicle and 1.25 mg/kg Δ^9-THC groups retched more frequently than any other group ($P<0.05$).

Ondansetron and Δ^9-THC

The combined pretreatment of OND+Δ^9-THC, at doses ineffective on their own, effectively suppressed cisplatin-induced vomiting and retching. Figure 3 (±SEM) presents the mean number of vomiting episodes, mean latency to first vomiting episode, and mean number of retches elicited by cisplatin in the shrews pretreated with vehicle, 0.02 mg/kg OND, 1.25 mg/kg Δ^9-THC and 0.02 mg/kg OND+1.25 mg/kg Δ^9-THC. The one-way ANOVA revealed that the number of vomiting episodes differed between groups [$F(3,23)=5.7$; $P<0.01$]. LSD post hoc comparison tests show that the combined OND+Δ^9-THC group (0.02 mg/kg OND and 1.25 mg/kg Δ^9-THC) vomited significantly fewer times than all other groups ($P<0.01$). The groups also differed on the basis of the latency to the first vomiting episode [$F(3,23)=8.0$; $P<0.01$]. LSD post hoc comparison tests revealed that group 0.02 OND+1.25 Δ^9-THC displayed a longer latency to the first vomiting episode than all other groups ($P<0.001$). Finally, the number of retches differed between groups [$F(3,23)=7.2$; $P<0.01$]. Post hoc LSD comparison tests show that the combined 0.25 OND+1.25 Δ^9-THC group retched fewer times then all other groups ($P<0.05$).

SR141716 and OND

SR did not reverse the effect on OND on cisplatin-induced vomiting. Figure 4 presents the mean frequency of vomiting episodes displayed by the relevant groups pretreated with vehicle prior to OND (solid bars) and the groups pretreated with SR prior to OND (open bars). There was only a significant effect of OND dose [$F(3,40)=9.90$; $P<0.001$]; shrews pretreated with vehicle

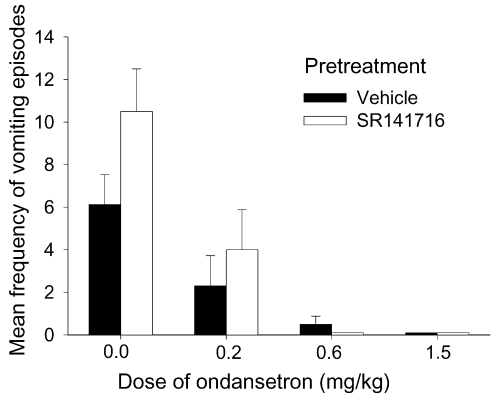

Fig. 4 Mean (±SEM) number of vomiting episodes displayed by shrews pretreated with vehicle (*solid bars*) or 2.5 mg/kg SR141716 and one of various doses of OND, 30 min prior to an injection of cisplatin (20 mg/kg)

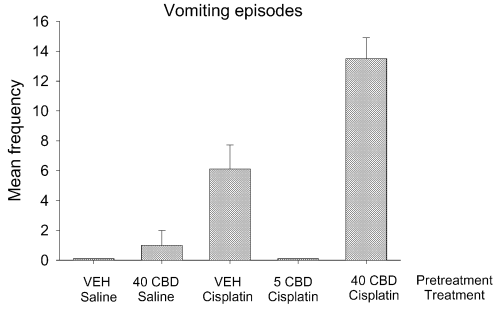

Fig. 5 Mean (±SEM) number of vomiting episodes displayed by shrews pretreated with CBD (5 or 40 mg/kg) or VEH 30 min prior to an injection of cisplatin (20 mg/kg) or saline

displayed significantly more vomiting than any other group ($P<0.01$).

CBD

CBD produced a biphasic effect on cisplatin-induced vomiting; a dose of 5 mg/kg suppressed vomiting, but a dose of 40 mg/kg potentiated vomiting (see Fig. 5). The ANOVA revealed a significant group effect [$F(4,29)= 25.6$; $P<0.001$]; LSD post-hoc comparison tests revealed that group Veh-Cisplatin displayed significantly more vomiting than groups Veh(40)-Saline ($P<0.001$), CBD(40)-Saline ($P<0.01$) or CBD(5)-Cisplatin ($P<0.001$) and significantly less vomiting than group CBD(40)-Cisplatin ($P<0.001$). It is also interesting to note that even when administered at a volume of 40 ml/kg, the vehicle did not produce emetic behaviors on its own.

