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Comparative Therapeutic Efficiency between Phenylbutazone and Dexamethasone in Chicks

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ABSTRACT

The current objective was to compare the antiinflammatory, analgesic, and antipyretic efficiency of phenylbutazone (PBZ) in contrast to dexamethasone (DMZ) in 7-15 days-old chicks. The analgesic ED50 value of PBZ and DMZ given alone were 5.60 and 0.63 mg/kg, i.p. PBZ and DMZ analgesic percentages were the same in the chicks while PBZ had a significantly more potent analgesic effects in comparison to DMZ regarding the post voltage of analgesia measured beside there is a significant value related to the pre and post-voltage measured in the PBZ group. Baker's yeast induces a significant pyresis 3 hour after its injection. PBZ gives rise to its significant antipyretic activity at 2, 3 and 4 hours after pyretic induction by baker's yeast while DMZ illustrates its antipyretic significantly at 4 hours of measured time. PBZ and DMZ exert their anti-inflammatory activity by 71 and 57%, respectively. PBZ and DMZ have a significant anti-inflammatory property through a significant reduction in delta-thickness in comparison to the control group besides the supremacy of PBZ over DMZ. Both PBZ and DMZ treatment for five consecutive days in the chicks have no significant difference in the concentrations of creatinine and uric acid (kidney function) besides AST and ALT (liver function) in comparison to the control group except the significant elevation in the creatinine concentration at the PBZ group. The net results of this comparative study indicated that PBZ has good, reliable and profound antiinflammatory, analgesic, and antipyretic efficiency than DMZ of the chickens model.

Keywords
analgesic; antipyretic; antiinflammatory; dexamethasone; phenylbutazone

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as PBZ, are a wide range of drugs that are used for several usages in veterinary medicine as anti-inflammatory, antipyretic, and analgesic (Bally *et al.*, 2017; Lanas & Chan, 2017; Bindu *et al.*, 2020). These properties are due to the non-selective mechanism through direct antagonism of the isoforms called the cyclooxygenase responsible for the synthesis of prostaglandin (PG) autacoids particularly the PGE_2 kind, from the arachidonic acid precursor, that is considered as a chemical mediator which plays a vital role in producing inflammation, fever, and pain (Botting, 2006; Finkel *et al.*, 2009; Smyth & FitzGerald, 2009; Hilal-Dandan & Brunton, 2014). PBZ pertains to high medications of NSAIDs which are bound to albumins (plasma proteins) approximately 99% with its stimulation properties of the microsomal enzymes (accountable for the phase-I of metabolism of the drugs) (Smyth & FitzGerald, 2009; Hilal-Dandan & Brunton, 2014).

On another hand, DMZ belongs to a corticosteroid drug which is similar to the biological hormone produced by the adrenal gland and it is frequently casted off to alleviates

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inflammatory issues with weak analgesia and antipyresis produced incomparable to NSAIDs (Sinniah *et al.*, 2021). DMZ acts through reducing the phospholipase A_2 enzyme which has a role in the transformation of the cell membrane phospholipids molecules to the unsaturated fatty acids which are arachidonic acid (the precursor of PG synthesis previously mentioned), thus inhibiting the PG production by the indirect action (Goppelt-Struebe *et al.*, 1989; Jang *et al.*, 2020). For that, DMZ and NSAIDs are used frequently due to their synergism against reducing the PG production (Raeeszadeh & Ghaffari, 2022).

The current objective of this study was to compare the anti-inflammatory, analgesic, and antipyretic efficiency between PBZ and DMZ of the chickens model.

Materials and methods

Animals conditions and drug preparation: Seven to fifteen days of broiler chicks were utilized in the study. The bodyweight of chicks were between 84-127 g with nonstopable light and kept at 31-34 ○C. The food and water were provided freely. PBZ (20%, Interchemie, Hohhand) and DMZ (0.2% VAPCO, Jordan) were diluted in a saline solution to acquire the desired dosages. The route of administration was intraperitoneally (i.p.) by 5 ml/kg as a volume of injection.

