Ganglioside GM1 (Porcine) Ameliorates Paclitaxel-Induced Neuropathy in Rats

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Background: *Paclitaxel, an anti-neoplastic agent effective against several solid tumors, has several side effects including peripheral neuropathy. So far, there are no effective treatments for this complication. Monosialic acid ganglioside (GM1) has been shown to protect neurons against injuries and degeneration. However, its efficacy in the treatment of paclitaxel-induced neuropathy has not been verified.*
Objective: *To evaluate the effect of porcine GM1 on neurophysiological abnormalities in rats receiving paclitaxel.*
Material and Method: *Fifty-four Wistar rats were divided into control, vehicle for paclitaxel (Cremophor EL), paclitaxel, and paclitaxel + GM1 groups. Paclitaxel 16 mg/kg/week for five consecutive weeks was given intraperitoneally. Treatment with 30 mg/kg 5 days per week of GM1 was started 3 days prior to the first dose and continued until 3 days after the last dose of paclitaxel. Tail and hind paw thermal thresholds including tail motor nerve conduction velocity (MNCV) were measured prior to and after the start of treatments. Histopathology of the sciatic nerve was also examined.*
Results: *Paclitaxel alone induced thermal hypoalgesia and reduced tail MNCV. Less severe abnormalities were also found with the vehicle. GM1 appeared to prevent the development of hypoalgesia and ameliorated the decreased MNCV without any evidence of Guillain-Barre Syndrome. Mild endoneurial edema and axonal degeneration in the sciatic nerve sections were seen in paclitaxel treated rats. Microtubule accumulation and activated Schwann cell were also presented in the paclitaxel treated groups.*
Conclusion: *These data suggest that porcine GM1 may be useful in the prevention and treatment of paclitaxel-induced neuropathy. However, the adverse effect of Cremophor EL should be of concern.*

Keywords: *Paclitaxel, Neuropathy, Ganglioside, GM1*

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Paclitaxel has been widely used as a chemotherapeutic drug against a variety of solid tumors including breast cancer[1], ovarian cancer[2], lung cancer[3], and cancers of the head and neck[4]. This anti-neoplastic property is achieved by stabilization of microtubule dynamics, thereby leading to mitotic arrest and blocking of the proliferation of tumor cells[5,6]. Despite these benefits, paclitaxel treatment is associated with several major side effects including bone marrow suppression, hypersensitivity reactions, and peripheral neuropathy[7-9].

Paclitaxel-induced neurotoxicity is dose-dependent and most commonly presents as distal symmetrical, predominantly sensory polyneuropathy. Symptoms in patients may range from numbness, paresthesia to allodynia[10-12]. Electrophysiological studies have shown impaired sensory nerve conduction after paclitaxel treatment[13]. In contrast, motor

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involvement is more subtle and may be evident later in the course of neuropathy[14]. Similarly, animals receiving paclitaxel show thermal hypo/hyperalgesia, mechanical allodynia including decreased motor and sensory nerve conduction velocities[15-18]. Currently, there are no effective treatments for this debilitating side effect.

Gangliosides belong to a family of sialic acid-containing glycosphingolipids. Monosialic acid ganglioside, GM1, has pleiotropic neurotrophic actions on several groups of neurons[19]. GM1 can rescue neurons from apoptosis[20,21] and promote recovery of spinal motor neurons after axotomy[22]. In addition, GM1 has been shown to correct neuronal abnormalities in experimental diabetic neuropathy[23-24]. The authors' previous study has shown that ganglioside mixture extracted from bovine brain can prevent thermal hypoalgesia and impaired sensory nerve conduction in the paclitaxel-treated rats[25]. However, there is concern about transmission of bovine neurological infectious diseases, especially bovine spongiform enchephalopathy (BSE). As a result, gangliosides prepared from porcine brain are favored but their efficacy on paclitaxel-induced neuropathy has not been tested. The aim of the present study was to investigate the effect of porcine GM1 on neurophysiological abnormalities observed in this toxic neuropathy.

