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Case definitions for human poisonings postulated to palytoxins exposure

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ABSTRACT

A series of case reports and anecdotal references describe the adverse effects on human health ascribed to the marine toxin palytoxin (PLTX) after different exposure routes. They include poisonings after oral intake of contaminated seafood, but also inhalation and cutaneous/systemic exposures after direct contact with aerosolized seawater during *Ostreopsis* blooms and/or through maintaining aquaria containing cnidarian zoanthids. The symptoms commonly recorded during PLTX intoxication are general malaise and weakness, associated with myalgia, respiratory effects, impairment of the neuromuscular apparatus and abnormalities in cardiac function. Systemic symptoms are often recorded together with local damages whose intensity varies according to the route and length of exposure. Gastrointestinal malaise or respiratory distress is common for oral and inhalational exposure, respectively. In addition, irritant properties of PLTX probably account for the inflammatory reactions typical of cutaneous and inhalational contact. Unfortunately, the toxin identification and/or quantification are often incomplete or missing and cases of poisoning are indirectly ascribed to PLTXs, according only to symptoms, anamnesis and environmental/epidemiological investigations (i.e. zoanthid handling or ingestion of particular seafood). Based on the available literature, we suggest a "case definition of PLTX poisonings" according to the main exposure routes, and, we propose the main symptoms to be checked, as well as, hemato-clinical analysis to be carried out. We also suggest the performance of specific analyses both on biological specimens of patients, as well as, on the contaminated materials responsible for the poisoning. A standardized protocol for data collection could provide a more rapid and reliable diagnosis of palytoxin-poisoning, but also the collection of necessary data for the risk assessment for this family of toxins.

1. Introduction

Palytoxin (PLTX) is a toxic marine compound, with a very complex structure, that was originally isolated from the cnidarian zoanthid *Palythoa toxica* in the Hawaiian Islands (Moore and Scheuer, 1971). PLTX and a series of its analogues, such as homopalytoxin, bishomopalytoxin, neopalytoxin, deoxypalytoxin, and 42-hydroxy-palytoxin were subsequently detected in several tropical *Palythoa* species (Ciminiello et al., 2009; Gleibs et al., 1995; Moore and Scheuer, 1971; Uemura et al., 1985). Furthermore, PLTX and its analogues, such as ostreocin-d, mascarenotoxin-a, -b and –c, and ovatoxin-a, -b, -c, -d and –e, were identified in various benthic dinoflagellate species belonging to the genus *Ostreopsis* (Ciminiello et al., 2010; Lenoir et al., 2004; Rossi et al., 2010; Ukena et al., 2001; Usami et al., 1995).

The main biological target of palytoxin seems to be the Na^+/K^+-ATPase, a plasma membrane pump involved in the maintenance of trans-membrane ionic gradients of animal cells, that is essential for cellular functions (Habermann, 1989; Rossini and Bigiani, 2011; Wu, 2009). Impairment of the pump by PLTX results in its conversion into a non-selective

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pore for monovalent cations, thereby destroying the transmembrane ionic gradient and triggering several adverse biological effects, some life threatening (Artigas and Gadsby, 2003; Habermann, 1989).

PLTX is widely known as one of the most toxic non-protein aceous compounds ever isolated, both for the results obtained during its first toxicological characterization in the 1970's (Wiles et al., 1974) and for the cases of lethal human poisonings ascribed to the toxin since then. In spite of that, the actual *in vivo* toxicity of the molecule is still poorly understood. The toxicity studies performed in the 1970's, even though on a broad range of animal species after several routes of administration, were performed on a semi-purified preparation of the molecule. The toxicological results obtained with that semi-purified material are difficult to completely evaluate because it is impossible to foresee what kind of influence the impurity could have caused. In this respect, a reduced or even increased toxicity of the pure molecule are both possible. Some data using PLTX of certified purity, of more recent origin, are available, but these data are limited mainly to PLTX after intraperitoneal or oral acute administration in mice (Munday, 2011).

