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Research Article

Side Effects of Ivermectin, a Drug Recently Used to Treat Humans Suffering from the Covid-19; A Study on Ants as Models

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Abstract

Ivermectin, a drug used for caring of persons suffering from parasitizes, has recently been found to potentially be used for treating the Covid-19 illness. Though the side effects of this drug used for treating parasitizes are known, those occurring when it is used for caring of persons suffering from the Covid-19 have not yet been sufficiently examined. Working on ants as models, we found that ivermectin decreases or largely impacts the individuals' food consumption, activity, locomotion, muscles functioning, sensitive perception, social relationships, cognition, learning and memory. No adaptation occurred to these side effects; ants developed no dependence on ivermectin consumption. In ants, the drug lost its effect in 30 hours without showing any sudden decrease. Since this drug is very useful for treating parasitizes and may be shortly efficient for treating the Covid-19 illness or preventing contracting it, side effects similar to those found in ants should be cautiously examined in humans. The dosages should be medically defined, and lastly but not the least, the toxic ecological impact of this drug should be reduced.

Keywords: Activity; Cognition; Memory; Muscles Functioning; Social Relationships

Abbreviations

ang.deg.: Angular Degrees; ang.deg./cm: Angular Degrees Per cm; mm/s: Millimeter Per Second; χ^2= chi-Square; *vs:* Versus; n°: Number; cm: Centimeter; mm: Millimeter; mL: Milliliter; µL: Microliter; mg: Milligram; kg: Kilogram; s: Second; min: Minute; h: Hour; t: Time; %: Percentage.

Introduction

Ivermectin is a macrocyclic lactone, issued from the fermentation of *Streptomyses avermitilis,* the chemical structure of which is given in figure 1. It is an efficient antihelmintical drug used for treating animals and more recently humans suffering from several parasitizes such as Loaloase, onchocerciasis [1,2]. This drug can easily be found, under the commercial label e.g. Mectizan®, Stromectol®, Ivomec®. It has recently been tried to allow caring of patients suffering from the Covid-19 illness and appeared to be rather efficient in several cases [3-5]. However, its efficiency is not recognized by some practitioners, is not unanimous, this being probably essentially due to the not enough rigorous character of the rapidly conducted medicinal analysis [6]. Moreover, it seemed to have adverse effects [7,8], and maybe due to its recent urgent use for caring of persons suffering from the Covid-19, its potential side effects seem to not have been meticulously examined [same references as above]. Reported side effects, concerning patients suffering from parasitizes, are essentially neurological ones leading to some ataxia (site Wikipedia) as well as (in the notice for use joined to the drug packages) weakness, muscular pain, drowsiness, tremors, loss of appetite, headache, mental disorders. No information is given for patients having the Covid-19 illness.

Since ivermectin is efficient for treating animals and humans suffering from severe parasitizes, since it will probably be used for caring of patients having the Covid-19, and since nothing has been reported as for the drug impact on the individuals' sensory perception, social relationships, learning and memory, adaptation to side effects, dependence on its consumption, loss of its effects after weaning, among others, we intended to examine the occurrence of such side effects of ivermectin on ants used as biological models. We have already studied the side effects of more than 40 products consumed by humans [9-13] and could each time confirm those observed in humans as well as provide new information and precision about several adverse effects. Here below, we briefly explain why using ants as models, which species we used and what we know on it, and which physiological and ethological traits potentially affected by ivermectin we intended to examine.

Basic biological processes are similar for all animals, including humans, i.e. genetics, metabolism, nervous cells functioning, muscles functioning. Invertebrates and vertebrates are thus used as models for studying biological traits [14-16]. Invertebrates are advantageously used due to their short life cycle, simple anatomy, and small dimension [17,18]. Some species are commonly used, e.g. the flatworm *Dendrocelium lacteum*, the nematode worm *Caenorhabdotes elegans*, the mollusk *Aplysia californica*, the beetle *Tribolium castaneum*, the fruit fly *Drosophila melanogaster*, the domestic bee *Apis mellifera*. Insects, especially social hymenoptera, are often used [19,20]. Ants are particularly convenient to be used as models. They can easily be maintained in a laboratory, at low cost. They are eu-social insects and present sophisticated biological traits, e.g. they navigate using learned cues, recruit nestmates, differently mark parts of their territory, take care of their brood and queens, clean their nest and manage cemeteries [21]. In the present study, the side effects of ivermectin will be very obvious since insects and particularly ants are very sensitive to that drug (Wikipedia).

We worked on the species *Myrmica sabuleti* Meinerts, 1861 the biology of which we know rather well. The workers of that species can recognize themselves in a mirror, are imprinted to the appearance of their congeners, learn several behaviors in the presence of older congeners [22,23], and have numerical abilities [24,25]. Their responses are influenced by the distance and the size effects, and the physiological law of Weber can be applied to them [26,27]. They can expect the following element of an arithmetic and a geometric sequence [28]. They mentally add visual cues when the latter are of the same kind, simultaneously seen i.e. located at maximally five (horizontal distance) or four (vertical distance) cm from each other [29,30]. However, all their cognitive abilities stay at a concrete level and never reach abstraction.

In the present work, we intend to examine, on the workers of the ant *M. sabuleti* as a model, the impact of ivermectin on food consumption, general activity, locomotion, orientation ability, audacity, tactile (pain) perception, social relationships, cognition, stress, learning ability and memory, as well as the adaptation to the side effects of ivermectine, the dependence on this drug consumption, and the decrease of its effects after its consumption was stopped. The used experimental protocols are similar to those employed in previous works [31-34]; they will be briefly related, without however avoiding some self plagiarism.

