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The effect of Phenobarbital and Diclofenac on Neurological Convulsion in Chicks as A model

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Abstract

Background: Phenobarbital is one of antiepileptic drugs. Diclofenac is one of NSAID. Objective: The purpose of carrying out this research was to determine the effect of both phenobarbital and diclofenac on the nervous convulsions resulting from the treatment of chicks with 4-aminopyridine in addition to determining the type of interaction between these two drugs. Methods: 4-aminopyridine was utilized to induce convulsion in chicks then we used Phenobarbital with diclofenac for prevent the occurrence of convulsion. Results: The chicks on which the experiments were conducted showed that the median lethal dose for 4-aminopyridine was 62.59 mg/kg i.p, while the median effective dose of 4-aminopyridine was 32.63 mg/kg. The median of anticonvulsant dose of phenobarbital in preventing nerve convulsions was 9.47 mg/kg i.m. These experiments also showed that the median of effective dose of diclofenac to prevent seizures was 7.48 mg/kg in chicks. Isobolographic analysis proved that the drug interaction between phenobarbital and diclofenac against induced nerve convulsions is synergistic interaction at 0.5:0.5 ratio this result recorded for first time in chicks, so the value of Y is lesser than one, Where the value of Y is calculated through a special equation. If the point falls on the line connecting the median doses of the two drugs, this means that the interaction is additive, and if it falls above the line, this indicates that the interaction is antagonistic, but if it falls below the line, it is synergistic interference. conclusion: our results indicate that phenobarbital and diclofenac have an effective role when used in therapy convulsion and it has synergistic interaction which is characterized by more effective in chicks in addition diclofenac has an essential side in convulsion therapy.

Keywords: Seizure, Phenobarbital, chicks, Diclofenac sodium, Convulsion

Introduction

Chickens and poultry are used in research in different fields including analgesia [1], pain [2], behavior, antioxidant levels [3,4] and toxicological studies [5]. In normal cases, the level of neurotransmitters is present in a balanced state, such that it is below the threshold value for consciousness. Any imbalance in this level could lead to the occurrence of seizures [6]. Any imbalance in neurotransmitters activity, whether irritating or inhibiting, such as serotonin, dopamine, glutamate, and other neurotransmitters can cause a seizure [7,8]. Force convulsions is characterized by the fact that it can occur in simple or complex form [9], Phenobarbital is one of the medicines used to prevent the formation of epileptic seizures [10-12]. This medication is belonging to the barbiturate family which distinguished by binds to their receptors and stimulate the occurrence of a hyperpolarization state by increasing the levels of chloride within the cell[13]. Diclofenac is a medicine belonging to the group of non-steroidal anti-inflammatory drugs, and it works as a pain reliever and anti-inflammatory [14-16]. Diclofenac inhibits the production of prostaglandins which responsible for pain, inflammation, high body temperature, and swelling by inhibiting the action of cyclooxygenase enzymes, which help treat pain. It may also affect the function of lymphocytes, and prevent the accumulation of moderate cells, which helps treat inflammation [17]. Inflammation led to convulsion [18,19]. Diclofenac works to inhibit the effectiveness of COX2, [20-23], as well as inhibiting the effectiveness of COX1, which leads to the appearance of side effects of diclofenac, like the pain and ulceration of the

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digestive system.4-aminopyridine is one from materials cause convulsion in various types of animals through the inhibition of potassium channels, it used to explain the activity of antiepileptic drugs in many researches . The lack of studies on its anticonvulsant effects in laboratory animals, encourage our research team to conduct this study and evaluate these effects of both phenobarbital and diclofenac on the nervous convulsions in chicks.

Material and method

Ethical approve

The ethics committee approval of the study (decision number: UM.VET.2023.046) .

Experimental chicks and medication

Eight-day, healthy broiler chicks, from two gender, utilized in the test, with body weight 44-120 g. The dilution of 4-aminopyridine (4-aminopyridin, Germany) and Phenobarbital (200 mg Phenobarbital, Iran, 75 mg Diclofenac, Iraq) in saline solution for give wanted dose via 5ml/kg.

Estimation median lethal dose of 4-aminopyridine in chicks

Eight chicks were utilized, aged 7-8 days, with a weight of 59-97 g. The first chick was given 4-aminopyridine at 100 mg/kg, i.p. this dose get depending on pilot study, enhanced with down the dose of 4-aminopyridine was a stable amount 10 mg/kg, By repeating this manner following primary alter for three animals is enough ,It was computed to establish ED_{50} of 4-AP [24] and via using this equation LD= XF+Kd ,(XF= final dose, K= table value, d= enhanced with down the dose of 4-aminopyridine was a stable amount) this method called Dixon method .

