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The Safety Profile of Flunixin and its Pharmacological Effects in Chicks

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Background: Flunixin meglumine is a non-steroidal anti-inflammatory drug used in the treatment of several conditions in veterinary medicine. Objective: The study was aimed to investigate the analgesic and anti-inflammatory effects of flunixin meglumine in chicks. **Methods:** The up and down method was used to assess the median lethal dose (LD_{50}) and effective median analgesic dose (ED_{50}) of flunixin meglumine administered intraperitoneally (i.p.) and orally (p.o.) in chicks. From the obtained values we determined the drug safety indices. Electric stimulation method was used to determination the dose-dependent analgesic effect of flunixin meglumine in chicks. Analgesic and anti-inflammatory effects were dignified via the formalin test. **Results**: The median lethal doses (LD_{50}) of flunixin were 143.24mg/kg intraperitoneally and 170.77mg/kg orally. The effective median analgesic doses (ED_{50}) of flunixin meglumine in chicks were 9.34 mg/kg and 11.75 mg/kg for intraperitoneally and orally respectively. The Therapeutic Index, Standard Safety Margin and Therapeutic Ratio of flunixin through intraperitoneal and oral route were (15.35 , 14.53), (0.15 , 0.14) and (5.11 , 4.84) respectively. The dose-dependent analgesic effect of flunixin meglumine at 9 mg/kg, 18 mg/kg ip and 12 mg/kg, 24 mg/kg p.o started at 15 min after treatment and lasted over 120 min of treatment. The analgesic effect peak of flunixin meglumine through intraperitoneal and oral routes was 30 minutes after treatment. In formalin test, flunixin meglumine caused a significant rise in the latency to lift right foot in comparison with the control value, along with a significant decline in foot lifting frequency. A substantial decrease in foot thickness compared to control value has been demonstrated by the anti-inflammatory effects of flunixin meglumine. **Conclusion**: These results shows that the flunixin has analgesic and anti-inflammatory effects and form the backbone for further pharmacological studies as well as the medication could be safely administered to chicken.

Keywords*:* Flunixin meglumine, LD_{50}, ED_{50}, Formalin test, Analgesia, Drug safety indices, Chicks.

Introduction

Animal pain assessment and treatment are critical to promoting their well-being in many situations where humans are ethically or legally bound[1]. Pain is a disagreeable sensory and emotional sensation related to tissue injury, real or probable [2]. Gentle and colleagues studied chicken neurophysiology systematically and found many parallels between avian and mammalian neurophysiology linked to pain [3]. If painful conditions are suspected or a painful operation is performed, analgesia should be provided [4].

In both human and veterinary medicine, non-steroidal anti-inflammatory agents (NSAIDs) are widely used [5]. NSAIDs work by inhibiting cyclo-oxygenase enzymes. There are two major isoforms of COX enzymes: COX-1 and COX-2. Cyclo-oxygenase-1 is constitutively expressed in many tissues and plays a role in maintaining

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renal function, gastric mucosa defense, and platelet aggregation control. Proinflammatory cytokines and growth factors are known to induce cyclo-oxygenase-2[6]. The COX reaction transforms arachidonic acid to prostaglandin G_2, and the peroxidase reaction reduces PGG_2 to prostaglandin H_2, which is then transformed to five biologically active PGs by various cell-specific isomerases and synthases: prostaglandin D_2 , prostaglandin E_2 , prostaglandin $F_{2\alpha}$, prostacyclin and thromboxane A_2[7]. Flunixin meglumine (FM) is non-steroidal anti-inflammatory drug, FM has great anti-inflammatory, anti-pyretic, and analgesic effects. In animals, it is commonly used in many conditions including mastitis, fever, lameness, and endotoxemia [8].

In the absence of precise studies on the analgesic and anti-inflammatory effect of flunixin meglumine in chicks, we conducted this study.