Figure 1: Realization of the solution of ivermectin given to the ants and ants drinking it. Successively: chemical structure of ivermectin, drug package and material for making a stock solution, one tablet of ivermectin duly scratched, material for making the daily solution of ivermectine, the tubes to be delivered to ants, and two ants drinking the sugared aqueous solution of ivermectin.

Materials and Methods

Collection and maintenance of ants

The experiments were performed on three colonies of *M. sabuleti* collected in May 2021 in an abandoned quarry located in the Aise Valley (Ardenne, Belgium). Two colonies, labeled A and B were used for performing all the experiments; one colony labeled

C was used for making the control experiment of the study of the ants' learning and memory. These colonies lived under stones and in grass, and contained about 500 workers, a queen and brood. They were maintained in the laboratory in one to three glass tubes half filled with water, a cotton plug separating the ants from the water. The nest tubes of each colony were set in a tray (34cm x 23cm x 4cm) which served as a foraging area. In them, pieces of *Tenebrio molitor* larvae (Linnaeus, 1758) were delivered three times per week, and a tube plugged with cotton containing an aqueous sugared solution was permanently present. The lighting in the laboratory equaled about 330 lux, the ambient temperature *ca* 20°C, the humidity *ca* 80%, and the electromagnetism 2 µWm^2. Such conditions were suitable to the used species, *M. sabuleti*. The ants are here often named workers or nestmates as commonly do researchers on social insects.

Solution of iverectine® given to the ants

A package of ivermectin EG® 3 mg (i.e. containing 3 mg of ivermectin) produced by the firm Europeenne de Pharmacotechnic-Europhartech (Lempdes, France) and authorized by EG LaBo (Le Quintet, Boulogne-Billancourt, France) was furnished by the pharmacist Wera (Brussels, Belgium). Humans treated with this drug generally consume 4 tablets of ivermectin over six months, thus 1 tablet over 45 days. Humans consume about one liter of water per day while insects, due to their physiology and anatomy, consume about ten less water. Therefore, to set ants under a diet with ivermectin equivalent to that of humans, they must receive a solution of 1 tablet of the drug diluted in 100 ml of sugared water over 45 days. Such a solution was made (Figure 1). Then, 1 ml of that solution was diluted into 44 ml of sugared water and the obtained solution (= 45 ml) was kept at -15°C. This final solution was delivered to the ants in their usual sugar water cotton plugged tubes. We refreshed the cotton plug of these tubes each 2-3 days, and renewed the entire solution every 7 days. We also checked each day if ants drunk the given solution, and they did. The control experiments were firstly conducted on the two colonies, then their sugar water was replaced by the diluted sugared aqueous solution of ivermectin, and the test experiments began on these two colonies after they had the drug solution at their disposal during 24 hours. Note that in 'http://agence-prd.ansm.sante.fr › php › ecodex › rcp', the recommended doze is 200µg per day. The doze we used was 3 mg/45 = 0.066 mg = 66 µg. We kept this low doze recommended in the notice joined to the drug package since ivermectin is highly toxic for insects.

Meat and sugar water consumption, general activity

For normal diet and a diet with ivermectin, during six days, six times per day, we counted the ants present on the meat food, present at the entrance of the sugar water tube, and being active at any location of their environment (foraging area, food sites, inside of the nest). For each of these three kinds of count, and for each kind of diet, the mean of these 6 times X 2 colonies = 12 counts was established (Table 1, the six first lines). The means of the six daily means were also calculated for each kind of count and each two diets (Table 1, last line).

The six daily means obtained for each kind of count under a diet with ivermectin were compared to the six corresponding daily means obtained under normal diet using the non-parametric test of Wilcoxon [35], the level of probability being set at 0.05.

Linear and angular speeds; orientation to a tied nestmate

These variables were assessed on ants walking in their foraging area, the speeds without stimulating the ants, the orientation while stimulating them with a nestmate tied to a piece of paper (Figure 2A). A tied ant emits its attractive mandibular glands secretion which acts as an alarm pheromone. To assess the ants' speeds during one experiment and their orientation during another experiment, the trajectory of 40 ants were recorded. These trajectories were analyzed using appropriate software [36] based on the following definitions. The linear speed (in mm/s) is the length of a trajectory divided by the time spent to travel it; the angular speed (in angular degrees/cm = ang.deg./cm) is the sum of the angles made by successive adjacent segments, divided by the length of the trajectory; the orientation (in ang. deg.) towards a location is the sum of successive angles made by the direction to the location and the direction of the trajectory, divided by the number of angles measured. If the obtained value of orientation is lower than 90°, the animal tends to orient itself towards the location; if the obtained value of orientation is larger than 90°, the animal tends to avoid the location. For each variable (linear speed, angular speed, and orientation), the median and the quartiles of the distribution of 40 values were established (Table 2, lines 1, 2, 3). The distributions obtained for ants under ivermectin diet were compared to the corresponding distributions obtained for ants under normal diet by using the non-parametric χ^2 test [35].

Audacity

A cylinder (height = 4 cm; diameter = 1.5 cm) vertically maintained on a square (9 cm^2), both in white Steinbach® paper, was deposited in the ants' foraging area [31-34] and the foragers present on this apparatus, at any place, were counted 10 times over 10 min (Figures 2B). The numbers obtained for the two colonies were added. The mean and extremes of the recorded numbers were established (Table 2, line 4). Also, the numbers of ants counted for the two colonies during two successive minutes were added, and the five summed values obtained for ants under ivermectin diet were compared to the five summed values obtained for ants under normal diet using the non-parametric test of Wilcoxon [35].

