

# 新驅蟲藥 Milbemycin Oxime 對廣東住血線蟲幼蟲之療效

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爲了解神經性藥物 milbemycin oxime 對廣東住血線蟲之治療效果，選擇不同劑量之 milbemycin oxime 5.0mg/kg×1、25.0mg/kg×1 及 5.0mg/kg×10 感染後第六天分別口服治療感染廣東住血線蟲第三期幼蟲之大白鼠，感染後第八週收集老鼠糞便檢查幼蟲數，第十五週解剖老鼠，計算肺臟重量與老鼠體重比、蟲體回收數；結果發現：對照組與治療組，其老鼠肺臟重量與老鼠體重比、蟲體回收數和幼蟲數都有顯著差異，而不同劑量之治療組之間，並沒有差異。

Key words: *Angiostrongylus cantonensis*, milbemycin oxime

## 前言

Milbemycin oxime 是 milbemycin oxime A3 與 oxime A4 以 20:80 混合而成的驅蟲藥，與 milbemycin D 同屬 macrocyclic lactone 系(1)。臨床上，已證明對犬絲狀蟲及對犬蛔蟲等之腸道線蟲類寄生蟲有良好的驅蟲效果(1-4)。在體外，從我們一連串有關 milbemycin oxime 之研究結果得知，它除了對線蟲類有效外（包括廣東住血線蟲），同時經 GABA 或 cholinergic 機轉，對條蟲類、吸蟲類均有抑制或興奮作用(5-6)。

廣東住血線蟲成蟲寄生在老鼠肺動脈，人類因食用其第三期幼蟲而感染，主要流行於氣候溫暖潮濕之地區，涵蓋的國家有台灣、中國大陸、泰國、馬來西亞、日本，並可達太平洋群島夏威夷、大溪地及澳洲北部(7-13)，爲造成當地居民嗜伊紅性腦膜炎及腦膜腦炎之主要原因(14)；在台灣主要感染途徑大多因食入未煮熟之非洲大蝸牛(7,15-16)，而造成民眾的危害；目前仍無適用之藥品，所以對廣東住血線蟲幼蟲有效之驅蟲藥亟待開發，本研究將進行了解 milbemy-

cin oxime 對廣東住血線蟲幼蟲之療效，提供廣東住血線蟲治療藥物之進一步參考。

## 材料和方法

### 一、動物感染

#### 1. 第三期幼蟲之收集

從實驗室中所感染廣東住血線蟲第一期幼蟲之螺螄 (*Biomphalaria glabrata*)，以人工胃蛋白消化液消化，收集感染性第三期幼蟲。

#### 2. 實驗動物分組

使用動物爲購自國科會動物中心之 Wistar strain 四週齡雄性大白鼠，分治療組及對照組。每組各五隻老鼠。

#### 3. 動物感染

治療組及對照組之大白鼠，每隻老鼠以口餵管餵食廣東住血線蟲 20 隻第三期幼蟲。

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## 二、藥物治療

對照組於感染後第六天以口餵管餵食生理食鹽水。

治療組分為三組，於感染後第六天以口餵管餵食(1)、Milbemycin oxime 5.0mg/Kg×1。(2)、Milbemycin oxime 25.0mg/Kg×1。(3)、Milbemycin oxime 5.0mg/Kg×10。

## 三、效果評估

1. 第一期幼蟲之檢查：感染後第八週連續三天收集大白鼠糞便，計算第一期幼蟲數目。
2. 成蟲蟲體回收數：感染後第十五週解剖大白鼠，計算老鼠肺動脈及心臟之成蟲數。
3. 大白鼠肺臟及體重之比例。

## 結果

所有資料均以統計學 One-Way-Anova Scheffe's test  $p < 0.05$  評估差異性，由表一可發現：感染後第八週，收集老鼠糞便檢查第一期幼蟲數，發現對照組每一公克幼蟲數為  $3651 \pm 438$ ，治療組分別是 5.0mg/Kg 治療一天每一公克幼蟲數為  $1068 \pm 210$ 、25.0mg/Kg 治療一天為  $952 \pm 180$  和 5.0mg/Kg 連續治療十天為  $795 \pm 60$ 。治療組三組之間並無區別，而治療組與對照組之間比較有顯著差異。感染後第十五週解剖老鼠，(一)、發現回收之蟲體數，對照組為  $17.1 \pm 1.8$  隻蟲體；治療組分別是 5.0mg/Kg 治療一天為  $7.3 \pm 2.1$ 、25.0mg/Kg 治療一天為  $9.6 \pm 2.2$  和 5.0mg/Kg 連續治療十天為  $8.3 \pm 1.6$  隻蟲體，三組治療組之間雖有數字上差異但沒有統計學上的意義，而治療組與對照組之比較有顯著差異；(二)、肺臟與體重之比例，對照組為  $3.26 \pm 1.66$ ；治療組分別是 5.0mg/Kg 治療一天為  $1.16 \pm 0.82$ 、25.0mg/Kg 治療一天為  $1.73 \pm 0.74$  和 5.0mg/Kg 連續治療十天為  $1.16 \pm 0.63$ 。未經治療之對照組其肺臟組織增生現象相當明顯，其肺臟與體重之比例比較，三組治療組之間仍然沒有差異，而治療組與對照組比較即有顯著差異。

