Acta Scientific Pharmacology

Volume 3 Issue 11 November 2022

Research Article

Side Effects of The Antiemetic Drug Motilium (Domperidone) Studied on Ants as Models

Marie-Claire Cammaerts*

Independent Researcher, Retired from the Biology of Organisms Department, University of Brussels, Belgium

***Corresponding Author:** Marie-Claire Cammaerts, Independent Researcher, Retired from the Biology of Organisms Department, University of Brussels, Belgium.

Received: October 10, 2022

Published: October 27, 2022

Abstract

The antiemetic active substance of Motilium, Domperidone, is very efficient, but is no longer authorized in France for children due to its side effects. These effects (reported e.g., in the notice for use joined to the drug package) concerns several health problems, but not many other physiological and ethological important traits which may be affected by Motilium consumption. We thus examined, on ants as models, if such impacts may occur. Motilium appeared to affect the ants' food intake, activity, locomotion, orientation ability, audacity, sensory perception, social relationships, state of stress, cognition, learning and memory. The ants did not adapt themselves to the drug side effects, and developed dependence on its consumption. Motilium partly lost its effect in two hours, then became inefficient in about 12 more hours. Thus, Domperidone have effectively a lot of severe side effects. Researchers have found clinical analyses which allow predicting if the patients will suffer from this drug side effects. Therefore, since Motilium is very efficient, we propose to go on using it, but before using it to check if the patients could no suffer from side effects, and during the treatment (with the smallest possible dose and during the shortest possible time period) to monitor the patients as for the occurrence of side effects, e.g., decrease of activity and audacity, locomotor problems, social interrelations problems, stress, and dependence.

Keywords: Addiction, Audacity; Cognition; Nausea; Sensory Perception; Social Relationships

Abbreviations

ang.deg.: Angular Degrees; ang.deg./cm: Angular Degrees Per cm; χ^2: Chi Square; cm: Centimeter; h: Hour; n°: Number; min: Minute; mg: Milligram; mm: Millimeter; mm/s: Millimeter Per Second; ml: Milliliter; %: Percentage; s: Second; t: Time; *vs*: Versus

Introduction

Motilium, the active substance of which is domperidone, is an antiemetic drug devoted to care of patients suffering from nausea, vomiting, dyspepsia or gastro-esophageal reflux. Its efficiency has been largely proved through many medicinal researches on different kinds of patients. Among others, children presenting gastro esophageal reflux and respiratory disorders were significantly in better health after having been treated with Motilium, and in addition, they presented no side effect [1]. In the same way, Domperidone was efficient and safe while caring of patients suffering from nausea, dyspepsia and vomiting [2]. Motilium also appeared to have a considerably 'sic the authors' efficient antiemetic effect in patients under chemotherapy [3]. Motilium could also prevent the gastro intestinal side effects of different drugs used in pulmonology [4]. This drug was also efficiently used to treat the gastro intestinal complains which occur during women's menopause [5]. A review of the pharmacological activity and the pharmacokinetics of Motilium once more revealed its efficiency to treat dyspepsia and as an antiemetic drug, and during this study, side effects seldom occurred [6]. A medicinal work, made for examining the benefits and side effects of domperidone while caring of 125 patients having several health problems, pointed out the efficiency of the drug, particularly for decreasing nausea, vomiting and stomach fullness. However, 12% of the patients presented some side effects [7]. A research work made in Great Britain showed that domperidone was efficient and induced side effects only if used at high dose. Since, at that time, in that land, the marketing of the drug was restricted to short term use, the authors concluded that their reported side effects were unlikely to occur [8]. Nevertheless, in the notice joined to Motilium packages, several side effects are reported, e.g., anaphylactic shock, anxiousness, nervousness, dizziness, drowsiness, headache, dry mouth, asthenia, akathisia, depression. In France (Europa), the drug is nowadays authorized only for patients weighing more than 35 kg; it can thus no longer be used for young children.

Among all the works carried out on Motilium, no information is given as for the impact of this drug on the consumers' audacity, sensory perception, social relationships, cognition, learning and memory, adaptation to the drug side effects, and decrease if the effect of the drug after its consumption was stopped. Consequently, on the basis of the available information related here above, and knowing the recurrent problems resulting from the confrontation between the side effects of drugs and their high-level marketing, we intended to examine, on ants as biological models, the potential side effects of Motilium on several physiological and ethological traits. Before relating this work, we explain why using ants as models, which species we used and what is known on it, and which traits we aimed to consider.

Use of ants as models

Genetics, nerve impulses, muscle contraction, sensory perception, memorization, and other fundamental biological processes are common to every animal species, including humans. This is why some invertebrates and vertebrates are often used as biological models for studying humans' problems [9,10]. Invertebrates are preferentially used because they are small, can easily be maintained in any room, and present a small generation time [11]. Insects are often used [12], for instance, the locusts, the mealworms, the fruit flies, the bees [12]. Ants can thus be used as models, the more so because their maintenance is very easy and not at all expensive, and because they detain several evolved biological characters on which the impact of products used by humans can be examined. Indeed, the ants can memorize visual and olfactory cues and use them for navigating, they emit specific chemical substances (pheromones) which inform nestmates, they can recruit congeners for efficiently collect food, they differently mark zones of their territorial area. In addition, they take care of their brood, build complex nests, clean them and manage cemeteries at the frontiers of their territory. They also detain many cognitive abilities (numerosity abilities, passing time perception …) and perform rather complex tasks (e.g., relocation of the nest including the transport of the brood) [13].

The species used and what is known on it

We here used the species *Myrmica sabuleti* Meinert, 1861. We know its recruitment system, navigation strategy, visual perception, visual and olfactory conditioning [14], and the ontogenesis of some of their abilities [15]. They can recognize themselves in a mirror [16]. The distance effect, size effect and Weber's law apply to their perception [17,18]. They detain many numerosity abilities [19-21]. However, their cognition always stays at a concrete level, without reaching abstraction.

The examined physiological and ethological traits.

The physiological and ethological traits on which Motilium could have an impact were the ants' food intake, general activity, locomotion, orientation ability, audacity, tactile (pain) perception, social relationships, stress, cognition, learning and memory. The ants' adaptation to the adverse effect of the drug and their dependence on its consumption were also examined. In addition, we defined the decrease of the effect of the drug after weaning. The experimental methods were similar to those used in previous works (e.g. [22-24]) (we have until now studied the effects of 53 products [25-31]). They are thus here rather briefly related, though without avoiding some self-plagiarism.

