



## The neurobehavioral effects of flumazenil in chicks

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### Abstract

Flumazenil is choosy and competitive GABA receptor blocker that serves as an antidote to benzodiazepines overdose. Its administration in humans and some animal's model is connected with nervousness, anxiety responses, or seizures attacks. The objective of this study was to scrutinize the neurobehavioral reaction as well as sedative and anxiolytic actions of flumazenil in chick's model. The Median effective dose of flumazenil injected chicks was 0.114 mg/kg i.p. Flumazenil at 0.04 and 0.08 mg/kg diminished the locomotors activity, prolonged the period of tonic immobility and have anxiolytic action in chicks. Flumazenil at 0.1, 0.2 and 0.4 mg/kg cause mild sedation in chicks. Flumazenil at 0.1 and 0.2 mg/kg have antagonistic effects in chicks sedated with diazepam at 10mg/kg. Flumazenil demonstrated fairly unexpectedly a depressant effect in the open field test and sedative and anxiolytic bias attention test in the chick's model. These findings indicate that the impact of flumazenil is indicative of the characteristics of partial agonists when given on its own and antagonist when given after diazepam according to the neurobehavioral tests.

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### Introduction

Flumazenil originated from antibiotic anthracycline (1), its works as a benzodiazepine receptor blocker (subunits  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$  and  $\alpha 5$ ) or as a partial agonist (subunits  $\alpha 4$  and  $\alpha 6$ ) (2). Flumazenil competitively prevents benzodiazepine-recognition action at the GABA/benzodiazepine receptor cluster, thus preventing the actions of benzodiazepines (3). The key therapeutic use for flumazenil is the management of diazepam overdosed and/or setback of benzodiazepine symptoms following anesthesia (4-6); A possible side effect is an anxiogenic action. Nevertheless, some publications have indicated that flumazenil itself also induces drowsiness and, to some degree, yield anxiolytic actions in rats (7), rabbit (8) particularly in anticipation anxiety (9). Amazingly, there is limited evidence of direct behavioral actions of flumazenil, following some notable findings in medical literature demonstrating the anxiolytic actions of this blocker. Prolong injection of flumazenil in rodents has been related with prevalently extended durations in open arms and

less fecal boluses in plus-maze experiments compared to the control group. In addition, flumazenil administered animals displayed enhanced exploratory activity through the hole-board trial and no improvement in drinking subsequent a 'pain encounter' in the drinking-punishment trial (10). Flumazenil anxiolytic activity has also been noticed in humans, where a double-blind test noticed substantially decreased fear due to the simulation of public speech (11). However, flumazenil was utilized as an effective reversal of the anesthetic effects of tiletamine-zolazepam in dogs (12). Flumazenil was utilized in persons, with a good outcome, to counteract ethanol and tegretol-trigger CNS depression (13). accordingly, it is reasonable to presume flumazenil also could be effective in small animals in such status (14). Flumazenil reduced the percentage of the feline that was asleep but did not reduce the duration to walk devoid of ataxia. Built on that report, it is not recommended that flumazenil be administered in a veterinary clinic at the doses examined to reduce and/or enhance midazolam and ketamine recovery in the sanitary feline (15).

There are several observations in the published literature that in some animal behavioral models flumazenil functions as a weak partial agonist. The goal of our research was to describe the neurobehavioral action of flumazenil in the chick's model as well as evaluate its sedative, anxiolytic, and antagonistic effects.

## **Materials and methods**

### **Animals**

Cobb chicks were obtained on the first day of hatching from a native hatchery and were reared up to they reached the time of life of a week or more, which is the age at which the experiments began. The chicks were put in a chamber at a temperature 33-35 °C, with constant lighting, and sawdust was put as a ground for the chicks, and fodder and water were available continuously. We used 93 chicks in our research. The studies have obeyed institutional rules. Addressing the use of animals, and the chicks got adequate courtesy and high-quality care.

### **Drugs preparation**

Ampules of flumazenil (0.5 mg/ml, Mylan, SAS, France) and Diazepam ampule (10 mg/2 ml, Albalsam Company, Syria) was moreover diluted in distilled water to achieve the required concentrations for dosing intraperitoneally (i.p.) in a volume of 10 ml/kg b.w. birds in control groups were treated i.p. by distilled water.

