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Histopathology and blood biochemical in sheep treated with an experimental intramuscular fasciolicide

Rosa Arias-García[1]
0000-0002-0459-4980
Froylán Ibarra-Velarde[1]*
0000-0001-5529-4702
Yolanda Vera-Montenegro[1]
0000-0002-9139-0133
Miguel Flores-Ramos[2]
0000-0002-8063-1165
Alicia Hernández-Campos[3]
Gerardo Leyva-Gómez[3]
0000-0002-7940-1100

[1] Universidad Nacional Autónoma de México. Facultad de Medicina Veterinaria y Zootecnia. Departamento de Parasitología. Ciudad de México, México.

[2] Universidad Nacional Autónoma de México. Escuela Nacional de Estudios Superiores-Unidad Mérida. Yucatán, México.

[3] Universidad Nacional Autónoma de México. Facultad de Química. Departamento de Farmacia. Ciudad de México, México.

*Corresponding author
Email address:
ibarraf@unam.mx

Abstract

The aim of present study was to determine whether intramuscular administration of injectable fasciolicide prodrug, fosfatriclaben, in a single dose at 6 mg/kg in mixed breed sheep, produces adverse reactions reflected in blood biochemical and histopathological profiles, particularly in tissues involved in drug metabolism. For this purpose, two sheep groups were formed. Group 1 (G1) of 15 sheep was treated, Group 2 (G2) of 5 sheep served as control. On days 0, 7, 14, 28, and 35 post-treatment, liver, kidney, and injection site samples were taken for histopathology, as well as blood samples for biochemical analysis. The results did not provide important histopathological changes or significant differences in blood biochemical ($P < 0.05$); analytes values remained within the reference range. It is estimated that the trial prodrug could have similar safety characteristics to its precursor, triclabendazole.

Keywords: *Fasciola hepatica*; Triclabendazole; Fosfatriclaben; Veterinary prodrug; Adverse drug reaction.

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Study contribution

In recent years, a multidisciplinary research group has experimented with a new fasciolicide, which is derived from triclabendazol, and whose name is fosfatriclaben. This new fasciolicide has shown advantages over its precursor such as high solubility, parenteral administration, lower dose, and high efficiency against *Fasciola hepatica* both in sheep and cattle. It is important to continue carrying out safety tests before marketing to ensure the absence of adverse reactions that would result in production losses for livestock farmers. Through histopathological and biochemical analysis, it is possible to detect any change or any other effects in liver in kidney function, or other consequences related to medication application. In this work, we confirm that experimental compound does not produce adverse reactions at the inoculation site, nor any findings in tissue or blood that suggest harm derived from its use. Therefore, we estimate a level of safety similar to that of its precursor, triclabendazole.

Introduction

Fasciolosis is the most important liver parasitosis in cattle and sheep due to trematode *Fasciola* spp.,causing serious animal health problems and significant financial losses due to productivity declines and considerable expenses to control this parasitosis.[1–3] *Fasciola hepatica*, present on all continents, infests a large number of mammals including humans, through the ingestion of plants and vegetables contaminated with the parasite.[4–6] Triclabendazole (TCBZ), also approved for humans,[7] is the most widely chosen fasciolicide due to its effectiveness against the adult trematode and its juvenile stage.[8, 9] Like all benzimidazoles, it is a very poor water-soluble compound.[10] A new prodrug, for now called fosfatriclaben (Figure 1) is a TCBZ derivative, highly soluble and water-stable. The first studies on its fasciolicidal efficacy have given promising results.[11–13]

