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ORIGINAL ARTICLE

COMPARATIVE NEUROPHARMACOLOGICAL EFFECTS OF DRUGS USED IN CHRONIC SUPPURATIVE OTITIS MEDIA IN WHITE ALBINO RATS

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ABSTRACT

Different antibiotics used in CSOM exerted neurotoxic effects. In present study, four antibiotics are selected which are either commonly employed or showed highest potential agent most prevalent organism in chronic suppurative otitis media in local population of Pakistan. For this purpose, white albino rats were randomly divided into different groups as G1: negative control (0.5ml normal saline), G2: ciprofloxacin (14.28mg/kg), G3: ceftizidime (15mg/kg), G4: co-amoxicillin (14.28mg/kg) and G5: amikacin (15mg/kg). Reference group was also included in the study in which animals were induced CSOM. All the drugs were administered intraperitonelly to healthy rats for seven days. Results showed that animals with CSOM showed significant decreased in neuropharmacological activities as compared with healthy rats of G1. All treated groups showed decreased in neuropharmacological activities as compared with healthy control in open field,light and dark cage,forced swimming test, maze and traction test. Co-amoxicillin, ceftazidime and amikacin produced mild to moderate depression, stress and anxiety but ciprofloxacin showed maximum depression and decreased locomotor activities. Therefore, these side effects of depression should be taken under consideration as CSOM itself causing depression. Therefore, present study may be helpful to select drug with lesser side effect of CNS depression in animal or patient with chronic or acute infection.

Keywords: Comparative neuropharmacological effects, cipro-floxacin, co-amoxicillin, ceftazidime, amikacin

INTRODUCTION

Chronic suppurative otitis media as chronic inflammation of mastoid cavity involving middle ear characterized by recurrent ear discharge through tympanic perforation is called chronic suppurative otitis media (WHO Genevia, 2004). Different antibiotics are being employed for CSOM such as penicillin, cephalosporins, quinolones, monobactams and carbapenems. In order to reduce the resistence of the drugs several drugs are being used in combination such as amoxicillin is used with clavulanic acid (Holten *et al.*, 2000, Elander *et al.*, 2003). Several studies showed that ciprofloxacin is one of the most effective agents against *Pseudomonas aeruginosa,* one of the most

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prevalent organisms found in CSOM in Pakistan (Abullah *et al.,* 2011). Co-amoxicillin is another well tolerated antibiotic use in otitis media in pediatric population (Easton *et al.*, 2003). Ceftazidime is a broad spectrum cephalosporin which is being employed to treat different bacterial infections across the world and included in the list of essential medicines of world health organization (WHO model list of essential medicine, 2011). Shamweel Ahmed showed that *S. aureus* (MSSA) was 100% sensitive to ceftazidime against pathogens isolated from patients of chronic suppurative otitis media (Ahmed, 2013). Few studies showed that sensitivity percentile of amikacin is very high against the causative organisms of chronic suppurative otitis media (Mansoor *et al.,* 2009).

Beside potential effects of above mentioned antibiotics, different neurotoxic effects are also reported. These drugs may influence the neurological activity in the patients due to several factors such as metabolism of drugs, blood flow to the tissue, pharmacokinetics and blood brain barrier of the patients (Snavely and Hodges, 1984). The neurotoxicity produced by ciprofloxacin is well established. It may induce insommia, seizure, headache, confusion, extrapyramidal effects and giat movement. Piperazine in ciprofloxacin and its inhibitory effects on GABA may contribute the behavioral and cognitive changes produced by it (Rezaei *et al.,* 2018). Therefore, the clinicians recognized that coamoxicillin can induce serotonin syndrome if taken with venlafaxine (Pinel-Ríos *et al.*, 2016). Neurotoxic effects of ceftazidime may include encephalopathy and non-convulsive status epilepticus (Grill, 2008). Amikacin is an aminoglycoside antibiotic and is reported to induce neurotoxic effects. it is associated with neuromuscular as well as autonomic transmission blockade (Mansoor *et al.,* 2009).

The aim of the current study is to evaluate the comparative neuropharmacological effects of drugs used in chronic suppurative otitis media which may be helpful to identify better selection of antibiotics in chronic suppurative otitis media.

MATERIALS AND METHODS

Drugs and dose

Drugs used in the current study ciprofloxacin co-amoxiclav amikacin ceftazidime were procured from the local supplier.