Estimation median convulsive dose of 4-aminopyridine in chicks

Six chicks were applying the Dixon design, weighing 64-91g.A first chick administered 4-aminopyridine 50 mg/kg, i.p., increase with decrease in the dose of 4-aminopyridine with a steady dose (10 mg/kg) [24], via using this equation LD= XF+Kd. The convulsant doses that led to the appearance of signs of nerve convulsions, such as muscle tension, were determined within 20 minutes after injection using the Dixon method.

Estimation median anticonvulsant dose of phenobarbital in chicks

Six chicks were applying the Dixon design, weighing 44-101g. A first chick administered phenobarbital 10 mg/kg, i.m., increase with reduce in the dose of phenobarbital with a steady dose (2 mg/kg) [24], via using Dixon equation, The anti-seizure dose was determined, and the chicks were monitored for 20 minutes, and the doses that prevented the occurrence of seizures were determined, in addition to the doses that did not prevent the appearance of signs of seizure and signs of poisoning with 4-aminopyridine, such as Defecation , urination, Lying on the sternum, screaming and seizures

Estimation median anticonvulsant dose of diclofenac in chicks

Seven chicks with the Dixon method, weighing 44-96g.A first chick administered diclofenac 10 mg/kg, i.m., increase with lessen in the dose of diclofenac with a steady dose (10 mg/kg) [24], Evaluation of anticonvulsant dose by Dixon equation. The chicks were observed for 20 minutes, during which the treated and untreated doses for convulsions were recorded, and the signs accompanying the convulsions, such as tension and relaxation of the body's muscles, were recorded.

Drug interaction at a ratio 0.5:0.5 of ED_{50} between Phenobarbital and diclofenac

The determination of drug interaction of phenobarbital with diclofenac was given at a ratio of 0.5:0.5 .The test was carried out in chicks weighing 57-120 g, and by using the Dixon table, first chick administered Phenobarbital and diclofenac 4.02 , 3.02 mg/kg, i.m. respectively, increase with lessen in the dose of Phenobarbital and diclofenac with a stable dose (1 mg/kg) [24].To determine the form of drug interaction of these drugs, The interaction index formula was used y=dA/Da +db/Db (Da:ED50 of Phenobarbital , Db:ED_{50} of diclofenac, da/db: ED_{50} of both Phenobarbital with diclofenac). By using isometric analysis, the average anticonvulsant doses were fixed for both phenobarbital and diclofenac, and the point at which the two doses meet was determined. If The location of the point was on the line connecting the ED50 of the two drugs. This indicates that the drug intervention at a ratio of 0.5:0.5 is an additive interference, and if the point falls outside the line (above the line), then the intervention is an antagonistic interference, whereas if the location is the point below the line is synergistic interference.

Statistical analysis

The figure draw via Microsoft Office Excel version 10.

Results

Estimation median lethal dose of 4-aminopyridine in chicks

The LD_{50} for 4-aminopyridine was 62.59 mg/kg, i.p., LD_{50} was establish with Dixon table after give the various doses of 4-aminopyridine (Table 1).

TABLE 1. Estimation median lethal dose of 4-aminopyridine in chicks.

Variables	Results
LD_{50}mg/kg	62.59
Average of doses mg/kg	100-60=40
first dose mg/kg	100
final dose mg/kg	70
Increase - decrease in dose mg/kg	10
Number of chicks	(XXXXOXOX) 8

X: dead, O: life

Estimation median convulsive dose of 4-aminopyridine in chicks

ED_{50} for 4-aminopyridine for stimulation of convulsion was 32.63mg/kg, i.p., The ED_{50} was establish with Dixon table after give different doses of 4-aminopyridine (Table 2).

TABLE 2. Estimation median convulsive dose of 4-aminopyridine in chicks

Variables	Results
ED_{50} mg/kg	32.63
Average of doses mg/kg	50-30=20
First dose mg/kg	5
Final dose mg/kg	4
Increase - decrease in dose mg/kg	1
Number of chicks	(XXOXOX) 6

X: convulsion, O: no convulsion

Estimation median anticonvulsant dose of phenobarbital in chicks

The ED_{50} for phenobarbital for avoiding of convulsion was 9.47mg/kg, i.m., ED_{50} was establish with Dixon table subsequent to give various doses of phenobarbital (Table 3).