Materials and Methods

One day-old chicks (Ross broiler) including both genders were obtained from a nearby hatchery (Mosul, Iraq). Chicks were housed for seven to twelve days previously the tests were finished. Birds were placed in poultry cages with availability a temperature of 32–35◦C, permanent lighting 24 hours light, and sawdust on the floor of the cage with the availability of water and food in an open manner. All tests were performed in compliance with institutional rules and the chicks were properly treated. The protocol of this study was reviewed and adopted by the Scientific Board of the Department of Physiology, Biochemistry and Pharmacology of the College of Veterinary Medicine, University of Mosul.

Flunixin meglumine (50mg/ml, UVEDCO CO., JORDAN) was extra diluted in saline solution (Pioneer Company for Pharmaceutical Industries, IRAQ) to gain the necessary drug concentrations. The volume of drug administration was 5 ml/ kg body weight given intraperitoneally (i.p.) or orally (p.o.).

Experiments

Determination of the oral and intraperitoneal median lethal dose (LD_{50}) of flunixin meglumine

Acute (24 h) LD_{50} of Flunixin has been calculated by the up and down approach after the oral and intraperitoneal treatment [9]. Two hours after flunixin meglumine dosed, the chicks have been observed individually for the clinical signs of toxicity. 24-hour lethality has been recorded [10].

Determination of the oral and intraperitoneal median effective dose (ED_{50}) of flunixin meglumine for the induction of analgesia in chicks

The up-and-down technique[9] was used to assess the analgesic effect of flunixin meglumine administered via oral and intraperitoneal routes in chicks. Following setting the frequency at 50Hz, the width at 5 Hz, and the amplitude pulse at 10 volts, analgesia with an electrical stimulator (SRI, Science and Research Instruments, United Kingdom) was measured by a rise in the pain threshold. The stimulator electrodes were gently placed under the wing in the featherless area that was moistened with distilled water. The response to inducing pain by the electrical stimulation device in the chicks was in the form of screaming or wing-flapping [11]. Each chick was exposed to the least voltage that triggered aversive pain response previously the flunixin meglumine treatment and then 30 min after the treatment (The triggered pain voltages were recorded before and after treatment). Each chick was evaluated for the increase or decrease in the voltage that causes a pain response. Generally, the positive analgesic response latency was evident in 2s following electrical stimulation. These doses were chosen grounded on the initial trials in chicks.

Determination of drug safety indices

From the values were obtained in the previous experiments, it is possible to calculate the drug safety indices for flunixin through used the following equations: The Therapeutic Index (TI) $=LD_{50}/ED_{50}$, Standard Safety Margin (SEM) $=LD_1/ED_{99}$ and Therapeutic Ratio (TR)= LD_{25}/ED_{75}[12].

Dose dependent analgesic effect of flunixin

Forty chicks were divided indiscriminately into five groups of eight birds. The chicks were treated with normal saline solution i.p. and p.o (Control) or with flunixin meglumine at 9 , 18 mg/kg i.p. and 12 , 24 mg/kg p.o. The doses of flunixin meglumine were the analgesic ED_{50} and two-fold of the analgesic ED_{50} of the drug (Grounded on the former experiment). We measured the minimum voltage for each chick that triggering aversive pain reaction at 0, 15, 30, 60, and 120 minutes after treatment. The increase in voltage was statistically tested in each group in order to determine the analgesic response of the chicks to flunixin.

Formalin test to determine flunixin analgesic and anti-inflammatory effect

Another method was used to measure the

analgesic and anti-inflammatory effects of flunixin meglumine (formalin test). Eighteen chicks were randomly divided into 3 groups of six birds. The three chicks groups were intraperitoneally treatment with flunixin at 0 (control), 9 and 18 mg/kg respectively. Fifteen-minute after treatment, the chicks were initiated with pain and inflammatory reactions by injection (0.05 ml) of 0.1 % formalin in the right foot plantar [13, 14]. The left foot plantar was injected with normal saline (0.05 ml) as a control. Directly when formalin injection and within 3 minutes the onset of raising right foot and the number of raising right foot in response to formalin injection were recorded. Accompanying, we evaluated flunixin meglumine anti-inflammatory effect through calculating foot thickness (mm) by digital caliber (Electronics Lab, China) before and one hour after formalin injection. The anti-inflammatory reaction was measured as following (percentage):

$$Anti-inflammatory\ response = \frac{alteration\ in\ control\ group\ foot\ thickness - alteration\ in\ treatment\ group\ foot\ thickness}{alteration\ in\ control\ group\ foot\ thickness} \times 100$$