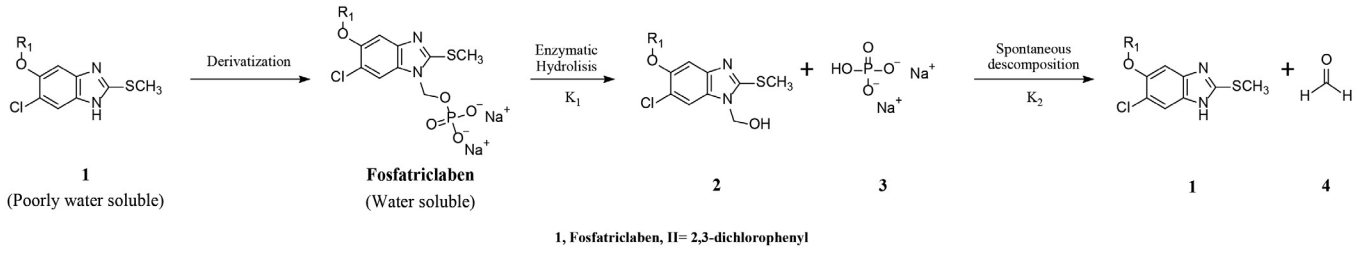

Figure 1. The bioconversion of fosfatriclaben to triclabendazole is done in two steps. First, a complete dephosphorylation with the enzyme alkaline phosphatase to generate the hydroxymethyl intermediary (2), and in a second step, the spontaneous chemical decomposition of 2 to give TCBZ (1) and formaldehyde.[11]

Because it is a newly developed compound, it is important to subject it to exhaustive testing and evaluation before registration and marketing to ensure its pharmacological activity, efficiency, safety, and quality, as well as to demonstrate its benefits or adverse reactions on organs particularly susceptible to drug-induced injury.[14–19] The drug effectiveness concerns both its efficiency or ability to produce

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the desired result, as well as absence or adverse response degree.[20] An adverse drug reaction (ADR or RAM for its Spanish acronym) is a harmful or unpleasant reaction, resulting from use of medicinal product in an individual, that predicts hazard from future administration and justifies prevention, treatment, dosage alteration, or product withdrawal.[21,22] This definition refers to all therapeutic and diagnostic substances, including pesticides and vaccines.[16]

ADRs can be minor, moderate, severe, or fatal; immediate, short-term, long-term, or permanent; and are caused by the active substance, contaminants, or excipients.[17, 21, 23] The moment of the onset of signs, the disease pattern, the outcomes of research, and new exposure may help attribute causality to a suspected ADR.[21] Most authors describe the terms allergy, side effects and toxicity as ADR forms: immunological, idiosyncratic, or due to dosage and time, respectively.[16, 17, 24–27]

ADRs are an important source of morbidity, mortality and increased healthcare costs.[24, 28] Research, diagnosis, and documented incidence of ADRs in veterinary medicine are much lower than in humans.[29] To protect public health it is necessary that all reactions observed during development and testing of a drug for food-producing animals be considered relevant and the association diagnosis with ADR can be specified.[15, 30, 31] Any organ or system could be affected by pharmacodynamic interactions,[32] however, liver and kidneys are often particularly susceptible to ADR due to their important role in drug metabolism and excretion.[33–36]

Through biotransformation reactions that modify the chemical structure medications, their water solubility and, hence their elimination increases.[36, 37] In this process the liver contributes with more than 70 %,[38] and the kidneys recapture drug from urine into the blood through renal tubular reabsorption, favoring its urinary excretion.[36, 39, 40] ADRs impact on livestock farming lies in productive profitability. Subacute or chronic alterations due to kidney or liver damage compromise animal productivity. The clinical condition and poor zootechnical performance of cattle can become complicated silently, and hence deteriorate the herd due to chronic toxicity, increase pharmacotherapy period and cost, and even lead to animals death.[32]

One alternative to determine possible ADRs in organs is histopathology, which through tissue biopsy analysis, allows determining alterations such as hepatocyte necrosis.[18, 40] Blood biochemical tests also provide useful information. Abnormal values with or without clinical signs could be due to a pathology or drug-induced enzyme alteration as damage sign to liver or kidney function.[21, 40, 41] In the live animal any reaction of pain, swelling, redness, heat, loss or decrease of function at the inoculation site, as well as any other visible or palpable changes, may be inspected.[18]

Materials and methods

Ethical statement

The authors affirm that all procedures carried out in this work comply with the ethical standards of national and institutional guidelines on the care and use of animals. This experimental protocol was approved by the Subcomité Institucional para el Cuidado y Uso de Animales Experimentales (SICUAE) of Facultad de Medicina Veterinaria y Zootecnia (FMVZ), Universidad Nacional Autónoma de México (UNAM);

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now called Comité Interno para el Cuidado y Uso de los Animales (CICUA), with protocol number SICUAE.DC-2020/3-2.

