

The Effect of The Pesticides Chlorpyrifos and Alphacypermethrin on The Development of Cutaneous Leishmaniasis Lesion in BALB/c Mice

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Abstract

Three groups of BALB/c mice were treated orally with 0.6, 1.0 and 6.0mg/kg body weight of chlorpyrifos (CPF), and 3 other groups were treated with 2.5, 6.25 and 25mg/kg bodyweight of alphacypermethrin (ACM), respectively, every other day for 1 week. Six other groups were treated similarly for 2 weeks. The treated groups and a control group for each pesticide were inoculated in the dorsum with *Leishmania major* promastigotes at their stationary phase. Lesions started to appear 2-3 weeks post-inoculation and their diameters were measured in all groups 1, 5, 9 and 14 days post-appearance (PA). The mean diameter of lesions (MDL) only in the 6.0mg group treated with CPF for 1 week was larger than that of the control group. In the groups treated for 2 weeks, the MDL of the 1.0 and 6.0mg groups were larger than those of the control group 5, 9 and 14 days PA while MLD of the 0.6mg group was larger than that of the control group only 5 days PA. MLD was larger in the 0.6mg group treated for 2 weeks than that in the group treated for 1 week 1 and 5 days PA. MLD was larger in the 1.0mg group treated for 2 weeks than that treated for 1 week 9 days PA. MLD was similar in the 6.0mg group treated for 1 and 2 weeks. The MDL only in the 25mg group treated with ACM for 1 week was larger than that of the control group 9 and 14 days PA. The MDL of the 6.25 and 25mg groups treated for 2 weeks were larger than those of the control groups 5 days PA and the MLD of the 25mg group was larger than that of the control group 9 and 14 days PA. The MLD was larger in the 2.5mg group treated for 2 weeks than that in the group treated for 1 week 5 days PA. The MLD was larger in the 6.25 and 25.0mg groups treated for 2 weeks than those treated for 1 week 1 and 5 days PA. Immunotoxicity and/or peripheral neurotoxicity caused by CPF and ACM might have caused aggravation of lesions in mice particularly those treated with the pesticides for 2 weeks.

Key words: Chlorpyrifos, organophosphates, alphacypermethrin, synthetic pyrethroids, *Leishmania major* lesion, cutaneous leishmaniasis, BALB/c mice.

Introduction

Cutaneous leishmaniasis (CL), caused by protozoan parasites of the genus *Leishmania*, is found in all continents except Australia and Antarctica especially in tropical and subtropical America, Africa, Asia and the Mediterranean countries (WHO, 1999). It is believed that 1.5 million new cases of CL are being reported yearly worldwide (Al-Jaser, 2005), a figure that does not include misdiagnosed, undiagnosed or unreported cases. This disease has significant morbidity that causes human suffering while the disease is active and psychological trauma from the disfigurement left

by the scars when it heals (Griffiths, 1987).

During her studies on the treatment of CL patients in Saudi Arabia, Al-Jaser (1995) observed that some patients do not respond to medical treatment. This unresponsiveness might be attributed to low sensitivity or high resistance of the parasite to the drug (Allen and Neal, 1989), modulation of the host immune system (Altes *et al.*, 1991; Gradoni

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and Gramiccia, 1994; Kocyyigit *et al.*, 2002) and/or to patient exposure to chemical pollutants such as pesticides (Breckenridge *et al.*, 1987).

Chlorpyrifos (CPF) (*O, O'*-diethyl 3, 5, 6-trichloro-2-pyridinyl-phosphoro-thioate), a broad-spectrum organo-phosphorous (OP) insecticide, has been widely used in the Kingdom of Saudi Arabia for the control of agricultural pests. OP compounds are highly toxic to vertebrates (Sultatos and Murphy, 1983; Spies *et al.*, 1988; Kousba *et al.*, 2004; Zhao *et al.*, 2006), and CPF is particularly considered to be neurotoxic (Albers *et al.*, 2004), cardiotoxic, hepatotoxic (Meyer *et al.*, 2004) and immunotoxic (Galloway and Handy, 2003).

