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LETTER TO EDITOR

Piperonylbutoxide as a Dubious Cause of Cardiac Manifestations in Pyrethroid Insecticide Poisoning; a Letter to Editor

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Dear Editor;

Some of the articles on cypermethrin poisoning manifesting with cardiac problems, published in 2020 and 2021, have attracted our attention (1, 2). In one of these papers, a 70-year-old female was presented with acute exposure to insecticide spray containing cypermethrin, tetramethrin and piperonylbutoxide, showing dyspnea as well as considerable chest pain. Based upon the preliminary evaluation of the patient, high-sensitivity troponin T increased within an hour; however, coronary artery disease was ruled out on coronary angiography. Hence, non-ST elevation myocardial infarction due to direct cardiotoxicity of cypermethrin was proposed as the reason (1). Another paper presented an eighteen-year-old male with acute cypermethrin poisoning showing bradycardia at a range of 45-54 bpm and some premature ventricular complexes. The only medication prescribed, was atropine sulphate. After 48 hours of admission his heart rate steadily normalized (2). In discussion of each paper, the authors cite some reports of different types of heart block in the field of pyrethroid exposure, as well as positive association between urinary pyrethroid metabolites and cardiovascular involvement (3-5).

As we know, cypermethrin is a synthetic pyrethroid used as an insecticide, which has neurotoxic properties in insects. Resistance to pyrethroid compounds is not rare and considering its synergic effect, piperonylbutoxide is added to many pesticide products to increase their insecticidal potency (1). Piperonylbutoxide has no insecticide effect itself (6). It is not sold as a commercial product in marketplace and it is usually ignored when clinicians are searching for ingredients of the insect killer product. However, it can lead to development of toxicological manifestations in humans if they are exposed to it. The only case for piperonylbutoxide toxicity in man was reported in 2000, and bradycardia was the main clinical manifestation (7). Interestingly, in one case of third-degree heart block discussed here, the pesticide formulation contained d-phenothrin, a pyrethroid, and piperonylbutoxide (2). However, in another case, no data regarding pesticide formulation is available (3). Searching for more evidence, we found only three other case reports of cardiotoxicity after exposure to pesticide products, in which when formulation is available, and piperonylbutoxide is the definitive ingredient (4, 5, 8).

The neuronal voltage-gated Na+ channel is the main site of action for pyrethroids. They bind to the channel when it is open, which leads to prolonged inward sodium transfer and extended action potentials (6). By searching in reputable scientific databases, we couldn't find any research about the cardiac effects of pyrethroid on mammalian heart; however, some studies were done on Dichlorodiphenyltrichloroethane (DDT) (9). Because pyrethroids and DDT both act by connecting to the same type of Na+ channels (6), their cardiac effects can be expected to be similar. In their study on whether the heart of animals exposed to DDT is prone to develop dysrhythmia, Jeyaratnam and Forshaw have found no electrocardiogram abnormalities in living samples, and the contractility of isolated heart muscle was not altered either. Yet, the administration of epinephrine caused unexpected bradycardia and dysrhythmia (9).

Interestingly, pyrethroid poisoning can cause stimulation of large-scale epinephrine and norepinephrine release, even in non-severe cases (10). We couldn't find any evidence indi-

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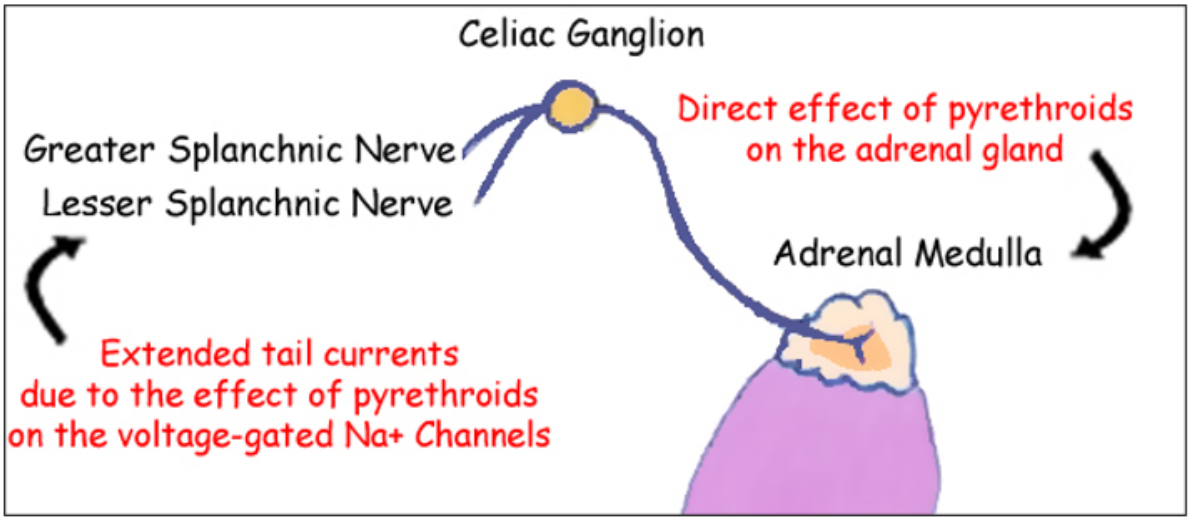

Figure 1: It isn't known whether pyrethroids produce a direct effect on the adrenal glands or they act through the stimulation of central nervous system to stimulate the release of norepinephrine and epinephrine.

cating whether pyrethroids produce a direct effect on the adrenal glands or they act through the stimulation of central nervous system (figure 1).

Pyrethroids are metabolized in the body by cytochrome P450 enzymes. Piperonylbutoxide has an inhibitory effect on this system (6), which causes a delay in elimination. Accordingly, epinephrine release may continue in the prolonged presence of pyrethroid compound, and cardiac abnormalities are caused by the provisional interaction between the toxin and epinephrine (10).

There is no well-proven scientific basis to conclude that the abovementioned case reports are biased in summarizing their articles. In conclusion, we think that pyrethroid poisoning may be seen with different faces, depending on the presence or absence of piperonylbutoxide in the commercial product. Hence it is necessary for all clinical toxicologists to determine suspicious ingredients when they are facing a doubtful manifestation.

1. Declarations

1.1. Acknowledgments

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1.2. Conflict of interest

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1.4. Authors' contribution

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