Study location

The present study was carried out at Centro de Enseñanza Práctica e Investigación en Producción y Salud Animal (CEPIPSA-UNAM) located in San Miguel Topilejo, Tlalpan, Ciudad de México.

Experimental compound

Experimental prodrug (Fosfatriclaben) was synthesized and formulated by our research group in the Facultad de Química, UNAM.

Animals

The study involved 20 clinically healthy mixed breed sheep, indistinct sex, between 8 and 12 months old, weighing an average weight of 25 kg each. They were born and housed at CEPIPSA-UNAM in covered pens with cement floors, open water and fed with alfalfa and concentrated sheep feed.

Treatments and necropsy

Two sheep groups were formed. Group 1 (G1) of 15 sheep was treated with fosfatriclaben injected at 6 mg/kg intramuscularly, single dose; G2 of 5 sheep remained as untreated control. Euthanasia was carried out by CEPIPSA-UNAM qualified personnel according to current health regulations,[42] using captive-bolt stunning on days 0, 7, 14, 28 and 35 post-treatment.[43, 44] On each of these days, three sheep were taken from G1 and one from G2. The determination of these times was based on the efficient use of the animals, according to the principle of reduction alternatives (fewer animals, 3R) to maximize the information obtained per animal without compromising animal welfare, and thus potentially limiting or avoid the subsequent use other animals.[45–47]

Therefore, in order to obtain the greatest number of experimental results with the fewest animals, sampling for this work was proposed within a sheep group acquired for adjacent research on residues in edible tissues, which will be carried out by high-performance liquid chromatography at the established slaughter times.

Sample collection and evaluation

For the histopathological processing of sectioned tissue sample for hematoxylin and eosin staining on slides, samples from all G1 and G2 sheep were collected. These samples, which measured 2 × 2 cm, were from the liver, the kidney, and the injection site (femoral muscles of the hind limb). These samples, were preserved in glass containers which contained 10 % formalin, 1:10 ratio.[48] For biochemical analysis, blood samples were taken from jugular vein of all sheep in G1 and G2 into heparinized Vacutainer tubes. On the days afore mentioned, they were centrifuged 10 minutes at 3 500 rpm, transferring plasma to Eppendorf vials of 2 mL.

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The basic blood biochemical profile included glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, conjugated bilirubin, unconjugated bilirubin, aspartate aminotransferase (AST), glutamate dehydrogenase (GDH), gamma-glutamyl transferase (GGT), creatine kinase (CK), total protein, albumin, globulins, calcium, phosphorus, sodium, potassium, chloride, bicarbonate, GAP anion, strong ion difference (SID), and osmolarity. All samples were sent under refrigeration to Department of Pathology at FMVZ-UNAM.

Statistical analysis

Blood biochemical results were analyzed using IBM® SPSS® Statistics, version 26-2019. Homogeneity of variance tests (Levene Statistic) and normality tests (Shapiro-Wilk) were applied. When differences were significant, means were compared using the nonparametric Kruskal-Wallis test to determine whether there were significant differences between the experimental and control groups. A P value < 0.05 was considered as critical level of significance for all procedures.

Results

Liver and kidney histological sections did not present evident pathological changes, neither in treated sheep nor in control group (Figures 2 A-B and 3 A-B). In microscopic description of skin and muscle from inoculation site of one treated sheep sampled on day 7, a small of amount of extravasated erythrocytes (hemorrhages) in the fascia was reported (Figure 4 A-B, comparison with a control tissue). From a clinical perspective, this finding was interpreted as normal because when administering any injectable medication, some blood vessels can be injured causing extravasation of their cellular components.

Blood biochemical statistical analysis (Table 1) rejected homogeneity of variances and normality in distribution (statistical significance $P < 0.05$). Therefore, the non-parametric Kruskal-Wallis test was carried out. No statistically significant differences were found between treated and control sheep, with a significance level of 5% ($P < 0.05$). Nor were any values outside of reference range provided by the Department of Pathology at FMVZ-UNAM.