表一. Effects of milbemycin oxime on larvae of *Angiostromylyus cantonensis* in rat

Drugs	No. exam.	LPG/female 8weeks	Rat BW at sacrifice	Rat lung-BW at ratio at sacrifice	No. of worms recovered
I. Control*	5	$3651 \pm 438$	$393.6 \pm 22.8$	$3.26 \pm 1.66$	$17.1 \pm 1.8$
II. 5mg/kg×1	5	$1068 \pm 210$	$418.8 \pm 10.9$	$1.16 \pm 0.82$	$7.3 \pm 2.1$
III. 25mg/kg×1	5	$952 \pm 180$	$416.3 \pm 12.1$	$1.73 \pm 0.74$	$9.6 \pm 2.2$
IV. 5mg/kg×10	5	$795 \pm 60$	$413.4 \pm 11.4$	$1.16 \pm 0.63$	$8.3 \pm 1.6$

Result are shown as mean±SD of four animals each.

\*I-II, I-III, I-IV, by Scheffe's test  $p < 0.05$

## 討論

老鼠為廣東住血線蟲自然界適當宿主，由口腔食入感染性第三期幼蟲，1-2 天幼蟲會到腦部發育，4-6 天形成第四期幼蟲，約 7-9 天形成第五期幼蟲，26-29 天移行至肺臟，繼續發育為成蟲，整個生活史約需 42-45 天(17)。人並非其適當宿主，在人體的發育大多僅形成第四、五期未成熟蟲體。

廣東住血線蟲症為人體重要之寄生蟲病，有多種藥物利用動物實驗研究其治療效果，包括 thiabendazole(18-19)、l-tetramisole(20)、mebendazole(21-22)、flubendazole(23)、avermectin B<sub>1a</sub>(24)、ivermectin(25)、milbemycin D(26)、albendazole(16) 和 PF1022A(27)；本實驗主要探討 GABA 類之驅蟲藥 milbemycin oxime 對於廣東住血線蟲幼蟲之治療效果。

GABA 類之驅蟲藥包括 VD-99-11、santquin、DEC、milbemycin D 和 PF1022A 等，在體外不同濃度對組織寄生蟲廣東住血線蟲分別具有抑制或興奮作用(28-31)；milbemycin oxime 在體外之研究，1991 年 Lec, et al 提出不同濃度會對線蟲類寄生蟲造成抑制或興奮作用(5)。1992 年又提出在低濃度時會興奮 GABA 機轉，轉而對廣東住血線蟲之蟲體，造成抑制作用(32)；有關 GABA 類之驅蟲藥對感染廣東住血線蟲老鼠之治療效果，milbemycin D 在感染廣東住血線蟲老鼠第六天給予口服 5.0mg/kg 連續治療十天，第七週和第九週糞便都沒有發現幼蟲數(LPG/female)、蟲體的回收數和肺臟與體重之比例，均明顯降低，有顯著治療效果(26)；

PF1022A 在感染廣東住血線蟲老鼠第一天給予口服

5.0mg/kg 連續治療五天或腹腔注射 0.5mg/kg 連續治療五天，糞便幼蟲數、蟲體的回收數和肺臟與體重之比例，均明顯降低，也具有顯著治療效果(27)；因此，我們爲了更深入探討 milbemycin oxime 對廣東住血線蟲幼蟲之治療效果，與 milbemycin D 同樣選擇在感染廣東住血線蟲老鼠第六天，給予不同劑量 5.0mg/Kg×1、25.0mg/Kg×1、5.0mg/Kg×10 的 milbemycin oxime 治療，由於感染廣東住血線蟲之老鼠會造成體重減輕和肺臟組織增生的現象(33)，因此，比較肺臟與老鼠體重之比例，來評估其治療效果；另外，同時也比較感染後第八週糞便幼蟲數(LPG/female)、蟲體的回收數。雖然，於感染後第六天給予 milbemycin oxime 治療，與 milbemycin D、PF1022A 同樣無法完全排除蟲體，但發現不論在糞便的幼蟲數、蟲體的回收數以及肺臟與老鼠體重比例之比較，對照組與不同劑量之治療組，統計學上均有顯著的差異；因此，milbemycin oxime 應可作爲治療廣東住血線蟲的參考藥物。

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# Efficacy of Milbemycin Oxime Against Larval Stage of *Angiostrongylus cantonensis*

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The main purpose of current study is to determine the efficacy of milbemycin oxime against *Angiostrongylus cantonensis* infection. Wistar rats with 20 infective larvae of the *Angiostrongylus cantonensis* were studied. Milbemyccin oxime was administered orally at dose 5.0mg/kg $\times$ 1, 25.0mg/kg $\times$ 1 and 5.0mg/kg $\times$ 10 in separate on the 6th days after post-infection. Fifteen weeks after post-infection, the worm are recovered from these rats. There is no significant difference ( $p > 0.05$ ) among the three treatment groups in the effectiveness of milbemycin oxime against larval stage of *Angiostrongylus cantonensis*. But there is significant difference between the control group and the treatment group ( $p < 0.05$ ).