Statistical Analysis

Data has been described as mean ± standard errors mean. Statistical analysis was carried out by using one-way variance analysis (ANOVA) accompanied by LSD test. P<0.05were considered to be significant. The measurements were conducted using the statistical software SPSS 17.

Results

The acute LD_{50} (24 h) of flunixin meglumine through intraperitoneal and oral routes in chicks were 143.425 mg/ kg, 170.775 mg/ kg, respectively (Table 1). The signs of acute toxicity involved anxiety, shouting, Apnea breathlessness (Shortly after the treatment) and then drooping of wings, dullness, shrunken eyes, recumbency before death.

The intraperitoneal and oral ED50 values of flunixin meglumine for the induction of analgesia in the chicks were 9.34 mg/kg, i.p. and 11.75 mg/ kg p.o., respectively (Table 2).

The Therapeutic Index (TI), Standard Safety Margin and Therapeutic Ratio of flunixin meglumine through intraperitoneal and oral route were (15.35 , 14.53), (0.15 , 0.14) and (5.11 , 4.84) respectively.

Following its intraperitoneally and oral administration, Flunixin meglumine produced a dose-dependent analgesic effect when given to chicks at 9, 18 mg/kg, i.p. and 12, 24 mg/kg p.o. in compare with the control group which treatment with normal saline only. The impact of the analgesic effect in all treatment groups began 15 minutes after administration and lasted over 120 minutes after administration. For all treatment groups, the peak analgesic effect was 30 minutes after administration (Fig.1). The observations are presented in Table 3.

In the formalin test, flunixin meglumine at 9 and 18 mg/kg i.p induced analgesia against pain persuaded by injection of formalin into chick's foot planter region. This was revealed through a significant increase in right foot lifting latency and a significant decrease in foot lift frequency relative to the control value (Table 4). A substantial decrease in thickness of foot compared to the control value was seen in the anti-inflammatory activity of flunixin meglumine. In comparison to the control group, the anti-inflammatory activity percentage was 87.5 and 90.6, respectively (Table 4).

TABLE 1. Determination of 24 h median lethal dose (LD_{50}) of Flunixin meglumine in chicks by the up-and-down method

Variable	Intraperitoneally	Orally
Median lethal dose (mg/kg)	143.42	170.77
Doses range (mg/kg)	100-150	150-200
Early dose(mg/kg)	100	150
Latest dose(mg/kg)	125	200
Increase or decrease in dose(mg/kg)	25	25
Total of chicks used	6 (OOXOXO)[a]	6 (XXOOXO)[a]

[a] X= death; O= survival.

TABLE 2. Determination of median effective dose (ED_{50}) of Flunixin meglumine in chicks by the up-and-down method after 30 min.

Variable	Intraperitoneally	Orally
Median effective dose(mg/kg)	9.34	11.75
Doses range(mg/kg)	5-10	10-7.5
Early dose(mg/kg)	10	10
Latest dose(mg/kg)	5	7.5
Increase or decrease in dose(mg/kg)	2.5	2.5
Total of chicks used(mg/kg)	6 (XXOXOX)[a]	5(XOXOX)[a]

[a] X= analgesic; O= non analgesic.