Tactile (pain) perception

Ants perceiving the uncomfortable character of a rough substrate walk there slowly, sinuously, with difficulty, often touching the substrate with their antennae (Figure 2C). An ant poorly perceiving the uncomfortable character of a rough substrate walks on it more quickly, less sinuously, more easily. Therefore, to assess the ants' tactile (maybe pain) perception, a duly folded piece (3 cm x 2 + 7 + 2 = 11 cm) of emery paper n° 280 paper was tied to the bottom and the borders of a tray (15 cm x 7 cm x 4.5 cm), dividing so the tray in three zones, a first 3 cm long zone, a second 3 cm long zone containing the emery paper, and a last 9 cm long zone. For making an experiment on a colony, 12 ants of that colony were deposited in the first zone of the apparatus, and when they walked on the emery paper, their trajectories were recorded and analyzed as explained in the subsection relative to the ants' linear and angular speeds. Two colonies being used, 24 ant trajectories were analyzed, for ants under normal diet then for ants under ivermectin diet. The median and quartiles of the obtained distributions of values were established (Table 2, lines 5, 6), and the distributions obtained for ants consuming ivermectin were compared to those obtained for ants under normal diet using the non-parametric χ^2 test [35].

Brood caring behavior

A few larvae of colonies A and B were removed from their nest and set outside near the entrance. For each colony, five of these larvae were observed during five minutes (Figures 2D). The larvae among these 5 observed ones not yet re-entered in the nest after 30 seconds, 1, 2, 3, 4 and 5 minutes were counted. The numbers obtained for the two colonies were added (Tables 3, line 1). The six summed values obtained for ants consuming ivermectin were compared to the six summed values obtained for ants living under normal diet using the non-parametric test of Wilcoxon [35].

Social relationship towards nestmates

Social insects pertaining to the same colony exhibit no aggressiveness towards one another. Drugs may affect this peaceful social relationship. To assess potential aggressiveness presented toward nestmates, five dyadic encounters of ants were performed for each two colonies A and B (total of encounters = 10). Each encountering was conducted in a cylindrical cup (diameter = 2 cm, height = 1.6 cm), the borders of which having been slightly covered with talc to prevent escaping. During each encountering, one ant of the pair was observed during 5 min and its behavior towards the other ant 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), tried to sting or stung the other ant (level 4) (Figure 2E). The numbers of these 5 behaviors obtained for the two colonies were correspondingly added (Tables 3, line 2). The sums relative to ants under ivermectin diet were compared to the sums relative to ants under normal diet by using the non-parametric χ^2 test [35]. Also, the ants' level of aggressiveness was quantified by a variable 'a', equaled to the number of recorded aggressiveness levels 2 + 3 + 4 divided by the number of recorded levels 0 + 1.

Cognition

To assess this trait on one colony, 15 ants were transported in an own apparatus (Figure 3A) consisting in a tray (15 cm x 7 cm x 4.5 cm) containing two duly folded pieces of white extra strong paper (Steinbach ®, 12 cm x 4.5 cm) which created a twists and turns path between a small area 2 cm long in front of that path and a larger area 8 cm long beyond the path. After the 15 ants had been set all together in the first small area, those still in this area and those having reached the large area beyond the difficult path were counted after 2, 4, 6, 8, 10 and 12 min. The numbers obtained for the two colonies were correspondingly added (Tables 3, line 3), and the sums obtained for ants consuming ivermectin were statistically compared to those obtained for ants under normal diet using the non-parametric Wilcoxon test [35].

Escaping from an enclosure

For each colony, six ants were set under a reversed polyacetate cup (h = 8 cm, bottom diameter = 7 cm, ceiling diameter = 5 cm) deposited in the foraging area. The ants were introduced into that enclosure through a hole (diameter = 3 mm) made in the ceiling of the glass. The inner surface of the glass had been slightly covered with talc for preventing the ants climbing on it. A notch (3 mm height, 2 mm broad) had been managed in the rim of the bottom of the cup (Figure 2F) to allow the ants escaping. Ants can do so if they do not stress too much and if their cognitive ability is not impacted. Assessing the ants' ability in escaping informs thus on their state of stress and on their cognition. The ants' escaping ability was assessed by counting after 2, 4, 6, 8, 10 and 12 min those which could escape. The numbers obtained for the two colonies were correspondingly added (Table 3, last line). The six sums obtained for ants consuming ivermectin were compared to those obtained for ants living under normal diet by using the non-parametric Wilcoxon test [35].