Alphacypermethrin (ACM) is a type II synthetic pyrethroid insecticide, consisting of 2 cis-isomers of alpha-cyano-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylate). This insecticide has been also widely used in Saudi Arabia for the control of agricultural pests. Synthetic pyrethroids are considered to have very low toxicity to vertebrates (Ecobichon, 1996; Dent, 2000). However, ACM is considered to be neurotoxic (Trainer *et al.*, 1997) and immunotoxic (Luty *et al.*, 2000).

In an attempt to clarify the possible morbidity of these insecticides in patients infected with CL, we studied the effect of exposure to CPF and ACM on the development of CL lesions in BALB/c mice.

Materials and methods

Male, 12-week-old BALB/c mice (weight 20-30g) were purchased from the animal breeding unit of King Faisal Specialist Hospital and Research Centre and housed in cages under controlled conditions of 12/12 hr light/dark cycle and 21±2°C. The pesticides CPF and ACM were purchased from the Arabic Company of Chemical Products (APCO, Kingdom of Saudi Arabia) and dissolved in corn oil. *L. major* (Z LON-4) parasites used in the present study were isolated from a patient attending the Dermatology Clinic in Al-Kharj and was cloned and propagated *in vitro* in Novy-MacNeal-Nicolle (3N) biphasic medium (Evans *et al.*, 1989). A growth curve was prepared to determine the stationary phase of the parasite.

Seven groups, each of 15 mice, were treated with CPF. Groups 1, 2 and 3 were given orally 0.6, 1.0 and 6.0mg of CPF/kg body weight, respectively [LD₅₀ in mice is 60mg/kg body weight (Gosselin *et al.*, 1984)], every other day for 1 week (3 doses). Groups 4, 5 and 6 were given similar

doses, respectively, every other day for 2 weeks (3 doses/week). Group 7 was the control group and was given corn oil every other day for 2 weeks.

Seven other groups, each of 15 mice, were treated with ACM. Groups 1, 2 and 3 were given orally 2.5, 6.25 and 25 mg of ACM/kg body weight, respectively [LD₅₀ in mice is 40mg/kg body weight (Varshney and Kanwar, 1995)], every other day for 1 week (3 doses). Groups 4, 5 and 6 were given similar doses, respectively, every other day for 2 weeks (3 doses/week). Group 7 was the control group and was given corn oil every other day for 2 weeks.

After completion of the exposure period to CPF and ACM, 10⁷ of stationary phase *L. major* promastigotes were inoculated into the mice dorsum at the base of the tail. The mice were observed daily for lesion appearance which started 2-3 weeks post-inoculation. The diameters of the lesions were measured on days 1, 5, 9 and 14 post-appearance (PA) using a micrometer (Pocotest[®] dial caliper gauge, Carbonze UK); lesions started to ulcerate 15 days PA. The mean and standard error of the lesion diameters on each day were calculated for each of the 14 groups. For each of CPF and ACM, the data obtained for treated mice were compared with the corresponding data of the control group using one-way ANOVA test.

All experiments were carried out in accordance with King Saud University Ethical Committee Acts.

Results

Treatment with CPF

In the case of mice treated with the 3 different doses of CPF for 1 week (Table 1), the mean lesion diameters (MLD) 1, 5 and 9 days PA were similar (P>0.05) to the MLD of the corresponding lesions of the control group. In the case of lesions measured 14 days PA, the MLD in mice of the 0.6 and 1.0mg groups were similar (P>0.05) to those of the control group while the MLD in the 6.0mg group was larger (P<0.01) than that of the control group. The MLD of the 1.0 and 6.0mg group were also larger (P<0.05-P<0.01) on days 9 and 14 than the MLD measured on days 1 and 5 PA.

In the case of mice treated with the three different doses of CPF for 2 weeks (Table 2), the MLD were similar (P>0.05) to that of the control group 1 day PA. In the case of lesions measured 5 days PA, the MLD in all groups treated with CPF were larger (P<0.05) than that of the control group. In the case of lesions measured 9 and 14 days PA, only the MLD in mice of the 0.6 groups was

Table 1. Effect of treatment with different doses of chlorpyrifos for one week on the diameter of cutaneous leishmaniasis lesion in BALB/c mice.

