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Adverse Drug Events in Puppies Following Treatment with Amoxicillin with or without Clavulanate

Fidelis A. Gberindyer[1,*], Felix K. Shima[2], Oladipo O. Omotosho[3], Temidayo O. Omobowale[3], Matthew O. Abatan[4]

[1]Department of Veterinary Pharmacology and Toxicology, Federal University of Agriculture, Makurdi, Nigeria
[2]Gan-Rovet Animal Hospital, Warri, Nigeria
[3]Department of Veterinary Medicine, University of Ibadan, Nigeria
[4]Department of Veterinary Pharmacology and Toxicology, University of Ibadan, Nigeria

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***Correspondence to:**
fidegber@yahoo.com

ABSTRACT

This study reports adverse drug events (ADEs) in puppies following treatment with amoxicillin with or without clavulanate. A prospective and observational multicentre study was conducted in five Veterinary clinics in Nigeria where 63 heterogeneous puppies with parvovirus enteritis were used. Puppies in group A (n=36) were treated with amoxicillin alone (n=16), or with clavulanate (n=20) by IV route, whereas group B (n=27) were administered amoxicillin alone by IM route. All puppies were administered a single dose of 15mg/kg, thereafter, observed for ADEs within 3 hours. Those that manifested ADEs were subsequently administered 2mg/kg IV single dose of diphenhydramine. Out of 63 puppies, 12(18.5%) had diarrhoea, hyper-salivation, cutaneous erythema, and swellings around eyelids and buccal areas within 5 minutes post-treatment. These were observed only in puppies treated by IV route, where 5/16(31.3%) of those administered amoxicillin with clavulanate, and 7/20(35%) of those treated with amoxicillin alone showed these signs, which resolved following diphenhydramine administration. No ADEs were observed after subsequent treatment of the affected puppies with amoxicillin alone by IM route. Although amoxicillin is usually well tolerated, this study recommends that veterinarians should be cautious when it becomes necessary to treat dogs with amoxicillin alone or with clavulanate by IV route to circumvent these ADEs.

1. INTRODUCTION

Adverse drug events (ADEs) are injuries resulting from medical intervention related to an administered drug which could be classified as medication errors, adverse drug reactions, allergic reactions, and drug overdose (Kohn et al., 2000; Neubeker et al., 2004). The Centre for Veterinary Medicine defined ADE as any side effect, injury, toxicity, or sensitivity reaction, or failure to perform as expected, that is associated with the use of an animal drug, whether or not determined to be attributable to the drug (FDA, 2017). Adverse drug events are categorised as allergic reactions (immunologically mediated effects), adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses), or unintentional overdoses (excessive doses or supra-therapeutic drug effects) (Budnitz et al., 2011). Previous reports attributed 42-60% of ADEs to excessive drug dosage for the patient's age, weight, underlying condition, and renal function (Classen et al., 1997). Also, age-related physiological changes, a greater degree of frailty, a larger number of coexisting conditions, and polypharmacy have been associated with an increased risk of ADEs (ElDesoky, 2007). Thus, adverse drug reaction is a special type of ADE in which a causative relationship can be shown.

Amoxicillin is a moderate-spectrum, bactericidal, and semi-synthetic β-lactam antibiotic

used to treat bacterial infections caused by susceptible microorganisms (Bush, 2003). Parvovirus enteritis is a seasonal and highly prevalent viral disease in Nigeria, which is associated with amoxicillin-susceptible secondary, Gram-negative and aerobic bacterial organisms such as *Escherichia coli*, *Salmonella spp,* and *Campylobacter spp* (Shima et al., 2015; Kahn, 2010). Out of the 1,050 antibiotic prescriptions for dogs diagnosed with parvovirus enteritis in Nigeria between 2010 and 2014, amoxicillin with or without clavulanate ranked fourth with the prescription rate of 12.6% (Gberindyer et al., 2017). There is dearth of documented clinical information on the incidences of ADEs in veterinary medicine, particularly in Nigeria. Most of the discussions on this subject are based on the information in the text books rather than clinical and prospective observational reports. The aim of this study was therefore to examine and report observable adverse drug events (ADEs) of amoxicillin with or without clavulanate in puppies.

