Dinotefuran: A Potential Neonicotinoid Insecticide Against Resistant Mosquitoes

VINCENT CORBEL,[1] STEPHANE DUCHON,[1] MORTEZA ZAIM,[2] AND JEAN-MARC HOUGARD[1]

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ABSTRACT Because pyrethroid, organophosphate, and carbamate resistance is more and more developed in mosquitoes of medical importance, there is an urgent need for alternative insecticides for vector control. Dinotefuran, a new neonicotinoid insecticide commercialized by Mitsui Chemicals (Tokyo, Japan), could be a useful candidate in public health because it shows low mammalian toxicity and great insecticidal activity against a broad range of pests. In this study, the intrinsic toxicity of dinotefuran was evaluated by larval bioassay and topical application against different mosquito strains of *Anopheles gambiae* Giles, *Culex quinquefasciatus* Say, and *Aedes aegypti* L. having none, one, or several resistance mechanisms, respectively, to insecticides. The results showed that dinotefuran was less toxic than most of the commonly used insecticides (e.g., deltamethrin, carbosulfan, and temephos) against the susceptible mosquitoes tested (between 6- and 100-fold at the LD_{50} level). However, the toxicity of dinotefuran was not strongly affected by the presence of common resistance mechanism, i.e., *kdr* mutation and insensitive acetylcholinesterase (resistance ratio [RR] from 1.3 to 2.3). More interestingly, the carbamate-resistant strain of *Cx. quinquefasciatus* was significantly more affected by dinotefuran than the susceptible strain (RR = 0.70), probably because the insensitive acetylcholinesterase is less efficient to degrade nicotinic substrates than normal acetylcholinesterase. Despite the relatively low toxicity of dinotefuran against susceptible mosquitoes, the absence of cross-resistance with common insecticides (pyrethroids, carbamates, and organophosphates) makes neonicotinoids potential candidates for disease vector control, especially in area where mosquitoes are resistant to insecticides.

KEY WORDS dinotefuran, insecticide resistance, *Anopheles gambiae*, *Culex quinquefasciatus*, *Aedes aegypti*

DINOTEFURAN BELONGS TO THE neonicotinoid insecticides, as do imidacloprid (Moriya et al. 1992) and thiamethoxam (Maienfisch et al. 1999). These compounds share a common mode of action. They are agonist of the nicotinic acetylcholine receptor, affecting the synapses in the central nervous system (Tomizawa and Yamamoto 1993). These insecticides are gaining widespread use for controlling insect pests of agricultural importance (Elbert et al. 1998). They are insecticides with stomach, contact and systemic action, with relatively low toxicity to mammals and nontarget organisms. Discovered in 1998, dinotefuran [MTI-446, 1-methyl-2-nitro-3-(tetra-hydro-3-furylmethyl) guanidine] is one of the most recent neonicotinoids (Kodaka et al. 1998) under development by Mitsui Chemicals (Tokyo, Japan). It has an especially high insecticidal activity against a broad range of hemipterous insects and a low mammalian toxicity (oral acute LD_{50} for rates between 2,000 and 2,800 and skin and eye acute percutaneous LD_{50} for rates >2,000 mg/kg; Tomlin 2000). Compared with other neonicotinoids, dinotefuran has been shown to be one of the most effective compounds against the adult male cockroach *Periplaneta americana* L. (Kiriyama and Nishimura 2002).

These characteristics make dinotefuran a promising candidate for the control of vectors and pests of public health importance, many of which have become resistant or multiply resistant to common insecticides. This is particularly relevant to mosquito vectors of dengue and malaria, for which vector control remains an important component of the global control strategy (Zaim and Guillet 2002).

Dengue and dengue hemorrhagic fevers are becoming increasingly important public health problems in the tropics and subtropics (WHO 2003). Exacerbated by urbanization, increasing population movement, and lifestyles that contribute to the proliferation of artificial larval habitats of the mosquito vector, the worsening epidemiological trends seem likely to increase. Control of the main mosquito vector, *Aedes aegypti* L., is currently the only option available for prevention and control of dengue, and it is carried out mainly by applying insecticides to larval habitats, destroying unwanted containers, and educating the pub-

[1] Institut de Recherche pour le Développement, 911 Av. Agropolis, B.P. 64501, 34394 Montpellier cedex 5, France.
[2] WHO/CDS/PVC, World Health Organization, 1211 Geneva 27, Switzerland.