Laboratory animal ethics: The scientific committee monitoring of the College of Veterinary Medicine / Mosul University has agreed the study and the usage of the experimental chicks.

Determination the median effective doses (ED_{50}s) of PBZ and DMZ causing of analgesia in the chicks: The analgesic ED_{50}s of either PBZ and DMZ were assessed for each drug alone. The first dosage of PBZ and DMZ were at 7 and 2 mg/kg, i.p. as illustrated according to the up-and-down technique (Dixon, 1980). The electro-stimulator device (Harvard apparatus, USA) was used to assess the occurrence of distress call in the chicks (as indicator to pain sensation). The chicks were assessed separately pre, and post 30 minutes of i.p. medications treatment (Mousa & Mohammad, 2012; Mousa, 2019; 2020). Then, according to the look or lack of the analgesia, the doses of the drugs will be decreased or increased as 2 and 0.5 mg/kg, correspondingly according to the initial dose used.

Comparing the analgesic effect produced by PBZ and DMZ:
According to the ED_{50} value of PBZ and DMZ measured in the previous experiment, two groups (6 chicks/group) were treated with 11.20 and 1.26 mg/kg, i.p. (that represented their ED_{100} respectively) for examining their comparative analgesia. The voltage (volt) induced by electrostimulation for each chick was documented pre, and post 30 minutes of treatment. Later, the percentage of analgesia occurred in each group of the chicks in addition to the delta voltage (the difference between voltage before and after injection of the drugs) were also recorded (Mousa *et al.*, 2019; 2021).

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Assessment of the antipyretic effects between PBZ and DMZ in chicks: The antipyretic effect of PBZ and DMZ was recorded by injection of baker's yeast at 135 mg/kg, i.p. (Abotsi *et al.*, 2016) for induction of pyresis. Three groups (6 chicks/each) were treated with 0 (normal saline), 11.20 (PBZ) and 1.26 mg/kg, i.p. (DMZ). The temperature was recorded before and after 1, 2, 3 and 4 hours by using the digital thermometer via the rectum.

Assessment of the anti-inflammatory effects between PBZ and DMZ in chicks: Three groups (6 chicks/group) of the control (normal saline injection) and treated (PBZ and DMZ injection) have been selected. PBZ and DMZ were injected at 11.20 and 1.26 mg/kg, i.p., respectively at 30 min. before induction of inflammation by using 0.05 ml injection of formaldehyde (1%, May and Baker Ltd Dagenham, UK) in the paw (Sufka *et al.*, 2001). The paw thickness will be admeasurement via the digital vernia as millimeters (mm) for pre, and post 60 min. of formaldehyde treatment besides the delta-thickness, which indicated the inflammatory occurrence (Collin *et al.*, 2001), was also measured in addition to its alteration percentage that reveals the antiinflammatory action of PBZ and DMZ.

Measurement of kidney and liver function in chicks after treatment with PBZ and DMZ for five consecutive days: After treatment with PBZ (11.20 mg/kg, i.p.) and DMZ (1.26 mg/kg, i.p.) for five consecutive days, the blood were taken from the two groups of chicks (6 chicks for each) in addition to the control group. Serum creatinine and uric acid were used to extrapolate the kidney function while the serum AST and ALT indicated the liver function (Plummer, 1987).

Statistical analysis: The two groups of parametric were analysed by paired and unpaired student T-tests besides the Man-Whitney U-test was applied to nonparametric data. The three groups of parametric data were analysed by one-way analysis of variance (Petrie & Watson, 2013). The p of less than 0.05 will be considered significant.

Results

The analgesic ED_{50}S of PBZ and DMZ in the chicks: Table 1 demonstrate the several results obtained from up-and down method. The analgesic ED_{50} of PBZ was 5.60 mg/kg, i.p. that exhibit analgesia in 50 % of the chicks whereas DMZ was 0.63 mg/kg, i.p.