Dose mg/kg	Mean lesion diameter in mm ± SE after (range)			
	1 day	5 days	9 days	14 days
Control*	8.42±0.520a** (6.1-11.0)	8.79±0.309a (6.9-10.2)	10.10±0.418b (8.3-12.3)	10.86±0.442b (8.7-13.4)
0.6*	8.19±0.314a (6.8-9.7)	9.12±0.352a (7.1-11.8)	10.44±0.371b (8.8-13.0)	11.44±0.399b (9.9-13.7)
1.0*	9.21±0.432a (5.0-11.1)	9.67±0.471a (5.7-12.4)	10.92±0.519b (6.7-14.0)	12.41±0.426b (9.9-14.2)
6.0*	9.22±0.197a (8.0-10.4)	9.92±0.421a (6.5-12.1)	11.82±0.623b (8.1-14.8)	13.30±0.419c (9.9-15.2)

*15 mice in each group.

** Data followed by similar letters are not significantly different ($P>0.05$), those followed by different letters are significantly different ($b=P<0.05$, $c=P<0.01$).

Table 2. Effect of treatment with different doses of chlorpyrifos for two weeks on the diameter of cutaneous leishmaniasis lesion in BALB/c mice.

Dose mg/kg	Mean lesion diameter in mm ± SE after (range)			
	1 day	5 days	9 days	14 days
Control*	8.42±0.520a** (6.1-11.0)	8.78±0.309a (6.9-10.2)	10.10±0.418b (8.3-12.3)	10.86±0.442b (8.7-13.4)
0.6*	9.5±0.282a (8.0-11.0)	10.35±0.211b (8.8-11.3)	11.20±0.618b (6.0-13.8)	11.80±0.265b (9.9-13.5)
1.0*	8.19±0.314a (6.8-9.7)	10.61±0.355b (7.7-13.3)	12.18±0.296c (10.6-14.2)	12.69±0.260c (10.7-14.7)
6.0*	8.91±0.248a (7.1-9.9)	10.72±0.186b (10.0-11.9)	12.52±0.292c (10.9-13.7)	13.64±0.106c (12.6-14.3)

*15 mice in each group.

** Data followed by similar letters are not significantly different ($P>0.05$), those followed by different letters are significantly different ($b=P<0.05$, $c=P<0.01$).

similar ($P>0.05$) to that of the control group while the MLD in the 1.0 and 6.0mg groups were larger ($P<0.01$) than those of the control group. In all treated groups, the MLD 5, 9 and 14 days PA were larger ($P<0.05$ - $P<0.01$) than those measured 1 day PA.

On comparing the MLD of the 0.6.0mg group treated with CPF for 1 week with those of mice treated for 2 weeks, the MLD were found to be larger ($P<0.05$) 1 and 5 days PA in mice treated for 2 weeks than those of mice treated for 1 week. On the other hand, the MLD 9 and 14 days PA were similar ($P>0.05$) in the groups treated with, PCF for 1 and 2 weeks.

The MLD of the 1.0mg group treated with CPF for 1 week was also compared with that of the group treated for 2 weeks. Although the MLD 1, 5 and 14 days PA were

similar ($P>0.05$) in the groups treated for 1 week and in those treated for 2 weeks, the MLD on day 9 PA was larger ($P<0.05$) in the group treated for 2 weeks than that of mice treated for 1 week.

On comparing the MLD of the 6.0mg group treated with CPF for 1 week with those treated for 2 weeks, the MLD were found to be similar ($P>0.05$) on days 1, 5, 9 and 14 PA.

Treatment with ACM

In the case of mice treated with the 2.5 and 6.25mg of ACM for 1 week (Table 3), the MLD 1, 5, 9 and 14 days PA were similar ($P>0.05$) to the MLD of the corresponding lesions of the control group. In the case of mice treated with 25mg, the MLD measured 9 and 14 days were larger ($P<0.01$) than

those of the control group and also larger ($P<0.01$) than the MLD of the same group measured 1 and 5 days PA.