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Table 1. Description of the mosquito strains used for larval and adult bioassay

Species	Strains	Origin	Status	Level of resistance (larval bioassay)
An. gambiae	KIS	Kenya	Susceptible	-
	VKPER	Burkina Faso	Resistant (*kdr*)	≈200-fold to permethrin
Ae. aegypti	BORA	French Polynesia	Susceptible	-
	LHP	Thailand	Resistant (*kdr*)	≈170-fold to permethrin
Cx. quinquefasciatus	SLAB	USA	Susceptible	-
	BKPER	Côte d'Ivoire	Resistant (*kdr* + oxidases)	≈300-fold to permethrin
	RLAB	France	Resistant ($Ace.1^R$)	≈1,900-fold to propoxur

lic. During epidemics, this is complemented by insecticide space-spraying against adult mosquitoes. The use of insecticides has resulted in emergence and spread of resistance to organophosphorus (OP) (Karunaratne and Hemingway 2001, Rodriguez et al. 2001), carbamate (Vaughan et al. 1998), and pyrethroid insecticides (Mebrahtu et al. 1997, Brengues et al. 2003), and this resistance is of great operational concern.

More than 0.7 million people, mainly children under the age of five, die from malaria each year (WHO 1995). This proportion is on the increase as a result of human intervention (e.g., deforestation and agriculture), breakdown in healthcare due to socioeconomic obstacles or wars, and increase and spread of resistance to drugs and insecticides (Snow et al. 2001). The use of insecticide-treated mosquito nets seems to be a method of choice in many parts of Africa, south of the Sahara, where >90% of malaria cases occur. This includes areas of intermediate or intense malaria transmission (Lines 1996). Pyrethroids are the only insecticides currently recommended for treatment of mosquito nets because of their rapid knockdown, high insecticidal potency at low dosages, and relative safety (Zaim et al. 2000). Pyrethroid resistance, however, has been reported in major malaria vectors (Sina and Aultman 2001), such as *Anopheles gambiae* Giles in West Africa (Chandre et al. 1999) and *Anopheles funestus* Giles in South Africa (Hargreaves et al. 2000). To be acceptable, insecticide-treated bed nets also should have a significant impact on nuisance from mosquitoes, including the multiresistant mosquito *Culex quinquefasciatus* Say. Because pyrethroids have less and less impact on this latter species, users frequently think that insecticide-treated bed nets are not effective and do not perceive their usefulness for malaria prevention and control.

In that context, and as a new insecticide, dinotefuran has been evaluated in the laboratory, against different strains of *Ae. aegypti*, *An. gambiae*, and *Cx. quinquefasciatus*, which present none, one, or several resistance mechanisms, respectively, to insecticides. This study, carried out within the framework of the joint WHO's Special Programme for Research and Training in Tropical Diseases and the Pesticide Evaluation Scheme initiative for research and development of alternative insecticides for vector control, examines the intrinsic toxicity of dinotefuran and its cross-resistance with commonly used insecticides.

Materials and Methods

Biological Material. Two laboratory strains of *Ae. aegypti*, two of *An. gambiae*, and three of *Cx. quinquefasciatus* were used in this study (Table 1). The susceptible reference strains of *An. gambiae* (KIS), *Cx. quinquefasciatus* (SLAB), and *Ae. Aegypti* (BORA) have been colonized for many years and are free of any detectable insecticide resistance mechanism. The pyrethroid-resistant strains of *An. gambiae* (VKPER), *Ae. aegypti* (LHP), and *Cx. quinquefasciatus* (BKPER) are homozygous for the knockdown resistance (*kdr*) gene (Martinez-Torres et al. 1998; Brengues et al. 2003; Chandre et al. 1998). The BKPER strain also shows an increased metabolic detoxification by the cytochrome P450-dependent monooxygenase (Chandre et al. 1998). The carbamate/OP-resistant strain of *Cx. quinquefasciatus* (RLAB) is homozygote for the gene encoding for an insensitive acetylcholinesterase ($Ace.1^R$) but remained fully susceptible to pyrethroids and DDT. This strain showed a genetic background identical to that of SLAB strain (Berticat et al. 2002). Resistant and susceptible strains were checked every 3 mo for resistance status and R-genotype.