### **Determination of the median effective dose of sedation induced by flumazenil**

The Median sedative dose (ED<sub>50</sub>) of flumazenil in chicks was calculated by up-and - down approach (16). The old of 5 chicks evaluated in this test ranged from 7-8 days. The primary dose of flumazenil was at 0.1 mg/kg, i.p. Later the treatment with flumazenil, We checked the chicks for sedation revealed as shut eyelids, drooping of the head, diminished motility or motionlessness and sternal recumbence (17-20).

### **Determination of the dose-response sedative effects of flumazenil in the chicks**

In this experiment the chicks were injected with flumazenil at 0.02, 0.04, and 0.08 mg/kg, flumazenil treated chicks separately supervised to notify beginning of sedation (shut eyelids) and its duration (17).

### **Open filed test and tonic immobility test**

In this experiment, the neurobehavioral and movement activity of 32 chicks were measured that randomly and equally divided into four groups. The old of the chicks evaluated in this test ranged from 7-8 days. All groups were treated with flumazenil at a dose of 0 (control), 0.02, 0.04, and 0.08 mg/kg. Behavioral measurements were taken 10 minutes after the injection of flumazenil. The test was carried out in the open field box for three minutes, and the

dimensions of the box were 60 x 60 x 30, and its floor is divided into 16 square. 50 grams of forage were spread on its floor, and after the end of the 3 minutes, the chicks were subjected to the tonic immobility test which is considered a kind of fear response in birds (21,22) and the time of immobility was registered.

### **Attention bias test**

32 chicks were divided into 4 groups of 8 birds each. The old of the chicks evaluated in this test ranged from 7-8 days. The chicks were administered flumazenil at 0 (control), 0.02, 0.04, and 0.08 mg/kg i.p. the chicks were given habituation sessions to the test box for 5 min before the attention bias test was performed (22-24). This was to minimize the chicks responding to the box itself versus the planned fear (alarm call playback). The 5-min open-field action of every chick was reported 10 min after the flumazenil administration at previous doses, the audio clips were edited into short playback files using the software Audacity 2.0.3. The alarm calls were played from a Bluetooth speaker for 10 seconds, it is worth noting that the chicks that have not been tested did not hear the alarm call because the test took place in an isolated room. After playing the alarm call in the open field container record the subsequent (i), the latency to move, and (ii) the onset to jump.

### **Flumazenil antagonism of diazepam sedation in chicks**

24 chicks were divided into three groups of 8 birds each. The old of the chicks evaluated in this test ranged from 7-8 days. The chicks were given diazepam at 10 mg/kg. Later 15 min of diazepam injections, the chicks were administered with flumazenil at 0 (distilled water), 0.1 and 0.2 mg/kg. The period of sedation has been registered for each chick in each group (25-27).

### **Statistical analysis**

The data were described as a mean + SEM. Statistical analysis was achieved using one-way variance analysis (ANOVA) accompanied via the least significant difference test,  $P < 0.05$  found to be significant.

## **Result**

### **Determination of the median effective dose of sedation induced by flumazenil**

Based on previous studies and pilot study, we selected the dose with which we started the median sedative dose for flumazenil, and the choice was made to start with a dose of 0.01 mg/kg i.p. and the test was performed in a noise-insulated room to show the proper effect of the drug and it appeared on flumazenil treated chick had mild sedation signs characterized by eyelid closure, Immobility, and signs of sedation started after injection 5-7 minutes. For this experiment, five chicks were used, aged 7-8 days, and the ED<sub>50</sub> value of flumazenil was calculated by the up and down method for chick sedation was 0.114 mg/kg, i.p (Table 1).

Table 1: The median sedative dose (ED<sub>50</sub>) of flumazenil injected intraperitoneally in chicks

Measurements	Results
ED <sub>50</sub> (mg/kg)	0.114
Range of the doses utilized (mg/kg)	0.1-0.08 = 0.02
Primary dose (mg/kg)	0.1
Final dose (mg/kg)	0.1
Number of birds utilized	5 (xoxox)
Signs of sedation	Eyelids closure, immobility or reduce mobility
Onset of the sedation signs (min)	5-7

X: sedation, O: no sedation, The ED<sub>50</sub> were calculated by the up-and-down approach

#### Determination of the dose-response sedative properties of flumazenil in chicks.

The onset of flumazenil sedation ranged from 1.47 min to 3.13 min and the duration of flumazenil sedation ranged from 13.4 min to 57 minutes (Table 2) flumazenil sedation that was characterized by mild sedation (eyelid closure and immobility).

