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Dexamethasone-Induced Changes in Phenylbutazone Absorption in Chicks

Dr. Hemlata Sharma[1], Mayur Porwal[2], Dr. Giresha AS[3]

[1]Assistant Professor, Department of Ayurveda, Sanskriti University, Mathura, Uttar Pradesh, India, Email id: hemlata.ayurveda@sanskriti.edu.in

[2]Associate Professor, College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India, Email Id: mayur.porwal1@gmail.com

[3]Assistant Professor, Department of Biochemistry, School of Sciences, JAIN (Deemed-to-be University), Karnataka, India, Email id: asgiresha@gmail.com

Abstract

The absorption of drugs in chicks, as in any animal species, can be influenced by various factors. The route of drug administration can significantly affect absorption. Chicks can receive drugs through different routes such as oral, parenteral or topical. The goal of the current research is to determine how Dexamethasone (DM) treatment affects phenylbutazone's (PB) pharmaceutical kinetics blood levels, and therapeutic activity in a chick species. The maximum effective doses (ED_{50s}) of the analgesics for DM and PB, respectively, were 5.61 and 0.64 mg/kg, IP. These ED_{50s} have been calculated to be 1.77 and decreased to 0.18 mg/kg, IP, correspondingly. The results of this research indicate that PB and DM combine pharmacologically in an additive way. Therefore, the plasma amounts of PB at a dose of 11.20 mg/kg, IP, were 39.85, 66.19, 48.02, 35.32, and 26.52 g/ml in the predicted periods of 0.26, 0.6, 1, 2, 4, and 24 hours. The levels increase to 57.01, 384.16, 210.68, 138.68, 65.51, and 50.1/ml, correspondingly, if DM 1.26 mg/kg, IP, is administered. The highest concentration (C_{max}) of PB increases by 426%, the area over the curve ($AUC_{0-\infty)}$ increases by 196%, the area over the time curve ($AUC_{0-\infty)}$ increases by 140%, the removal rate variable (K_{el}) increases by 50%, and the area under the curve ($AUC_{0-\infty)}$ increases by 140% as a consequence of the changed pharmacokinetics of PB. The average duration of residence (MRT), a continuous state of the amount of dispersion ($t_{1/2\beta}$) clearance rate, and half-life are all reduced to 33%, 18%, 78%, and 60%, respectively. The total results show that PB and DM combine pharmacologically in a way known as synergism. Additionally, PB's blood levels and kinetics have changed, which has improved the drug's therapeutic effectiveness in the chick type.

Keywords: Chicks, Phenylbutazone, Dexamethasone, Pharmacokinetics, Pharmacodynamics

Introduction

The simultaneous use of many drugs has the possibility of causing drug interactions, in which another may change the effects of one medication. Optimizing treatment results and reducing side effects need an in-depth knowledge of these relationships. The wellness management of many kinds of animals, especially chicks, represents the field of veterinary medicine (1). In the field of veterinary medicine, two drugs are often used: PB, a nonsteroidal anti-inflammatory drug (NSAID), and DM, a synthetic corticosteroid. DM is commonly recommended for the treatment of a broad range of illnesses in both people and animals due to its robust antibacterial and cytotoxic characteristics. Although there is detailed research on the interactions between DM and PB, especially in chicks, each compound's impact and utilization are widely known (2). Being a young and growing species, chicks may react differently to treatment than mature animals. A variety of carriers absorb these tiny parts. In the infancy and early life of grilled chickens, these pathways for carbohydrates and protein are being discovered (3). Clinical pharmacology uses pharmacokinetics (PK) and