Discussion

In this work, we determined that treatment with fosfatriclaben administered intramuscularly to sheep at 6 mg/kg, did not produce pain signs or inflammation at the animal's inoculation site, nor histopathological or biochemical findings that could be related to any ADR. Anticipating the ADR profile allows implementing strategies to reduce risks, while maintaining favorable pharmacological properties.[49] In humans, the clinical features, liver injury patterns, and diagnostic criteria for drug-induced liver injury are well described.[17, 40] In animals some hepatocellular toxicity diagnoses, such as that of carpofen in dogs, are based on hyperbilirubinemia, AST, ALT, and ALP increases, along with clinical signs of jaundice, vomiting, and anorexia.[40]

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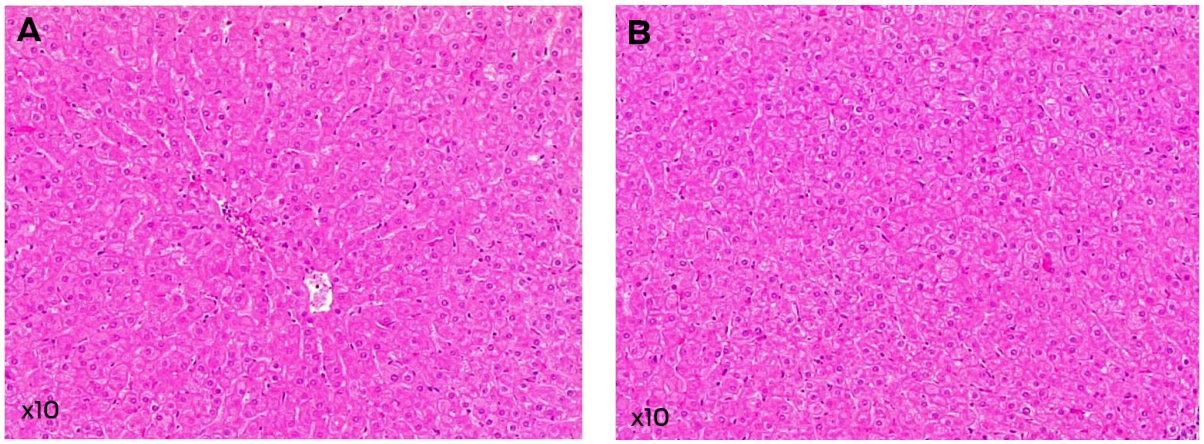

Figure 2. Cross-sectional histological sections stained with hematoxylin and eosin. A. Sheep liver from group treated with experimental fasciolicide. B. Sheep liver from control group. In both cases the tissues are normal with no pathological changes.

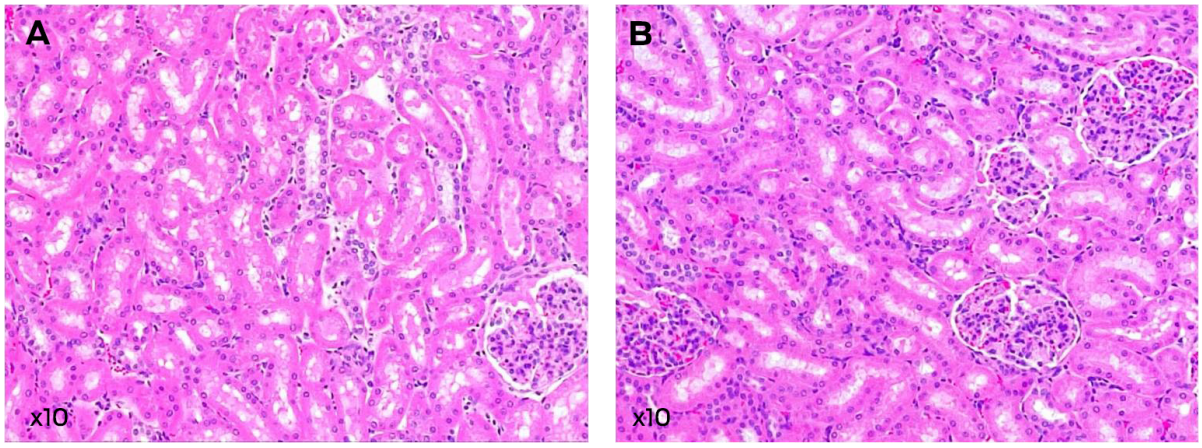

Figure 3. Cross-sectional histological sections stained with hematoxylin and eosin. A. Sheep kidney from group treated with experimental fasciolicide. B. Sheep kidney from control group. Both tissues are normal with no pathological changes.