Discussion

Both ondansetron and Δ^9-THC dose-dependently suppressed cisplatin-induced vomiting in the *Suncus murinus*. Furthermore, doses of the two drugs that were ineffective alone (0.02 mg/kg OND and 1.25 mg/kg Δ^9-THC) produced complete suppression of vomiting and retching when they were combined. This suggests that a combination treatment of lower doses of these agents may be an effective alternative treatment for vomiting in chemotherapy patients.

Since the cannabinoid and serotonin systems have been shown to interact in the solitary tract nucleus (Himmi et al. 1996, 1998) as well as in the gut (Fan 1995) and that CB1 receptors are coexpressed with 5-HT_3 receptors (Herman et al. 2002), we evaluated the potential of the CB1 antagonist SR 141716 to reverse the antiemetic effects of OND. However, we found that the antiemetic effect of ondansetron was not reversed by a dose of SR141716A that reversed the anti-emetic effect of the agonist WIN 55,212 (Darmani 2001c) and Δ^9-THC (Parker et al. 2004), suggesting that the effect of OND is not CB_1 receptor mediated. It is not known whether the combined effect of THC and OND is mediated by a synergistic action on a single system or by an additive action of their effects on several systems.

Interestingly, not only did the intoxicating component of marijuana, Δ^9- THC, reduce vomiting, but also the non-intoxicating component, CBD. As we have previously demonstrated with lithium-induced vomiting, CBD produced a biphasic effect with a low dose (5 mg/kg) suppressing cisplatin-induced vomiting and a high dose (40 mg/kg) potentiating cisplatin-induced vomiting. Since CBD does not bind with known CB receptors, this antiemetic effect does not appear to be mediated by CB_1 or CB_2 activity.

This report is the first direct comparison of the effectiveness of combined doses of cannabinoids and serotonin antagonists in the control of acute vomiting and retching. Our results suggest that a combination of subthreshold doses of these agents can prevent acute vomiting and may be of use in clinical treatment. Additionally, the non-intoxicating component of cannabis, CBD, also prevented acute cisplatin-induced vomiting in the shrew. Our results, however, do not address the effects of these agents (or their combination) on phases of nausea and vomiting that are resistant to treatment with serotonin antagonists: a) anticipatory nausea and vomiting experienced during re-exposure to chemotherapy related cues, and b) the delayed phase of nausea and vomiting produced by chemotherapy treatment (Tyc et al. 1997; Morrow et al. 1998; Fabi et al. 2003). It is conceivable that these phases of nausea and vomiting may be more effectively treated by THC or CBD than OND. Indeed, in an animal model of anticipatory nausea and vomiting, Parker and Kemp (2001) demonstrated that THC suppressed anticipatory retching in the *Suncus murinus*. It is not known if OND would produce a similar effect. Animal models for delayed nausea and vomiting are difficult to develop because of the individual variability inherent in the onset of bouts of vomiting and retching that follow the acute phase. Future experiments will

attempt to shed light on better treatment regimes for these phases of chemotherapy-induced nausea and vomiting.

Acknowledgements The research was supported by the research grant from the Canadian Institute of Health Research (CIHR) to LP and from the Israel Science Foundation and the National Institute on Drug Abuse to R.M. We thank Marion Corrick for breeding and excellent care of the shrews.

References

Abrahamov A, Abrahamov A, Mechoulam R (1995) An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci 56:2097–2102

Andrews P, Torii Y, Soit H, Matsuki N (1996) The pharmacology of the emetic response to upper gastrointestinal tract stimulation in *Suncus murinus*. Eur J Pharmacol 307:305–313

Andrews P, Okada F, Woods A, Hagiwara H, Kakaimoto S, Toyoda M, Matsuki N (2000) The emetic and anti-emetic effect of the capsaicin analogue resiniferatoxin in *Suncus murinus*, the house musk shrews. Brit J Pharm 130:1247–1254

Darmani NA (1998) Serotonin 5-HT_3 receptor antagonists prevent cisplatin-induced emesis in *Cryptotis parva*: a new experimental model of emesis. J Neural Transm 105:1143–1154

Darmani NA (2001a) Delta-9-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB_1 receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacology 24:198–203

Darmani NA (2001b) Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-insuced emesis and indices of motor function via cannabinoid CB_1 receptor in the least shrew. Pharmacol Biochem Behav 69:239–249

Darmani NA (2001c) The cannabinoid CB_1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212–2. Eur J Pharmacol 430:49–58

Fabi A, Barduagni M, Lauro S, Portalone L, Mauri M, Marinis F, Narduzzi C, Tonini G, Giampaolo M, Pacetti U, Paoloni F, Cognetti F (2003) Is delayed chemotherapy-induced emesis well managed in oncological clinical practice? Support Care Cancer 11:156–161

