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Clinical Study on Penicillin Anaphylaxis and Role of Oxidative Stress and Pro-inflammatory Markers: An Implication for Therapy

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ABSTRACT

Background: Penicillin belongs to the β-Lactam group of antibiotics which is used as a first-line drug in veterinary medicine. The occurrence of penicillin anaphylaxis and its pathophysiology is rarely reported in ruminants.

Methods: In the present study, oxidative stress and pro-inflammatory response were investigated in 4 cases (Jersey crossbred) of penicillin hypersensitivity by assessing oxidative stress biomarkers and pro-inflammatory cytokines. Animals in the current experimental plan were divided into three groups, group I included penicillin hypersensitive (n=4), group II included penicillin tolerant (n=6) and group III (n=10), included healthy control animals.

Result: Mean values of temperature, heart rate and respiration were significantly ($p<0.05$) elevated in the penicillin-sensitive group compared to the penicillin tolerant and control group. The present study revealed significantly ($p<0.05$) elevated levels of lipid peroxidation (MDA), xanthine oxidase (XO), nitric oxide (NO), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), while as levels of glucose-6-phosphate dehydrogenase (G6PD), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were significantly reduced in the penicillin-sensitive group. Levels of G6PD showed significant positive correlation with GPx ($r=0.54$, $P<0.001$) and catalase ($r=0.34$, $P<0.05$) while as significant negative correlation with XO ($r=0.39$, $P<0.05$) was observed. Collectively, these findings indicate that the pathophysiology of penicillin hypersensitivity involves anti-oxidant imbalance and enhanced pro-inflammatory response and targeting these pathways can have therapeutic implications for penicillin hypersensitivity.

Key words: Hypersensitivity, Oxidative stress, Penicillin, Pro-inflammatory response.

INTRODUCTION

Penicillin was derived from Penicillium fungi and the historical importance of penicillin lies in that it was among the first drugs found to be effective against many previously untreated diseases Wise *et al.* (1965). Benzylpenicillin is most commonly used in ruminant medicine owing to its relative inexpensiveness (Bhattacharya 2010), wide safety margin (Omidi 2009), diverse formulation availability Broesby-Olsen *et al.* (2015), maintenance of long term therapeutic concentration Hooper *et al.* (2004) and well tolerance capacity (Allpress and Heathcote 1986).

In human medicine, antibiotics are observed to cause adverse drug reactions including sulphonamide, vancomycin fluoroquinolones, macrolides, tetracyclines and glycopeptides (Strom *et al.*, 2003, Gomes *et al.*, 2004, Mockenhaupt *et al.*, 2008, Zhou *et al.*, 2016). In addition to antibiotics, drugs especially nonsteroidal anti-inflammatory drugs Brown *et al.* (2004) vaccines and bacterins Turnquist *et al.* (1993) have been reported to cause adverse drug reactions.

To the best of our knowledge, adverse reactions caused by penicillin alone and other preparations of penicillin used in combination with other drugs have been rarely reported in livestock Broesby-Olsen *et al.* (2015). However, some earlier studies have reported penicillin anaphylaxis in equines Olsen *et al.* (2007) sheep Radostits *et al.* (2007)

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and a single report in cattle (Omidi 2009). There are a limited number of studies that have reported the role of oxidative stress in some allergic diseases which include asthma, atopic dermatitis and angioedema Kharitonov *et al.* (1995). These studies have found an increased number of eosinophils and mast cells and increased levels of lipid per-oxidation with concurrent decreased levels of anti-oxidant defense mechanism Gomes *et al.* (2004). Furthermore, there is a paucity of literature available on the role of oxidative stress and pro-inflammatory markers on the pathophysiology of penicillin anaphylaxis and their possible role in the therapeutic implication of adverse drug reactions. Based on these lacunas, the aim of the current study was to investigate the possible role of oxidative stress and pro-inflammatory cytokines in the pathophysiology of penicillin anaphylaxis.

Highlights

- Penicillin anaphylaxis and its pathophysiology in ruminants is discussed.
- Oxidative stress and pro-inflammatory response were investigated.
- Results show pathophysiology of penicillin hypersensitivity involve anti-oxidant imbalance and enhanced pro-inflammatory response.
- Further investigations are required.