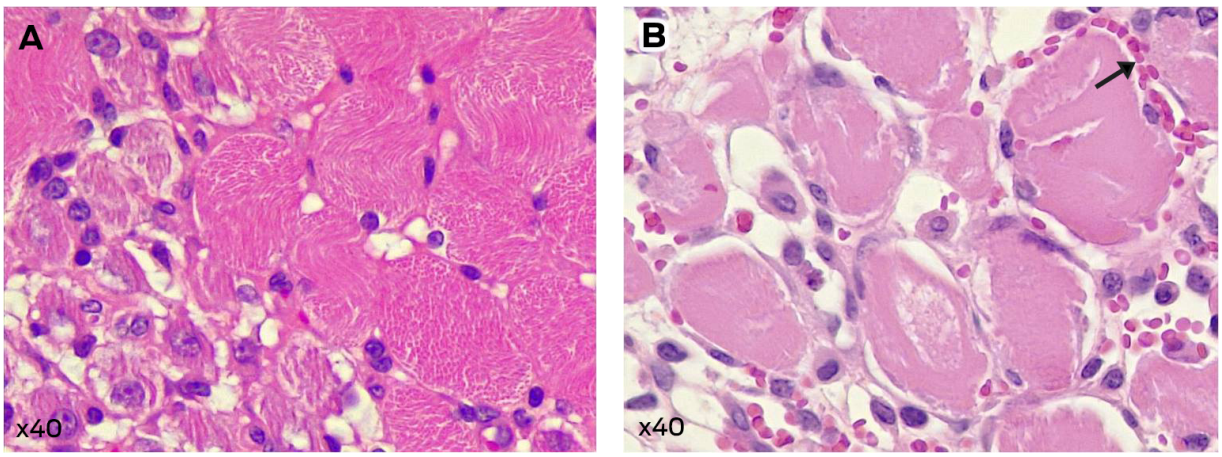

Figure 4. Cross-sectional histological sections stained with hematoxylin and eosin. A. Femoral muscle of the hind limb from a control sheep (injection site in treated sheep). B. Inoculation site of a treated sheep presents minimal red blood cell extravasation (arrow), a common finding with injectable medications.

Photographs provided by Dr. Elizabeth Morales Salinas (Figures 2-4).

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Table 1. Blood biochemical report results of sheep treated with fosfatriclaben at 6 mg/kg intramuscularly and untreated sheep

Analyte	Unit	Treated sheep[a]	Control sheep[a]	Reference value
Glucose	mmol/L	4.1	4.3	2.8–4.4
BUN	mmol/L	6.5	6.3	3.6–6.7
Creatinine	mmol/L	106.6	106	106–168
Total bilirubin	mmol/L	2.0	2.1	1.1–8.5
Conjugated bilirubin	mmol/L	1.1	1.6	0–6.84
Unconjugated bilirubin	mmol/L	0.9	0.5	0–5.13
AST	U/L	77.7	78	<180
GDH	U/L	8.5	3	<32
GGT	U/L	47.1	54	<56
CK	U/L	225.7	155	50–451
Total protein	g/L	60.2	62	60–79
Albumin	g/L	25.3	28	24–30
Globulins	g/L	35.1	36	35–57
Calcium	mmol/L	2.6	2.7	2.59–3.24
Phosphorus	mmol/L	2.3	2.34	1.61–2.35
Sodium	mmol/L	143.9	144	136–154
Potassium	mmol/L	4.8	5	4–6
Chloride	mmol/L	106.4	106	98–115
Bicarbonate	mmol/L	25.2	21	22–27
GAP anion	mmol/L	16.8	22	9–31
SID	mosm/kg	37.5	38	30–40
Osmolarity	mmol/L	287.9	290	282–292

UV-visible spectrophotometry, Dirui CS-T240, dcL-SEKISUI reagents, FMVZ, UNAM.
[a]Averages
BUN: blood urea nitrogen. AST: aspartate aminotransferase. GDH: glutamate dehydrogenase. GGT: gamma-glutamyl transferase. CK: creatine-kinase. SID: strong ion difference