Visual conditioning and memory

For colony C (control experiment) and for colonies A and B (test experiment), at a given time, a green hollow cube, build in strong green paper (Canson®), was set at the nest entrance (Figure 3B, training), the ants being thus able to associate the cube (= the cue) and the nest entrance (= the reward) and undergoing so visual operant (operative) conditioning. From the time of the cube deposit, the ants were tested over their conditioning acquisition, then after the cue removal, over their loss of conditioning. To do so, ten ants of each colony were individually tested in a Y-apparatus (Figure 3B, test) set in a tray (30 cm x 15 cm x 4 cm, made of strong white paper), their sides having slightly been covered with talc, and their floor covered with a thin paper changed between each test. A green hollow cube was randomly set in the left or the right branch of each Y-apparatus. An ant's choice of the branch containing the green cube was considered as being a correct response. Control experiment was performed on colony C and not colonies A and B because once an individual had been conditioned, it is no longer naïve for the used cue and its conditioning ability under a novel situation (here under ivermectin diet) can no longer be examined. To make a test on a colony, 10 ants of that colony were one by one transferred into the part of the Y-apparatus lying before the two branches, and for each ant, it was recorded if it turned into the branch containing the green cube (correct response) or into the other branch (wrong response). After having been tested, the ant was kept into a cup until the 10 ants of its colony were tested for avoiding testing twice the same ant. After 10 ants had been tested, all of them were replaced back into their foraging area, near their nest entrance. For each test, the numbers of ants of colony C (n = 10) or of colonies A and B (n = 20) having given the correct or the wrong response allowed calculating the proportion of ants' correct responses (= their conditioning score) (Table 4). Having no distribution of values at our disposal, the successive numbers of correct responses obtained for ants consuming ivermectin were statistically compared to those obtained for ants living under normal diet using the non-parametric Wilcoxon test [35].

Adaptation (tolerance) to ivermectin adverse effects

Adaptation to a drug or a situation occurs when an individual less and less suffers from the adverse effects of this drug or situation over their use. To study potential adaptation to a drug, a trait impacted by this drug must be assessed soon after the start of its consumption, and then again after several days of its consumption. In the present work, the ants' linear and angular speeds were impacted by ivermectin. These traits were thus again assessed after 6 days of ivermectin consumption, exactly as they had been assessed after one day of consumption (Table 5, upper part). The results obtained after 6 days of consumption were compared to those obtained after one day of consumption using the non-parametric χ^2 test [35].

Dependence on ivermectin consumption

An individual becomes dependent on a drug or a situation when it wants going on using this drug or situation, enjoys doing so and finally can no longer live without using it. Dependence on ivermectin was examined after the ants had consumed the drug during 8 days. To do so, for colonies A and B, 15 ants were deposited in a tray (15 cm × 7 cm × 5 cm) containing two cotton-plugged tubes (h = 2.5 cm, diam. = 0.5 cm), one filled with sugar water, the other filled with the sugared solution of the drug they consumed since 8 days. The tube containing the drug was located on the right in the tray of one colony, and on the left in the tray of the other colony (Figure 3C). Every minute during 15 minutes, the ants of each colony present at the entrance of each tube were counted, and the 15 counts made on the two colonies were correspondingly added (Table 5, lower part). The sums of the counts made for the two colonies were compared to the numbers expected if the ants randomly visited the two provided tubes using the non-parametric χ^2 goodness-of-fit test [35].

Decrease of the effects of ivermectin after its consumption was stopped

This decrease was studied after the ants had consumed ivermectin during 10 days. The experimental protocol was identical to that used in previous studies, e.g. in [31-34]. The ants were provided with a fresh solution of the drug 12 hours before weaning, and after these 12 hours, the ants' linear speed was assessed as it had previously been assessed during this work except that 20 instead of 40 ants' trajectories were analyzed for being able to finalize all the assessments in the course of the study of the decrease. After this assessment (made at t = 0h), weaning started: the sugared solution of the drug was removed and replaced by an aqueous sugared solution. From this time, the ants' linear speed was assessed every three hours until it became similar to that of ants under normal diet, and the median and quartiles of the values recorded at each test were established (Table 6, Figure 4). The distributions of the linear speed values obtained over time after weaning were compared to that obtained just before weaning (at t = 0) as well as to that obtained for ants under normal diet (i.e. control) using the non-parametric χ^2 test [35].

Days	Under normal diet			Under a diet with ivermectin		
	Meat	Sugar water	Activity	Meat	Sugar water	Activity
I	1.25	4.50	16.50	0.50	1.00	5.50
II	1.75	4.17	17.75	0.50	0.50	5.00
III	1.50	3.50	9.75	0.08	0.50	5.50
IV	1.75	2.50	9.00	0.50	1.00	5.25
V	1.50	2.25	10.75	0.25	0.75	6.00
VI	1.50	2.25	10.50	0.75	1.00	5.25
I-VI	1.54	3.19	12.37	0.43	0.79	5.42

Table 1: Impact of ivermectin on the individuals' food consumption and general activity. The table gives the mean numbers of ants counted, during 6 days, on their meat, their sugar water, and being active, as well as the means of these six daily means for the three considered counts. Ivermectin largely impacted the three considered physiological traits.

Traits	Under normal diet	Under a diet with ivermectin
Linear speed (mm/s)	10.3 (9.4 - 10.8)	6.0 (5.3 - 6.4)
Angular speed (ang.deg./cm)	104 (94 - 113)	183 (157 - 210)
Orientation (ang.deg.)	37.1 (27.9 - 43.8)	63.4 (50.0 - 80.7) 69.2 (60.6 - 84.8)
Audacity (n°)	1.80 [1 - 3]	1.35 [0 - 3]
Tactile (pain) perception: Linear speed (mm/s)	5.4 (4.3 - 6.5)	5.5 (5.1 - 6.2)
Angular speed (ang.deg./cm) on a rough substrate	282 (252 - 317)	193 (172 - 214)

Table 2: Impact of ivermectin® on five individuals' ethological and physiological traits. The table gives the median (and quartiles) or the mean [and the extremes] of the recorded data. Ivermectin impacted the five considered traits, the less impacted being the audacity, the more one being the ants' tactile perception. Details are given in the text, and three photos can be seen in figure 2.