Bioassays. The intrinsic activity of dinotefuran against larvae (larval bioassays) and adults (topical applications) was measured using forced contact tests to avoid any side effects linked to the insect behavior (WHO 1996). All bioassays were made by using a 89.8% technical grade of dinotefuran (Mitsui Chemicals).

Larval Bioassays. Batches of third instars were exposed to 1 ml of insecticide solution diluted in 99 ml of distilled water. Five lots of 20 larvae per concentration and five to eight concentrations per test, providing mortalities ranging from 0 to 100%, were run. Temperature was maintained at 27°C throughout the test, and larval mortality was recorded after 24-h exposure and then corrected for control mortality (Abbott 1925). Three replicates with insect larvae from different rearing batches were made at different times, and the results were pooled. The data were subject to a computerized log-probit analysis (Raymond et al. 1997) to determine the LC_{50} and LC_{95} values as well as their 95% confidence intervals (CI). Two mosquito strains of the same species were considered as having the same susceptibility to dinotefuran when 1) their probit lines were parallel (parallelism test not rejected at 95% CI), and 2) the ratio between their LC_{50} (resistance ration $[RR]_{50}$) or LC_{95} (RR_{95}) had confidence limits including the value 1.

Table 2. Comparative toxicity of dinotefuran against susceptible and resistant strains of *An. gambiae*, *Ae. aegypti*, and *Cx. quinquefasciatus* tested at the larval stage (larval bioassays)

Species	Strains (*N*)	LC_{50} (mg/l) (95% CI)	LC_{95} (mg/l) (95% CI)	Slope ± SE Parallelism test[a]	RR_{50} (95% CI)	RR_{95} (95% CI)
An. gambiae	KIS (S) (301)	0.17 (0.16–0.18)	0.32 (0.30–0.34)	5.90 ± 0.27		
	VKPER (R) (297)	0.17 (0.16–0.18)	0.31 (0.29–0.33)	6.20 ± 0.26 accepted	1.01 (0.92–1.11)	[b]
Ae. aegypti	BORA (S) (302)	0.21 (0.20–0.22)	0.81 (0.72–0.94)	2.84 ± 0.13 –		
	LHP (R) (293)	0.40 (0.39–0.42)	0.96 (0.90–1.06)	4.34 ± 0.20 rejected	1.88 (1.76–2.02)	1.18 (1.00–1.40)
Cx. quinquefasciatus	SLAB (S) (295)	0.34 (0.32–0.35)	0.71 (0.67–0.76)	5.04 ± 0.22 –		
	BKPER (R) (302)	0.44 (0.43–0.45)	0.80 (0.77–0.84)	6.23 ± 0.27 rejected	1.30 (1.20–1.40)	1.13 (0.98–1.29)
	RLAB (R) (299)	0.14 (0.13–0.15)	0.26 (0.23–0.29)	5.18 ± 0.04 accepted	0.42 (0.36–0.47)	[b]

N, number tested; S, susceptible; R, resistant.
[a] Parallelism test rejected if slopes between susceptible and resistant strains of the same species are significantly different at 95% CI.
[b] RR_{95} not statistically different from RR_{50} because regression lines between susceptible and resistant strains are parallel ($P > 0.05$).

Topical Applications. Insecticide solution (0.1 μl) in acetone was dropped with a microcapillary onto the upper part of the pronotum of each adult mosquito that was briefly anesthetized with CO_2 and maintained on a cold table. Doses were expressed in nanograms of active ingredient per milligram of mosquito body weight. In total, 50 individuals (nonblood-fed females, 2–5 d old) were used per dose, with at least five doses providing between 0 and 100% mortality. After treatment, the females were maintained at 27 ± 2°C and 80% ± 10% RH in plastic cups with honey solution provided. Mortality was assessed after 24 h and then corrected for control mortality (Abbott 1925). As for larval bioassays, each test was replicated three times, and the data were subjected to a computerized log-probit analysis (LD_{50} and LD_{95} and 95% CIs). Parallelism tests and resistance ratios (RR_{50} and RR_{95}) also were compared between each strain of the same species.