#### Open filed test and tonic immobility experiment

The chicks were injected by flumazenil at 0, 0.02, 0.04 and 0.08 mg/kg ip. 10 minutes after injection the chicks' behavior was assessed in the open field for the time of three minutes. As there was a substantial rise in the time needed to transfer out of the median square compared to the control group, there's likewise a decline in the total of lines cut across with together feet compared to the control group.

Flumazenil injection also resulted in prolonged periods of tonic immobility depending on the dose in comparison with the control group (Table 3).

Table 2: Sedation effect of flumazenil in chicks

Flumazenil mg/kg (ip)	Start of sedation (min)	Length of sedation (min)
0.1	3.13± 0.35	13.4 ± 0.62
0.2	1.72± 0.17 *	18.5 ± 1.47
0.4	1.47±0.25*	57 ± 5.51*a

Results are mean± SE. N= 8 chicks/group. \* significantly dissimilar of flumazenil at 0.1 mg/kg, P<0.05. a significantly dissimilar of flumazenil at 0.2 mg/kg, P<0.05.

Table 3: Flumazenil effects in chicks on the open field test and tonic immobility test

Measurements	Flumazenil mg/kg i.p.			
	0 (distilled water)	0.02	0.04	0.08
Latency to move (seconds)	24.9± 2.41	26.6±2.03	32.6±2.27	60.4±5.42*ab
Lines crossed	12.8±1.23	10.4±0.86	8.5±0.42*	6.1±0.79*a
Duration of tonic immobility test (second)	2.9±0.39	11±1.15	16.4±2.19*	55±5.63*ab

Results are mean ± SE of 8 chicks/group. All chick was undergoing to open field action test 10 min later the flumazenil administration, then by the tonic immobility test. \* significantly dissimilar of the respective control value, P<0.05. a significantly dissimilar of the respective value of the flumazenil at 0.2 mg/kg, P<0.05. b significantly dissimilar of the respective value of the flumazenil at 0.4 mg/kg, P<0.05.

#### Attention bias test

The aim of the attention bias experiment was to examine the anxiolytic effect of flumazenil in the chicks at 0.02,0.04, and 0.08 mg/kg ip significantly and dose- depending caused anti-anxiety effect by increasing the time needed to move after the alarm call was triggered for 10 seconds in comparison with the control group. Injection of flumazenil to the chicks at the above mentioned doses also reduced the time needed to jump out of the box. The two groups injected with Flumazenil 0.04 and 0.08 did not jump out of the box during the 5-minute test period (Table 4).

#### Flumazenil antagonism of diazepam sedation in chicks

In this experiment, the effects of flumazenil 0.1 and 0.2 mg/kg were administered to minimize the duration of the sedation 15 minutes after diazepam 10 mg/kg was injected intraperitoneally. Before the administration of flumazenil, all chicks attained lateral recumbence and the period of sedation was greatly shorter with flumazenil groups compared to the control group diazepam 10mg/kg+ normal saline (Table 5).

Table 4: Flumazenil effects in chicks on the bias attention test

Measurements	Flumazenil mg/kg i.p.			
	0 (distilled water)	0.02	0.04	0.08
Latency to move (min)	4.38±0.08	2.94±0.10*	2.59±0.30*	2.25±0.22*a
Latency to jump	3.35±0.73	2.92±0.42	0±0*a	0±0*a
% chicks jump	87.5	75	0	0

Results are mean ± SE of 8 chicks/group. All chicks were undergone to attention bias test 10 min later the flumazenil injection. \*Significantly dissimilar of the respective control value, P<0.05. a Significantly dissimilar of the respective value of the flumazenil at 0.2 mg/kg, P<0.05.

Table 5: Antagonistic effect of flumazenil in chicks sedated with diazepam

Groups	Variable	Duration of sedation
Group 1	Diazepam10 + distilled water	111.1±4.8
Group 2	Diazepam10 + 0.1 flumazenil	54±3.5*
Group 3	Diazepam10 + 0.2 flumazenil	35.9±2.5*a

Results are mean ± SE for 8 chicks/group. \*significantly dissimilar from the group 1, P<0.05. a significantly dissimilar from the group 2, P<0.05.

## Discussion

At beginning of our experiments, we had to perform a pilot test to show the pharmacological effect. The median effective dose for sedation of flumazenil was 0.114 mg/kg body weight and this dose was the basis for the choice of doses in subsequent studies. The open-field test in chicks is one of the most important behavioral experiments that provide useful information into the activity of drugs that need to be tested for effects and whether the medication has a stimulating or inhibitory effect in the nervous system (28-30).