Material and Method

Animals

Fifty-four male Wistar rats (200-250 g, National Laboratory Animal Center, Mahidol University, Thailand) were housed in aluminum cages on a 12 h light-dark cycle with free access to food and water. The room temperature was maintained at 25 $\pm$ 2°C. This experiment was approved by the institutional ethics committee and was carried out in accordance with the guidelines of the National Research Council of Thailand. All efforts were done to minimize pain or discomfort.

Drug administration

The rats were randomly divided into four groups: control (C, n = 13), vehicle (V, n = 13), paclitaxel only (P, n = 14), and co-treatment of paclitaxel and GM1 (PG, n = 14). Paclitaxel (Taxol®, Bristol-Myers Squibb, in Cremophor EL® and ethanol) was diluted with normal saline to a final concentration of 1.2 mg/ml just before use and given to the P and PG groups 16 mg/kg intraperitoneally (i.p.) once a week for five consecutive weeks. Thus, the accumulative dose of paclitaxel was 80 mg/kg/rat. This treatment protocol has been previously shown to induce neuropathy in the rats[15].

Ganglioside GM1 (TRB Pharma s.a., Argentina) was also administered 30 mg/kg/day i.p. to the PG group. The previous study has demonstrated that this dose regimen of GM1 was beneficial to motoneurons in spinal cord after axotomy[22]. The GM1 treatment was started 3 days prior to the first injection of paclitaxel and, then, 5 days (Monday-Friday) per week for 5 consecutive weeks. This was continued until 3 days after the last injection of paclitaxel. A mixture of Cremophor EL and ethanol (1:1 v/v) as a vehicle was administered to the V group in the equivalent volume using the same schedule as in the P group. No treatment was given to the C group.

Assessment of general toxicity

Baseline body weight was recorded for each animal prior to the first injection of paclitaxel and once a week thereafter until the last week of the present study (the week after the fifth injection). In addition, the rats were examined daily to detect any morbidity such as limb weakness or piloerection and mortality.

Hind paw thermal threshold

The hot plate analgesia meter (Harvard Apparatus, UK) was used to measure the hind paw thermal threshold. Before the first injection of paclitaxel, the rats were allowed to familiarize with the test procedure and apparatus. Baseline values were obtained before the start of any treatment and, then, once a week just before each paclitaxel injection until after the last injection. During the test, temperature was maintained at 55°C. The rat was placed on the hot plate within a transparent plastic cage and a timer was started. When the rat licked its hind paw on either side, the timer stopped and the animal was removed from the apparatus. Elapsed time was recorded as latency. A cut-off duration of 30 s was used to avoid skin injury. The test was repeated at least four times with an interval of 5 min and, then, an average latency was calculated for each rat.

Tail thermal threshold

The tail-flick test was employed to determine the tail thermal threshold. The rat was placed on the tail-flick analgesic meter (Ugo Basile, Italy) with its tail on the photocell. When the infrared lamp was activated, a timer was automatically started and duration monitored until the rat flicked its tail out of the beam. A cut-off time of 10 s was used to avoid skin burn. The test was

repeated at least four times for each rat with a 5 min interval. An average latency was obtained. This test was done prior to the first dose, weekly just before each dose and after the last dose of paclitaxel.

Electrophysiological study

Tail motor nerve conduction velocity (MNCV) was determined prior to the start of any treatment as baseline, after the second injection of paclitaxel and after the end of treatment. The rat was anesthetized using halothane. Rectal temperature was maintained at 37 $\pm$ 0.3°C using a heating pad and digital rectal thermometer. A pair of recording ring electrodes was placed at approximately 5 cm from the tail base. Then, a bipolar stimulating surface electrode was placed at approximately 2 cm proximal to the recording electrodes. A ground electrode was placed between the stimulating and recording electrodes. All these electrodes were connected to the oscilloscope (Neurostar, Oxford Instrument). The tail nerve was stimulated with a supramaximal stimulus and a latency was measured from the start to the top of the positive peak of compound muscle action potential. An average latency, designated L1, was derived from at least five stimulations. Subsequently, the stimulating electrode was moved exactly 20 mm more proximally. The average latency, L2, was determined. The tail MNCV was calculated by dividing the distance of 20 mm by the latency difference (L2-L1).

Histopathological study

At the end of the experiment, the sciatic nerve was collected and processed for light and electron microscopic examination.