Ciprofloxacin 14.28 mg/kg, co-amoxicillin 14.28 mg/kg, amikacin 15mg/kg and ceftazidime 15mg/kg (according to adult's dose). All the drugs were administered intraperitonelly for seven days as per recommended doses. (Ahmed *et al*., 2020)

Instruments

Instruments used in the present study were TC-96+ELISA Microplate Reader, centrifugation machine, microscope (Olympus bh2) and Beckman coulter analyzer.

Chemicals/ kits used in Elisa neuro-immunological assay were purchased from (Calibiotech and glory Science Ltd) Company (IgE catalog no. T1244, IL8-95419, IL6 10140, TNF gamma 12089, serotonin 97117).

Animals

Male Sprague-dawley rats (191.5g ± 12) were purchased from Dow University of health sciences. The animals were locally bred and housed individually under 12 hour light dark cycle and controlled room temperature (22±2ºC) with the access of cubes of standard rodent diet and water under the recommendations of NIH for the Care and Use of Laboratory Animals as approved in the protocol of higher education. Animals were randomly selected to serve any group (Saleem *et al.,* 2018).

Dosing Protocol

Neuropharmacological, biochemical and liver function tests alongwith histological examination were performed on healthy rats divided into different groups as G1: negative

control (0.5ml normal saline), G2: ciprofloxacin (14.28mg/kg), G3: ceftizidime (15mg/kg), G4: co-amoxicillin (14.28mg/kg) and G5: amikacin (15mg/kg). All the drugs were administered intraperitonelly to healthy rats for seven days.

Induction of chronic suppurative otitis media

Animals of reference group were given anesthesia with ketamine (100mg/kg) with diazepam (0.1 mg/kg) given intraperitonelly. otitis media was induced by the inoculation of 0.04 ml of 6.4 * 10^7 CFU of *Pseudomonas aeruginosa* intoear (tympanic bulla) and kept the animals under the guidlines of NIH for two weeks. (Trinidad *et al.*, 2005, Bhutta *et al.,* 2012).

Neuropharmacological effects on drugs used in CSOM

Neuro-pharmacological activities (open field test, light and dark cage activities, force swimming test, traction and memory test) were performed in peaceful and calm environment. Observations were taken after treatment at eighth day.

Open field test

The open field apparatus consists of 76 × 76 cm of square area having 42 cm high walls. The floor is equally divided into 25 squares. To evaluate the activity, animal is placed in the centre of the open field and number of squares crossed by the animals with all four paws was counted for 30 minute (Ahmad *et al.,* 2013).

Light and dark cage activity test

This apparatus consist of one light compartment of transparent plastic and another dark portion of black translucent plastic, each measure 26× 26× 26 cm with 12× 12 cm passageway and provided a source of white light. The animal behavior is monitored under peaceful, quiet and controlled temperature. The reading is observed when the animal is introduced in the light area of the activity cage and the total time spent in the light compartment is noticed for a cut off time of 10 minutes (Porsolt *et al.,*1977).

Forced swim monitoring test

The force swimming test was conducted in a glass cylinder (40 cm height, 17 cm diameter) containing water (21°C) to a height of 30 cm, a little modified process described by Porsolt *et al.*The cut off time is 6 minutes to notice the mobility after a 15 minutes training session conducted before 24 hours on day 1 (Porsolt *et al.,*1977).

Traction test

The process of recording the traction time on static rod very much resembled the procedure described by Bogo V. in which rat was place the mouse at the far end of a rod. The orientation time was the time taken to orientate 180° from the starting position and the transit time was the time taken to travel to the end of the rod, both the orientation and transit times were recorded considering 120 seconds as cut off (Porsolt *et al.,*1977).

Maze test

This tets is also called short-term episodic memory in the rat; object recognition task The animal under observation was tested for memory via a procedure very much similar to the process described by Ennaceur and Delacour, consisting of a uniformly lit hardboard enclosure (65 × 45 × 45 cm). Rat was placed at the starting point of the apparatus and a recognized object was placed at the end point of the board. The exploration was taken under consideration when rat had its head within 2 cm of the object while 15 minutes were considered as cut off time (Porsolt *et al.,* 1977).