TABLE 3. Estimation median anticonvulsive dose of phenobarbital in chicks

Variables	Results
ED_{50}mg/kg	9.47
Average of doses mg/kg	10-6=4
First dose mg/kg	10
Final dose mg/kg	8
Increase - decrease in dose mg/kg	2
Number of chicks	(OOXOXO) 6

X: convulsion , O: no convulsion

Estimation median anticonvulsant dose of diclofenac in chicks

Table 4 showed the ED_{50} for diclofenac for evading of convulsion was 7.48mg/kg, i.m., Median dose was fixed with Dixon table after give the various doses of phenobarbital.

TABLE 4. Estimation median anticonvulsive dose of diclofenac in chicks

Variables	Results
ED_{50}mg/kg	7.48
Average of doses mg/kg	10-4=6
first dose mg/kg	10
final dose mg/kg	6
Increase - decrease in dose mg/kg	2
Number of chicks	(OOOXOXO) 7

X: convulsion, O: no convulsion

Drug interaction at a ratio 0.5:0.5 of ED_{50} between Phenobarbital and diclofenac

The doses producing a 50% of anticonvulsive effect in convulsion chicks for Phenobarbital and Diclofenac were 7.48 and 9.47 mg/kg, respectively, through Dixon method (Tables 3 and 4). Synergistic effect of phenobarbital and diclofenac was evaluated via Isobolographic analysis , The ED50 numbers was recorded (Table 5). Moreover, the data of Y was calculated with an equation that was establish to be less than 1 (Figure 1).

TABLE 5. Parameters of Isobolographic Analysis for phenobarbital and diclofenac in chicks

Variables	Phenobarbital	Diclofenac
ED_{50} mg/ kg	4.02	3.02
Rate of doses mg/kg	5.73-4.73=1	4.74-3.74=1
Initial dose mg/ kg	4.73	3.74
last dose mg/ kg	4.73	3.73
Raise or decline in dose mg/kg	1	1
Number of chicks	(XOXOX)5	(XOXOX)5
Y value	0.82	

X: convulsion, O: no convulsion

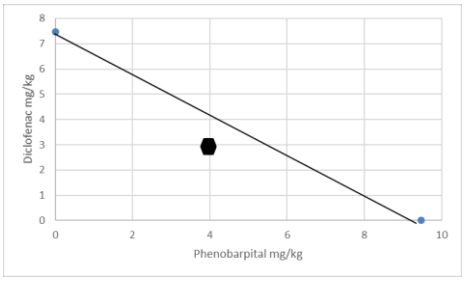

Fig. 1. Isobolographic analysis for phenobarbital and diclofenac by dixon method.

Discussion

Previous studies were limited to using rats and mice as a model for inducing nerve convulsions and using anticonvulsant drugs to prevent them from occurring. In a normal state, excitatory and inhibitory neurotransmitters are in a state of balance and

stability within the body. Preventing the occurrence of nerve convulsions can occur through the use of a wide range of drugs such as anticonvulsants [4]. Neurology in both humans and animals, showed that the convulsions after exposure to 4-aminopyridine may occur as a result of a change in the concentrations of neurotransmitters such as glutamate, (GABA) and serotonin [26-28], Moreover, the imbalance in the level of dopamine inside the body in rodents, may result in the occurrence of convulsions [24], which acting on inhibiting potassium channels and its effect on opening calcium and sodium channels [28]. Our results show that the effective phenobarbital dose was 9.47 mg/kg. This result did not agree with that of a study conducted on rats [28], which indicated that the average dose of phenobarbital was 18.1 mg/kg in rats. It also did not agree with a study conducted on rats [29], which shows that the average dose of phenobarbital was 32 mg/kg in rats, and this difference may be the result of a difference in the type of animals, The role of phenobarbital in preventing the occurrence of convulsions may be due to its action on GABA receptors, as there are many studies in veterinary medicine that have shown that nerve convulsions may arise from a low level of GABA in the body [31-33]. Whereas GABA is the common target of action of both phenobarbital and GABA [34,35] This may be the answer to how phenobarbital works in preventing seizures inside the body of the organisms [36]. These effects may also be due to its action on glycine, the amount of it increases with treatment with anticonvulsants in many studies [27]. The anti-inflammatory property of diclofenac occurs through inhibiting the synthesis of Prostaglandins: Diclofenac inhibits the COX enzyme and thus stops the synthesis of prostaglandins and thrombaxane. During the occurrence of neurological convulsions accompanying epilepsy, the presence of any inflammation in the body may have an impact on the occurrence of these convulsions [37-39] Many studies have indicated a relationship between inflammation and seizures, as one of the causes that result convulsions is nerve inflammation.[40]. Since the seizure threshold may decreased as a result of the presence of inflammatory mediators [41], a study conducted on mice demonstrated that intestinal inflammation led to an increase in the number of seizures [42]. In normal, non-pathological conditions, the levels of cytokines in the serum are very low, while in the presence of any neurological defect, this will lead to an increase in their levels in the body [43]. This work has a very important effect on preventing the appearance of nervous convulsions using diclofenac, through its role in inhibiting the production of cytokines, and this gives us evidence of the effectiveness of using diclofenac, or an NSAID in general, in preventing the occurrence of neurological seizures in animals by preventing the production of cytokines in the body [44-45].