Results

Data from larval bioassays are shown in the Table 2. No significant difference was noted in the toxicity of dinotefuran between the susceptible and pyrethroid-resistant strains of *An. gambiae.* Dinotefuran, however, showed slightly higher toxicity against the susceptible strain of *Ae. aegypti*, compared with the pyrethroid-resistant strain, particularly at the LC_{50} (about two-fold). The same trend was noted with pyrethroid-resistant *Cx. quinquefasciatus*, although the difference was less marked. Conversely, dinotefuran was ≈3 times more toxic against the carbamate-resistant strain of *Cx. quinquefasciatus* than the susceptible one, both at the LC_{50} and LC_{95} levels (as probit lines were parallel, $P > 0.05$). When comparing interspecific toxicity, *An. gambiae* was shown to be slightly more affected by dinotefuran (2–2.5-fold) than the two other species, both at the LC_{50} and LC_{95} levels. Few differences were noted between *Ae. aegypti* and *Cx. quinquefasciatus;* the ratio varied according to the LC considered.

Data from topical applications (Table 3) showed slightly more marked differences between the susceptible and pyrethroid-resistant strains of each mosquito species. Dinotefuran proved to be slightly more toxic (about two-fold) against the susceptible *An. gambiae* and *Cx. quinquefasciatus* strains than against the pyrethroid-resistant strains, both at the LD_{50} and LD_{95} levels. The same trend was noted with *Ae. Aegypti*, despite probit lines were not parallel. As with larval bioassays, a slight difference was noted with the carbamate-resistant *Cx. quinquefasciatus*, which was shown to be slightly more affected by dinotefuran than the susceptible strain (RR_{50} = 0.7). It is also interesting to note that dinotefuran was as much as 35 and 75 times more toxic to *An. gambiae* than to *Cx. quinquefasciatus* and *Ae. Aegypti* adults, respectively, whereas mosquito larvae were only <2 times different in sensitivity.

Discussion

When comparing the larval activity of dinotefuran to other chemicals of public health interest (Table 4), this compound seems much less toxic against the susceptible reference strains than most of them (100-fold), except for DDT and propoxur, which are of similar range of activity. The same trend was noted with topical applications, but the differences were less important (six-fold for BORA and 30-fold for SLAB). However, dinotefuran was as toxic as permethrin and bifenthrin against susceptible adults of *An. gambiae.* More interesting, we noted large difference in adult toxicity of dinotefuran between species (*An. gambiae* being significantly more affected than *Ae. aegypti* and *Cx. quinquefasciatus*). This unusual and unexplained phenomenon may have significant implications for a potential use of neonicotinoids for bed net treatments.

Table 3. Comparative toxicity of dinotefuran against susceptible and resistant strains of *An. gambiae*, *Ae. aegypti*, and *Cx. quinquefasciatus* tested at the adult stage (topical applications)

Species	Strains (*N*)	LD_{50} (ng/mg female) (95% CI)	LD_{95} (ng/mg female) (95% CI)	Slope ± SE Parallelism test[a]	RR_{50} (95% CI)	RR_{95} (95% CI)
An. gambiae	KIS (S)	0.18	0.73	2.70 ± 0.18		
	(149)	(0.16–0.19)	(0.63–0.88)			
	VKPER (R)	0.30	1.44	2.44 ± 0.36	1.71	[b]
	(152)	(0.26–0.36)	(0.92–2.33)	accepted	(1.36–2.15)	
Ae. aegypti	BORA (S)	7.14	24.54	5.01 ± 0.39		
	(151)	(6.33–8.07)	(17.77–34.62)			
	LHP (R)	12.57	41.60	3.17 ± 0.24	1.76	1.68
	(144)	(11.56–13.63)	(35.22–51.70)	rejected	(1.50–2.01)	(1.10–2.55)
Cx. quinquefasciatus	SLAB (S)	13.75	28.20	5.27 ± 0.75		
	(149)	(12.73–14.78)	(23.15–34.70)			
	BKPER (R)	31.16	65.37	5.11 ± 0.39	2.29	[b]
	(148)	(29.69–32.62)	(59.03–74.77)	accepted	(1.81–2.90)	
	RLAB (R)	9.49	21.06	4.75 ± 0.32	0.70	[b]
	(149)	(8.96–10.02)	(19.07–23.89)	accepted	(0.54–0.88)	

N, number tested; S, susceptible; R, resistant.
[a] Parallelism test rejected if slopes between susceptible and resistant strains of the same species are significantly different at 95% CI.
[b] RR_{95} not statistically different from RR_{50} because regression lines between susceptible and resistant strains are parallel ($P > 0.05$).