MATERIALS AND METHODS

Experimental design

A study was conducted between June 2017 to January 2020 in animals presented to Teaching Veterinary Clinical Services Complex, (TVCSC), Faculty of Veterinary Sciences and Animal Husbandry (Faculty of Veterinary Sciences and Animal Husbandry, SKUAST-K). Throughout the period four calves exhibited adverse drug reactions towards penicillin injection. So current study was designed to observe the role of oxidative stress and pro-inflammatory cytokines in the pathophysiology of penicillin anaphylaxis. To accomplish it, animals in the current study were divided into three groups, group I (n=4; male-3, female-1; age-4.02±2.52; Crossbred) as penicillin hypersensitive group (after intramuscular administration) showing overt signs/symptoms of penicillin anaphylaxis. Group II (n=6; male-4, female-2; age-3.56±1.34; Crossbred) was a penicillin tolerant group and animals in this group were injected penicillin prior to a surgical intervention *i.e.*, Vasectomy. Group III (n=10; male-10; age-0.98±0.54; Crossbred) comprised of control group and animals in this group were evaluated for normal health check-ups without giving any medicinal formulation.

Clinical examination

All animals in the present study were examined by distant and near clinical examination and vital parameters examined included temperature, pulse rate and respiration rate. The distant examination included gait, posture and behavior while near examination included examination of the mucous membrane, examination of all body parts, rumen motility and respiratory sounds.

Sample collection

Blood samples were collected from the jugular vein and were transported to the laboratory in ice buckets. Blood samples collected were centrifuged @ 1500 rpm in a cooling centrifuge for 15 mins. Serum obtained was stored at 40°C until used for estimation of pro-inflammatory cytokines and serum levels of NO (Nitrous oxide).

Assessment of markers of oxidative response and glucose-6-phosphate dehydrogenase (G6PD)

Erythrocyte lysate was prepared as per method Nabi *et al.* (2021) oxidative stress markers were estimated in erythrocyte lysate. Lipid peroxidations (MDA), reduced glutathione (GSH), glutathione peroxidases (GPx) activity, glutathione reductase (GSSG) activity, Superoxide Dismutase (SOD) activity Xanthine oxidase (XO) and Catalase (CAT) activity in erythrocyte lysate were accessed as per the method of Jollow *et al.* (1974), Marklund and Marklund (1974); Carlberg and Mannervik, (1975); Wright *et al.* (1981), Mohandas *et al.* (1984); Nabi *et al.* 2021 and Claiborne, (1985) respectively. G6PD was estimated as per the method described by Beutler, (1984).

Measurement of NO (Nitric oxide)

NO concentration in serum was estimated by measuring the concentration of nitrite (an indicator of NO) and concentration of nitrite was evaluated from a $NaNO_2$ curve obtained by Green *et al.* (1982).

Serum proinflammatory cytokine analysis

Concentrations of pro-inflammatory cytokines (TNF-α-Tumour Necrosis Factor-Alpha, interleukin-6) in serum were estimated using commercially available ELISA kits (Sigma Aldrich) as per instructions of the manufacturer.

Statistical analysis

The results from each group were presented as mean and standard error. Differences between different groups were analyzed by using ANOVA followed by the Tukey-Kramer multiple comparison test with the minimum criterion for statistical significance at $p<0.05$.

RESULTS AND DISCUSSION

Animals in the penicillin-sensitive group (Group I) showed severe dyspnoea (4/4), urticaria (2/4), oedema (3/4), lacrimation (4/4). Oedema was noticed in the eyelids (Fig 1a), lips, brisket region (Fig 1b), face, perianal and anal region (Fig 1c and 1d) in group I. Rectal body temperature of animals in the penicillin-sensitive group (102.50±0.64°F) was significantly elevated compared to animals in Penicillin Tolerant (98±0.36°F) and control group (98.4±0.40°F), while the non-significant difference in rectal body temperature of animals in group II and group III were observed (Table 1). A similar trend was also observed in the case of heart rate (131.75±2.95 beats in group I, 90.33±3.07 beats in group II

Fig 1: Effect of penicillin on different body parts. 1a shows Conjunctival angioedema, 1b shows brisket edema, urticaria and perianal edema is shown in 1c and facial angioedema is shown in 1d.