RESULTS AND DISCUSSION

Open field test

In open field test, decreased locomotor activities were observed by all treated groups in contrast with control group. The mean values of number of squares covered by G1 (negative control), G2 (ciprofloxacin), G3 (ceftazidime), G4 (co-amoxicillin) and G5 (amikacin) were 237.66 ±5.55, 196.01±21.21, 223.3±31.09, 226.6±12.22 and 217.62±23.35, respectively (table 1).

The maximum decrease in number of squares was observed in G2: (ciprofloxacin) with 17.52% drug response and minimum decrease was observed by G4: (co-amoxicillin) with 4.65% drug response.

The effects of drugs on open field test was significant at p=0.00 and F=8.898.

Light and dark cage activity test

In light and dark cage activity test, decreased in time was observed in light area was observed by all treated groups. The mean value of time (minutes) spent in light by G1 (negative control), G2 (ciprofloxacin), G3 (ceftazidime), G4 (co-amoxicillin), G5 (amikacin) and was 4.18 ±0.55, 3.22±0.57, 3.13±0.49, 2.52±0.41 and 3.05±0.44, respectively (table 2).

Ciprofloxacin treated group spent maximum time in light with 39.71% drug response and minimum co-amoxicillin treated group with 22.96% drug response.

The effects of drugs on time spent in light in light and dark cage activity test was significant at p=0.00 and F=219.027.

Forced swim test

In forced swim test, decreased in mobility time was observed by all treated groups as compare to the negative control. The mean value of mobility time (minutes) by rats of G1 (negative control), G2 (ciprofloxacin), G3 (ceftazidime), G4 (co-amoxicillin), G5 (amikacin) and was 4.51 ±0.42, 4.44±0.37, 4.03±0.43, 4.37±0.42, 4.27±0.39 and respectively (table 3).

The decreased mobility time was observed by G2 (ciprofloxacin) with 1.55% and by G3 (ceftazidime) with 10.64% drug response.

The effects of drugs on open field test was significant at p=0.00 and F=42.1.26

Maze test

In maze test, increased in time was observed by all treated groups in contrast with control group. The mean value of time (minutes) taken by rats to reach the goal of G1 (negative control), G2 (ciprofloxacin), G3 (ceftazidime), G4 (co-amoxicillin) and G5 (amikacin) was 6.11±1.80, 7.15±0.57, 6.58±0.43, 5.28±0.43 and 7.02±0.33 respectively (table 4).

The maximum delayed time was observed in G2 (ciprofloxacin) with 17.02% drug response and minimum by G3 (ceftazidime) with 7.69% drug response.

The effects of drugs on open field test was significant at p=0.00 and F=341.957.

Traction test

In traction test, increased time to cover the distance was observed by all treated groups in contrast with control group. The mean value of time (seconds) by rats of G1 (negative control), G2 (ciprofloxacin), G3 (ceftazidime), G4 (co-amoxicillin) and G5 (amikacin) was 25 ±0.12, 32.66±0.57, 27.49±0.43, 21±0.41 and 31±0.43 respectively (table 5).

The maximum time to reach the target was observed in G2 (ciprofloxacin) with 30.64% and minimum by G3 (ceftazidime) with 9.96% drug response, respectively. Imipramine showed increase in time in traction test (14.08%) whereas bromazepam showed slight decreased time (7.32%). The effects of drugs on open field test was significant at p=0.00 and F=135.0.

In the present study four commonly used antibiotics were selected on the basis most commonly found causative agent *Psuedomonas auregenosa* of CSOM in local population of Pakistan (Mansoor *et al.,* 2009). Ciprofloxacin is drug of choice due to its efficacy in CSOM (Indudharan *et al.,* 1999, Abdullah *et al.,* 2011), co-amoxicillin is commonly used in pediatric patients of CSOM which developed low resistance as compared to amoxicillin alone (Abdullah *et al.,* 2011). Amikacin and ceftazidime are very sensitive to the pathogenic strain found in CSOM (Mansoor *et al.,* 2009).

Table 1: Effects of antibiotics (ciprofloxacin, ceftazidine, co-amoxicillin and amikacin) in open field (30 min) in different groups.