Materials and Methods

Collection and maintenance of ants

We experimented on two colonies of *M. sabuleti* collected in 2021, during the spring, from an abandoned quarry located in Ardenne (Belgium) in the Aise valley. Each colony contained *ca* 500 workers, a queen and brood. They were maintained in one to three glass tubes half-filled of water, with a cotton plug separating the water from the space devoted to the ants. The nest tubes of each colony were deposited in a tray (34 cm x 23 cm x 4 cm). These trays constituted the ants' foraging area; in them, pieces of *Tenebrio molitor* larvae (Linnaeus, 1758) were delivered three times per week, and a cotton-plugged tube filled with sugar water was permanently set. The lighting of the room varied between 110 and 330 lux, the temperature equaled *ca* 20°C, the humidity *ca* 80%, and the electromagnetic field *ca* 2 µWm², these environmental conditions being suitable to *M. sabuleti*. Here, the words 'workers' and 'nestmates' were often used instead of 'ants' as commonly done by researchers on social insects.

Solution of Motilium (Doperidome) given to the ants

A package of 30 tablets containing each one 12.72 mg Domperidone maleate (= 10 mg Domperidone) was furnished by the pharmacist Wera (1170 Bruxelles, Belgium). The drug was manufactured and authorized by Johnson & Johson Consumer NV/SA, Antwerpseweg, 15-17, 2340, Beerse, Belgium. Its number is BE109986. Humans are advised to consume maximally 3 tablets of 10 mg Domperidome per day. Humans drink about one liter of water per day. Thus, when treated with Motilium, they consume 30 mg of this drug together with one liter of water. Insects, and so ants, consume about ten times less water than mammals due to their anatomy (cuticle) and physiology (excretory apparatus). Therefore, for setting ants under a Motilium diet similar to that of patients cared of with that drug, they must be provided with a solution of three tablets of Motilium 10 mg Domperidome in 100ml of water. We needed only about 30 ml for making our experimental work. Consequently, one tablet of Motilium was duly crushed (Figure 1) then dissolved into 33 ml of the ants' usual sugared water, and the drug solution was delivered to the ants in their usual cotton-plugged tubes. The plug of these tubes was refreshed every 2-3 days, and the entire solution was renewed every 7 days. Each day, we checked if the ants drunk the delivered solution, and they little did. The control experiments were firstly made on the two colonies maintained under normal diet. Then, the tubes filled of sugar water were replaced by tubes filled of the sugared solution of Motilium, and the experiments started after the ants had this solution at their disposal for 24 hours.

Figure 1: Realization of the solution of Motilium (Domperidone) given to the ants. Successively, from left to right, upper part: the chemical structure of Domperidone, a package of Motilium; lower part: the material used to make the solution, a tablet of Motilium duly crushed, the tubes filled with the solution, ready to be given to the ants.

Meat and sugar water consumption, general activity

For ants under one then the other kinds of diet, the workers being on the meat food, those staying at the entrance of the sugar water tube, and those being active in the foraging area, at the nest entrance, or inside of the nest) were separately counted four times per day (twice during the day, twice during the night) for each two colonies, as e.g.., [22-24]. The total number of each kind of count equaled 6 days x 2 colonies x 4 counts per day = 48 counts. For each diet and each kind of count, the means of the six daily counts was established (Table 1, lines I - VI), and for each kind of count, the six means obtained for ants consuming Motilium were compared to the six means obtained for ants living under normal diet using the non-parametric test of Wilcoxon [32]. In addition, for each diet and count, the mean of the six daily means was calculated (Table 1, I-VI = last line).

Linear and angular speeds; orientation to a tied nestmate

These physiological traits were assessed, as in e.g., [22-24], on ants moving in their foraging area, the speeds without stimulating them, the orientation while presenting them a nestmate tied to a piece of paper (Figure 2 A). A tied nestmate emits its alarm attractive mandible glands pheromone, and the workers being in its surroundings soon moved towards it. For assessing the ants' speeds on one hand and their orientation on the other hand, 40 ants' trajectories were recorded and analyzed thanks to appropriate software. The latter assessed the three variables on the basis of the following definitions [33]. The linear speed (measured in mm/s) is the length of a trajectory divided by the time spent to travel it; the angular speed (measured in ang.deg./cm) is the sum of the angles made by successive adjacent segments, divided by the length of the trajectory; the orientation to a defined point (measured in ang. deg.) is the sum of successive angles made by the direction of the trajectory and the direction towards the defined point, divided by the number of measured angles. When the orientation value is inferior to 90°, the animal tends to orient itself toward the defined point; when the orientation value is superior to 90°, the animal tends to avoid the defined point. For each three considered variables, the median and the quartiles of the 40 recorded values were established (Table 2, lines 1, 2, 3). Also, for each three considered variables, the distribution of the values obtained for ants maintained under a diet with Motilium were compared to that obtained for ants living under normal diet using the non-parametric χ^2 test [32].

Audacity

This ethological trait was evaluated through the ants' tendency in coming onto an unknown apparatus, as in e.g., [22-24]. A cylinder (height = 4 cm; diameter = 1.5 cm) vertically tied to a squared platform (9 cm^2), both in Steinbach® white paper, was set in the foraging area of the two used colonies. Then, the ants present on this apparatus were counted 20 times over 10 minutes (i.e., each 30 seconds) (Figure 2B). For ants on each kind of diet, the mean and the extremes of the recorded counts were established (Table 2, line 4). Also, the numbers obtained for the two colonies were chronologically added and then, the numbers relative to each two successive minutes were summed, what provided ten successive sums. These sums obtained for ants under a diet with Motilium were compared to those obtained for ants under normal diet using the non-parametric Wilcoxon test [32].

Tactile (pain) perception

This physiological trait was assessed through the ants moving on an uncomfortable substrate. Indeed, ants duly perceiving the rough character of substrate walk on it slowly, sinuously, with difficulty, and often touch the substrate with their antennae (Figure 2, C1). On the contrary, ants poorly perceiving the rough character of a substrate walk on it more frankly, more easily, more rapidly and less sinuously, and seldom touch the substrate with their antennae. Therefore, as in e.g., [22-24], to assess the ants' tactile (pain perception), their linear and angular speeds were quantified while they were walking on a rough substrate. A piece (3 cm x 2 + 7 + 2 = 11 cm) of n° 280 emery paper was adequately folded and set in a tray (15 cm x 7 cm x 4.5 cm) dividing this tray in a first small 3 cm long one, a second zone 3 cm long one covered with the emery paper, and a third zone 9 cm long zone. For making an experiment on a colony, 20 ants of that colony were transferred into the first small 3 cm long zone of the apparatus, and 20 of their trajectories were recorded while they walked in the zone covered with the emery paper. Their linear and angular speeds were then quantified as these two variables have been previously assessed (see the subsection relative to the ants' speeds). Since two colonies were used, a total of 40 values of linear and of angular speeds were recorded. For each of speed, the median and quartiles of the obtained values were established (Table 2, lines 5, 6). In addition, for each speed (linear and angular), the distribution of the values obtained for ants consuming Motilium was compared to the corresponding distribution obtained for ants maintained under normal diet using the non-parametric χ^2 test [32].