Table 1. The results of analgesic ED_{50}s of PBZ and DMZ in the chicks

Parameters	PBZ	DMZ
ED_{50} *	5.60 mg/kg, i.p.	0.63 mg/kg, i.p.
First dosage	7 mg/kg	2 mg/kg
Latest dosage	7 mg/kg	1 mg/kg
± in the doses	2 mg/kg	0.5 mg/kg
Range of the dosages	7-5= 2 mg/kg	2-0.5= 1.5 mg/kg
Overall chicks	5 (XOXOX)	7 (XXXOXOX)

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[*] ED_{50} = Latest dosage + (table value of Dixon × increased or decreased in the doses)
X indicate analgesia while O means no analgesia
Volt documented pre, and post 30 min. of PBZ and DMZ treatment

Comparing the analgesia between PBZ and DMZ in the chicks: The analgesic percentages of the PBZ and DMZ were the same in the chicks while PBZ had a more significantly potent analgesic effect in comparison to DMZ regarding the post voltage of analgesia measured beside the significantly variation among the pre, and post voltage in the PBZ group (Table 2).

Table 2. Comparing the analgesia between PBZ and DMZ in the chicks

Parameters	PBZ	DMZ
Analgesia (%)	100 (6/6)	100 (6/6)
Prevoltage	11.33 ± 0.33	10.00 ± 0.37
Postvoltage	14.17 ± 0.17 [#]	11.33 ± 0.61[*]
Deltavoltage	2.83 ± 0.48	1.67 ± 0.33

Numbers categorized for mean ± Std.E (6 chicks/ group)
[*] dissimilar significantly than the PBZ group at $p < 0.05$
[#] dissimilar significantly than the prevoltage for the similar group at $p < 0.05$
PBZ and DMZ were injected at 11.20 and 1.26 mg/kg, i.p., respectively

The antipyretic effects between PBZ and DMZ in chicks: Baker's yeast induces a significant pyresis 3 hour after its injection. PBZ give rise of its antipyretic activity at 2, 3 and 4 hours after pyretic induction by baker's yeast while DMZ illustrates its antipyretic significantly at 4 hours of measured time besides PBZ has a significant superiority of antipyretic action in comparison to DMZ at 3 hours of baker's yeast injection (Table 3).

Table 3. The antipyretic effects between PBZ and DMZ in chicks

Parameters	Control	PBZ	DMZ
Pre-temperature	40.68 ± 0.32	40.95 ± 0.21	41.30 ± 0.13
Post-temperature (1h)	40.60 ± 0.16	40.40 ± 0.26	40.17 ± 0.14 [#]
Post-temperature (2h)	40.63 ± 0.15	39.72 ± 0.28 [*,#]	40.27 ± 0.27 [#]
Post-temperature (3h)	41.82 ± 0.13 [#]	39.60 ± 0.20 [*,#]	40.55 ± 0.16 [a,#]
Post-temperature (4h)	41.05 ± 0.15	39.90 ± 0.24 [*,#]	40.17 ± 0.30 [*,#]

Numbers categorized for mean ± Std.E (6 chicks/ group)
[*] dissimilar significantly than the control group at $p < 0.05$
[a] dissimilar significantly than the PBZ group at $p < 0.05$
[#] dissimilar significantly than the pre-temperature for the similar group at $p < 0.05$
PBZ and DMZ were injected at 11.20 and 1.26 mg/kg, i.p., respectively
Baker's yeast was injected at 135 mg/kg, i.p.

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The anti-inflammatory effects between PBZ and DMZ in chicks: PBZ and DMZ exert their anti-inflammatory activity by 71 and 57%, respectively. PBZ and DMZ have a significant anti-inflammatory property through a significant reduction in delta-thickness in comparison to the control group besides the supremacy of PBZ over DMZ (Table 4).