TABLE 3. Effect of Flunixin meglumine on electro-stimulation in chicks

Groups	Increase in voltage caused pain after				
	0 min	15 min	30 min	60 min	120 min
Control	10.37±0.18[a]	10.75±0.16[a]	10.12±0.12[a]	10.12±0.12[a]	10.12±0.12[a]
Flunixin 9mg/kg ip.	10.75±0.16[a]	13.87±0.12[c]	15.87±0.22[d]	14.12±0.12[c]	12.87±0.12[b]
Flunixin 18mg/kg ip.	11.00±0.00[a]	15.37±0.32[c]	19.25±0.25[d]	15.62±0.18[c]	14.62±0.18[b]
Flunixin 12mg/kg p.o.	10.75±0.16[a]	12.87±0.12[b]	16.36±0.26[d]	14.12±0.22[c]	12.62±0.26[b]
Flunixin 24mg/kg p.o.	11.00±0.00[a]	14.50±0.26[c]	18.87±0.39[e]	16.00±0.26[d]	13.00±0.00[b]

Values represent mean±SE for 8chicks/group.
At the 5 percent significance level, the values of different letters in each column indicate the significant difference.

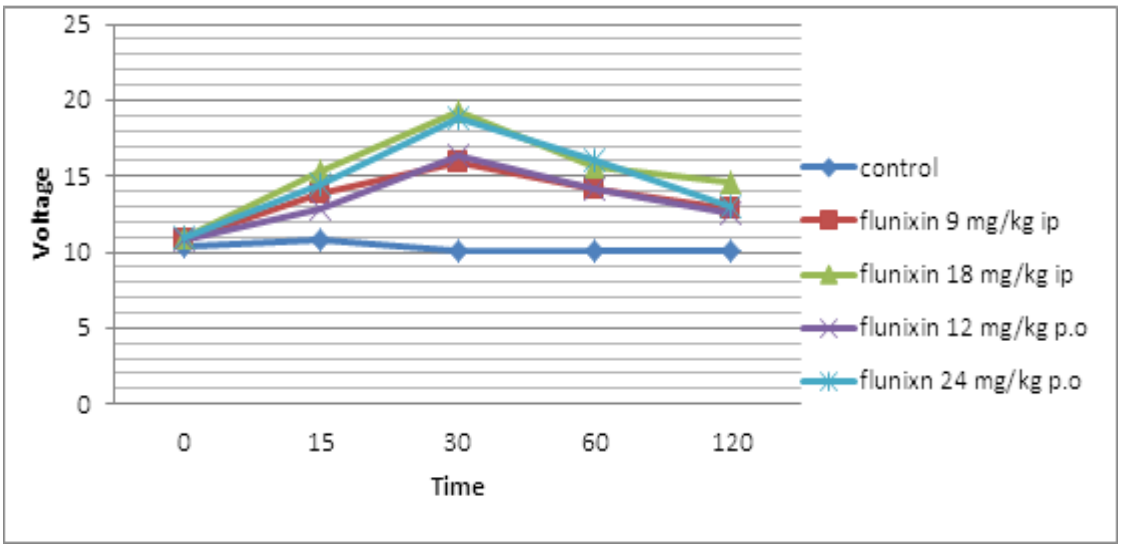

Fig. 1. Dose response curve of flunixin meglumine.

TABLE 4. Onset of raising right foot, number of raising right foot, increase in paw thickness and the anti-inflammatory activity % in the chicks treated with flunixin meglumine.

Groups	Onset of raising right Foot (sec.)	Number of raising right foot (3min)	The increase in paw thickness (mm)	The anti-inflammatory activity %
Control	1.00±0.00[a]	36.00±3.08[a]	0.64±0.13[a]	0
Flunixin 9 mg/kg ip.	2.66±0.76[a]	21.66±1.72[b]	0.08±0.01[b]	87.5
Flunixin 18 mg/kg ip.	5.83±1.64[b]	13.00±1.96[c]	0.06±0.02[b]	90.6

Values represent mean±SE for 6 chicks/group.
At the 5 percent significance level, the values of different letters in each column indicate the significant difference.