Groups	Dose	No. of squares covered (Mean±S.D)	*P* value	Percentage response (%)
G1: Negative control (Normal saline)	0.5ml (oral)	237.66±5.5	-	-
G2: (ciprofloxacin)	14.28mg/kg (I/P)	196.01±21.21	0.00	17.52
G3: (ceftazidime)	15 mg/kg (I/P)	223.3±31.09	0.99	6.04
G4: (co-amoxicillin)	14.28mg/kg (I/P)	226.6±12.2	1.00	4.65
G5: (amikacin)	15 mg/kg (I/P)	217.6±23.35	0.714	8.44

One way ANOVA is applied to evaluate the effect of drugs at p <0.05) and post hoc (Tukey) for group comparasion.

Table 2: Effects of antibiotics (ciprofloxacin, ceftazidine, co-amoxicillin and amikacin) on tiime (minutes) in light and dark cage activity test (10 min) in different groups.

Groups	Dose	Time (minutes) spent in light (Mean ±S.D)	*P* value	Percentage response (%)
G1: Negative control (Normal saline)	0.5ml (oral)	4.18±0.52	-	-
G2: (ciprofloxacin)	14.28mg/kg (I/P)	2.52±0.41	0.00	39.71
G3: (ceftazidime)	15 mg/kg (I/P)	3.13±0.49	0.00	25.11
G4: (co-amoxicillin)	14.28mg/kg (I/P)	3.22±0.57	0.00	22.96
G5: (amikacin)	15 mg/kg (I/P)	3.05±0.44	0.00	27.034

One way ANOVA is applied to evaluate the effect of drugs at p <0.05) and post hoc (Tukey) for group comparasion.

Table 3: Effects of antibiotics (ciprofloxacin, ceftazidine, co-amoxicillin and amikacin) on mobility time (minutes) in force swim test (6 min) in different groups.

Groups	Dose	Mobility time (minutes (Mean ±S.D)	*P* value	Percentage response (%)
G1: Negative control (Normal saline)	0.5ml (oral)	4.51±0.42	-	-
G2: (ciprofloxacin)	14.28mg/kg (I/P)	4.44 ±0.37	0.689	1.55
G3: (ceftazidime)	15 mg/kg (I/P)	4.03±0.43	0.00	10.64
G4: (co-amoxicillin)	14.28mg/kg (I/P)	4.37±0.42	0.142	3.10
G5: (amikacin)	15 mg/kg (I/P)	4.27±0.39	0.080	5.32

One way ANOVA is applied to evaluate the effect of drugs at p <0.05) and post hoc (Tukey) for group comparasion

Table 4: Effects of antibiotics (ciprofloxacin, ceftazidine, co-amoxicillin and amikacin) on time (minutes) in maze test in different groups

Groups	Dose	Time in minutes (Mean ±S.D)	*P* value	Percentage response (%)
G1: Negative control (Normal saline)	0.5ml (oral)	6.11±1.80	-	-
G2: (ciprofloxacin)	14.28mg/kg (I/P)	7.15±0.57	0.05	17.02
G3: (ceftazidime)	15 mg/kg (I/P)	6.58±0.43	0.304	7.69
G4: (co-amoxicillin)	14.28mg/kg (I/P)	5.28±0.43	0.00	13.58
G5: (amikacin)	15 mg/kg (I/P)	7.02±0.33	0.00	14.89

One way ANOVA is applied to evaluate the effect of drugs at p <0.05) and post hoc (Tukey) for group comparasion

Table 5: Effects of antibiotics (ciprofloxacin, ceftazidine, co-amoxicillin and amikacin) on time (seconds) in traction test in different groups

Groups	Dose	Time (seconds) (Mean ±S.D)	*P* value	Percentage response
G1: Negative control (Normal saline)	0.5ml (oral)	25±0.12	-	-
G2: (ciprofloxacin)	14.28mg/kg (I/P)	32.66+0.57	0.00	30.64
G3: (ceftazidime)	15 mg/kg (I/P)	27.49±0.43	0.095	9.96
G4: (co-amoxicillin)	14.28mg/kg (I/P)	21±0.41	0.00	16.0
G5: (amikacin)	15 mg/kg (I/P)	31.33±0.43	0.00	25.32

One way ANOVA is applied to evaluate the effect of drugs at p <0.05) and post hoc (Tukey) for group comparasion