Traits	Normal diet	Diet with Ivermectin
Brood caring: n° of not re-entered larvae over 5 minutes	t: 30s 1 2 3 4 5 min 8 6 4 2 1 0	t: 30s 1 2 3 4 5 min 10 10 10 8 7 5
N° of aggressiveness 0-4 levels towards nestmates, variable 'a'	levels 0 1 2 3 4 'a' 64 45 12 0 0 0.11	levels 0 1 2 3 4 'a' 38 48 37 1 0 0.44
Cognition: n° of ants in front and beyond a twists and turns path over 12 minutes	t: 2 4 6 8 10 12 min in front 25 21 16 12 10 8 beyond 0 1 2 4 5 6	t: 2 4 6 8 10 12 min in front 27 23 20 19 15 14 beyond 0 0 0 0 0 1
Stress and cognition: n° of ants escaped over 12 minutes	t: 2 4 6 8 10 12 minutes 2 4 6 8 10 12	t: 2 4 6 8 10 12 minutes 1 1 2 3 4 5

Table 3: Impact of Ivermectin on four ethological and physiological traits. The drug affected the four examined traits, i.e. the ants' brood caring behavior and their aggressiveness against nestmates, thus their social relationships, as well as their ability in crossing a twists and turns path and in escaping from an enclosure, thus their cognition. Details (0-4 levels, 'a' etc...) are given in the text and photos can be seen in figures 2 and 3.

Results

Food consumption, general activity

These three physiological traits were largely impacted by ivermectin (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. These three impacts were statistically significant: each time: N = 6, T = -21, P = 0.016. Each of them should be considered while treating humans with ivermectin.

Linear and angular speeds

These two physiological traits relative to the individuals' locomotion were affected by ivermectin consumption (Table 2, Lines 1, 2). Ants consuming this drug walked far less slowly and more sinuously than while living under normal diet, and these two differences were statistically significant: linear speed: $\chi^2 = 42.00$, df = 2, P < 0.001; angular speed: $\chi^2 = 46.50$, df = 1, P < 0.001. Such an impact of ivermectin on the individuals' locomotion (movement) should be taken into account when treating humans with this drug.

Orientation

This ethological and physiological trait was affected by ivermectin consumption (Table 2, line 3; Figure 2 A). Under this drug diet, the ants oriented themselves less well towards a tied nestmate than when living under normal diet and this decrease was significant: $\chi^2 = 26.98$, df = 2, P < 0.001. The experiment was repeated and leaded to an identical result (Table 3, line 3 italics). Such an impact may be due to the ants' change of locomotion under ivermectin consumption, but may also be caused by a decrease of the perception of the species' attractive alarm pheromone. The impact of the drug on the individuals' sensitive perception was examined in a following experiment (see below the subsection relative to tactile (maybe pain) perception). In any way, attention should be paid to humans treated with ivermectin as for their orientation, direction of movement and maybe sensitive perception.

Audacity

This ethological trait was slightly affected by ivermectin consumption (Table 2, line 4; Figure 2 B). Compared with ants living under normal diet, somewhat less workers consuming the drug came onto the risky apparatus, and the difference was at the limit of significance (N = 5, T = -13.5, P = 0.078). However, a behavioral difference could be observed between the ants living under one or the other kind of diet: ants under ivermectin diet coming on the apparatus immediately climbed on the tower and several ones which did so fell down (Figure 2 B2 indicated by an arrow). This demonstrated two impacts of the drug on the individuals' physiology, one on their movement, their walking (maybe their muscles functioning) (and this has already been detected here above: see the subsection relative to linear and angular speed), and the other one on their estimation of a potential danger, of the risky character of an act. The latter impact, *a priori* not obvious, might occur in humans treated with ivermectin, and attention should thus been paid to the behavior of these patients who find themselves in a risk situation.

Tactile (pain) perception

This physiological trait was largely impacted by ivermectin consumption (Figure 2 C). Under normal diet, the ants walked on the rough substrate at a far lower linear speed and far larger angular speed than on a normal substrate. These differences were highly significant: linear speed: χ^2 = 32.85, df = 1, P < 0.001; angular speed: χ^2 = 60.07, df = 1, P < 0.001. On the contrary, while consuming ivermectin, the ants walked on a rough substrate only slightly less quickly and more sinuously than on a normal substrate: linear speed: χ^2 = 2.08, df = 1, 0.10 < P < 0.20; angular speed: χ^2 = 2.28, df = 2, 0.30 < P < 0.50. Such an impact of the drug on the individuals' sensitive perception can explain, at least partially, the ants' poor orientation towards a tied nestmate (see above, the subsection relation to the orientation) and should be taken into account while treating humans with this drug.

Brood caring behavior

This behavioral trait appeared to be affected by iverectin consumption (Table 3, line 1; Figure 2 D). More larvae were not reentered in the nest when ants consumed this drug than when they lived under normal diet, and this difference was significant (N = 6, T = +21, P = 0.016). However, this difference was apparently not essentially due to a lack of interest in the larvae by the ants consuming ivermectin (these ants touched the encountered larvae and tried to take them in their mandibles), but mostly to some difficulties presented by these ants for holding and correctly transporting the larvae (the transported larvae often touched the ground, being not high enough lifted, Figure 2 D2). Such an impact of ivermectin was in agreement with that on the ants' locomotion and their climbing on a tower (see the two above subsections relative to these two traits); the muscles functioning may be affected. Nevertheless, the ants consuming ivermectin might be less interested in the larvae than ants living under normal diet; their usual social behavior might be affected by the drug consumption. The next experiment examined this possibility (see the here under subsection).