Discussion

At the beginning of the research, we determined the median lethal dose in chickens through different administration routes via peritoneal cavity and mouth, which is an important parameter in pharmacology. Acute toxicity is involved in the calculation of LD_{50}(the dose that proved to be lethal (causing death) to 50 percent of the animal group tested). In the assessment and evaluation of the toxic properties of all compounds, the determination of acute oral toxicity is generally an initial screening stage [15]. Shortly after the treatment, we noticed the signs of acute toxicity involved anxiety, shouting, breathlessness. After one hour the signs of toxicity were observed (drooping of wings, dullness, shrunken eyes) which compatible with Patel in his study[16].

Somatic pain is the pain emanating from the walls of the body, it is called superficial pain/cutaneous pain if pain originates in the skin or superficial tissues, cutaneous nociceptors terminate just beneath the skin and create a well-defined, limited pain of a short period due to the great density of nerve endings. Generally, it is described as sharp, stabbing, and well-localized [17].

Electric shock induces intense pain with some vocalization, resulting in aggressive avoidance actions including forceful escape efforts (i.e. jumping and wing flapping)[18]. For this reason, the electrical stimulator was used to create local pain and limited to a very short period (electric prick). Thus, the median effective dose of flunixin meglumine to induce analgesia is calculated which was not determined before. Previous studies suggested that flunixin meglumine was given in the range of 3.0 to 12.0 mg⁄kg intramuscular and it is effective in reducing chickens' arthritic pain [19]. In our current research, we were able to accurately determine the effective median analgesic dose via intraperitoneal and oral administration.

Cyclooxygenase (COX) converts arachidonic acid into prostanoids such as prostaglandins, prostacyclines, and thromboxane. Prostanoids are vital mediators that regulate the various functions of the cardiovascular, gastrointestinal, urogenital and nervous systems and play a crucial role in inflammation [20]. PGE2 and PGI2 improve the sensitivity of pain receptors (or nociceptors) in the periphery thus enhance the activity of different pain mediators[21]. Flunixin meglumine blocks both cyclooxygenase-1 (COX-1) and COX-2. it is widely used in the management of several inflammatory and non-inflammatory diseases such as arthritis, cardiovascular disease, post-operative pain and post-traumatic pain in animals and humans[22].

Flunixin meglumine has rapid effects and can alleviate pain within 15 min[23]. This is in consistent with what we have achieved; where the analgesic effect was observed after 15 minutes and reached a peak at 30 minutes in the manner of dose depend.

We discovered that flunixin is safe and has a reasonable margin of safety based on the results of TI, SSM, and TR decided in this study. The therapeutic index of a drug is the proportion of the lethal drug dose in 50% of subjects (LD_{50}) to the effective drug dose in 50% of subjects (ED_{50}) [12]. From the results we obtained, there is a high level of safety when using flunixin meglumine in chicks through oral and intraperitoneal routes and up to fifteenfold.

Pain has an inflammatory component. In our

research, flunixin meglumine has demonstrated important analgesic and anti-inflammatory effects in chicks (using the formalin test).The formalin test is being used as an inflammatory model of tonic pain[24]. Subcutaneous paw injecting of formalin causes biphasic nociceptive reactions. Although Phase I is known to indicate acute nociceptive pain caused by direct stimulation of the nerve by formalin, Phase II is related to a combination of continuous inflammatory-associated peripheral tissue afferent feedback and functional changes in the spinal horn (central sensitization)[25]. The first phase, which is temporary, is initiated by the direct effect of formalin on the transient receptor potential ankyrin subtype 1 receptors (TRPA 1). The second prolonged phase is associated with the peripheral tissue variety of an inflammatory reaction. This reaction triggers the release of nociceptive mediators such as serotonin, histamine, bradykinin, and prostaglandins, resulting in central neuron sensitization leading to changes in the central pain control processes[26]. Through the results of the formalin experiment, it is clear that flunixin meglumine suppresses pain resulting from the first and second phases.