Brood caring behavior

As in e.g., [22-24], a few larvae and nymphs of each two used colonies removed from the nest and deposited in front of the entrance. For each colony, five of these removed larvae and nymphs were monitored during five minutes. The ants' behavior towards these larvae or nymphs were cautiously observed (e.g., their finding, caring of, and holding them) (Figure 2 D) and those not yet re-entered inside the nest were counted after 30 seconds, 1, 2, 3, 4, and 5 minutes. Only five larvae or nymphs of each two colonies were so tracked because they must be so simultaneously. Also, the observation was not repeated because removing larvae and nymphs out of the nest induced a great perturbation to the colonies which could imperil the survival of the ants' brood. The six numbers of not re-entered larvae or nymphs obtained for the two colonies were correspondingly summed (Table 3, line 1), and the six sums obtained for ants consuming Motilium were compared to the six sums obtained for ants maintained under normal diet using the non-parametric test of Wilcoxon [32].

Social relationships (interactions between nestmates)

Nestmates, i.e., ants belonging to the same colony, are normally not aggressive towards one another. However, some factors (e.g., drugs) may alter this usual peaceful behavior. Therefore, to examine the impact of Motilium on these nestmates' usual peaceful interactions, we conducted, as in e.g., [22-24], five dyadic encounters of nestmates for each two colonies. Each encounter occurred in a cup (diameter = 2cm, height = 1.6cm) the borders of which being lightly covered with talc to prevent ants from escaping. During each encounter, one of the two encountered nestmates was observed during 5 minutes, and its behavior was characterized by the numbers of times it did nothing (level 0 of aggressiveness), touched the other ant with its antennae (level 1), opened its mandibles (level 2), gripped and/or pulled the other ant (level 3), and tried to sting or stung the other ant (level 4) (Figure 2, E). The numbers obtained for each colony and each ant were correspondingly added (Table 3, line 2). The obtained distribution of these added numbers recorded for ants provided with Motilium was compared to the equivalent distribution recorded for ants living under normal diet using the non-parametric χ^2 test [32]. In addition, for each kind of diet, the ants' potential aggressiveness was evaluated thanks to a variable 'a' which equaled the number of aggressiveness levels 2 + 3 + 4 divided by the number of aggressive levels 0 + 1 (Table 3, line 2).

State of stress and cognition through escaping ability

For being able to escape from an enclosure, an individual must be calm, not stress, and look for a potential exit. Also, their cognitive abilities must be intact, not affected by any factor. Consequently, to assess the ants' state of stress and cognition, as in e.g., [22-24], six workers of each colony were enclosed under a reversed polyacetate cup (= an enclosure, height = 8cm, bottom diameter = 7 cm, ceiling diameter = 5 cm, the inside surface having been slightly covered with talc) set in their foraging area. A notch (3 mm height, 2 mm broad) had been created in the rim of the bottom of the cup for giving to the ants the possibility of escaping (Figure 2 F). For each colony, the workers which could escape after 2, 4, 6, 8, 10 and 12 minutes were counted and the numbers obtained for the two colonies were correspondingly added (Table 3, line 3). The six successive sums obtained for ants having Motilium at their disposal were compared to the six ones obtained for ants maintained under normal diet using the non-parametric Wilcoxon test [32].

Cognition

This trait was assessed through the ants' ability to navigate a twists and turns path. To do so, as in previous works (e.g., [22-24]), two pieces of paper (Steinbach®, 12 cm x 4.5 cm) adequately folded were inserted inside a tray (15 cm x 7 cm x 4.5 cm) in order to create a twists and turns path between a first 2cm long area in front of this path and a second 8 cm long one beyond it. Such an apparatus was constructed for each colony. To make an experiment on a colony, 15 workers were transferred into the area lying in front of the twists and turns path (Figure 3 A), and since that time, the ants still there and those having reached the area lying beyond he twists and turns path were counted after 2, 4, 6, 8, 10 and 12 minutes. The numbers obtained for the two colonies were correspondingly added (Table 3, line 4). For the zone lying in front of the difficult path as well as for that lying beyond this path, the numbers obtained for ants consuming Motilium were compared to those obtained for ants living under normal diet using the non-parametric Wilcoxon test [32].

Visual operant conditioning and memory

As previously conducted (e.g., [22-24]), for the two colonies having a solution of Motilium at their disposal, at a given time, a green hollow cube made in strong paper (Canson®) was set above the entrance of the tube filled with this drug solution and the pieces of mealworms were transferred near that tube and the green cube (Figure 3 B 2). Since that time, the ants underwent operant visual conditioning. The control experiment was previously made on another colony of *M. sabuleti* collected from the same site at the same date and maintained under normal diet. Doing so is required because when an ant has acquired conditioning to a stimulus, it keeps it during minimally two to three days and also, after having lost its conditioning, it more quickly than usually acquires it again. In other words, an ant once conditioned to a stimulus can no longer be used for quantifying its acquisition of conditioning. In the course of the ants' conditioning acquisition, then after the green cube removal, in the course of their loss of conditioning, the ants of each of each used colony were tested in an own Y-apparatus (made of strong white paper, with its sides slightly covered with talc) deposited in a separated tray. A green hollow cube was set randomly in the left or the right branch of the Y-apparatus. To make a test on a colony, 10 ants were transferred one by one in the Y-maze, about 2 cm before its division in two branches, and for each tested ant, its first choice of one or the other branch of the Y-apparatus was recorded (Figure 3 B 2). Choosing the branch containing the green cube was giving the correct response. Each tested ant was maintained in a cup until 10 ants of its colony were tested for avoiding testing twice the same ant. For each colony, after 10 ants were tested, they were transferred back into their foraging area. For each considered conditioning time period, the 10 responses given by the ants used for the control experiment were used as they were, while the 10 responses given by the ants of colonies A and B were added (total n° of responses for each conditioning time period = 10 control responses, and 10 x 2 = 20 test responses) and the proportions of correct responses (= the conditioning scores) was each time established (Table 4). The successive scores obtained for ants consuming Motilium were compared to the successive scores previously obtained for ants living under normal diet using the non-parametric test of Wilcoxon [32].

Adaptation (tolerance) to motilium adverse effects

An individual can adapt itself to the adverse effects of a drug when it less and less suffers from these adverse effects over its drug consumption. For studying such an adaptation, a trait impacted by the drug must be quantified soon after then a longer time after the individual consumes the drug., and the results of the two quantifications must be compared. In the present work, the traits particularly impacted by Motilium were the ants' locomotion and essentially their linear speed, as well as their food intake and general activity.

Consequently, the ants' linear and angular speeds were again quantified after the ants had consumed the drug during seven days exactly as they had been quantified after the ants had the drug at their disposal during 12 hours (Figure 3 C 2). For each kind of speed, the median and quartiles of the obtained values were established (Table 5, upper part), and the distributions of the recorded values were compared to those obtained after 12 hours of Motilium consumption using the non-parametric χ^2 test [32].