In the case of mice treated with the 3 different doses of ACM for 2 weeks (Table 4), the MLD of all of the treated groups were similar ($P>0.05$) to that of the control group 1 day PA. In the case of lesions measured 5 days PA, the MLD in the 6.25 and 25mg groups were larger ($P<0.05$) than that of the control group. In the case of lesions measured 9 and 14 days PA, the MLD in mice of the 2.5 and 6.25mg groups were similar ($P>0.05$) to those of the control group while the MLD of the 25mg group were larger ($P<0.01$) than those of the corresponding MLD of the control group. The MLD of 2.5mg group measured 9 and 14 days PA were

larger ($P<0.05$) than those measured 1 and 5 days PA. Also the MLD of the 6.25 and 25mg groups measured on days 5, 9 and 14 PA were larger ($P<0.05$ - $P<0.01$) than those measured 1 day PA.

On comparing the MLD of the 2.5mg group treated with ACM for 1 week with those of mice treated for 2 weeks, the MLD was found to be larger ($P<0.01$) 5 days PA in mice treated for 2 weeks than that of mice treated for 1 week.

The MLD of the 6.25 and 25.0 groups treated with ACM for 1 week were also compared with those of the groups treated for 2 weeks. The MLD 1 and 5 days PA were larger ($P<0.05$ - $P<0.01$) in the groups treated for 2 weeks than those of mice treated for 1 week.

Table 3. Effect of treatment with different doses of alphacypermethrin for one week on the diameter of cutaneous leishmaniasis lesion in BALB/c mice.

Dose mg/kg	Mean lesion diameter in mm \pm SE after (range)			
	1 day	5 days	9 days	14 days
Control*	10.62 \pm 0.465a** (7.9-14.7)	11.45 \pm 0.399a (8.4-13.2)	12.53 \pm 0.307b (10.3-14.6)	13.31 \pm 0.266b (11.0-14.8)
2.5*	9.70 \pm 0.348a (7.7-11.5)	10.80 \pm 0.457a (8.0-14.1)	12.57 \pm 0.327b (10.1-14.8)	13.59 \pm 0.307b (11.2-15.2)
6.25*	9.45 \pm 0.680 a (7.2-12.7)	11.79 \pm 0.529a (9.6-15.5)	13.32 \pm 0.455b (10.2-15.3)	13.61 \pm 0.494b (10.6-16.6)
25*	8.85 \pm 0.799 a (6.8-13.4)	11.22 \pm 0.410a (9.4-14.2)	14.01 \pm 0.191c (12.7-15.2)	14.28 \pm 0.253c (12.9-16.4)

*15 mice in each group.

** Data followed by similar letters are not significantly different ($P>0.05$), those followed by different letters are significantly different (b= $P<0.05$, c= $P<0.01$).

Table 4. Effect of treatment with different doses of alphacypermethrin for two weeks on the diameter of cutaneous leishmaniasis lesion in BALB/c mice.

Dose mg/kg	Mean lesion diameter in mm \pm SE after (range)			
	1 day	5 days	9 days	14 days
Control*	10.62 \pm 0.465a** (7.9-14.7)	11.45 \pm 0.399a (8.4-13.2)	12.53 \pm 0.307b (10.3-14.6)	13.31 \pm 0.266b (11.0-14.8)
2.5*	10.37 \pm 0.471a (7.6-14.1)	12.35 \pm 0.329a (9.0-14.1)	13.39 \pm 0.298b (11.2-15.1)	13.72 \pm 0.271b (11.6-15.5)
6.25*	11.57 \pm 0.507a (9.6-15.5)	13.32 \pm 0.455b (10.2-15.3)	13.66 \pm 0.463b (10.6-16.6)	13.95 \pm 0.468b (10.9-16.8)
25*	10.97 \pm 0.394a (8.4-13.1)	13.89 \pm 0.167b (12.7-15.2)	14.28 \pm 0.253c (12.9-16.4)	14.63 \pm 0.241c (13.3-16.7)

*15 mice in each group.

** Data followed by similar letters are not significantly different ($P>0.05$), those followed by different letters are significantly different (b= $P<0.05$, c= $P<0.01$).