2. MATERIALS AND METHODS

2.1. Study design

A multicentre observational prospective clinical study was carried out in five Veterinary clinics in Nigeria between 3 November 2015 and 24 April 2016 with 63 dogs on parvovirus enteritis management. The study was approved by the University of Ibadan Animal Care and Use Research Ethics Committee (UI-ACUREC/App/2015/027).

2.2. *Inclusion criteria*

Dogs enrolled into this study were those without history of being treated with any of the β-lactams from birth. In addition, they were not administered any drug for at least two weeks prior to presentation. None of the dogs was on a concurrent medication with amoxicillin, except 5% dextrose saline and/or lactated ringer's infusions.

2.3. Animals

A total of 63 dogs of different breeds (Alsatian [n=11], Rottweiler [n=13], Boerboel [n=20], Samoyed [n=1], Lhasa Apso [n=2], and Mongrel [n=16] breeds), mixed sexes, with median body weight and age of 6.0kg (2.4-28.1kg) and 4 months (2-10 months), respectively that met the inclusion criteria were enrolled for this clinical study. All the puppies were those diagnosed with parvovirus enteritis, where the diagnosis was based on the vaccination history, clinical presentations, and rapid chromatographic Enzyme Linked Immunosorbent Assay (SNAP® Parvo, IDEXX Laboratories, USA) for the detection of parvovirus antigen in their faeces.

2.4. Treatment and monitoring

Puppies in Group A (n=36) were administered amoxicillin with (n=16) or without (n=20) clavulanate by IV route. Whereas those in group B (n=27) were treated with amoxicillin alone by IM route. The amoxicillin formulation (with or without clavulanate potassium) used was from the same source and at the required dose of 15mg/kg body weight for dogs. Afterwards, treated puppies were observed for any ADE within 3 hours post treatment. Apart from fluids and electrolytes, all the indicated medications were administered after the 3-hour period of observation for the ADEs in order to circumvent any likely interfering effect of other medications. Those that manifested cutaneous ADEs were treated with diphenhydramine by IV route at a single dose of 2mg/kg, depending on the severity of the clinical manifestations of the ADEs.

3. RESULTS

Results showed that only 12(18.5%) of the 63 puppies manifested various forms of gastrointestinal and cutaneous ADEs concurrently. Specifically, 5/16(31.3%) of the puppies administered amoxicillin containing clavulanate intravenously manifested ADEs inform of diarrhoea (Figure 1A) and hyper-salivation (Figure 1B), as well as swellings around the eyelids and oral commisures (Figure 2B), and erythema of the eyelids (Figure 2B) within 5-10 minutes post treatments. Also, 7/20(35%) puppies treated with amoxicillin alone by IV route manifested similar signs post treatments. However, those puppies administered amoxicillin only by IM route showed none of the ADE signs observed in those treated with amoxicillin in combination with or without clavulanate by IV route. Result also revealed that only Boerboel (n=9), Lhasa Apso (n=2), and Samoyed (n=1) breeds showed ADEs. Again, the drug events were completely resolved 24 hours after treatment with diphenhydramine.

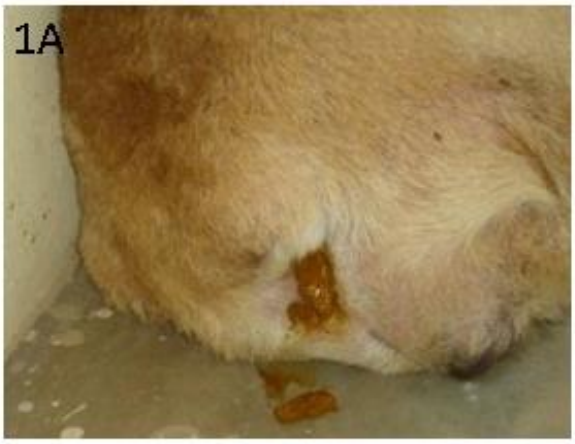

Figure 1A: Diarrhoea following treatment with amoxicillin alone by intravenous route.