Many drugs belong to the class of NSAIDs may possess other mechanisms that have a relationship with monoaminergic, nitric oxide, endocannabinoids, serotonergic and cholinergic systems and endogenous opioid pathways [27]. This gives us the hypothesis of the effect of flunixin meglumine on the acute pain created by electrical stimulation and formalin test.

Conclusions

We conclude that flunixin meglumine has analgesic and anti-inflammatory effects in chickens and can be used safely for the wide difference between the therapeutic dose and the lethal dose, with the recommendation of more studies to come up with a clear treatment schedule.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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دلائل الامان للفلونكسين وتأثيراته الدوائية في افراخ الدجاج

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

الفلونكسين ميكلومين هو عقار مضاد للالتهابات غير ستيرويدي يستخدم في علاج العديد من الحالات في الطب البيطري. هدفت الدراسة إلى الكشف عن التأثيرات المسكنة والمضادة للالتهاب للفلونيكسين ميكلومين في افراخ الدجاج. تم استخدام طريقة الصعود والنزول لتحديد الجرعة المميتة الوسطية (LD_{50}) والجرعة الفاعلة المسكنة الوسطية (ED_{50}) للفلونكسين ميكلومين والمعطاة داخل الخلب وعن طريق الفم، ومن ثم تحديد مؤشرات السلامة الدوائية. وباستخدام طريقة التحفيز الكهربائي تم الكشف عن التأثير المسكن المعتمد على الجرعة للفلونيكسين ميكلومين . وتم الكشف عن التأثيرات المسكنة والمضادة للالتهابات باستخدام اختبار الفورمالين.

كانت الجرعة المميتة الوسطية للفلونكسين ميكلومين في افراخ الدجاج ١٤٣,٤٢ ملغم / كغم داخل الخلب و ١٧٠,٧٧ ملغم / كغم عن طريق الفم. وكانت الجرعة الفاعلة المسكنة الوسطية (ED_{50}) للفلونيكسين ميكلومين في افراخ الدجاج ٩,٣٤ ملغم / كغم و ١١,٧٥ ملغم / كغم داخل الخلب وفموياً على التوالي. كان المؤشر العلاجي وهامش الأمان القياسي والنسبة العلاجية للفلونيكسين داخل الخلب وفمويا (١٥,٣٥ ، ١٤,٥٣) ، (٠,١٥ ، ٠,١٤) و (٥,١١ ، ٤,٨٤) على التوالي. بدأ التأثير المسكن للفلونكسين ميكلومين للجرع ٩ ملغم / كغم و ١٨ ملغم / كغم داخل الخلب و ١٢ ملغم / كغم و ٢٤ ملغم / كغم بعد ١٥ دقيقة من المعاملة واستمر لأكثر من ١٢٠ دقيقة . كانت ذروة التأثير المسكن للفلونكسين ميكلومين عن طريق الخلب والفم بعد ٣٠ دقيقة من المعاملة. في اختبار الفورمالين ، ادى الفلونكسين ميكلومين الى ارتفاع معنوي في الوقت اللازم لرفع القدم اليمنى مقارنةً بمجموعة السيطرة ، إلى جانب انخفاض معنوي في عدد مرات رفع القدم اليمنى، وكذلك انخفاض معنوي في سمك القدم مقارنةً بمجموعة السيطرة نتيجة التأثير المضادة للالتهابات للفلونكسين ميكلومين. تظهر هذه النتائج أن الفلونكسين له تأثيرات مسكنة ومضادة للالتهابات ويشكل العمود الفقري لمزيد من الدراسات الدوائية وكذلك يمكن إعطاء الدواء بأمان للدجاج.

الكلمات المفتاحية: فلونكسين ميكلومين، الجرعة المميتة الوسطية، الجرعة الفاعلة المسكنة الوسطية، hاختبار الفورمالين،التسكين، مؤشرات آمان الدواء، افراخ الدجاج.