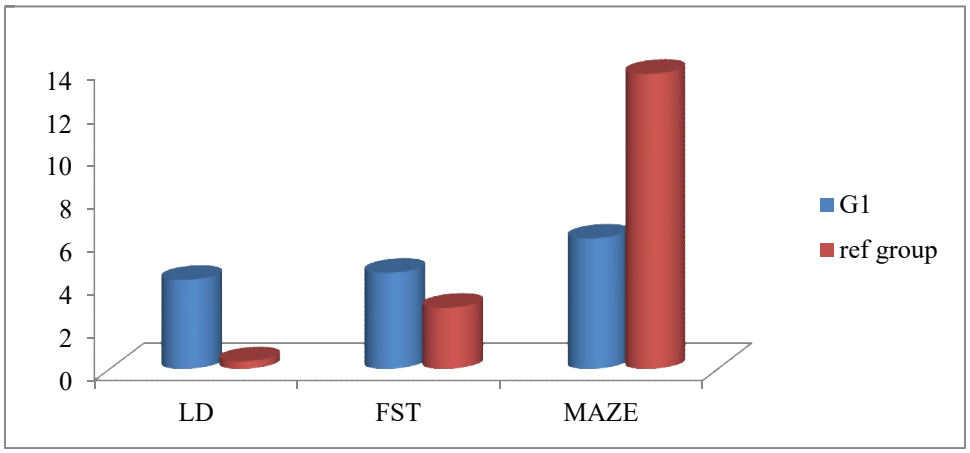

Fig. 1: Comparative neuropharmacological responses by G1 (healthy control) and reference group induced with CSOM in light and dark cage activities (LD) and forced swimming test (FST) and in MAZE test in minutes.

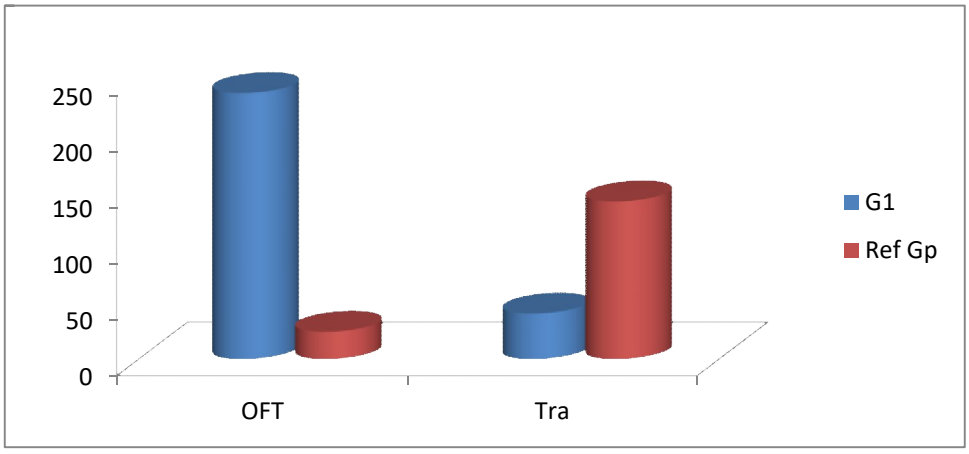

Fig. 2: Comparative neuropharmacological responses by G1 (healthy control) and reference group induced with CSOM in open field (LD) in no of squares covered and forced swimming test (FST) in seconds.

Ciprofloxacin showed decreased in movement (17.29 %) in open field test. In light and dark cage activity it showed significant decreased in time spent in light (39.71%). Ciprofloxacin showed insignificant decreased in mobility time in forced swimming test (1.55%, delayed time in maze test (17.02 %) and traction test (30.64 %). Ceftazedime slight decreased activity in open field (6.04%), forced swim test (10.64%), exposure to the light area (25.11%) in light and dark cage activity test, delayed time traction (9.96%) and maze test (7.69%). Co-amoxicillin insignificantly decreased activity in open field (4.65%) and significant increased time spent in light by light and dark activity (22.96%). It did not effect on memory in maze test (13.58%), mobility in force swim test (3.10 %) and traction time (16 %). Amikacin showed insignificant decreased activity in open field (8.44%), mobility in forced swim test (5.32%), exposure to light in light and dark cage activity box (27.03%), delayed memory in maze test (14.89%) and increased traction time (25.32%). Overall, neuropharmacological studies (table1 to 6) showed that ciprofloxacin had maximum effects to decrease activity followed by amikacin and ceftazidime. However co-amoxicillin showed negligible effects on behavioral changes.