The ants' food intake and general activity were also again assessed after that the ants consumed fluvoxamine for eight days, exactly as they had been during the first six days of the drug consumption, except that the six new assessments were made over 24 hours (i.e., 6 times 12 counts over 24 hours). For each examined trait, the mean of these six assessments was established (Table 5, lower part), and the value of the six assessments were compared to the six corresponding ones obtained during the six first days of the drug consumption using the non-parametric Wilcoxon test [32].

Dependence on motilium consumption

An individual becomes dependent on a drug use when it enjoys consuming this drug, tries to have it always at its disposal, uses it even if suffering from its adverse effects, and finally can no longer live without consuming the drug. In the present work, the ants' dependence on Motilium was examined after the ants consumed it during 9 days. To do so, 15 ants of each colony were deposited into an own tray (15cm ×7 cm × 5cm) into which two cotton-plugged small tubes (h = 2.5 cm, diam. = 0.5 cm) had been set. One of the tubes contained sugar water, the other one contained the sugared solution of Motilium used all over the entire experimental work (Figure 3 D 2). The tube containing the drug was located on the right in one tray and on the left in the other tray. After the ants' deposit in the tray, for the two colonies, the workers present at the entrance of each tube were counted 15 times over 15 minutes, and the 15 counts obtained for the two colonies were correspondingly added (Table 5, lower part). Then, the total numbers of ants sighted in front of each tube wee separately added. The two obtained sums allowed calculating the proportion of ants having visited the tube containing the drug and the tube containing the drug-free solution. The two obtained sums were compared to the two numbers which would have been obtained if the ants have randomly gone near one and the other kind of tube, this using the non-parametric χ^2 goodness-of-fit test [32].

Decrease of the effects of motilium after its consumption was stopped

This decrease was studied after the ants consumed the drug during 11 days using the ants' linear speed as physiological trait impacted by the drug. Twelve hours before starting this study, a fresh solution of Motilium was delivered to the ants. After these 12 hours, at t = 0, the ants' linear speed was assessed as it had been after 1 and 8 days of the drug consumption, except that 20 and not 40 ants' trajectories were recorded and analyzed. This sample reduction was made for being able to make the successive assessments over the decrease of the effect of Motilium and so, to evaluated the situation at any time. After the assessment made at t = 0, the ants' tubes containing the sugared solution of Motilium were replaced by tubes filled of a drug-free aqueous sugar solution, and weaning so started. The ants' linear speed was then assessed every two hours, until this trait became similar to that of ants living under normal diet (= the control value). For each record, the median and quartiles of the 20 obtained values were established (Table 6). The successively obtained distributions of values were compared to that obtained at t = 0 and to the control one using the non-parametric χ^2 test [32]. In addition, the mathematical function which could best describe the decrease of the effect of Motilium on the ants' linear was empirically established.

Results and Discussion

Meat and sugar water consumption, general activity

These three physiological traits were affected by Motilium consumption (Table 1). While consuming this drug, the ants eat less meat, drunk less sugar water, and were far less active than when living under normal diet. This was statistically significant (for each of the three traits: N = 6, T = 21, P = 0.016). This is not in favor of the drug use.

Days	Normal diet			Diet with Motilium		
	Meat	Sugar water	Activity	Meat	Sugar water	Activity
I	0.38	1.50	14.50	0.13	0.25	9.00
II	0.38	1.12	13.88	0.13	0.13	6.00
III	0.50	1.00	13.50	0.25	0.13	5.50
IV	0.63	1.00	15.50	0.13	0.13	6.25
V	0.50	1.25	16.00	0.25	0.13	6.00
VI	0.63	0.88	16.50	0.25	0.00	4.50
I-VI	0.50	1.13	14.98	0.19	0.13	6.21

Table 1: Impact of Motilium (Domperidone) on the ants' food intake and activity. For each considered trait, the table gives the means of eight daily counts (lines I to VI) as well as the average of these six means (line I-VI). The drug appeared.

Traits	Normal diet	Diet with Motilium
Linear speed (mm/s)	8.3 (7.8 - 9.8)	4.9 (4.3 - 5.2)
Angular speed (ang.deg./cm)	96 (88 - 112)	115 (92 - 130)
Orientation (ang.deg.)	26.6 (22.2 - 31.5)	70.7 (55.7 - 83.7)
Audacity (n°)	2.50 [1 - 5]	0.75 [0 - 2]
Tactile (pain) perception linear speed	4.0 (2.9 - 4.5)	4.5 (4.1 - 4.7)
Angular speed on a rough substrate	267 (238 - 287)	141 (117 - 167)

Table 2: Impact of Motilium (Domperidone) on five ants' physiological and ethological traits. The table provides the median (and quartiles) or the mean [and extremes] of the recorded values. Briefly, the drug appeared.

Linear and angular speeds

The ants' linear speed was obviously impacted by Motilium consumption (Table 2, line 1). While under that drug diet, the ants walked very slowly, with hesitation and difficulty, often touching the substrate with their antennae, stopping, lifting their gaster, behaving as if suffering. They did not walk very sinuously, but their linear speed being slow, their trajectories were short, what leaded to a somewhat larger sinuosity. In fact, for the observers, they simply walked slowly and unusually. The numerical and statistical results confirmed these observations. Indeed, the linear speed of ants consuming Motilium was statistically highly lower than that of ants living under normal diet (4.9 *vs* 8.3; χ^2 = 76.10, df = 1, P < 0.001) and the angular speed of the former ants was slightly higher than that of the latter ants (115 *vs* 96; χ^2 = 10.61, df = 2, P < 0.01). Seven days later, it was checked if ants could adapt themselves to this impact of the drug on their locomotion (see the subsection relative to the ants' adaptation).

Orientation to a tied nestmate

This physiological and ethological trait was affected by Motilium consumption (Table 2, line 3; Figure 2 A). While under normal diet, the ant soon and correctly oriented themselves towards a tied nestmate, when they lived under a diet with the drug, they poorly did so, and the decrease of orientation ability was statistically significant (χ^2 = 46.07, df = 2, P < 0.001). This was surely due to the impact of the drug on the ants' locomotion (see the above subsection), but could also be due to a decrease of the ants' perception and maybe to an impact of the drug on their social relationships. These two latter presumptions were investigated thanks to two following experiments (see the subsections relative to the ants' tactile perception and to their social relationships).

Audacity

Motilium affected this ethological trait (Table 2, line 4; Figure 2 B). Ants living under normal diet went onto the provided unknown apparatus and stay on it a few seconds. Ants consuming the drug were rather reluctant in doing so: they seldom went onto the apparatus and if doing so, they rapidly went back, away from the apparatus. Also, contrary to the ants maintained under normal diet, those consuming Motilium never climbed on the tower. The difference of behavior between the ants living under one and the other kinds of diet was significant: N = 10, T = 55, P = 0.001. This decrease of audacity may impact the ants' escaping behavior and their ability to cross a twists and turns path, two presumptions examined through the experiments relative to these two latter ethological traits.