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pharmacodynamics (PD) to assess and comprehend drug-specific adverse effects. In a specific space, such as blood, cerebrospinal fluid, or subcutaneous tissues, drug concentration-time courses are described by pharmacokinetics Volume of distribution and clearance, which are the two main PK factors, control the concentration time course when the systemic circulation is taken into account. The relationship between medication levels and effects or adverse effects as time passes is described by pharmacodynamics (4). There aren't many Foods and Drug Administration (FDA) approved medications that can really be used on backyard chicks. NSAID are among the most often given medications by doctors to treat inflammation as well as pain in backyard chickens. NSAIDs are drugs that are often given to both people and animals. They are well-known for having antipyretic, analgesic, and antiphlogistic effects. This group of medications is used to treat allergic reactions, decrease fever, and lessen discomfort (5). An immune-suppressive drug called dexamethasone (DM) is a synthetic glucocorticoid. It's been applied to study how different kinds of chicken react to pressure and cause oxidative damage. In avoiding oxidative damage and alleviating the suppression of the immune system brought on by DM, dietary antioxidants may have favorable effects and advantages (6). The purpose of this research is to examine any possible alterations in chicks' phenylbutazone absorption brought on by DM treatment. A deeper comprehension of the potential drug-drug relationships among these two treatments may be attained by analyzing the absorption kinetics and any changes in pharmacokinetic characteristics, such as solubility and publication (7). The results of this research will further our understanding of how medications are used in chicks, and they could have consequences for tailoring drug treatment for this group.

Related Works

The article (8) suggests effects of Voltaren on kidney fluid movement and the kidney's outflow were evaluated using a sudden exposure paradigm. In the initial stage of a two-phase study employing similar birds, ordinary hens were given a subcutaneous injection of a (PAH-para-amino hippuric acid) and (IOH-iohexol) combination. Voltaren, it is discovered, alters the perfusion of the kidneys and kidney blood circulation, lowering fatalities brought on by secretion from the tubes to essentially nonexistent operating over a prolonged period of period. The article (9) discussed the fundamental categories and physical properties are used to assess the information set's relevancy to medical therapeutics. A large number of medications, based on studies, contain properly optimized physicochemical characteristics that point to a higher possibility of favorable drug metabolism and pharmacokinetic qualities, notably great oral uptake. The study (10) mentioned the benefits of using just-born pigs in drug discovery, paediatric disease, creating pharmacology, and pharmaceutical safety testing, as well as the parallels and contrasts among postpartum growth in pigs and humans. This huge animal model's drawbacks and untapped potential are also highlighted. The possibilities of newborn and young pigs as nonclinical safety models for developing pediatric medications are currently underutilized. The study (11) mentioned glucocorticoids and AMPK cooperate to control the liver bile acid production route. The development performance of broiler chicks was reduced by therapy. The article (12) examined the link between the transcriptome and

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proteome, except for the spleen-specific components of DM-induced hypertension in chicks, both of which have been well-researched. To analyze the process of protein and transcript diversification by analysis of this resource, this has increased our knowledge of the intricate nature of the mechanisms underlying stress-related immunosuppression. The study (13) examined thirteen miRNAs that circulate that are connected to the IBDV and were chosen for this investigation in order to examine their levels, potential roles, and processes in dexamethasone (DM)-induced immunosuppressed chicken that had received an IBDV-modified vaccination. The purpose of the research was to ascertain if the amount of miRNAs in circulation associated with IBDV and stress-related immunosuppressive are connected. The articles (14) mentioned order to comprehend the process of stress brought on the research was done on the stools of broiler poultry using gastrointestinal specimens from a previous examination and the results of adding arginine, glutamine, and amino to diets with little protein and using the synthetic corticosteroid DM. The study (15) examined with general chick embryos and in vitro-grown preosteoblast nuclei, the crowd looked at how DM affected the development and specialization of osteoblasts during the development of bones. They first showed using 17-day chick eggs that DM therapy could reduce the length of bones in life besides blocking the transcription of genes that regulate bone development.

Materials and Methods

Laboratory animals

The investigation was conducted on broiler chicks of males and females that were bought from a nearby hatchery when they were seven to fourteen days old and weighed around 90 and 130 g. The chicks were well-provided for in a 29–33 °C range of temperatures with enough illumination. The chicks had unrestricted access to food and water, and the ground's litter was made out of wood chips.

Ethics

The University of Mosul's Disciplinary Council for Utilising samples is one of the research methods that have been authorized by the College of Veterinary Medicine.

Preparation of medications

Salicylic acid (SA) was added to DM 0.2% VAPCO with PB 20% Interchemie, Holland, Jordan to provide the required concentration, which was then given intraperitoneally (IP) as a 5 ml/kg delivered dosage.