Table 4. The antiinflammatory effects between PBZ and DMZ in chicks

Parameters	Control	PBZ	DMZ
Anti-inflammatory effect (%)	_____	71	57
Pre-thickness (mm)	10.72 ± 0.31	10.86 ± 0.24	10.83 ± 0.20
Post-thickness (mm)	11.33 ± 0.25 #	11.06 ± 0.24 #	11.14 ± 0.24 #
Delta-thickness	0.70 ± 0.05	0.20 ± 0.01*	0.30 ± 0.07 *

Numbers categorized for mean ± Std.E (6 chicks/ group)
* dissimilar significantly than the control group at $p < 0.05$
[a] dissimilar significantly than the PBZ group at $p < 0.05$
PBZ and DMZ were injected at 11.20 and 1.26 mg/kg, i.p., respectively
Formaldehyde was injected at 0.05 ml of 0.1% in the right paw

Measurement of kidney and liver functions in chicks after treatment with PBZ and DMZ for five consecutive days: Table 5 explains that creatinine and uric acid (kidney function) in addition to AST and ALT (liver function) concentrations for both groups of chicks which were treated for five consecutive days have no significant difference in the concentrations in comparison to the control group except the significant elevation in the creatinine concentration at the PBZ group with notice that one and three of chicks were dead during the treatment pattern of PBZ and DMZ, respectively.

Table 5. Kidney and liver function in chicks after treatment with PBZ and DMZ for five consecutive days

Parameters	Control	PBZ	DMZ
Creatinine (mg/dl)	0.35 ± 0.02	0.42 ± 0.02 *	0.41 ± 0.03
Uric acid (mg/dl)	39.10 ± 8.40	41.75 ± 5.61	52.10 ± 11.98
AST (U/L)	137.84 ± 13.91	157.53 ± 4.82	159.03 ± 19.52
ALT (U/L)	29.37 ± 0.75	27.34 ± 1.71	27.90 ± 2.74

Numbers characterized as mean ± SE for 6, 5 and 3 chicks for the control, PBZ and DMZ groups, respectively
* dissimilar significantly than the control group at $p < 0.05$
PBZ and DMZ were injected at 11.20 and 1.26 mg/kg, i.p., respectively for five consecutive days

Discussions

The current objective was to compare the anti-inflammatory, analgesic, and antipyretic efficiency between PBZ and DMZ used at the chicks model. As found in this

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study, the values of ED_{50}s for PBZ and DMZ values given each were 5.6 and 0.63 mg/kg, i.p., respectively that of benefit to alleviate analgesia in 50 % of the chicks casted-off as the model of laboratory animals, and this is reported here firstly in chicks. When comparing the analgesic, antipyretic and anti-inflammatory properties between PBZ and DMZ in this study, we notice that PBZ have the superiority over DMZ for alleviation of pain, fever and inflammation in the chicks model and this are attributed to the direct mechanism of action related to PBZ for direct reducing the PG synthesis that responsible for these situations (Botting, 2006; Finkel *et al.*, 2009; Smyth & FitzGerald, 2009; Hilal-Dandan & Brunton, 2014) rather than the reducing effects of DMZ causing analgesic, antipyretic and anti-inflammatory effects was assumed to the indirect effect on reducing the PG synthesis (Goppelt-Struebe *et al.*, 1989; Jang *et al.*, 2020). DMZ affects a wide variety of autacoids biosynthesis in the body (rather than inhibiting PG production) such as leukotriene through blocking the phospholipase A_2 enzyme (Goppelt-Struebe *et al.*, 1989; Jang *et al.*, 2020) which weakens his action toward the relieving of pain and fever conditions in comparison to PBZ. PBZ was known to induce the cytochrome enzymatic system responsible for the phase-I metabolism through accelerating the PBZ metabolism to other active metabolites called oxyphenbutazone (Tobin *et al.*, 1986) and this also attributed to increasing the efficacy of PBZ in comparison to DMZ effects. Other attributed reasons discussing the difference of PBZ in contrast to DMZ may be ascribed to the difference in the pharmacokinetic properties especially the high protein binding of PBZ of 99% (Smyth & FitzGerald, 2009; Hilal-Dandan & Brunton, 2014) rather than the DMZ protein binding of 60.5% (Ayyar *et al.*, 2019) which have a an immediate effect upon the distribution volume and subsequent increases the amount of free drugs reaching the target receptors.

Conclusion

The net results of this comparative study indicated that PBZ has good, reliable and profound antiinflammatory, analgesic, and antipyretic efficiency than DMZ of the chickens model.

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