These results showed that ciprofloxacin produced depression, decreased muscular movement and muscular co-ordination, memory deficit and decreased in body balance. It exhibited more time in dark area in light and dark cage activity which showed that ciprofloxacin has anxiogenic behavior. Previous studies showed ciprofloxacin may cause different disorders related to CNS depression such as delirium, oro-facial dyskinesias, gait movement, insommia, seizure, headache, confusion, extrapyramidal effects and psychosis (Grill and Maganti, 2008). The possible mechanism of these disorders might be due to fluoroquinolone mediated CNS toxicity. Ciprofloxacin is a fluoroquinolone which inhibit GABA-A receptors or activation of excitatory NMDA receptors (Rezaei *et al.,* 2018). Other possibility of depression and anxiety could be due to dopamine and opiod receptor activation causing the decreased mobility by ciprofloxacin (Takayama *et al.*, 1995). Some studies also showed that this may be due to the presence of piperazine structure in ciprofloxacin molecule which is well known for its CSN depressant effects (Rezaei *et al.,* 2018). In addition to this, ciprofloxacin also produced oxidative stress which may also be responsible to memory deficit in maze test (Ilgin *et al.*, 2015).

Ceftazidime neither alter behavior in animals (rats) nor induced significant depression. Mild reduce in activity may be due to alteration in alteration in GABA receptors (Joseph and Vimala, 2015). Ceftazidime belongs to third generation of cephalosporin and postulated mechanism for its side effects involved induction of endotoxins and activate glutamate (Grill and Maganti, 2008).

Results showed that co-amoxicillin caused slightly decreased in activities. Co-amoxicillin was involved in different neurological disorder associated with depression. Moreover, co-amoxicillin, belongs to penicillin group which cause psychological problems such as confusion, disorientation and seizure (Grill and Maganti, 2011). Connor (2003) reported that co-amoxicillin caused uncontrolled movement (Connor, 2003). The proposed epileptogenic activity due to the resemblance of beta lactam ring to the GABA produced inhibitory effects on GABA (Rezaei *et al.,* 2018).

These results also showed that amikacin might produced depression related to locomotor activity and muscular movement. Reported studies showed that amikacin induced neurotoxic effects by such as ototoxicity, peripheral neuropathy, encephalopathy, neuromuscular and autonomic transmission blockade. Ototoxic effects of amikacin produced due to oxidative stress. (Grill and Maganti, 2008).The proposed mechanism for neurotransmitter blockade (acetylecholine) was the binding of the drug post junctionally with acetylcholine receptor

and inhibition of release of acetylecholine at presynaptic junction (Grill and Rama, 2011).

Co-amoxicillin, ceftazidime and amikacin produced mild to moderate depression, stress and anxiety but ciprofloxacin showed maximum depression and decreased locomotor activities. However, co-amoxicillin, ceftazidime and amikacin are usually not reported as drug of choice for CSOM due to several reasons such as high resistance associated with co-amoxicillin (Abdullah *et al.,* 2011) and ototoxicity induced by ceftazidime and amikacin (Watanabe *et a.l,* 1978).

Co-amoxicillin, ceftazidime and amikacin produced mild to moderate depression, stress and anxiety but ciprofloxacin showed maximum depression and decreased locomotor activities. However, co-amoxicillin, ceftazidime and amikacin are usually not reported as drug of choice for CSOM due to several reasons such as high resistance associated with co-amoxicillin (Abdullah *et al.,* 2011) and ototoxicity induced by ceftazidime and amikacin (Watanabe *et al.,* 1978).

Figures1 and 2 showed that rats induced with CSOM showed significant decreased in activities in open field, light and dark cage, forced swimming test, maze and traction test (p>0.01) as compared to healthy animals of control group. Therefore, during selection of antibiotics should be done with caution as CSOM itself produced depression and drugs used in CSOM also causing depression and decreased neuropharmacological activities.

CONCLUSION

Co-amoxicillin, ceftazidime and amikacin produced mild to moderate depression, stress and anxiety but ciprofloxacin showed maximum depression and decreased locomotor activities. Therefore, these side effects of depression should be taken under consideration as CSOM itself causing depression. Therefore, present study may be helpful to select drug with lesser side effect of CNS depression in animal or patient with chronic or acute infection.

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