Discussion

The results of the present study show that relatively large doses of CPF (6.0mg/kg body weight) or ACM (25mg/kg body weight) given for 1 week may aggravate CL lesions developing in experimentally infected mice as shown from the larger lesions observed 14 days PA in the case of CPF and 9 and 14 days PA in the case of ACM in these mice. They also show that administration of small CPF doses as well as large doses of CPF or ACM for a longer period of 2 weeks may aggravate lesion development in these mice. Such aggravations might be attributed to alteration of the immune system of the infected mice since CPF and ACM have been reported to be immunotoxic (Luty *et al.*, 2000; Galloway and Handy, 2003); alteration of the immune system was reported to interfere with treatment of CL in AID's patients (Altes *et al.*, 1991, Gradoni and Gramiccia, 1994).

CPF and ACM inhibit acetylcholine esterase (AChE) in animals and humans (Vijverberg and Bercken, 1990 and Zhao *et al.*, 2006). In mice, CPF affect neurotransmission to vital organs such as the heart and liver (Meyer *et al.*, 2004). Sufficient inhibition of AChE in the central and peripheral nervous systems by CPF or ACM probably causes excessive accumulation of acetylcholine which in turn results in neurotoxicity. A neurotoxic effect of CPF or ACM on the peripheral nerves supplying the cutaneous area of the lesion may have contributed to the aggravation of lesion development.

CL is a common health problem in Saudi Arabia, and commonly affects agricultural workers (Al-Gindan *et al.*, 1984; Peters and El-Zahrani, 1987; Peters, 1988; Dye *et al.*, 1989). Al-Jaser (1995) observed that not all patients treated for CL in Al-Kharj responded properly and equally to medical treatment. The possible effect of the presence of pesticides in the body of patients unresponsive to medical treatment should be investigated.

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تأثير ميدي الأفات كلوربيريفوس و ألفاسبيرمثرين على تطور بثره الليشمانيا الجلدية في الفئران BALB/c

أسياء نعمة آل داوود ومي حمد الجاسر و جلييلة مصطفى خليل

قسم علم الحيوان- كلية العلوم- ص.ب. ٢٤٥٥- جامعة الملك سعود
الرياض ١١٤٥١- المملكة العربية السعودية

المخلص

في هذه الدراسة تم بحث تأثير تعرض الفئران من سلالة BALB/c لكل من المبيدين كلوربيريفوس chlorpyrifos و ألفاسبيرمثرين alphacypermethrin- الذين ينتشر استعمالهما بالمملكة العربية السعودية - على تطور بثره الليشمانيا الجلدية التي يسببها طفيل الليشمانيا العظمى *Leishmania major*. وقد تم استخدام سبع مجموعات من الفئران تشمل كل منها ١٥ فأرا لاختبار أثر كل من المبيدين، و تم إعطاء ست منها جرعات مختلفة من المبيد المذاب في زيت الذرة عن طريق الفم وإعطاء المجموعة السابعة (الضابطة) زيت الذرة فقط. وكانت جرعات المبيد كلوربيريفوس ٠,٦ و ١,٠ و ٦,٠ مجم لكل كجم من وزن الجسم أعطيت يوما بعد يوم لمدة أسبوع واحد (ثلاث مجموعات) أو أسبوعين (ثلاث مجموعات). وكانت جرعات مبيد ألفاسبيرمثرين ٢,٥ و ٦,٢٥ و ٢٥ مجم لكل كجم من وزن الجسم أعطيت كذلك يوما بعد يوم لمدة أسبوع واحد (ثلاث مجموعات) أو أسبوعين (ثلاث مجموعات). وبعد ذلك تم حقن كل من الفئران بطفيل الليشمانيا في طوره أمامي السوط في مرحلته الثابتة stationary phase في منطقة الظهر أمام قاعدة الذيل. وقد بدأت البثرات في التكون بعد فترة تراوحت بين أسبوع وأسبوعين من تاريخ الحقن، وتم قياس قطر كل منها بعد يوم واحد و ٥ و ٩ و ١٤ يوما بعد تكون البثره، كما تم حساب المتوسط والخطأ المعياري لقطر البثرات في كل من هذه الأيام لجميع المجموعات. وبمقارنة متوسط قطر البثرات في كل من المجموعات بذلك في المجموعة الضابطة اتضح أن متوسط قطر البثرات في الفئران المعالجة بالكلوربيريفوس لمدة أسبوع واحد كان أكبر من ذلك في المجموعة الضابطة فقط في حالة المجموعة التي أعطيت ٦,٠ مجم/كجم بعد ١٤ يوما من تكون البثرات. و في حالة المجموعتين اللتين أعطيتا ١,٠ و ٦,٠ مجم/كجم من المبيد لمدة أسبوعين كان متوسط قطر البثرات فيها أكبر من ذلك في المجموعة الضابطة عندما قيست في الأيام ٥ و ٩ و ١٤ بعد تكون البثره، بينما كان متوسط قطر البثرات في المجموعة التي أعطيت ٠,٦ مجم/كجم أكبر من ذلك في المجموعة الضابطة عندما قيست في اليوم الخامس فقط بعد تكون البثرات. وعند مقارنة قطر البثرات في المجموعات التي أعطيت المبيد لمدة أسبوعين بتلك التي أعطيت المبيد لمدة أسبوع واحد كان متوسط قطر البثرات في المجموعة التي أعطيت ٠,٦ مجم/كجم لمدة أسبوعين أكبر من ذلك في المجموعة التي أعطيت المبيد لمدة أسبوع واحد عندما قيست بعد يوم واحد أو ٥ أيام من ظهور البثره. أما في المجموعة التي أعطيت ١,٠ مجم/كجم فقد كان متوسط قطر البثرات في المجموعة التي أعطيت المبيد لمدة أسبوعين أكبر من ذلك في المجموعة التي أعطيت المبيد لمدة أسبوع واحد عندما قيست بعد ٩ أيام من تكون البثره، بينما لم يختلف متوسط قطر البثرات في المجموعتين اللتين أعطيتا ٦,٠ مجم/كجم لمدة أسبوع أو أسبوعين.