Social relationship towards nestmates

This ethological trait was affected by ivermectin consumption (Table 3, line 2; Figure 2 E). While living under normal diet, the tested nestmates often stayed side by side, doing nothing or making antennal contacts. While consuming the drug, the two observed ants seldom stayed side by side; they were generally far from one another, and when they were close to one another, they often opened their mandibles. These differences between ants under one and the other kinds of diet were significant: χ^2 = 22.58, df = 2, P < 0.001. The variable 'a' assessing the ants' aggressiveness equaled 0.11 for ants under normal diet and 0.44 for ants consuming ivermectin. Such an impact of the drug on the ants' social relationships partly explained the above reported poor efficiency of the ants under that drug diet in re-entering larvae removed from the nest as well as their poor orientation to a tied nestmate (see the preceding subsections relative to these two traits). Such an impact of ivermectin on social interaction might occur in humans treated with this drug and attention should thus be paid to their social behavior.

Cognition

Ivermectin affected this trait (Table 3, line 3; Figure 3 A). While 6 ants under normal diet among 30 could cross the twists and turns path over the 12 experimental minutes, only 1 ant consuming ivermectin could do so. The difference of ability in navigating a twists and turns path between ants under one and the other kinds of diet was significant: in front of the difficult path: N = 6, T = +21, P = 0.016; beyond the path: N = 5, T = 15, P = 0.031. The ants consuming ivermectin often came back on their way in the difficult path instead of going on trying to cross it. The drug affected thus the ants' cognitive abilities, a presumption again examined thanks to the two following experiments (see below).

Escaping from an enclosure

This ethological trait was affected by ivermectin consumption (Table 3, line 4; Figure 2 F). Under normal diet, the enclosed ants first walked all around the area of the enclosure, then more calmly along its rim. They so walked in front of the managed notch and they then often escaped. While consuming the drug, the ants also first walked all around the enclosure, then rather calmly along its rim, but they often stopped walking, and when coming in front of the notch, they very seldom escaped. This showed that the ants did not particularly stressed, were not inclined in walking (what is in agreement with the previous result on the ants' speeds), and did not guess that the notch could allow them escaping. Ivermectin might thus impact the ants' cognitive abilities, a presumption already issued from the previous experiment (see above) and again examined thanks to the next experiment (see below). It was also observed that foragers moving outside the enclosure had a tendency to enter the enclosure, a behavior revealing their non estimation of a potential danger as it has already been revealed thanks to the experiment relative to the ants' audacity (see the above subsection relative to this trait).

Figure 2: Some photos of the experiments made to examine the impact of ivermectin on six ants' ethological and physiological traits. 1: ants under normal diet, 2: ants consuming ivermectin. A: ants coming towards a tied nestmate, less well while consuming the drug. B: ants coming onto a risky apparatus, and felling down the tower while consuming the drug. C: an ant walking on a rough substrate with difficulties and touching the substrate with its antennae while under normal diet, and walking easily without touching the substrate

Figure 3: Some photos of the experiments made to examine the impact of ivermectin on three ethological and physiological traits. 1: ants under normal diet, 2: ants consuming iverectin. A: 3 ants under normal diet vs 1 one consuming the drug having been able to cross a twists and turns path. B: ants trained to a green hollow cube set at their nest entrance; an ant under normal diet giving the correct response and an ant under ivermectin diet giving the wrong response when tested in the presence of such a cube. C: ants not preferentially choosing the sugar solution containing the drug (red dot), and being thus not dependent on its consumption.

Time	Normal diet	Diet with ivermectin
7 h	6 *vs* 4 60%	5 *vs* 5 and 5 *vs* 5 50%
24 h	6 *vs* 4 60%	5 *vs* 5 and 4 *vs* 6 45%
31 h	7 *vs* 3 70%	6 *vs* 4 and 4 *vs* 6 50%
48 h	7 *vs* 3 70%	4 *vs* 6 and 5 *vs* 5 45%
55 h	8 *vs* 2 80%	5 *vs* 5 and 5 *vs* 5 50%
72 h	9 *vs* 1 85%	6 *vs* 4 and 5 *vs* 5 55%
Cue removal		
7 h	9 *vs* 1 85%	
24 h	8 *vs* 2 80%	
31 h	8 *vs* 2 80%	
48 h	8 *vs* 2 80%	could not be examined
55 h	8 *vs* 2 80%	
72 h	8 *vs* 2 80%	

Table 4: Impact of ivermectin on learning and memory. The control experiment on ants under normal diet was made on colony C; the test experiment on ants under a diet with ivermectin was made on colonies A and B. Under the drug diet, the ants never acquired conditioning, the learning and memorizing abilities being thus affected by ivermectin. Since, under the drug diet, the ants learned nothing, their middle-term memory could not be assessed.

Adaptation	Normal diet	Ivermectin diet for 2 days	Ivermectin diet for 8 days
Linear speed (mm/s)	10.3 (9.4-10.8)	6.0 (5.3-6.4)	6.2 (5.6-6.5)
Angular speed(ang.deg./cm)	104 (94-113)	183 (157-210)	185 (159-209)

Dependence	Drug-free solution	Drug solution
Colony A	30 ants' visits	18 ants' visits
Colony B	19 ants' visits	10 ants' visits
Total	49 → 63.64% ants' visits	28 → 36.36% ants' visits

Table 5: Adaptation to and dependence on ivermectin consumption. The ants did not adapt themselves to the impact of the drug on their locomotion (upper part of the table): after 8 days of ivermectin consumption, they still walked slowly and sinuously exactly like after 2 days of consumption. The ants did not develop dependence on the drug consumption (lower part of the table); on the contrary, they slightly more visited the drug-free solution.