Conclusions

The results of present study indicated that diclofenac made anticonvulsant effects on convulsion in chicks. In addition, diclofenac has synergizes effect when mixed with phenobarbital, thus providing a supportive advance to convulsion therapy.

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Conflict of interest

The creator indicate that they without conflict of interest

Funding statement

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تأثير الفينوباربيتال والدايكلوفيناك على الاختلاجات العصبية المستحدثة في نموذج أفراخ الدجاج

زهير سالم احمد و ماب عزمي فاضل

فرع الفسلجة والكيمياء الحياتية والادوية - كلية الطب البيطري - جامعة الموصل - الموصل - العراق.

الخلفية العلمية: الفينوباربيتال هو أحد الأدوية المضادة للصرع. الدايكلوفيناك هو أحد مضادات الالتهاب غير الستيرويدية.

الهدف: الغرض من إجراء هذا البحث هو تحديد تأثير كل من الفينوباربيتال والدايكلوفيناك على الاختلاجات العصبية الناتجة عن علاج الأفراخ مع 4-أمينوبيريدين بالإضافة إلى تحديد نوع التفاعل بين هذين الدوائين. **طرائق العمل:** تم استخدام 4-امينوبيريدين لإحداث الاختلاج في الأفراخ ثم استخدمنا الفينوباربيتال مع الدايكلوفيناك لمنع حدوث الاختلاج.

النتائج: أظهرت الافراخ التي أجريت عليها التجارب أن الجرعة المميتة الوسطية لمركب 4-أمينوبيريدين كان 62.59 ملغم/كغم من وزن الجسم، بينما كان الجرعة الفعالة الوسطية لمركب 4-أمينوبيريدين 32.63 ملغم/كغم. وكان متوسط جرعة الفينوباربيتال المضادة للاختلاج في الوقاية من الاختلاجات العصبية 9.47 ملغم/كغم في العضل. كما أظهرت هذه التجارب أن الجرعة الفعالة الوسطية من الدايكلوفيناك لمنع النوبات كان 7.48 ملغم/كغم في الأفراخ. أثبت تحليل الأيزوبولوكرافيك أن التداخل الدوائي بين الفينوباربيتال والدايكلوفيناك ضد الاختلاجات العصبية المستحثة هو تفاعل تآزري بنسبة 0.5:0.5 وسجلت هذه النتيجة لأول مرة في الأفراخ، فإن قيمة Y أقل من واحد، حيث يتم حساب قيمة Y من خلال معادلة خاصة. إذا وقعت النقطة على الخط الواصل بين الجرعة الفعالة الوسطية للعقارين، فهذا يعني أن التداخل إضافة، وإذا وقعت فوق الخط، دل ذلك على أن التفاعل تضادي، أما إذا وقعت تحت الخط، فإنه تداخل تآزري.

الخلاصة: تشير نتائجنا إلى أن الفينوباربيتال والدايكلوفيناك لهما دور فعال عند استخدامهما في علاج الاختلاجات، كما أن لهما تفاعل تآزري يتميز بأنه أكثر فعالية في الأفراخ، بالإضافة إلى أن للدايكلوفيناك جانب أساسي في علاج الاختلاجات.

الكلمات الرئيسية: النوبة ، الفينوباربيتال ، الأفراخ، دايكلوفيناك الصوديوم ، الاختلاج .