Drug-induced nephrotoxicities may appear as glomerulonephritis, tubular degeneration, interstitial nephritis, proximal tubular necrosis, and acute renal failure.[21, 24, 25, 40, 50–52] Aminoglycosides, NSAIDs and tetracyclines often accumulate in kidneys, and cause nephrotoxicity increasing serum concentrations and exacerbating toxicity.[29, 53] The increase in plasma creatinine or blood urea nitrogen (BUN), due to reduction in glomerular filtration rate, are suggestive findings of nephrotoxicity; measurement urine output and osmolarity constitute part of the diagnosis.[25, 29, 35, 52] Local reactions at inoculation site (muscle necrosis, abscesses, inflammation, induration, pain) are also common, as well as hypersensitivity (skin reactions, skin and mucous membrane modifications).[29] Penicillin and its derivatives are frequent causes of cutaneous and anaphylactic ADRs.[54, 55] In Australia severe reactions have been informed in sheep vaccinated against anthrax: necrotizing cellulitis and abscesses at injection site which progressed to severe systemic signs and death in some animals.[16] Other well-known ADRs are dry mouth due to antihistamines and ototoxicity due to aminoglycosides.[29]

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Generally, ruminants antiparasitics are relatively safe. Nevertheless, it is advantageous to evaluate for potential ADRs. Levamisole has been reported to cause anaphylaxis, local irritation, tremors, and paralysis.[41] Closantel may cause nervous signs and pain.[56] TCBZ is highly safe. ADRs documented in humans are short-lived and limited to abdominal pain, headache, nausea and fatigue,[57] attributed to expulsion of dead or dying helminths from hepatobiliary system into the intestinal tract,[58–60] a claim supported by ultrasound studies showing dilated intrahepatic bile ducts caused by transient biliary obstruction associated to flukes expulsion.[61]

To date (2025), no changes in liver or kidney function tests or in hematological indices attributable to TCBZ have been reported in human clinical trials; and in animals no evidence of dose-related toxicity has been observed.[61] It is inferred that since fosfatriclaben is a TCBZ derivative, there could be an equivalence in the high safety index that TCBZ has.[62] In previous studies, fosfatriclaben presented high fasciolicidal efficiency close to 100% in reducing *F. hepatica* eggs and adults[11, 13] compared to best commercial fasciolicides including its precursor, TCBZ.

The neutral pH, high solubility and aqueous stability of fosfatriclaben make it suitable for parenteral administration, and so far, no signs of pain in the animal's inoculation site, side effects, or toxicity have been observed,[11, 12] which was corroborated in this work. Its intramuscular application has advantages of facilitating administration to large animals groups and requiring a reduced dose compared to TCBZ (oral route), while maintaining high fasciolicidal activity.[12] This prodrug is undergoing various current and planned trials on pharmacokinetic evaluation, stability, toxicity, and withdrawal periods, which together, will determine its full potential as a fasciolicide alternative for sheep and cattle.

Conclusions

The TCBZ clinical safety has been consistently demonstrated. And in this work, it was confirmed that fosfatriclaben, being a TCBZ derivative, did not produce pain signs or inflammation at the animal's inoculation site, nor histopathological or biochemical findings, which would lead to interpretation of some ADR caused by this experimental parasiticide, hence we can estimate that its safety characteristics are similar to its precursor, TCBZ. It is recommended to continue similar studies to confirm the safety of this compound.

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Data availability

The original dataset used in this research are deposited and available for download at the SciELO Dataverse doi: 10.48331/scielodata.CPFAF4.

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Conflicts of interest

The authors have no conflict of interest to declare in regard to this publication.

Author contributions

Conceptualization, investigation, methodology, project administration, validation: R Arias-García, F Ibarra-Velarde, Y Vera-Montenegro.
Data curation and formal analysis: R Arias-García.
Funding acquisition: F Ibarra-Velarde.
Resources: F Ibarra-Velarde, M Flores-Ramos, A Hernández-Campos, G Leyva-Gómez.
Visualization and Writing-original draft: R Arias-García.
Writing-review and editing: R Arias-García, F Ibarra-Velarde, Y Vera-Montenegro.

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