وعند مقارنة متوسط قطر البثرات في الفئران المعالجة بالألفاسبيرمثرين لمدة أسبوع واحد بذلك في المجموعة الضابطة اتضح أن متوسط قطر البثرات في الفئران المعالجة بالمبيد كان أكبر من ذلك في المجموعة الضابطة فقط في حالة المجموعة التي أعطيت ٢٥ مجم/كجم بعد ٩ و ١٤ يوما من تكون البثرات. و في حالة المجموعتين اللتين أعطيتا ٦,٢٥ و ٢٥ مجم/كجم من المبيد لمدة أسبوعين كان متوسط قطر البثرات فيها أكبر من ذلك في المجموعة الضابطة عندما قيست في اليوم الخامس بعد تكون البثره، بينما كان متوسط قطر البثرات في المجموعة التي أعطيت ٢٥ مجم/كجم فقط أكبر من ذلك في المجموعة الضابطة عند قياس قطر البثرات في اليومين ٩ و ١٤ بعد تكونها. وعند مقارنة قطر البثرات في المجموعات التي أعطيت المبيد لمدة أسبوعين بتلك التي أعطيت المبيد لمدة أسبوع واحد كان متوسط قطر البثرات في المجموعة التي أعطيت ٢,٥ مجم/كجم لمدة أسبوعين أكبر من ذلك في المجموعة التي أعطيت المبيد لمدة أسبوع واحد عندما قيست في اليوم الخامس من ظهور البثره. أما في المجموعات التي أعطيت ٦,٢٥ و ٢٥ مجم/كجم فقد كان متوسط قطر البثرات في المجموعتين اللتين أعطيتا المبيد لمدة أسبوعين أكبر من ذلك في المجموعتين اللتين أعطيتا المبيد لمدة أسبوع واحد عندما قيست في اليومين الأول والخامس بعد تكون البثره. ويظهر أن معالجة الفئران بأي من المبيدين بجرعات صغيرة لمدة أسبوعين قد يسبب تسارع تطور البثرات بينما المعالجة بجرعة عالية نسبيا لمدة أسبوع واحد كان كافيا لتسارع تطور البثرات عن تلك في المجموعة الضابطة. وقد يرجع هذا التسارع إلى السمية المناعية immunotoxicity أو السمية العصبية neurotoxicity الطرفية لهذه المبيدات أو إلى كلا النوعين من السمية مجتمعين.