The pharmacological relationship between PB and DM

DM and PB analgesic were both administered individually and evaluated using the up-and-down method. PB and DM were first administered at doses of 7 and 2, accordingly, per kilogram, intraperitoneally. Prior to and following every medication's 30-minute therapy, the chicks were put to examination using an electro-stimulator (Harvard equipment, USA). In the chick model, an agonizing cry represented the signs of suffering. Depending on whether or not there was discomfort, the entire dosage of the two drugs was either raised or lowered by

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2, and the initial dose was 0.5 mg/kg. Following that, using a holographic examination, chicks in ED_{50} values of a 1:1 combination of DM and PB were computed. The first dosages of DM and PB, 5.61 mg/kg and 0.64 mg/kg, IP, respectively, were assessed. Due to the previously mentioned effect, the amounts of the two drugs were altered from their beginning dosages by 25% at 1.4 and 0.16 mg/kg, respectively.

Examining the isobolograms of PB and DM

The straight line of connection between the ED_{50} results for DM (0.64 mg/kg, IP) and PB (5.61 mg/kg, IP) on the y and x directions suggests that the holographic investigation should be performed using the ED_{50} doses of DM and PB individually. Although the mark is too focused on antagonism, the investigation stated as the mark under the line is still deemed cooperation. Use the equation da / Da + db / Db to ascertain the Y symbol's classification as an associate director. DM and PB both have an analgesic ED_{50} when administered by themselves. Db and Da are their combined ED_{50s} (Table 1). Resonance exists if the Y value is smaller than 1, according to the formula. If Y is bigger than 1, an antagonistic link will be taken into account.

DM has an impact on PB levels in the blood measurement.

PB was injected into the initial batch at a rate of 11.20 mg/kg, while DM was injected into the remaining group at a rate of 1.26 mg/kg, both intravenously. Blood was drawn from jugular veins in each group at various intervals of 0.26, 0.6, 1, 2, and 4 during the course of 24 hours.

The buffered permanganate solution is made.

During the examination, the BPS was applied. The pH was lowered to 12.4 by adding either HCl or NaOH after the solution of Potassium permanganate, 1.6 grammas of NaOH, and 15.2 grammas of Na2HPO4.12 H2O in 100 milliliters of distilled water was used to establish the solution.

PB standards preparation

PB was in order to get the necessary PB quantity, mixed with BPS of pH 12.4, before being used to create the PB samples at 25, 50, 100, 200, 400, and 800 g/ml quantities. The sample was evaluated using a spectrum analyzer (314 nm in wavelength), as opposed to the BPS blank. The linear regression equation of the PB standards served as the basis for the calibration curve. As shown in Figure 1, “the equation is as follows: y = a + b x, coefficient of determination (R2) = 0.9468”, where y stands for instances of absorbance, for the intercept (0.0765), b for slope (0.0011) of the calibration curve, and x for an unnamed blood PB concentration.

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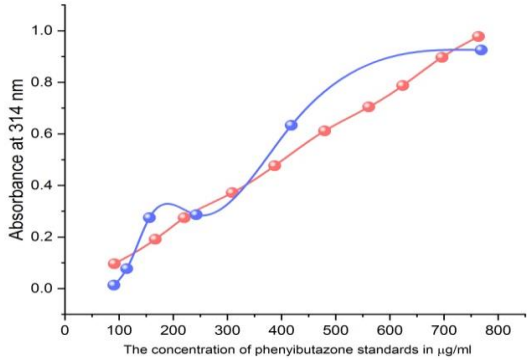

Figure (1): "The calibration curve for the absorbance (314 nm) of the PB standards at 25, 50, 100, 200, 400, and 800 g/ml"

Liquid-liquid extraction of PB

The liquid-to-liquid extraction method for PB was used for obtaining the plasma samples. It is easy, accurate, and acceptable. In order to prepare 0.5 ml of examples, 1 ml of HCl, together with 5 ml of n-heptane, was used. Following a 30-minute period of shaking, the tube underwent a 5-minute centrifugation at 3000 rpm. "A different transparent tube holding 3 ml of 0.5 molars NaOH and 4 ml of the n-heptane top stage was added". The top phase of the n-heptane was removed after 5 minutes of vigorous shaking of the tube. Applying the steps outlined above, 5 ml of BPS that had been made earlier in a separate glass tube were combined with 2.5 ml of the aqueous phase. The tubes in question were given a water bath for five minutes at 65 OC, after which they were chilled. To the centrifuged contents from the previous stage, after adding 2 ml, the mixture was stirred for 20 minutes. second glass tube contains the n-heptane stage was moved and kept at the ambient temperature for a period of three hours. In contrast to the empty, which was composed of heptane, a spectrum analyzer was used to find the end result at 314 nm.