Tactile (pain) perception

Motilium appeared to affect this physiological trait (Table 2, lines 5, 6; Figure 2 C). Looking to the tested ants allowed deducing that they walked on a rough substrate nearly as on their foraging area. A detail analysis of their locomotion revealed that they walked, on a rough substrate, at a linear speed equivalent to (χ^2 = 0.01, df = 1, 0.30 < P < 0.50) and at an angular speed slightly higher than (χ^2 = 6.71, df = 2, 0.02 < P ≤ 0.50, i.e., at the limit of significance) that on their foraging area. This means that ants consuming the drug less perceived the uncomfortable of the rough substrate, and walked on it as on a normal substrate, though somewhat more sinuously due to the difficulty in walking on such a substrate. This decrease of perception could partly explain the ants' poor orientation towards a tied nestmate (see the subsection relative to the ants' orientation), i.e., they less perceived the emitted attractive alarm pheromone, and might impact their social interactions (see the following subsections relative to the ants' brood caring and social relationships)

Traits	Normal diet	Diet with motilium
N° of not re-entered larvae over time	30s 1' 2' 3' 4' 5' 8 6 5 3 0 0	30s 1' 2' 3' 4' 5' 12 11 10 8 7 7
N° of aggressive levels 0 to 4, variable 'a'	0 1 2 3 4 'a' 52 58 10 0 0 0.09	0 1 2 3 4 'a' 20 29 47 0 0 0.96
N° of ants escaped over time	2 4 6 8 10 12 1 5 8 9 11 12	2 4 6 8 10 12 0 0 0 1 2 5
N° of ants in front (f) and beyond (b) a twists and turns path over time	2 4 6 8 10 12 f: 19 16 13 12 9 7 b: 0 0 2 4 6 8	2 4 6 8 10 12 f: 20 18 19 17 17 16 b: 0 0 0 0 0 1

Table 3: Impact of Motilium (Domperidone) on four ants' ethological and physiological traits. The table gives the numbers of not re-entered larvae over time, of the observed levels of aggressiveness, of the ants being over time in front as well as beyond a twists and turns path, and on ants escaped over time. Details are given in the text, and photos are shown in Figures 2 and 3. In short, the drug appeared to affect all the examined traits, i.e., the ants' social interrelations, state of stress and cognition.

Figure 2: Some photos of the experiment conducted for examining the side effects of Motilium (Domperidone). 1: ants under normal diet, 2: ants under a diet with Motilium. A: ants walking towards a tied nestmate duly when under normal diet, not well while consuming the drug. B: ants coming onto an unknown apparatus rather frankly while under normal diet, with reluctance while consuming the drug. C: an ant walking with difficulty on a rough substrate while living under normal diet, and rather easily (not perceiving the uncomfortable character of the substrate) while consuming the drug. D: an ant under normal diet transporting a larva, and have difficulty to do so while consuming the drug. E: two nestmates staying peacefully while under normal diet, and presenting aggressive behavior (opening their mandibles) while consuming the drug. F: an ant under normal diet escaping from an enclosure, and hesitating to do so while consuming the drug.

Brood caring behavior

Motilium appeared to impact this ethological trait. While consuming this drug, the ants presented difficulties for correctly holding the larvae, for transporting them, and for finding the nest entrance (Figure 2 D). Consequently, after the five experimental minutes, all the 10 removed larvae were re-entered in the nest by ants living under normal diet, while 7 ones were not yet so by ants consuming the drug (Table 3, line 1). We even observed that, for the latter ants, 5 larvae were not yet re-entered after half an hour. The difference as for the numbers of not re-entered larvae over time between the ants maintained under one and the other kinds of diet was significant: N = 6, T = 21, P = 0.016. This observation was in agreement with that relative to the ants' locomotion (see the subsection relative to the ants' speeds), and is not in favor of the drug use.

Social relationships towards nestmates

This ethological trait was affected by Motilium consumption (Table 3 line 2; Figure 2 E). Indeed, while ants under normal diet stayed side by side with no aggressive behavior, those consuming the drug seldom stayed so, and if doing so, they then nearly each time largely opened their mandibles. The latter behavior also occurred on the ants' foraging area and during most of the conducted experiments. The difference of behavior between the ants maintained under one and the other kinds of diet was significant: $\chi^2 = 44.85$, df = 2, P < 0.001. Also, the variable assessing the ants' aggressiveness equaled 0.09 for ants living under normal diet and 0.96 for ants consuming Motilium. This may be due to a decrease of the individuals' perception, as already suggested on the basis of the results of the experiments relative to the ants' orientation and tactile perception (see the two subsections relative to these two traits). This is not in favor of the drug use.

State of stress and cognition through escaping from an enclosure

Motilium affected these physiological traits (Table 3, line 3; Figure 3 F). While ants under normal diet soon became rather calm in the enclosure, walked along its rim, found the exit and went out, those consuming the drug stressed, poorly found the exit, and even when finding it, did not go out. Also, sometimes they approached the exit and had a tendency to go out, but went back on their way, i.e., inside the enclosure. They thus present stress and hesitation, two behaviors already observed in the course of our experimentation and general maintenance of these ants consuming Motilium. The difference as for the numbers of ants escaped over time between the ants maintained under one and the other kinds of diet was significant: N = 6, T = 21, P = 0.016. The fact that the ants consuming Motilium poorly escaped from an enclosure may also result from an impact of the drug on their cognitive abilities, a presumption examined through the two following experiments.

Cognition

Motilium appeared to affect this physiological and ethological trait (Table 3, line 4; Figure 3 A). Under normal diet, the ants entered rather soon the twists and turns path, walked inside of it rather frankly and so reached the zone lying beyond this difficult path. While consuming Motilium, the ant delayed in entering the twist and turns path (they walked up to its entrance then came back on their way). If they entered the difficult path, they often stopped, turned back and moved back in the zone lying in front of the path. Only one ant could cross the twists and turns path while eight ants living under normal diet could do so. The difference between the ants maintained under one and the other kinds of diet as for the numbers of ants counted over time in the zone lying in front of the path was highly significant (N = 6, T = 21, P = 0.016), and in the zone lying beyond the path was at the limit of significance due to the smallness of the sample (N = 4, T = -10, P = 0.063). This result was in agreement with that relative to the ants' poor ability in escaping from an enclosure (see the above subsection relative to this trait). The impact of Motilium on the ants' cognitive abilities was again examined thanks to a following experiment (see the below subsection)

Visual operant conditioning and memory

Ants consuming Motilium could not acquire conditioning. Indeed, when tested in the Y-maze, they continuously hesitated to enter the branch containing the green cube, they moved towards that branch then they came back on their way. They often stopped, opened their mandibles, turned their head and body towards one then the other branch of the Y-maze, and finally, either they went away from the division of the maze into its two branches, or went with an equal proportion either into the left or the right branch of the maze (Table 4, Figure 3 B 2). The difference between the ants maintained under normal diet and under a diet with Motilium as for their successive conditioning scores over time was significant: N = 6, T = 21, P = 0.016. Motilium affected thus the ants' short-term memory through its impact on the ants' audacity, ability to make new tasks, capability to take a decision. This observation was in agreement with those on the ants' audacity, escape behavior, and cognition (see the three subsections relative to these three traits). Since ants under Motilium diet could not acquire conditioning, the impact of this drug on their middle-term memory could not be examined.