Figure 1B: Hyper-salivation following treatment with amoxicillin alone by intravenous route.

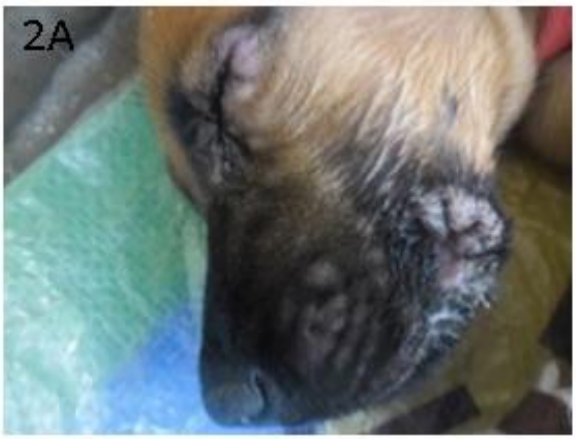

Figure 2A: Swellings around the eyelids and oral commisures following treatment with amoxicillin in combination with clavulanate by intravenous route.

Figure 2B: Erythema around the eyelids following treatment with amoxicillin alone by intravenous route.

4. DISCUSSION

Most cutaneous drug reactions in human and small animals are associated with antibiotics where β-lactams are amongst the most implicated (Bigby, 2011). However, Wilcke and Davis independently reported that ADEs associated with penicillin in veterinary medicine are rare (Wilcke, 1986; Davis, 1987). Again, a previous study showed that of the 115 dogs treated with amoxicillin, 25(21.7%) manifested adverse drug reactions (ADRs) post treatment, whereas out of the 34 cats treated, 15 (44.1%) were observed with ADRs (Iraguen et al., 2010). In addition, ulcerations, crusting, and pruritus on the head following a course of amoxicillin with clavulanate have been reported in cats (Voie and Lavergne, 2012). Nevertheless, lack of recognition of cutaneous ADEs in animals may be because of the mild lesions and hairy characteristic of these patients. Furthermore, a myriad of clinical signs of some diseases presented at the clinics for therapeutic interventions could contribute to the misdiagnosis of ADEs.

Diarrhoea and vomiting are cardinal clinical presentations of parvovirus enteritis (Isogai et al., 1989). This study revealed that all the patients observed with ADEs following treatment with amoxicillin with or without clavulanate presented gastrointestinal and

cutaneous signs simultaneously few minutes post treatments. An additive effect of amoxicillin and the presenting disease condition on the gastrointestinal tract could have explained the observed diarrhoea and hyper-salivation few minutes post treatment. Again, patients that manifest ADEs often have serious diseases requiring polypharmacy, making incrimination of a particular drug challenging. This is applicable to those used in this study that were diagnosed with parvovirus enteritis requiring symptomatic management with array of drugs such as antibiotics, antiemetic, analgesics, and fluid and electrolytes. Even though ADE could be related to an underlying disease, polypharmacy, or other non-drug related causes (ElDesoky, 2007), none of the puppies was administered the investigated drug (amoxicillin with or without clavulanate) with another before and during the period of observation for the ADEs. These to a reasonable extent suggest the role of amoxicillin with or without clavulanate in the observed ADEs. However, considering the fact that the same form and extent of ADEs were observed in puppies treated with amoxicillin alone or amoxicillin in combination with clavulanate intravenously, we propose that amoxicillin alone was the cause of those ADEs.

Adverse drug events due to β-lactams, including amoxicillin with or without clavulanate in man have been reported to occur a few minutes to an hour following treatment, but much earlier when the IV route is employed (Hoigne et al., 1984). This corroborates our observations where ADEs in form of diarrhoea, hyper-salivation, and varying forms of cutaneous manifestations were observed between 5 and 10 minutes post IV treatment with amoxicillin alone or in combination with clavulanate. Most ADEs are self-limiting, but could be severe, and/or serious. Nielsen *et al*. reported five deaths out of 11 horses that showed ADEs following IM treatments with procaine penicillin G (Nielsen et al., 1988). Conversely, no mortality was recorded in any of the puppies enrolled for this study. Also, only those puppies administered amoxicillin with or without clavulanate through IV route showed ADEs. No ADEs were observed after subsequent treatment (24 hours after the first encounter) of the same puppies with amoxicillin alone by IM route thereby suggesting drug allergy and excluding hypersensitive reactions. This again supports an earlier report that inadvertent IV injection of large dose of penicillin G is one of the causes of acute ADRs (Wilcke, 1986). The high serum concentration of drug rapidly attained following IV route of administration could be an appropriate explanation to this.