The Pharmacokinetics of PB are affected by the injection of DM

The PK Solver tool and "a non-compartmental physiological system were used in this study to ascertain the pharmacokinetic characteristics of PB whether it was given alone or in combination with DM". The ratios assessed for each of these factors varied in both directions in the two sets that obtained PB shots either alone or together with DM.

Statistical analysis

The statistical studies' values for the two sets were examined and linked using the separated student T-test. A value is considered meaningful while p is lower than 0.05.

Results

Isobolographic analysis of PB and DM

Table 1 shows that although PB solo had a painful ED_{50} value of 5.61 mg/kg, IP, DM solo had an analgesic has an IP ED_{50} value of 0.64 mg/kg. The significant ED_{50} values, if PB and

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DM had been given simultaneously at a ratio of 1:1 from their ED_{50s}, were 1.77 and 0.18 mg/kg, IP, respectively (Table 1).

Table (1): PB and DM's analgesic ED_{50s} administered separately

Variables	DM	PB
ED_{50} *	0.64 mg/kg, IP	5.61 mg/kg, IP
± doses (d)	0.7 mg/kg	2 mg/kg
Dosages value (mg/kg)	2-0.6=1.6 mg/kg	8-6=2 mg/kg
Animal used	8 (XXXOXOX)	6 (XOXOX)
The first dosage	2 mg/kg	7 mg/kg
Final dosage (xf)	2 mg/kg	8 mg/kg

DM and PB interact pharmacologically

In Table 2 and Figure 2, it is evident that PB and DM combine pharmacologically in a beneficial way since the relationship index Y symbol is less than 1, as demonstrated. O denotes no analgesic effect, while X in the list denotes analgesia. Before and after PB and DM therapy for 30 minutes, factors were noted. Additionally, +Da and Db denote the ED_{50} for DM and PB alone, accordingly, whereas da and db denote their auxiliary ED_{50}. A hostile interaction is indicated by the resultant connection gauge, which might be either 1 or more.

Table (2): Analysis between PB and DM

Variables	DM	PB
ED_{50} *	0.20 mg/kg , IP	1.77 (mg/kg), IP
± doses (d)	0.18 mg/kg	1.42 (mg/kg)
Dosages value (mg/kg)	0.64-0.17=0.50	5.61-1.5=4.2
Animal used		8 (XXXOXOX)
The first dosage	0.65mg/kg	6.61 (mg/kg)
Final dosage (xf)	0.31 mg/kg	2.82 mg/kg
$+Y = da/Da + db/Db$	-	0.62

DM and PB plasma levels may be administered singly or in combination.

Comparatively to its blood concentration, if PB is administered by itself, the plasma concentration of PB rises dramatically while PB is administered in addition to DM. PB levels in the blood was 11.20 mg/kg, IP was assessed in the current investigation at intervals of 0.26, 0.6, 1, 2, 4, and 24 hours as 39.85, 66.19, 48.1, 35.31, 26.51, and 13.34 g/ml. According to Table 3, PB and DM 11.20 and 1.26 mg/kg, IP, respectively increased the blood concentration by 44, 427, 340, 295, 148, and 279% to 57.01, 384.16, 210.68, 138.68, 65.51, and 50.11 g/ml and 50.11 g/ml, etc.

PB pharmacokinetics with and without DM

If coupled with PB, DM increases these levels by 196, 140, 50, and 426%, making them as follows: "2570.03 g.h/ml, 49660.79 g.h 2 /ml, 0.06 h -1, and 348.17 g/ml". According to the overall results, PB and DM combine pharmacologically in a way called cooperation. Additionally, a modification in the blood levels of PB and its pharmacokinetics that enhances

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the curative effects of PB in the chick model is noted (Table 3). "The ED_{50} value of PB (5.61 mg/kg, IP) is represented by the y axis, while the ED_{50s} of DM (0.64 mg/kg, IP) are represented by the x-axis. For both medications 1.77 and 0.18 mg/kg, IP for PB and DM, respectively, the triangle point reflects 1:1 of ED_{50s} combinations (Figure 2)".