Statistical analysis

Data were analyzed using SPSS for Windows version 10. ANOVA followed by Tukey's post hoc test was used to compare means $\pm$ standard errors of mean (SEM) among different experimental groups. However, if the distribution of data was not normal, the non-parametric Kruskal-Wallis test was used instead. Statistically significant difference was noted when $p < 0.05$.

Results

General toxicity

Two rats in the P group and four rats in the PG group died after the third and fourth injections, respectively. All other animals survived until the end of the experiment. A decrease in motor activity was observed in a few rats in the P and PG groups but no limb weakness was detected. The body weight of the P and PG groups was significantly lower than that of the C group from after the first injection of paclitaxel until the end of the present study (Fig. 1). There was no difference in the weight gain between the C and V groups at any time point.

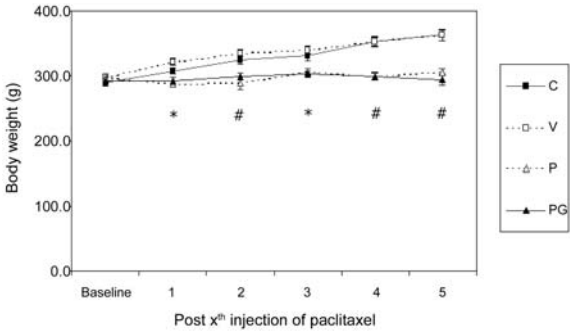

Fig. 1 Changes in the body weight of rats in the control (C), vehicle (V), paclitaxel (P) and paclitaxel + GM1 (PG) groups. Means with SEM are expressed for each time point after the weekly injection of paclitaxel. * $p < 0.05$ C vs. P and $p < 0.01$ V vs. P, # $p < 0.01$ C vs. P and V vs. P

Hind paw thermal threshold

At baseline, there were no significant differences in the mean latency between groups (Fig. 2). After the third injection of paclitaxel, the latency of the P group started to be significantly prolonged compared with that of the C group. This trend remained until the last dose of paclitaxel although the differences were not statistically significant. It was worth noting that transient increase in the latency of the V group was observed only after the fourth injection of paclitaxel. The latencies of all groups were not different at the end of the present study. As for the PG group, the latency was not different from that of the C group at all time points except a trend toward an increase after the last injection.

Tail thermal threshold

There were no differences in the baseline latencies of the tail thermal response among the animal groups (Fig. 3). The mean latency of the P group was prolonged relative to that of the C group after the first dose of paclitaxel and returned to the baseline value after the fourth injection. Significantly prolonged latency of the V group was also temporarily detected

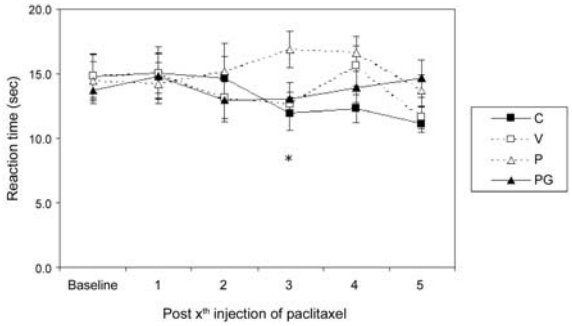

Fig. 2 Alteration in the hind paw thermal threshold of rats in the control (C), vehicle (V), paclitaxel (P) and paclitaxel + GM1 (PG) groups. Means with SEM of reaction time are expressed for each time point after the weekly injection of paclitaxel. * $p < 0.05$ C vs. P

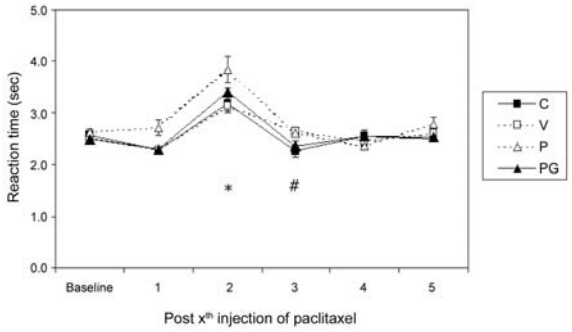

Fig. 3 Alteration in the tail thermal threshold of rats in the control (C), vehicle (V), paclitaxel (P) and paclitaxel + GM1 (PG) groups. Means with SEM of reaction time are expressed for each time point after the weekly injection of paclitaxel. * $p < 0.05$ C & V vs. P, # $p < 0.05$ V & P vs. C