Fan P (1995) Cannabinoid agonists inhibit the activation of 5-HT_3 receptors in rat nodose ganglion neurons. J Neurophysiol 73:907–910

Feigenbaum JJ, Richmond S A, Weissman Y, Mechoulam R (1989) Inhibition of cisplatin-induced emesis in the pigeon by a non-psychotropic synthetic cannabinoid. Eur J Pharmacol 169:159–165

Gurley RJ, Aranow R, Katz M. (1998) Medicinal marijuana: a review. J Psychoact Drugs 30:37–147

Hermann H, Marsicano G, Lutz B. (2002) Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience 109:541–460

Higgins GA., Kilpatrick GJ., Bunce KT, Jones BJ, Tyers MB (1989) 5-HT_3 receptor antagonists injected into the area postrema inhibit cisplatin-induce emesis in the ferret. Br J Pharmacol 97:247–255

Himmi T, Dallaportam M, Perrinm J, Orsini J (1996) Neuronal responses to delta-9-tetrahydrocannabinol in the solitary tract nucleus. Eur J Pharmacol 312:273–279

Himmi T, Perrin J, Ouazzani T, Orsini J (1998) Neuronal responses to cannabinoid receptor ligands in the solitary tract nucleus. Eur J Pharmacol 359:49–54

Ito C, Isobe Y, Kijima H, Kiuchi Y, Ohtsuki H, Kawamura R, Tsuchida, K, Higuchi S (1995) The anti-emetic activity of GK-128 in *Suncus murinus*. Eur J Pharmacol 285:37–43

Kimura T, Ohta T, Watanabe K, Yoshimura H, Yamamoto I (1998) Anadamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5-HT) receptor. Biol Pharmaceut Bull 21:224–226

Matsuki N, Wnag C, Okada F, Tamura M, Ikegaya Y, Lin S, Hsu Y, Chaung L, Chen S, Saito H (1997) Male/female differences in drug-induced emesis and motion sickness in *Suncus murinus*. Pharmacol Biochem Behav 57:721–725

McCarthy LE, Borison HL (1981) Antiemetic activity of N-methyllevonantradol and nabilone in cisplatin-treated cats. J Clin Pharamcol 21:30S-37S

Morrow GR, Roscoe JA, Kirshner JJ, Hynes HE, Rosenbluth RJ (1998) Anticipatory nausea and vomiting in the era of 5-HT_3 antiemetics. Support Care Cancer 6:244–247

Ozaki A, Sukamoto T (1999) Improvement of cisplatin-induced emesis and delayed gastric emptying by KB-R6933, a novel 5-HT_3 receptor antagonist. Gen Pharmacol 33:283–288

Parker LA, Kemp SWP (2001) Tetrahydrocannabinol (THC) interferes with conditioned retching in *Suncus murinus*: an animal model of anticipatory nausea and vomiting (ANV). Neuroreport 12:749–751

Parker LA, Kwiatkowska M, Burton P, Mechoulam R (2004) Effect of cannabinoids on lithium-induced vomiting in the *Suncus murinus* (house musk shrew). Psychopharmacology 171:156–161

Rudd J, Tse J, Wai M (2000) Cisplatin-induced emesis in the cat: effect of granisetron and dexamethasone. Eur J Pharmacol 391:145–150

Simoneau II, Hamza MS, Mata HP, Siegel EM, Vanderah TW, Porreca F, Makriyannis A, Malan Jr PT (2001) The cannabinoid agonist WIN55, 212-2 suppresses opioid-induced emesis in ferrets. Anesthesiology 94:882–887

Soderpalm A, Schuster A, DeWit H (2001) Antiemetic efficacy of smoked marijuana: subjective and behavioral effects on nausea induced by syrup ipecac. Pharmacol Biochem Behav 69:343–350

Torii Y, Saito H, Matsuki N (1991) Selective blockade of cytotoxic drug-induced emesis by 5-HT_3 receptor antagonists in *Suncus murinus*. Jpn J Pharmacol 55:107–113

Tramer MR, Carroll D, Campbell FA, Reyonold DJM, Moore RA, McQuay HJ (2001) Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 323:1–8

Tyc VL, Mulhern Rk, Barclay DR, Smith BF, Bieberich AA (1997) Variables associated with anticipatory nausea and vomiting in pediatric cancer patients receiving ondansetron antiemetic therapy. J Pediatr Psychol 22:45–58

Van Sickle MD, Oland LD, Ho W., Hillard, CJ, Mackie K, Davison JS, Sharkey KA (2001) Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology 121:767–774

Weddington WW, Miller NJ, Sweet DL (1982) Anticipatory nausea and vomiting associated with cancer chemotherapy. N Engl J Med 307:825–826