Table 1: Clinical and biochemical parameters (mean±SE) of penicillin hypersensitivity in penicillin hypersensitive, penicillin tolerant and control group (bovine calves).

Parameter	Group I (n=4)	Group II (n=6)	Group III (n=10)
Temperature (°F)	102.50±0.64^{a}	98±0.36^{b}	98.4±0.40^{b}
Heart rate (BPM)	131.75±2.95^{a}	90.33±3.07^{b}	87.50±2.72^{b}
Respiration rate (bpm)	35.00±3.48^{a}	26.33±1.87^{b}	24.77±1.31^{b}
MDA (nmol/g Hb)	30.72±2.05^{a}	27.35±2.38^{ab}	21.45±1.37^{b}
Catalase (IU/g Hb)	6.91±0.46	7.20±0.50	9.58±0.43
XO (mU/mL)	0.38±0.02^{a}	0.25±0.03^{ab}	0.16±0.01^{b}
SOD (IU/mg Hb)	20.66±2.49^{a}	22.52±1.61^{a}	28.41±1.74^{b}
GPx (IU/mg Hb)	28.19±3.57^{a}	56.88±4.12^{b}	59.24±5.01^{b}

F: Fahrenheit; BPM: Beats per minute; bpm: Breaths per minute; Group I; Penicillin hypersensitive, Group II; Penicillin tolerant, Group III; Control. Results with different superscripts (ab) vary significantly (P<0.05) across different groups.

and 87.50±2.72 beats in group III) and respiration rate (35.00 ±3.48 breaths per minute (bpm) in group I, 26.33±1.87 bpm in group II and 24.77±1.31 bpm in group III). These clinical manifestations of penicillin hypersensitivity observed in the present study are in concurrence with findings of earlier studies (Radostits *et al.*, 2007, Omidi 2009, Boonk *et al.*, 1982). Elevated body temperature and urticaria have been attributed to muscle tremors and are mediated by IgE directed against allergic determinants generated from oxidative damage (Omidi 2009) and oxidative metabolites Boonk *et al.* (1982) of the culprit drug. An interesting clinical finding of the current study was three animals out of four in the penicillin hypersensitivity group (2 female and 1 male) showed odema in the brisket region. These findings are supported by the study of (Omidi 2009), who proposed increased vascular permeability and leakage of albumin in chlorogenic acid hypersensitivity in rats.

Our results indicated that erythrocytes lysate from penicillin-hypersensitive animals were having higher ROS (Reactive oxygen species) as compared to the other two groups. Animal in groups I (30.72±2.05 nmol/g Hb) treated with penicillin was having significantly (P<0.05) increased levels of MDA (Malondialdehyde) in comparison to groups III (21.45±1.37 nmol/g Hb). While as MDA levels in groups II (27.35±2.38 nmol/g Hb) were comparable with values in groups III and groups II (Table 1). SOD (20.66±2.49 IU/mg Hb in group I and 28.41±1.74 IU/mg Hb in group II) and GPx (28.19±3.57 IU/mg Hb in group I and 59.24±5.01 IU/mg Hb in group II) content in the penicillin-hypersensitive group was significantly (P<0.05) depleted compared to group III. Penicillin administration in group I resulted in significantly (P<0.05) increased levels of NO production (59.72±7.79 µmol/L) as compared with the group II (38.61±4.44 Mmol/L) and group III (33.78±4.12 µmol/L). We observed that there was no appreciable significant difference in NO levels in groups II and III (P<0.05) (Fig 2a). The concentration of XO (Xanthine Oxidase) was significantly elevated (P<0.05) in group I (0.38±0.02 mU/mL) compared to group III (0.16±0.01 mU/mL) so it can be postulated that Penicillin treatment