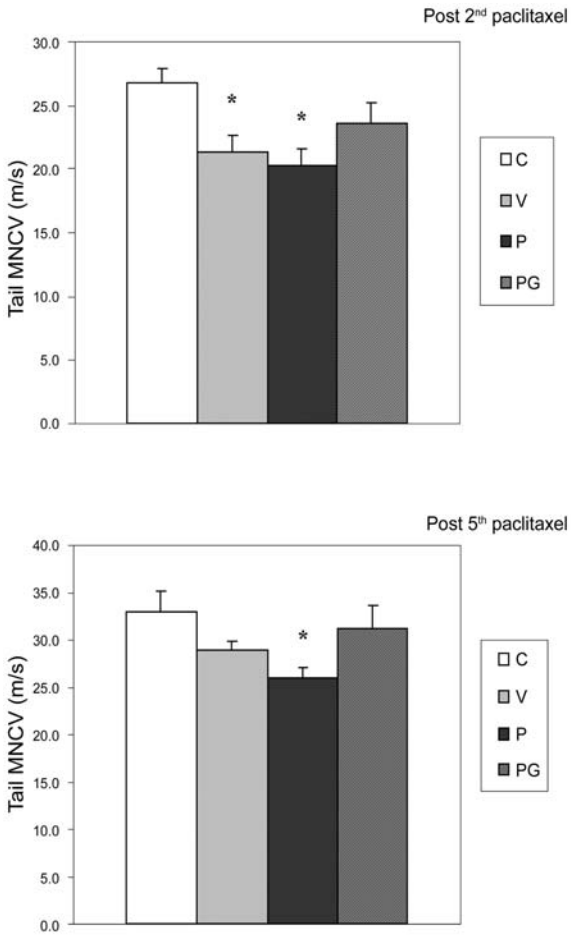

Fig. 4 Tail motor nerve conduction velocity (MNCV) of rats in the control (C), vehicle (V), paclitaxel (P) and paclitaxel + GM1 (PG) groups after the second (upper panel) and fifth (lower panel) injections of paclitaxel. Means and SEM are expressed. * $p < 0.05$ vs. C

after the third injection of paclitaxel. The latencies of the PG group were not significantly different from those of the C group throughout the present study.

Tail motor nerve conduction velocity

Before treatments, tail motor nerve conduction velocities (MNCV) were not different among the groups. After the second dose of paclitaxel, the P group had a significantly lower tail MNCV than the C group and this reduction remained significant until after the last injection of paclitaxel (Fig. 4). In addition, the tail MNCV of the V group was decreased relative to that of the C group at both time points with a significant difference only after the second administration of paclitaxel. The value of the PG group was between those of the C and P groups.

Histopathological study

The sciatic nerve was examined under the light and electron microscopes. Minimal degenerative axonal change in the V, P, and PG groups, and mild endoneurial edema in the P and PG groups were observed. Microtubule accumulation and its tendency to surround the mitochondria were present in the P and PG groups. Activated Schwann cells were also seen in those groups.

Discussion

Weekly intraperitoneal injection of 16 mg/kg paclitaxel for five weeks used in the present study was adopted from Authier et al, 2000[15]. The reason was this dosing regimen could clearly induce neurophysiological alterations without causing severe general toxicity. Although two and four rats in the P and PG groups died before the end of the present study, weight loss in other animals did not exceed 15%. These findings were similar to what were reported by Authier et al[15]. Moreover, mildly decreased motor activity without weakness was observed in our and their studies. Hence, this model of paclitaxel-induced neuropathy was reproducible and suitable for further testing the effect of GM1. It is worth noting that loss of rats in the PG more than in the P groups was likely due to the higher frequency of intraperitoneal injection of both paclitaxel and GM1. More severe general toxicity was unlikely as weight loss was not different between these two groups. This finding also indicates that GM1 did not have any effect on the general toxicity associated with paclitaxel.