Adaptation (tolerance) to Motilium adverse effects

Briefly, the ants did not adapt themselves to the side effects of Motilium (Table 5, upper part; Figure 3 C 2, D 2). Concerning the ants' locomotion, after having had the drug at their disposal during seven days, the ants walked at a linear speed even lower (χ^2 = 10.77, df = 1, 0.001 < P < 0.01) and, consequently, at an angular speed rather higher (χ^2 = 9.53, df = 2, 0.001 < P < 0.01) than those presented after one day under that drug diet. They thus not at all adapt themselves to the impact of Motilium on their locomotion. This was very obvious to observers and is not in favor of the drug use. On the basis of this result, the ants' linear speed was chosen as the trait impacted by Motilium for studying the decrease of the effect of that drug over time after weaning. Concerning the ants' food intake, after having Motilium at their disposal for eight days, the ants continued to eat very little meat and to drink very little sugar water, just like when having had the drug for one to six days. The difference as for the numbers of ants counted on the meat and at the entrance of the tube filled with sugar water between the two times of observation (1 - 6 days *vs* day 8) was not significant (meat: successively 0.13, 0.13, 0.25, 0.00, 0.25, 0.13 → N = 2, NS; sugar water: successively 0.13, 0.13, 0.13, 0.13, 0.50, 0.13 →N = 3, NS). As for the ants' general activity, after having had Motilium at their disposal for eight days, the ants were even less active than when having had this drug for one to six days. This decrease was significant: after 8 days, successively 3.88, 5.00, 5.00, 4.00, 4.25, 4.25 ⟶ N = 6, T = -21, P = 0.016). Such a decrease of activity may result from the ants' less food intake, and all this is not in favor of the drug use.

Figure 3: Some photos of four experiments performed for knowing the impact of Motilium ((Domperidone) on the ants 'cognition (A), conditioning acquisition (B), adaptation to the drug side effects (C, D), and dependence on its consumption (E). The drug impacted the ants' cognition (ants are near the red circles) conditioning acquisition (the ants hesitated to act adequately). The ants did not adapt themselves to this impact of the drug on their locomotion (upper photo: after 1 day of consumption, lower photo: after 7 days). Also, over their consumption of the drug, the ants went on drinking less sugar water (upper photo: after two days, lower photo: after 7 days). The ants developed dependence on the drug: they essentially went onto the tube containing the drug (red dot).

Time (hours)	Under normal diet conditioning score	Under a diet with Motilium; n° correct *vs* wrong responses for colony A colony B conditioning scores
7 h	60%	5 *vs* 5 6 *vs* 4 55%
24 h	60%	5 *vs* 5 5 *vs* 5 50%
31 h	70%	4 *vs* 6 5 *vs* 5 45%
48 h	70%	6 *vs* 4 5 *vs* 5 55%
55 h	80%	5 *vs* 5 4 *vs* 6 45%
72 h	85%	5 *vs* 5 5 *vs* 5 50%
cue removal		
7 h	85%	
24 h	80%	
31 h	80%	Not examined due to the non-acquisition of conditioning
48 h	80%	
55 h	80%	
72 h	80%	

Table 4: Impact of Motilium on the ants conditioning acquisition. The table gives the control conditioning scores, as well as the right *versus* the wrong responses given by the experimented ants and their resulting conditioning scores. The drug impacted the ants' conditioning acquisition, i.e., no conditioning could be acquired.

<table>
<tr><th>Traits</th><th>Normal diet</th><th colspan="2">+ Motilium for 1 or 1-6 days</th><th colspan="2">+ Motilium for 7 or 8 days</th></tr>
<tr><td>Locomotion:
Linear speed
Angular speed
Intake: meat
Sugar water
Activity</td><td>
8.3 (7.8 - 9.8)
96 (88 - 112)
0.50
1.13
14.98</td><td colspan="2">
4.9 (4.3 - 5.2)
115 (92 - 130)
0.19
0.13
6.21</td><td colspan="2">
4.2 (3.5 - 4.6)
133 (117 - 188)
0.17
0.19
4.39</td></tr>
<tr><td colspan="2">Dependance
N° of ants sighted on the drug solution
versus on the drug-free solution</td><td>Colony A
24 vs 6</td><td>Colony B
41 vs 19</td><td>Total n°
65 vs
25</td><td>Total %
72.2% vs
27.8%</td></tr>
</table>

Table 5: Ants' adaptation to side effects of Motilium (Domperidone) and dependence on its consumption. The upper part gives the ants' linear and angular speed after one and seven days of the drug consumption (median and quartiles), as well as the ants' food intake and activity after these two time periods (n° of ants (same legends as those of Table 1 and 2). The ants did not adapt themselves to the impact of the drug on these physiological traits. The lower part of the table shows that the ants developed dependence on Motilium consumption. Photos are shown in figure 3.

Dependence on Motilium consumption

Briefly, the ants developed some dependence on Motilium consumption (Table 5, lower part; Figure 3 E 2). In details, during the experiment, 24 ants of colony A were counted in front of the drug solution while 6 ones were counted in front of the drug-free solution. At the same time, 65 ants of colony B were sighted at the entrance of the tube containing the drug solution and 25 ones at the entrance of the tube containing the drug-free solution. In total, 65 ants were seen on the drug solution and 25 ones on the drug-free solution, what leaded to 72.2% of the ants' counts for the drug solution and 27.8% for the drug-free solution. The two total of counted numbers of ants (65, 25) statistically differed from those (45, 45) expected if the ants had equally gone onto the two presented tubes ($\chi^2 = 8.43$, df = 1, $0.001 < P < 0.01$). The ants presented thus some slight though statistically significant dependence on Motilium consumption, what is not in favor of the drug use.