Visual conditioning and memory

This physiological and ethological trait was affected by ivermectin consumption (Table 4, Figure 3 B). While under normal diet, the ants of colony C soon acquired conditioning and reached in fine a conditioning score of 85%, those (of colonies A and B) consuming ivermectin never acquired conditioning. The difference of behavior between the ants maintained under one and the other kinds of diet was significant: N: 6, T = -21, P = 0.016. In the course of this experiment, the ants living under the drug diet learned and memorized nothing, and consequently, their middle-term memory could not be assessed. However, these ants went on returning to their nest and going to their food sites. It could thus be presumed that their long-term memory was not or only slightly impacted by ivermectin. In any way, a potential impact of the drug on the memorization capability of human patients treated with this drug should be examined.

Adaptation (tolerance) to ivermectin adverse effects

The ants did not adapt themselves to the impact of ivermectin on their locomotion (Table 5, upper part). After having consumed the drug during 6 days, they still walked at a low linear speed and very sinuously, just like they did after having consumed the drug during 2 days. There was no statistical difference between the two locomotion assessments: linear speed: $\chi^2 = 0.80$, df = 1, 0.30 < P <

0.50; angular speed: $\chi^2 = 0.06$, df = 2, $0.95 < P < 0.98$. The decrease of the effect of ivermectin after weaning was thus examine on the basis of its impact on the ants' linear speed (see the below subsection relative to this decrease).

Dependence on ivermectin consumption

The ants developed no dependence on ivermectin consumption (Table 5, lower part; Figure 3 C). During the experiment, 30 ants of colony A were counted on the drug-free solution and 18 ones on the drug solution, while 10 ants of colony B were counted on the drug solution and 19 ones on the drug-free solution. Such numbers leaded to 63.64% of ants sighted on the drug-free solution and 36.36% of them sighted on the drug solution. Though ants more visited the drug-free solution, this preference was not statistically significant: the recorded numbers did not statistically differ from those expected if the ants randomly went onto the two kinds of solution (38.5, 38.5) ($\chi^2 = 2.39$, df = 1, $0.10 < P < 0.20$). Such a non dependence on ivermectin consumption is in favor of its use and allows minimizing its potential adverse effects since the patients treated with this drug will not be tempted to abuse it.

		Statistics					
Time (h=hours)	Ants' linear speed (mm/s)	vs t = 0			vs control		
		χ^2	df	P	χ^2	df	P
t = 0	5.5 (4.3 - 6.2)	-	-	-	-	-	-
3h	5.2 (4.7 - 5.6)	1.38	1	0.10<P<0.20	47.08	1	< 0.001
6h	5.7 (5.2 - 6.8)	0.43	1	0.50<P<0.70	30.00	1	< 0.001
9h	6.1 (5.3 - 7.0)	1.67	1	0.20	24.34	1	< 0.001
12h	6.9 (6.1 - 7.5)	8.12	1	0.001<P<0.01	10.58	1	- 0.001
15 h	7.2 (6.6 -7.6)	15.0	1	< 0.001	13.15	1	< 0.001
18h	7.8 (7.2 - 8.6)	15.0	1	< 0.001	13.15	1	< 0.001
21 h	7.9 (7.0 - 8.5)	21.54	1	< 0.001	12.83	1	< 0.001
24 h	8.9 (7.4 - 9.9)	21.54	1	< 0.001	4.17	1	0.10<P<0.20
27 h	9.7 (8.7 - 8.5)	21.54	1	< 0.001	0.30	1	0.50<P<0.70
30 h	10.3 (9.1 - 11.1)	40.0	1	< 0.001	0.028	1	0.80<P<0.90
Control	10.3 (9.4 - 10.8)	-	-	-	-	-	-

Table 6: Loss of effect of ivermectin after its consumption was stopped. The table gives the median (and quartiles) of the ants' linear speed obtained over the loss of effect. t = 0: staring of the weaning; control = under normal diet. The effect of the drug became statistically different from its initial one 12 hours after weaning, no longer differed from the control situation 24 hours after weaning, and fully vanished in a total of 30 hours. This slow decrease accounts for the absence of dependence on ivermectin consumption. The present results are graphically illustrated in figure 4. Details (e.g. the mathematical function of the decrease) are given in the text.

Decrease of the effects of ivermectin after its consumption was stopped

Numerical and statistical results are detailed in Table 6; results are graphically illustrated in Figure 4. The effect of ivermectin kept its initial value for about 5 hours after weaning. Then, it slowly decreased, becoming different from its initial value 12 hours after weaning, and not different from the control situation 24 hours after weaning. The effect of the drug fully vanished in 30 hours. The decrease, slow just after weaning, seemed to become somewhat more rapid over time. Mathematically, though approaching a linear function, the decrease of the effect of ivermectin after its consumption ended could best be described by a quadratic function, i.e.:

$E_t = E_i - t^{0.022}$

With t = time (in hours), E_t = effect at time 't', E_i = initial effect

explanation of the '0.022' value:

$E_{final} - E_{initial} = 10.3 - 5.3 = 5 = t_{final}{}^{x} - t_{initial}{}^{x} = 30^x - 0^x = 30^x \rightarrow 5 = 30^x \rightarrow$ x = Log 5/30 = Log 0.166 = 0.022