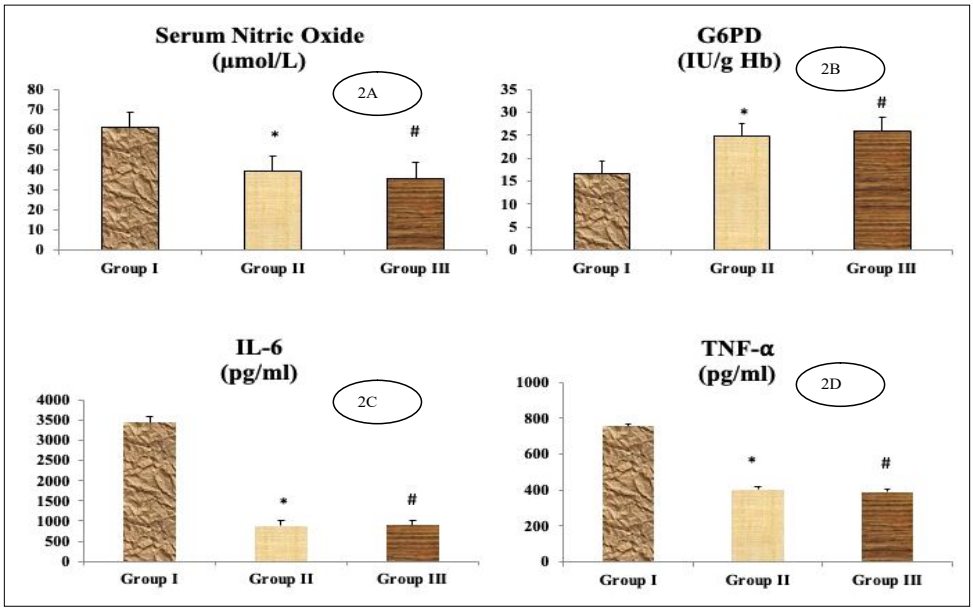

Fig 2: Group I (n=4): Penicillin hypersensitive group; group II (n=6): Penicillin tolerant group; group III (n=10): control group; Data were expressed as mean±SD. Nitric Oxide (µmol/L), TNF-α (pg/ml) and IL-6 (pg/ml) levels were significantly increased (*P<0.05) in penicillin hypersensitive group (group I) as compared with group II and group III. Glucose-6-Phosphate Dehydrogenase levels (IU/g Hb) were significantly decreased (*P<0.05) in penicillin hypersensitive group (group I).

significantly increased the activity of XO in group I (P<0.05) (Table 1). In the present study significantly reduced levels of G6PD (16.22±1.42 IU/gHb) were found in the penicillin hypersensitivity group compared to the penicillin tolerant and control group (Fig 2b). The results of current study indicate significant positive correlation between G6PD with GPx (r=0.547, P<0.01) and SOD (r=0.34, P<0.05). While a significant negative correlation was found between G6PD with XO (r=0.39, *P*<0.05). Furthermore, XO and SOD (r= -0.32, P<0.01) exhibited a significant negative correlation. Catalase (r=-0.43, P<0.01) and GPx (r=-0.43, P<0.01) and values of XO showed significantly positive correlation with NO (r=0.40, P<0.05) (Table 1).

Excessive generation of ROS leads to depletion of antioxidant enzymes Nabi *et al.* (2021) therefore it may be proposed that injection of culprit drugs in penicillin-sensitive patients results in oxidative stress because of excessive generation of ROS and depletion of the antioxidant defense system. Radostits *et al.* (2007) has earlier proposed the "reactive metabolite hypothesis" according to their study reactive oxidative species generated in adverse drug reactions activate the immune system in drug-induced hypersensitivity. In the current study, SOD activity was observed to be significantly decreased in the penicillin-sensitive group. Analysis of peripheral mononuclear cell resistance to adverse drug reaction was found to have elevated levels of SOD in erythrocyte homogenate Cornejo-Garcia *et al.* (2016). Human Immunodeficiency Virus (HIV) infected individuals sensitive to adverse drug reactions were found to have significantly lower levels of antioxidant enzymes Buhl *et al.* (1989). Increased levels of nitric oxide in the penicillin-sensitive group (59.09±13.89) are supported by experimental study of Radostits *et al.*, 2007 (2014) on induced cardiac anaphylaxis in the rat model and the study concluded that elevated levels of nitric oxide (NO) play a pivotal role in immune dysregulation via ROS acting as a stimulus for the clonal proliferation of mast cells. In the present study, we could not observe any significant difference in values of reduced glutathione, catalase and glutathione reductase across different experimental groups.