Generally, very little is known about the pathogenesis of allergic drug reactions in animal, consequently limiting diagnostic and then treatment options. Yet, the relatively limited knowledge on this subject in human is often extrapolated to animals. In most cases, ADEs resulting from β-lactams are described by an immunoglobulin E (IgE)-mediated mechanism (Mirakian et al., 2008). It is presumed that interaction of drugs, including the β-lactams, its metabolite, drug-protein complex, or metabolite-protein complex with specific IgE bound to the surface of mast cells and possibly basophils result to mast cells degranulation and consequently release of stored inflammatory mediators such as histamine, neural proteases, cytokines, and others (Friedmann et al., 2003; Jakate et al., 2006). Mast cells are distributed in many tissues, including the gastrointestinal mucosa and the skin (Stevens and Austen, 1986). Increase in mucosal mast cells above 20 mast cells per high field power (mastocytosis) using immunostaining for CD117 has been linked with enterocolitis and its associated clinical presentations, including diarrhoea (Jakate et al., 2006). Mast cell inflammatory mediators from the gastrointestinal mucosa have been reported to increase gastrointestinal motility and hyper-secretion culminating in diarrhoea and abdominal pain via gut-brain inter-neuronal interactions (Wood, 2004). Specifically, elevated histamine levels have been associated with allergic mastocytic gastroenteritis and colitis in human (Akhavein et al., 2012). Furthermore, release of the stored inflammatory mediators following degranulation of the cutaneous mast cell by the parent drug or its metabolite results in vasodilatation with increased vascular permeability, producing redness and edema in the skin clinically presenting as urticarial and angioedema (Omidi, 2009).

Viral Reactivation theory of the pathogenesis of drug allergy has been proposed postulating that a relationship exists between viral diseases and drug allergies (Shiohara and Kano, 2007). Underlying viral infections, such as herpes virus may increase susceptibility of patients to ADRs (Chung et al., 2004). Antiviral T cells may be implicated in stimulating an immune response that causes drug hypersensitivity. However, this could be possible in similar vesicular viral infections such as pest des petit ruminates (PPR) in goats.

Consequently, treatment of these conditions has been tailored towards mast cell membrane

stabilisation employing cromolyn sodium, and histamine receptor (H) antagonists such as diphenhydramine, and cetirizine (H1 blocker), ranitidine or famotidine (H2 blocker) for cutaneous and gastrointestinal forms of ADEs, respectively (Zachariae et al., 1981; Ramsay et al., 2010). A single intravenous dose of diphenhydramine alone effectively resolved the clinical signs observed in this study within 24 hours, thus defining the events as "severe" but "not serious" as earlier specified in the Australian Pesticides and Veterinary Medicines Authority (APVMA) for small animals (APVMA, 2017).

Lack of awareness of drug adverse events in veterinary clinical practice has led to an underestimation of their severity and frequency. This study has therefore demonstrated that IV administration of amoxicillin with or without clavulanate could result in cutaneous and/or gastrointestinal forms of adverse drug events. This was observed in Boerboel, Lhasa Apso, and Samoyed breeds of dogs. However, these drug reactions were "severe" but not "serious", and not observed following a second treatment with amoxicillin alone by IM route, hence could be defined as drug allergic reactions due to amoxicillin. Although amoxicillin is usually well tolerated, the present clinical study presents an alert to veterinarians regarding the potential role of amoxicillin in adverse drug events in dogs, particularly following IV administration. Consequently, veterinarians should be cautious when it becomes obligatory to treat dogs with amoxicillin alone or in combination with clavulanate by IV route in order to circumvent these adverse drug events.

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