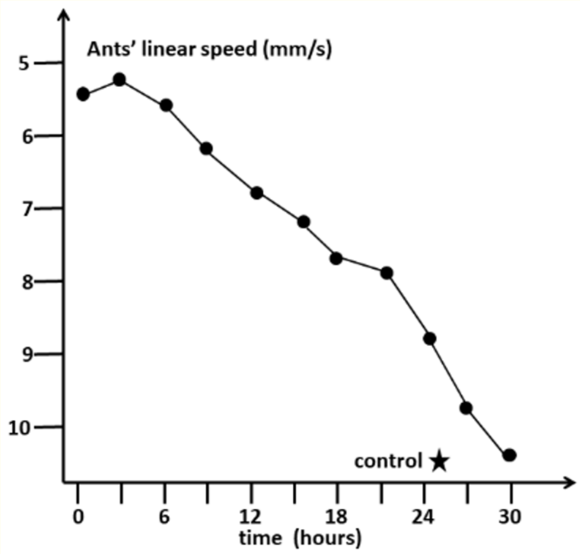

Figure 4: Loss of the effect of ivermectin after its consumption was stopped. The drug kept its initial effect during about 5 hours then lost it in a total of 30 hours. Its effect statistically became different from its initial one 12 hours after weaning and similar to the control situation 24 hours after weaning. The decrease appeared to become somewhat more rapid over time, and could thus be described by a quadratic function though approaching a linear one. Details are given in the text and numerical values can be found in Table 6.

Such a decrease, with no sudden quick loss of effect, accounts for the absence of dependence on the drug consumption [37]. Also, daily doses of ivermectin (dosages for time periods of 24 hours) could be defined for caring of differently aged persons more or less severely suffering from the Covid-19 illness or for preventing humans contracting this illness.

Discussion

Ivermectin is a drug used for treating humans suffering from parasitizes such as Loaloase, onchocerciasis, galla etc… In addition to the examples given in the introduction section, let us cite the works of Prod'hon., *et al*. [38], Chippaux., *et al*. [39], Prod'hon., *et al*. [40], Boussinesq [41] and Chandre., *et al*. [42]. Recently, ivermectin has been found to be useful for caring of persons suffering from the newly emerged Covid-19 illness. This discovery is a particularly providential case of serendipity. However, the efficiency of ivermectin in its newly discovered use is not yet fully admitted and recognized; its novel use is not unanimous but seems to be very promising (see the introduction section). Other drugs, products and chemical compounds are in the same case. No doubt that research will continue for finding efficient and easily available drugs allowing treating patients suffering from the Covid-19 illness and probably for preventing humans catching this illness, as well as for understanding the mode of action and for knowing the side effects of such new drugs.

Several adverse effects of ivermectin occurring in patients suffering from parasitizes have been reported (see the introduction section), but nothing has yet been reported as for the potential side effects which occurs when the drug is used to care patients suffering from the Covid-19 illness.

On ants used as models, we found that ivermectin reduces the individuals' food intake, activity, locomotion, appreciation of a danger, sensory perception, muscles functioning, and largely impacts their social relationships, cognition, learning and memory. Ants never adapted themselves to these effects, and did not develop dependence on ivermectin consumption. The effect of the drug slowly vanished in 30 hours after weaning according to the quadratic function $E_t = E_i - t^{0.022}$. All these side effects observed in ants may occur in humans. They thus should be examined in a valuable number of humans, in the course of duly conducted medicinal studies, before planning a large scale use of the drug for caring of patients suffering from the Covid-19. Also, the most appropriate daily dose should be established on one hand for caring of patients having the Covid- 19 illness and on the other hand for preventing not ill persons contracting this illness. Some potential habituation to the wanted effect of the drug should also be studied before a massive use of ivermectin. Moreover, concerning the half-live time of ivermectin, researches should still be conducted because the times reported in internet largely varies according to the consulted internet links: 3-6 hours (https://pharmacomedicale.org › par-specialites › item), 12 hours (https://www.hug.ch › coronavirus › documents › i..; http://www.astrium.com › fiches-maladies › ivermectine; http://agence-prd.ansm.sante.fr › php › ecodex › rcp; https://fr.wikipedia.org › wiki › Ivermectine), 18 hours (https://www.merck.ca › STROMECTOL-PM_F), 57 hours (https://www.creapharma.ch › Médicaments), and 5.5 days (http://www.ircp.

anmv.anses.fr › rcp › NomMedicament). This drug is not an antidepressant as are several other drugs proposed for treating the Covid-19 illness (e.g. paroxetine, fluoxetine, flavoxetine …). Another additional problem, also valuable for many humans' drugs, is the presence of ivermectin in waste water and thus in natural water in the wild [43]. This problem should not be overlooked because ivermectin is very toxic for the insects and thus for the environment. Processes for eliminating residues of ivermectin from waste water should thus be elaborated, the so more if the drug, already widely used for treating parasitizes, becomes in a near future, largely, worldwide used for preventing humans contracting the Covid-19 illness and for caring of the illness persons.

Conclusion

To conclude, ivermectin is without doubt very efficient for treating persons suffering from parasitizes, and will probably become useful for caring of those having the Covid-19 illness. This drug must still be used, but researches should be conducted for precisely knowing its adverse effects when it is used for caring of patients having the Covid-19 illness or for preventing humans contracting that illness. It should also be necessary to define the most adequate dosages for using ivermectin as a preventive or as a medicine for patients with varying degrees of Covid-19, to check if any potential habituation occurs to the effect of ivermectin, and to eliminate the residue of this drug from waste water.

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