Decrease of the effects of Motilium after its consumption was stopped

Numerical and statistical results are given in Table 6 and are illustrated in figure 4. As soon as 2 hours after weaning, the effect of Motilium became statistically different from its initial one. Its effect stayed different from the control situation until 12 hours (P < 0.001) as well as 14 hours (P < 0.01) after weaning. It became no longer statistically different from the control situation 16 hours after weaning, and identical to that situation 18 hours after weaning. In fact, the effect of Motilim first quickly decrease during 2 hours, then from 4 to 14 hours after weaning linearly decreased (see below), and finally from 14 to 18 hours after weaning rapidly decreased until reaching the control value. The linearly decrease occurring from 4 to 14 hours after weaning obeyed to the following function:

$E_t = E_{4h} - 0.2t$ with E_t = effect at time t, E_{4h} = effect at 4 hours after weaning, t = time (in hours)

The two quick decreases of the efficacity of Motilium occurring during its loss of effect could be perceived by consumers who will then be tempted to intake again the drug, increasing so its adverse effects.

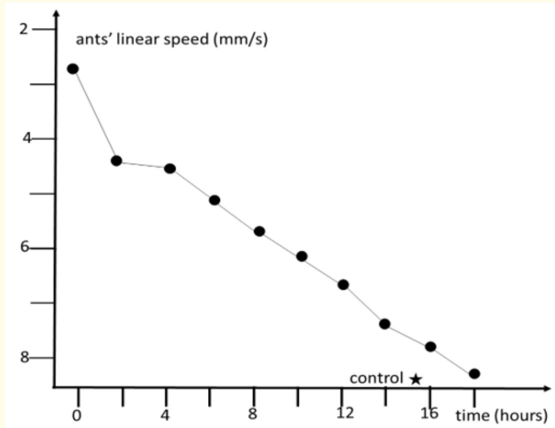

Figure 4: Decrease of the effect of Motilium (Domperidone) after its consumption was stopped. Numerical and statistical results are given in Table 6. The effect of the drug first rapidly decreased, then linearly decreased more slowly, and finally, from about 12 to 18 hours after weaning quickly and totally vanished.

Time hours	Linear speed (mm/s)	*Versus* t = 0			Stastitics *versus* control		
		χ^2	df	P	χ^2	df	P
T = 0	2.7 (2.5 - 4.1)	-	-	-	59.65	1	< 0.001
2 h	4.4 (4.1 - 5.0)	15.00	1	< 0.001	59.65	1	< 0.001
4 h	4.5 (4.2 - 5.4)	10.00	1	≤ 0.001	46.99	1	< 0.001
6 h	5.1 (4.6 - 5.4)	21.54	1	< 0.001	59.65	1	< 0.001
8 h	5.8 (5.3 - 6.4)	21.54	1	< 0.001	16.50	1	< 0.001
10 h	6.1 (5.7 - 6.6)	18.03	1	< 0.001	21.16	1	< 0.001
12 h	6.7 (5.8 - 7.2)	21.54	1	< 0.001	13.32	1	< 0.001
14 h	7.2 (6.4 - 7.8)	21.54	1	< 0.001	8.42	1	< 0.01
16 h	7.6 (7.1 - 8.7)	21.54	1	< 0.001	2.14	1	< 0.20
18 h	8.2 (7.2 - 9.9)	21.54	1	< 0.001	0.16	1	≤ 0.70
Control	8.3 (7.8 - 9.8)	21.54	1	< 0.001	-	-	-

Table 6: Decrease of the effect of MOtilium after its consumption was stopped. The table gives, for each testing time, the median (and quartiles) of the recorded values of the ants' linear speed (mm/s) (column 2), as well as the results of non-parametric χ^2 tests made between these values and those obtained and t = 0 and the control ones (column 3). Briefly, the effect of Motilium soon became lower than its initial one, stayed different from the control situation until about 15 after weaning, and fully vanished in a total of 18 h. These results are detailed in the text and illustrated in Figure 4.

Discussion - Conclusion

Discussion

Motilium, the active substance of which is Domperidone, is a very efficient antiemetic drug which is now authorized for only patients weighting more than 35 Kg (see the Introduction section). In addition to the references given in that section, let us add the review of Reddymasu and co-authors which once more shows the efficiency of Domperidone [34]. However, this drug presents several adverse effects. They are reported essentially in the notice for use joined to e.g., Motilium package (see the Introduction section). In the present work, we found that, in ants, this drug reduced the food intake, activity, speed of locomotion, orientation capability, audacity, sensory perception, social relations, cognition, learning, and short-term memory. The drug increased the ants' state of stress and reduced their tendency to make novel tasks. The ants did not adapt themselves to the adverse effects of Motilium, and developed dependence on its consumption. The effect of Motilium fully vanished in a total of 18 hours, decreasing very rapidly during the two first hours and somewhat quickly during the four last hours. In the notice joined to the drug package, a demi-live time of 8 hours is reported, what is in agreement with our own estimation. The correlation between a rapid decrease of effect and the occurrence of dependence is once more observed [35]. The obtained numerical and statistical results were in agreement with the observation of the experimented ants (see the photos given in the figures) and the results of the different conducted experiments were in agreement with one another. Most of our results are in agreement with the side effects reported in some works relative to Domperidone and in the notice joined to that drug package: e.g., nervousness, anxiousness, dizziness, drowsiness, asthenia, akathisia. Other ones are novel, not yet reported: e.g., locomotor disorder, decrease of the sensory perception, social relationships problems, reluctant for making new tasks, decrease of the short-term memory and of the learning, no adaptation to side effects, development of some dependence. An observed but not quantified observation which may correspond to what occurs for humans is that the young ants obviously more suffer from the side effect of Motilium than the old ants (i.e., those of about two years old).

Nevertheless, Domperidone is a very efficient drug and should be used for caring of patients who suffer from vomiting. A solution is possible. Parkman and co-authors have found through medicinal experimenting how to know if patients will suffer or not from define side effects induced by this drug [36]. An adequate exam of patients should thus be undertaken before treating them with Domperidone, and/or patients under treatment should monitored as for the occurrence of detected possible side effects. An *in vitro* study of the enzymes catalyzing Domperidone N-dealkylation and hydroxylation also concluded that a high variability exists between patients as for their tolerance of this drug, and that increased risk of adverse effects as well as decreased of efficiency could be anticipated [37].

Conclusion

Due to its efficiency, Motilium should be used to treat vomiting, nausea and some gastrointestinal problems. Since this drug presents several severe adverse effects, and since a clinical analysis of patients nowadays can predict the occurrence of most of these side effects, these potential patients should be adequately medicinally examined before being treated with the drug. In all cases, patients must be monitored as for the occurrence of side effects (e.g., locomotion problems, stress, reluctance to make new tasks, dependence etc…) all along their treatment, and the latter should be based on a small amount of the drug (i.e., only twice a half table per day) and should be limited in time (i.e., only for maximally three days).

Conflict of Interest

We have no conflict of interest as for the use of Motilium or any other similar drugs. We work on ants, on their behavior and cognitive abilities, and receive no money for doing so. We maintain the ants in the laboratory under the best possible conditions, and collect in field the smallest amount of required ant colonies.