In addition, it has been noted that the toxicity of dinotefuran was not strongly modified by the two common insecticide resistance mechanisms, i.e., *kdr* mutation and insensitive acetylcholinesterase. When comparing with previous data obtained by Corbel et al. (2004) on mosquito larvae, dinotefuran was shown to be 10 times more toxic than permethrin and 1000 times more toxic than propoxur against the pyrethroid- (BKPER) and carbamate (RLAB)-resistant *Cx. quinquefasciatus*, respectively. This finding is of great importance in development of alternative insecticides for field applications because pyrethroid and organophosphate/carbamate resistance is now widely developed in mosquitoes (Chandre et al. 1998, 1999; Brengues et al. 2003; N'Guessan et al. 2003). Because neonicotinoids have a different mode of action as common insecticides, such chemicals also could contribute to a better management of insecticide resistance. However, one cannot exclude that increased metabolic detoxification, such as elevated oxidase or esterase activities, might be involved in neonicotinoid resistance. Indeed, Kiriyama and Nishimura (2002) showed increased toxicity of dinotefuran when adding piperonyl butoxide, an oxidase inhibitor. The slightly lower activity of dinotefuran against the pyrethroid-resistant strains of *Ae. Aegypti* and *Cx. quinquefasciatus* may be due to a higher metabolic detoxification through the cytochrome P450-dependent monooxygenases. Increased monooxygenase activity has not been investigated in the LHP strain but has already been detected in the BKPER strain (Chandre et al. 1998).

It was also interesting to note that dinotefuran was slightly more toxic against the carbamate-resistant strain of *Cx. quinquefasciatus* than the susceptible one. This could be explained by the fact that mosquitoes showing an insensitive acetylcholinesterase ($Ace.1^R$ gene) were less efficient at degrading nicotinic sub-

Table 4. Comparative larval and adult toxicity of several insecticides against susceptible reference strains of *An. gambiae*, *Ae. aegypti*, and *Cx. quinquefasciatus*

	Larval bioassays (LC_{50}, mg/l)			Topical applications (LD_{50}, ng/mg female)		
	An. gambiae	*Ae. aegypti*	*Cx. quinquefasciatus*	*An. gambiae*	*Ae. aegypti*	*Cx. quinquefasciatus*
Organochlorine						
DDT	—	0.106	0.023	—	—	—
Organophosphates						
Temephos	0.0047	0.0017	0.0015	—	195	—
Chlorpyrifos ethyl	0.0013	0.0021	0.0016	—	—	—
Carbamates						
Carbosulfan	0.0014	0.0097	0.0032	—	—	—
Propoxur	0.11	0.39	0.15	—	—	—
Pyrethroids						
Permethrin	0.011	0.0011	0.0015	1.02	0.24	2.21
Deltamethrin	0.00044	0.00012	0.00012	0.018	—	0.14
Bifenthrin	0.0087	0.00045	0.00069	0.14	0.077	0.16
Fiprols						
Fipronil	0.0059	0.028	0.0034	0.040	0.020	0.014
Neonicotinoids						
Dinotefuran	0.17	0.21	0.34	0.18	7.1	13.6

—, data not available.
Source: Chandre and Duchon, personal communication.

strates than susceptible individuals of the same species (Bourguet et al. 1997). In the presence of a neonicotinoïd insecticide such as dinotefuran, the concentration of acetylcholine (ACh) at the synaptic level could increase more rapidly with the carbamate-resistant strain (RLAB) than the susceptible strain (SLAB). This higher concentration of ACh in the synapses probably leads to an earlier saturation of the nicotinic receptors (which leaves the ACh receptor permanently open), resulting in higher mortality of the R-LAB strain.

The knockdown activity, which is a key factor in the prevention of mosquito bites, has been demonstrated with dinotefuran against the cockroach *P. americana* (Mori et al. 2001). This activity needs to be confirmed in mosquitoes, particularly against *kdr*-resistant *An. gambiae*, which are susceptible to dinotefuran. The excito-repellent effect, which is another characteristic of pyrethroid activity and key element in personal protection of insecticide-treated mosquito nets, has to be further investigated for dinotefuran. Comparison of the mosquitocidal activities of dinotefuran with other neonicotinoids is also of relevance to ensure that the compound is representative of this class group of insecticides.

Despite that dinotefuran is somewhat less toxic to mosquitoes than other insecticides, its low mammalian toxicity and good activity against pyrethroid- and carbamate-resistant mosquitoes makes it potential candidate for further study for control of mosquito-borne disease.

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