Pro-inflammatory cytokines particularly TNF-alpha and IL-6 have important roles pathology of drug-induced hypersensitivity. Penicillin injection in the penicillin-sensitive group caused significant (p<0.05) elevation in the serum levels of TNF-alpha, (757.75±52.80 pg/ml) and IL-6 (3389.75 ±283.73 pg/ml) as compared to the healthy control group and the penicillin-resistant group (Fig 2c and 2d). The levels of pro-inflammatory markers (TNF-α and IL-6) were significantly elevated in the penicillin-sensitive group compared to the penicillin-resistant group and control group. It may be proposed from the present study that the generation of ROS may activate the inflammatory cascade which sensitizes the host cells to an allergen in drug-induced hypersensitivity. To support these speculations, the results of the present study observed significantly increased levels of pro-inflammatory cytokines (TNF-α and IL-6) in penicillin-sensitive patients. There are various indirect pieces of evidence for the role of oxidative stress in hypersensitivity reactions (Rieder *et al.*, (1989); Cribb and Spielberg (1992) proposed that in the initial stage of hypersensitivity oxidative metabolite of the culprit drug form covalent bonding with endogenous host macromolecules and resulting (oxidative

metabolite-endogenous macromolecule) addict functions as an allergic determinant to initiate hypersensitivity reaction. Adeyanju *et al.* (2018) has postulated oxidation of sulfhydryl and disulphide bond in endogenous proteins by free radical generated in drug-sensitive subjects' results in the generation of allergens. Furthermore, Rieder *et al.* (1989) proposed that lowered oxidative defense/redox imbalance inhibits various enzymatic pathways involved in cellular defense and hence causes immune sensitization of host cells. These assumptions are further validated by the use of anti-oxidants which ameliorate the drug-induced hypersensitivity reaction and concurrently lowered allergic adduct in blood Samitas *et al.* (2018). These propositions are further supported by Yanagawa *et al.* (2017) who proposed that mast cell degranulation can be triggered by ROS generated during oxidative stress. The role of oxidative stress markers like NO and XO have been studied in allergic and anaphylactic conditions Frijhoff *et al.* (2015) and effective inhibition of these markers has shown pronounced clinical improvement in these conditions Bayer *et al.*, (2013). As reported by previous studies numbers Samitas *et al.* (2013) of oxidative stress markers have been found to play an important role in anaphylaxis so for effective treatment of anaphylaxis there is an urgent need to understand pathogenetic hotspots activated by oxidative stress markers.

G6PD functions as an indirect antioxidant as the enzyme is involved in the activation of NADPH + H^+-SOD and GSH-Px Beutler (2002). Results of our study showed a significantly positive correlation between G6PD activity and major antioxidants (SOD and GSH-Px) and its negative correlation with ROS suggests a contributory role of G6PD in oxidative damage and henceforth hypersensitivity. G6PD has a sparing effect on SOD activity and supplies NADPH to the cellular microenvironment which keeps GSH-Px and other enzymes in a reduced state Rezaei and Naghadeh (2006). Decreased G6PD activity has been proposed to cause oxidative damage to reticuloendothelial cells and the release of endogenous factors results in immune dysregulation Roth *et al.* (1988). However, there were some limitations of the present study which includes a sample size.

In the present study, the sample was less, so there is a need to study the role of ROS in a large sample size and hypersensitivity induced by vehicles used in common medicinal preparations.

CONCLUSION

Based on the results of the present study it can be postulated that both Oxidative stress markers and pro-inflammatory cytokines are involved in diseases mediated by immune dysregulation. These parameters need to be standardized and used as routine screening tests for patient susceptibility in the development of drug-induced hypersensitivity. However, further study in laboratory animal models is warranted for a better understanding of the pathophysiology of penicillin-induced hypersensitivity.

Conflict of interest: None.

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