Hind paw and tail thermal hypoalgesia was transiently found in the P group. Increased thermal threshold was previously observed with either similar dosing regimen[15] or lower accumulative doses[25,26]. However, in the presented animals, the hind paw thermal hypoalgesia disappeared within one week after the last injection of paclitaxel, whereas it was still evident until at least 2 weeks after the last dose in Authier et al, 2000. The explanation of this discrepancy might be the different degree of neuropathy. GM1 likely prevented an increase in the latencies of both hind paw and tail withdrawal since the values in the PG group were not different from those of the C group at any time point.

Electrophysiological tests showed that tail MNCV was significantly reduced in the P group compared with that of the C group. Slower motor as well as sensory NCV after paclitaxel treatment have been reported by several studies[15,17,26]. Unlike the thermal hypoalgesia, reduced tail MNCV was more persistent and was observed until the end of the present study. Similarly, Authier et al observed a decrease in sciatic MNCV after five injections of 16 mg/kg/week and it was still present two weeks later[15]. Treatment with GM1 partially restored the tail MNCV at both time points studied.

As described above, GM1 appeared to ameliorate the deterioration of thermal perception and motor nerve conduction induced by paclitaxel. GM1 has been shown to have beneficial effects on nervous system degeneration from various causes[22-24]. Moreover, sensory abnormalities in the paclitaxel-treated rats were improved with the mixed gangliosides from bovine[25]. The result of the present study of using porcine GM1 was not different from the previous study[25]. Despite these benefits of GM1, some studies have found that administration of GM1 prepared from bovine brain induced the production of anti-GM1 antibody leading to acute motor axonal neuropathy in rabbits and Gullain-Barre syndrome (GBS) in patients[27,28]. Since motor weakness was not observed, this immune-mediated neuropathy was unlikely to be associated with the GM1 treatment in the present study. This was similar to most of the studies using rodents. Therefore, it appears that motor neuropathy associated with anti-GM1 antibody develops in a species-specific manner with GM1 extracted from bovine brain. Nevertheless, this issue must be considered when GM1 is to be considered for clinical trials. The histopathologic change in the P and PG groups were similar to those described previously[16,29,30].

The underlying mechanisms of neuroprotection exerted by GM1 are still unclear. Several mechanisms have been proposed. First, GM1 has been shown to possess neurotrophic actions by stimulating the trk receptors and release of some neurotrophins [20,31-33]. Its supplementation has been shown to ameliorate neuronal injuries[34-37]. Furthermore, prevention of mitochondrial damage in hippocampal slices during incubation in the recording chamber by GM1 was demonstrated[38]. Recently, mitochondrial swelling and dysfunction in the nerve of paclitaxel-treated rats has been proposed[39]. Paclitaxel was hypothesized to cause this mitochondrial abnormality by triggering the mitochondrial permeability transition pore (mPTP) to open leading to the release of calcium into the cytosol. Increased intracellular calcium was thought to result in hyperalgesia observed in the rats receiving paclitaxel. Hence, GM1 might protect the mitochondria in this situation. Moreover, GM1 has been shown to play a role in the regulation of intracellular calcium and this has been linked to the cytoprotective effect[40,41]. Therefore, it is possible that GM1 also exerts the beneficial effects on sensory and motor deficits in the PG group by counteracting the disturbed calcium homeostasis induced by paclitaxel. These hypotheses, however, need to be proved.

It is noteworthy that the vehicle, Cremophor EL with ethanol, had an adverse effect on sensory tests and tail MNCV. The authors found that there was transient hypoalgesia in the hind paw and tail

including slight continuous reduction in the tail MNCV. These effects were unlikely ascribed to the general toxicity as the mean body weight of the V group was not different from the C group at any time point. Evidence of Cremophor EL-induced neurotoxicity has been previously reported[42]. In the rats receiving Cremophor EL, Authier et al observed the mechanical hyperalgesia of hind paw, tail hypoalgesia, and histopathological changes in the nerve similar to those of the paclitaxel group[15]. Accordingly, it cannot be denied that the neuropathy seen in the P group may be due to the vehicle. However, data from another study[15] and the present study showed the difference in the severity of neuropathy between the vehicle and paclitaxel groups suggesting that paclitaxel must have additional effects. Nevertheless, this toxic property of Cremophor EL should be considered in the future studies and replacement with other solvents would exclude this confounding factor.