Data that describes the effects in human intoxications are similarly controversial, in particular after oral exposure to contaminated seafood. The uncertainty in the definition of case reports arises from the difficulty in performing analyses for the confirmation/quantification of the toxins directly in leftover food or in clinical samples. This issue of uncertainty of PLTXs toxicity was recently highlighted in temperate coastal waters in connection with blooms of benthic micro-algae of the genus *Ostreopsis* (Durando et al., 2007; Gallitelli et al., 2005). Concomitant to algal blooms, unusual incidences of respiratory syndrome and systemic symptoms were recorded in people exposed to marine aerosols. In addition, recent cases describe the effects of PLTX after cutaneous or inhalational exposure of hobbyists that have cnidarian zoanthids, typically of the genus *Palythoa*, in their aquaria. These cases describe the intoxication that may occur after handling toxic organisms or inhalation of steam after cleaning the aquarium from these organisms with boiling water.

In this review we present a description of human intoxications due to postulated presence of PLTX along with relevant symptoms. Based on the available literature data, we suggest a "case definition of PLTX poisonings" according to the main exposure routes, suggesting the main symptoms to be checked, the performance of specific hemato-clinical analyses, and direct toxin detection in the causative agents.

2. Methods of literature review

A systematic review of the literature on human poisonings ascribed to PLTXs exposure was performed with no time restriction, even though the structural elucidation of palytoxin was not defined until 1981 (Moore and Bartolini, 1981; Uemura et al., 1981). The electronic databases (PubMed, Scopus and ToxLine) and the references of identified articles were used as data sources. Inclusion criteria were all the papers in English, Japanese, French, Spanish and Italian languages. For each exposure route, the cases of human poisoning were examined considering the following criteria: (1) direct detection of PLTXs in the causative agents of poisoning through biological and/or chemical methods of analysis; (2) indirect detection of PLTXs in the causative species through the analysis of samples collected after or before the poisoning episodes and/or in different places; (3) attribution of PLTXs involvement in the cases of human poisoning only on the basis of clinical signs and symptoms in concomitance to ingestion of seafood and/or exposure to *Ostreopsis* sp. and cnidarian zoanthids.

Very little information was available on the direct detection of PLTX in human biological specimens due mainly to methodological problems for toxin detection in this matrix.

3. Human poisonings after consumption of postulated palytoxins contaminated seafood

Human illness and death due to consumption of seafood contaminated or suspected to be contaminated with palytoxin and/or its analogues have been reported in some tropical and subtropical areas. However, only a few cases are documented in the literature through palytoxin detection directly in the seafood leftovers that caused the poisoning. Other cases of intoxication were ascribed to PLTXs on the basis of screening tests that were performed on seafood samples collected or purchased after or before the poisoning episode, rather than directly on leftovers. In addition, palytoxin and/or its analogues have been considered responsible of a high number of human seafood-borne poisonings, without a confirmatory analysis aimed to toxin identification, but only on the basis of clinical observations, signs and symptoms.

3.1. Cases of human poisoning ascribed to contaminated seafood: direct identification of PLTXs in leftovers

Episodes of human poisoning ascribed to PLTX and supported by a direct analysis of meal remnants are summarized in Table 1. A fatal case after ingestion of a crab (*Demania reynaudii*) occurred in the Philippines, where a man (49 years old) reported a metallic taste after consuming the crab and, shortly after, developed a general malaise that initially involved the gastrointestinal apparatus (Alcala et al., 1988). The patient experienced nausea, tiredness, diarrhoea, and vomiting followed by dizziness, numbness of the extremities, muscle cramps and restlessness. After hospitalization he experienced alternating periods of normal heart rate and severe bradicardia (30 beats/min), rapid and shallow breathing, and cyanosis around the mouth and hands. Finally, despite the administration of atropine, benadryl, demerol and adrenaline, anuria occurred and the patient died 15 h after the crab ingestion. In this case, analyses of the food were performed directly on the cooked leftovers and, after bioassay oriented extraction, toxin detection in the 1-butanol fraction indicated the absence of tetrodotoxin and saxitoxin. The causative toxin was suggested to be PLTX mainly on the basis of the chromatographic properties as well as the dose-survival time relationship at the mouse bioassay (Alcala et al., 1988).

In the same period, Noguchi et al. (1987) described a case of a man and a woman that were poisoned after