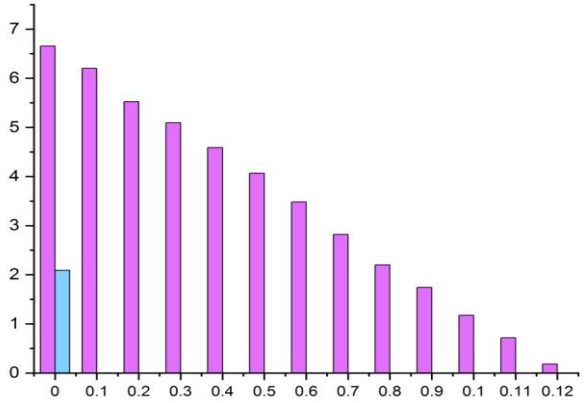

Figure (2): "Isobolographic study of PB and DM's analgesic interaction"

Table (3): DM and PB plasma levels in combination or separately in the chicks

Time (h)	DM on plasma focused of PB (%)+	Groups ($\mu g/ml$)	
		PB + DM	PB
0.26	44	57.01 ± 6.80*	39.85 ± 4.52
0.6	427	384.16 ± 27.58 *	66.19 ± 3.75
1	340	210.68 ± 28.91*	48.01 ±4.88
2	295	138.68 ± 11.42*	35.31 ± 2.04
4	148	65.51 ± 7.74*	26.51 ± 2.06
24	279	50.11 ± 7.50*	13.34 ± 2.35

Discussion

DM's impact on PB's levels in the blood and its pharmacokinetic features are both the subject of this investigation. Furthermore, the holographic research is used to investigate the probable pharmacological interaction in the chick species. In this study, the ED_{50s} for PB and DM combined have been shown to be lower than their values, indicating a rise in the painkillers performance required to induce a pharmacological reaction in 50% of the test-subject examining chicks. It is possible to identify the analgesic connection between two drugs using the holographic research method. The results of the research indicate that PB and DM have a synergistic pharmacological communication, as determined by examining the relationship value combined as a Y sign. If taken together with DM at the identical time, PB causes an increase in plasma levels as well as variations in the different pharmacokinetic parameters (AUC and AUMC). This paper provides the first account of this. The pharmacological effects of DM and PB may be increased by this important extra factor. Because of close rivalry at protein-binding locations on albumins in general which impacts

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the visible amount of movement of PB and DM, the pharmacokinetic characteristics of PB have changed. This shift is related to an increase in plasma amounts of the unbound medication. Competition at protein-binding sites on albumins could be to blame, which are a hallmark of PB and DM (99% proteins bound), the former of which was discovered in a different study to have a high protein adsorption rate of 60.5%. This raises the quantity of PB -free medication that is permitted to attach to the binding locations on receptors in order to increase the therapeutic effectiveness of PB with a potential for harm and change its level of safety (Table 4). The results also show that DM directly affects several significant pharmacokinetic factors; including intake, digestion, and removal, as well as other elements including the drug's authorization, stable values for half-life, average occupancy duration, and elimination rate. DM, according to other research, increases the effectiveness of other medications used to produce anesthesia following surgery, including opiates.

Table (4): Characteristics of PB alone or with DM in the chicks

Variables	Units		Groups	
		Influence of dexamethasone (%)*	Phenylbutazone + dexamethasone	Phenylbutazone
$AUMC_{0-\infty}$	$\mu g.h^2/ml$	141 (+)	50661.80	20700.04
MRT	h	19 (-)	20.33	25.53
C_{max}	$\mu g/ml$	427 (+)	350.18	67.18
$t_{1/2\beta}$	h	33 (-)	12.60	18.23
$AUC_{0-\infty}$	$\mu g.h/ml$	198 (+)	2571.04	868.72
T_{max}	h	0	0.7	0.7
CI	L/h /kg	60 (-)	0.05	0.01
K_{el}	h^{-1}	50 (+)	0.07	0.05

Conclusion

The specific details regarding drug absorption, including phenylbutazone, in chicks are influenced by various factors such as the route of administration, gastrointestinal physiology, drug formulation, drug interactions, and the age of the chicks. According to the results of the current investigation, PB and DM combine pharmacologically in a way known as cooperation. The research also demonstrates a shift in PB's blood levels and pharmacokinetics, enhancing the drug's efficacy for therapy in chicks.

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