In conclusion, porcine GM1 appeared to prevent the development of hypoalgesia and partially blocked the reduction in MNCV induced by paclitaxel without the presence of immune-mediated motor neuropathy. Therefore, the presented data suggests that GM1 has a potential to prevent the neuropathy, which is one of the major side effects of paclitaxel. However, the underlying mechanisms of GM1-mediated neuroprotection remain to be elucidated. In addition, the adverse effect of the Cremophor EL and the possible induction of GBS by GM1 treatment in humans must be concerned.

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แกงกลิโอไซด์จีเอ็มหนึ่ง (ผลิตจากสมองหมู) แก้ไขโรคของเส้นประสาทที่เกิดจากยาพาคลิแทคเซลในหนูให้ดีขึ้น

วิไล ชินธเนศ, ณัฐภาณินี ถนอมศรีเดชชัย, ณัฐธรา ดวงมาตย์พล, สิทธิพร แอกทอง, อทิตยา แก้วเสมา, ศุภางศ์ มณีศรี เลอกรองด์

ภูมิหลัง: *Paclitaxel ซึ่งเป็นยาที่ใช้รักษามะเร็งหลายชนิด ก่อให้เกิดผลข้างเคียงหลายประการรวมทั้ง neuropathy ในปัจจุบันยังไม่มีวิธีการรักษาที่ได้ผล มีหลักฐานว่า GM1 หรือ monosialic acid ganglioside มีผลดีต่อการบาดเจ็บและการเสื่อมของเซลล์ประสาท อย่างไรก็ตามยังไม่ได้มีการศึกษาประสิทธิภาพของ GM1 ในภาวะ neuropathy จาก paclitaxel*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของ GM1 ที่ผลิตจากสมองหมูต่อภาวะ neuropathy ที่เกิดจาก paclitaxel ในหนูทดลอง*

วิธีการศึกษา: *แบ่งหนู Wistar ทั้งหมด 54 ตัว เป็นกลุ่มควบคุม กลุ่มที่ได้ vehicle ของ paclitaxel (Cremophor EL) กลุ่มที่ได้ paclitaxel และกลุ่มที่ได้ทั้ง paclitaxel และ GM1 โดยขนาดของ paclitaxel ที่ให้ คือ 16 mg/kg เข้าช่องท้องสัปดาห์ละครั้งติดต่อกัน 5 สัปดาห์ ส่วน GM1 ให้ในขนาด 30 mg/kg เข้าช่องท้อง 5 วันต่อสัปดาห์โดยเริ่ม 3 วันก่อนให้ยาถึง 3 วันหลังการให้ paclitaxel ครั้งสุดท้าย ทำการวัด thermal threshold ที่หางและฝ่าเท้า รวมทั้งความเร็วการนำกระแสประสาท motor ที่หางทั้งก่อนและหลังให้การรักษาต่าง ๆ เส้นประสาท sciatic ได้ถูกตัดออกมาเพื่อศึกษาทางพยาธิวิทยากายวิภาค*

ผลการศึกษา: *Paclitaxel ทำให้เกิด thermal hypoalgesia และการลดลงของความเร็วการนำกระแสประสาท นอกจากนี้ยังพบความผิดปกติเหล่านี้แต่รุนแรงน้อยกว่าในกลุ่มที่ได้ vehicle การรักษาด้วย GM1 ช่วยป้องกันการเกิดความผิดปกติเหล่านี้ได้โดยไม่พบลักษณะของ Guillain-Barre syndromeในเส้นประสาท sciatic พบการบวมที่ชั้น endoneurium เล็กน้อยและมีบาง axon เสื่อมในกลุ่ม P และ PG microtubule มีการเกาะกลุ่มกัน มากขึ้นและพบ activated Schwann cell ในกลุ่มดังกล่าวด้วย*

สรุป: *ข้อมูลเหล่านี้บ่งชี้ว่า GM1 น่าจะมีประโยชน์ในการป้องกันหรือรักษาภาวะ neuropathy ที่เกิดจาก paclitaxel อย่างไรก็ตามจำเป็นต้องคำนึงถึงผลข้างเคียงของ Cremophor EL ด้วย*