Bibliography

1. Dupont C., *et al*. "Treatment using Motilium of gastro-esophageal reflux associated with respiratory manifestations in children". *Annales de Pédiatrie* 36.2 (1989): 148-150.
2. Reyntjens AJ., *et al*. "Domperidome , a novel and safe gastrokinetis anti-nauseant for the treatment of dyspepsia and vomiting". *Arzneimittelforschung* 28.7 (1978): 1194-1196.
3. Cha JJ., *et al*. "Antiemetic effects of Metoclopramide and Motilium suppository in patients perceiving Cisplatin based chemotherapy: a randomized crossover trial". *Journal of Korean Cancer Association* 22.2 (1990): 307-316.

4. Vadasz I., *et al*. "Examination of Motilium in the prevention of gastro-intestinal side-effects of different drugs in pulmonology". *Therapia Hungarica* 36.4 (1988): 202-205.
5. Huber G. "Treatment of gastro-intestinal complaints accompanying menopause with Motilium film-coated tablets". *Therapy Hung* 35.4 (1987): 227-231.
6. Brogden RN., *et al*. "Domperidone. A Review of its Pharmacological Activity, Pharmacokinetics and Therapeutic Efficacy in the Symptomatic Treatment of Chronic Dyspepsia and as an Antiemetic". *Drug Evaluation* 24 (1982): 360-400.
7. Schey R., *et al*. "Domperidone to Treat Symptoms of Gastroparesis: Benefits and Side Effects from a Large Single-Center Cohort". *Digestive Diseases and Sciences* 61 (2016): 3545-3551.
8. Cann PA., *et al*. "Galactorrhoea as side effect of domperidone". *British Medical Journal* 286 (1983): 1395-1396.
9. Wehner R., *et al*. "Biologie et physiologie animales". Eds. De Boeck Université, Thieme Verlag, Paris, Bruxelles (1999).
10. Russell WMS., *et al*. "The Principles of Humane Experimental Technique". Johns Hopkins University, (2014).
11. Wolf FW., *et al*. "Invertebrate models of drug abuse". *Journal of Neurobiology* 54 (2003): 161-178.
12. Andre RG., *et al*. "Insect Models for Biomedical Research". In: Nonmammalian Animal Models for Biomedical Research. Woodhead AD, editor, Boca Raton, FL: CRC Press, (1989).
13. Passera L., *et al*. "Les fourmis : comportement, organisation sociale et évolution". *Les Presses Scientifiques* du CNRC, Ottawa, Canada, (2005).
14. Cammaerts MC., *et al*. "Comparative outlook over three Myrmica species' biotopes and foragers' know-how". *Biologia* 69 (2014): 1051-1058.
15. Cammaerts MC., *et al*. "The acquisition of cognitive abilities by ants: a study on three Myrmica species (Hymenoptera, Formicidae)". *Advanced Studies in Biology* 7 (2015): 335-348 + synopsis: 349-350.
16. Cammaerts MC., *et al*. "Are ants (Hymenoptera, Formicidae) capable of self-recognition?". *Journal of Sciences* 5.7 (2015): 521-532.
17. Cammaerts MC., *et al*. "Non numerical distance and size effects in an ant". *Journal of Biology and Life Science* 11.2 (2020): 13-35.
18. Cammaerts MC., *et al*. "Weber's law applied to the ants' visual perception". *Journal of Biology and Life Science* 11.2 (2020): 36-61.
19. Cammaerts MC., *et al*. "Ants' numerosity ability defined in nine studies". *Journal of Biology and Life Science* 11.1 (2020): 121-142.
20. Cammaerts MC., *et al*. "Summary of seven more studies on numerosity abilities in an ant, four of them relating to human competence". *Journal of Biology and Life Science* 11.2 (2020): 296-326.
21. Cammaerts MC., *et al*. "A synthesis of six recent studies on numerosity abilities in an ant". *Journal of Biology and Life Sciences* 13.1 (2022): 1-23.
22. Cammaerts MC., *et al*. "R. Ethological and physiological effects of the recently most used analgesic, ibuprofen; a study on ants as models". *EC Pharmacology and Toxicology* 6.4 (2018): 251-267.
23. Cammaerts MC., *et al*. "Safety of glucosamine, examined on ants as models". *MOJ Biology and Medicine* 3.4 (2018): 132-142.
24. Cammaerts MC., *et al*. "Side effects of chloroquine and hydrochloroquine examined on ants as models". *EC Pharmacology and Toxicology* 8.11 (2020): 57-82.
25. Cammaerts MC. "Ants as biological models for studying effects of substances used by humans". *JSM Anatomy and Physiology* 1 (2016): 1003.
26. Cammaerts MC. "Some findings on ants as models, which should be considered for caring of humans". *MOJ Biology and Medicine* 1.5 (2017): 00027.
27. Cammaerts MC. "Ants as models for examining potential adverse effects of products used by humans". *JSM Anatomy and Physiology* 3.1 (2018): 1016.
28. Cammaerts MC. "Brief report of the effects of seven human drugs studied on ants as models". *MOJ Biology and Medicine* 4.2 (2019): 42-47.

29. Cammaerts MC. “Harmful effects of humans’ environmental factors and drugs, and advices for a safer live; a study on ants as models”. *World Journal of Pharmaceutical Sciences* 9.1 (2021): 34-45.

30. Cammaerts MC. “Side effects of drugs studied on ant models: a mini review”. *MOJ Biology and Medicine* 7.1 (2022): 1-7.

31. Cammaerts MC. “Not sufficiently revealed side effects of three largely used drugs, i.e. furosemide, Apranax, Metformin, studied on ants as models”. *EC Pharmacology and Toxicology* 10.6 (2022): 75-83.

32. Siegel S., *et al*. “Nonparametric statistics for the behavioural sciences”. Singapore: McGraw-Hill. (1988).

33. Cammaerts MC., *et al*. “An easy and cheap software-based method to assess two-dimensional trajectories parameters”. *Belgian Journal of Zoology* 142 (2012): 145-151.

34. Reddymasu SC., *et al*. “Domperidone: review of pharmacology and clinical applications in gastroenterology”. *American Journal of Gastroenterology* 102 (2007): 2036-2045.

35. Cammaerts MC. “Physical dependence on a substance occurs when the effect of this substance rapidly decreases after withdrawal”. *JSM Anatomy and Physiology* 3.1 (2018): 1017.

36. Parkman HP., *et al*. “Domperidone Treatment for Gastroparesis: Demographic and Pharmacogenetic Characterization of Clinical Efficacy and Side-Effects”. *Digestive Diseases and Sciences* 56 (2011): 115-124.

37. Bryan A., *et al*. “Characterization of human cytochrome P450 enzymes catalyzing domperidone N-dealkylation and hydroxylation in vitro”. *British Journal of Clinical Pharmacology* 58.3 (2004): 277-287.