Based on the symptoms noticed in flumazenil injected chicks, the central nervous calming task of the flumazenil in birds has been demonstrated. Sedation marks (closed eyelids, immobility, decreased motility, or sternal recumbent) have been recorded in rats and rabbits treated with flumazenil (8). However, Discomfort, anxiety, or convulsions are related with the flumazenil use in humans (31), cats (32), and rodents (33).

In the current study, the anxiolytic influence of flumazenil is evaluated by using an attention bias test, for recent attention bias test, latency measurements of motor activity performance are included; the more fitting anxiety evaluation test is conducted by exposing the chicks to an alarm call that simulates a predator attack. Flumazenil has been shown to have an anti-anxiety effect in sub-sedative doses, illustrated by a decrease in the time needed to move and a decrease in the time taken to leap out of the box. In truth, sedative action was associated with high doses, while anxiolytic action was associated with low doses (34). this

study was conducted with a simple adjustment of the original researcher to match the behavior of the chicks (23).

It is very important to research the paradoxical influence of drugs in animal models as well as in humans; the paradoxical influence of flumazenil on actions is attributed to the properties of the endogenous ligands of the BZD binding sites (7).

Additional studies we performed showed the dose-dependent properties of flumazenil and duration of achievement in the creation of sedation in chicks. The mechanism of the sedation action of flumazenil has been suggested to be related the purported endogenous moiety of the BZD binding domain of the GABA receptor seems to have inverse agonistic characteristics. Mostly on one side, BZD domain site agonists are blocked by flumazenil; on the other side, flumazenil is expected to blocker signs caused by benzodiazepine pulling out (9,35,36).

Flumazenil has been proposed to 'reset' GABAA receptors for the usual function (37). In addition, our findings have shown that flumazenil can improve the reduction of diazepam sedation in chicks, consistent with previous research in rats (38), mice (39), fangs (26), dogs (40) and cats (40,41).

## Conclusion

Flumazenil had an unexpected sedative effect and had an inhibitory effect in the open field test and was anti-anxiety in the attention bias test. Flumazenil also demonstrated a reverse effect on the hypnotic effect of diazepam in the chick's model. More clinical researches are required to determine possible flumazenil applications in the bird in association with interaction with other drugs that affect CNS.

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## Conflict of interests

The authors report that they have non-rival interests.

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أعراض الهيجان والقلق وبعض الاختلاجات. كان الهدف من أجراءنا للدراسة الحالية هو الكشف عن التأثيرات العصبية السلوكية للفلومازينيل فضلا عن التأثيرات المسدرة والمزيلة للقلق في نموذج الأفراخ. كانت الجرعة المسدرة الوسطية للفلومازينيل عن طريق الحقن في الخلب هي ٠,١١٤ ملغم/كغم في الخلب. أدى حقن الأفراخ بالفلومازينيل بجرع ٠,٠٢, ٠,٠٤, ٠,٠٨, ٠,٠٨ ملغم/كغم في الخلب إلى تثبيط النشاط الحركي داخل الميدان المفتوح وإطالة زمن عدم الحركة الشدي وكان للفلومازينيل بالجرع المذكورة أنفا تأثيرات ضادة للقلق بالمقارنة مع مجموعة السيطرة. وأدى حقن الأفراخ بالفلومازينيل بجرع ٠,١ و ٠,٢ ملغم/كغم في الخلب إلى تقليل زمن النوم للأفراخ المحقونة بالدايزيبام بجرع ١٠ ملغم/كغم في الخلب. أظهر الفلومازينيل تأثيرات غير متوقعة تمثلت بتثبيط النشاط الحركي وتأثيرا مزيلا للقلق وتأثيرا عاكسا للفعل المسدر للدايزيبام وتشير نتائجنا إلى أن للفلومازينيل تأثيرا شادا جزئيا عند حقنه منفردا وتأثيرا عاكسا عند حقنه بعد الدايزيبام في نموذج الأفراخ.

## التأثيرات السلوكية العصبية للفلومازينيل في أفراخ الدجاج

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### الخلاصة

يعد الفلومازينيل من الأدوية الضادة التي تعمل تنافسيا وانتقائيا على مستقبلات الكابا ويعد الترياق المناسب عند اخذ جرع عالية من مركبات البيزودايزيبام. إن استخدامه في الأنسان وبعض الحيوانات قد يؤدي إلى