Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20172017

Original Research Article

Comparative analysis of cutaneous drug reactions among different fluoroquinolones: an experimental study

Susandhya Devadarshini, Kali Prasad Pattnaik*, Rajashree Samal, Jigyansa Mohapatra, Swayam Sourav Sahoo

Department of Pharmacology, SCB Medical College, Cuttack, Odisha, India

Received: 18 April 2017
Accepted: 24 April 2017

***Correspondence to:**
Dr. Kali Prasad Pattnaik,
Email:
drkaliprasad@yahoo.co.in

ABSTRACT

Background: Fluoroquinolones are generally well tolerated; most adverse effects are mild and common are GI upset. But recent literatures suggest increase reports of Cutaneous Drug reactions (CDRs) including SJS with Fluoroquinolones. However there is insufficient data both in animal and clinical study regarding comparative Analysis of CDRs among different Fluoroquinolones. Hence the present study was under taken to evaluate incidence of comparative CDRs among different Fluoroquinolones.
Methods: 96 Albino mice were divided into 16 groups of 6 each. Ciprofloxacin, Ofloxacin, Levofloxacin and Moxifloxacin were administered in Group 1-4, 5-8, 9-12 and 13-16 at the dose of 50/100/150/200mg/kg respectively. The following parameters were observed i.e. Number and % of mice developed CDRs with type and severity. Duration of exposure till development of CDRs, time to Recovery and Mortality in each group.
Results: Ofloxacin produced maximum number of CDRs i.e. in 33.3% mice which was significantly higher than that with levofloxacin (p=0.006*). The incidence of CDRs with Ciprofloxacin was 16.67 % and Moxifloxacin16.67 %, but no statistically significant difference than Ofloxacin. The onset for CDRs was significantly earlier with Ofloxacin among the Fluoroquinolones (P=0.013*). The reactions varied from severe dermatitis to serious exfoliation of the skin with ofloxacin and Ciprofloxacin, Alopecia with Moxifloxacin but no cutaneous reactions to Levofloxacin. Mortality was found only with Ofloxacin (12.5%).
Conclusions: CDRs are common and may present as severe skin exfoliation or Alopecia with Fluoroquinolones. The CDRs are Maximum with Ofloxacin without significant difference from ciprofloxacin but significantly higher than levofloxacin which has least potential for CDRs. Fatality may occur with Ofloxacin.

Keywords: Cutaneous drug reactions, Fluoroquinolones, Epidermal necrolysis, Mice model

INTRODUCTION

Cutaneous drug reactions are one of the most common types of adverse reaction to drug therapy, with an overall incidence of 1-5 %.[1] The Fluoroquinolones as a class are generally well tolerated; most adverse effects are mild in severity, self-limiting and rarely result in treatment discontinuation.[2] The most commonly occurring effects are GI upset (nausea, vomiting, diarrhoea, constipation and abdominal pain; less than 7% total). Less common effects may include central nervous system (CNS) events (less than 5%), blood disorders (approximately 5%), renal disturbances (approximately 4.5%), and skin hypersensitivity and photosensitivity effects (approximately 2%).[3] Steven Johnson Syndrome associated with administration of Ofloxacin had been reported.[4] Similar reactions have been documented with ciprofloxacin and levofloxacin (a L-racemic isomer of ofloxacin).[5] In a systematic review of cutaneous drug reactions on Indian Population Patel et.al. have shown that the major suspect groups were antimicrobials (45.46%), NSAIDs (20.87%) and antiepileptic (14.57%), commonly implicated drugs were sulphonamides (13.32%), β-lactams (8.96%), carbamazepine (6.65%),

phenytoin (6.46%) and Fluoroquinolones (5.12%).[6] But recently use of Sulphonamides drugs is reduced and Fluoroquinolones are preferred agents in number of situations i.e. Urinary Tract Infection (UTI), Respiratory Tract Infections (RTI), Gastro Intestinal Tract infections and various Sexually Transmitted Diseases. Different Fluoroquinolones i.e. ciprofloxacin, ofloxacin, Levofloxacin and Moxifloxacin are indicated for the above conditions and also used for prolonged therapy in Pulmonary Koch's. The literature search for relative incidence of cutaneous drug reactions among different Fluoroquinolones did not reveal sufficient information either in animal studies or in clinical studies. So study of comparative incidence of cutaneous drug reactions (CDRs) with different Fluoroquinolones may help in selecting one over the other. Hence initially an animal study was planned to find out the relative incidence of cutaneous drug reactions among different commonly used Fluoroquinolones. Mice is used as animal models for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, skin from UVB-exposed C57BL/6J mice showed features resembling human photo damage.[7,8] Mouse is also used as models for alopecia areata for review of preclinical drug screening.[9] Taking all these into account we used Mice as the animal model for study of relative incidence of cutaneous drug reactions among different commonly used Fluoroquinolones.

METHODS

This study was conducted in Department of Pharmacology, SCB Medical College, Cuttack in collaboration with Department of Dermatology, over a period of six months from June 2008 to December 2008. Experimental protocol was approved by the Institutional Animal Ethics Committee.

Design of the study was an open level prospective experimental study.

Study procedure

Selection of animals

96 albino mice of either sex weighing between 25-35 gm were selected. They were randomly divided in to sixteen groups of 6 mice in each group. All the mice were provided free access to food and water and maintained under standard laboratory conditions.

Selection of drugs

Four Fluoroquinolones which are available in I.V formulations i.e. Ciprofloxacin - 500 mg/100ml, Ofloxacin - 200 mg/100ml, Levofloxacin - 500 mg/100ml and Moxifloxacin - 400 mg/100ml were selected for the study.

Administration of the drugs

Ciprofloxacin was administered in Group 1 to 4, Ofloxacin in Group 5 to 8, Levofloxacin in Group 9 to 12 and Moxifloxacin in Group 13 to 16 mice at the dose of 50,100,150 and 200mg/kg respectively. All the drugs were administered intraperitoneal to the mice daily till cutaneous drug reactions appeared or till the end of 10 days. After CDRs appeared in any mice the drug was discontinued. The mice were kept in separate cages for observation.

Precautions taken to avoid photosensitive and photo toxic effects: The mice were not exposed to direct sun rays and the drugs are given daily in the evening to avoid photo sensitive and photo toxic effects.[10]

The following parameters were observed:

- Number and % of mice developed (CDRs) in each group
- Mortality in each group
- Type and Severity of CDRs
- Duration of exposure till development of CDRs and Time to Recovery

Statistical analysis

The incidence (Percentage) of Cutaneous Drug Reactions(CDRs)in the mice, among the different Fluoroquinolones were compared by applying Chi Square Test with Yates Correction. The duration of onset of CDRs among different Fluoroquinolones were compared by ANOVA.

RESULTS

The details of cutaneous drug reactions with different Fluoroquinolones are depicted in (Table 1) and the summary of the observations is presented in (Table 2). The following observations were made from the study.

Analysis of CDRs

Figure 1: Ciprofloxacin induced skin exfoliation.

Ciprofloxacin 50 mg/kg did not produce any CDRs. But serious CDRs including skin exfoliation (resembling Epidermal Necrolysis) developed in 16.67% (4 out of 24) mice treated with different doses of Ciprofloxacin (Figure 1). The mean duration of exposure before exfoliation was 78±12 hours, and no death have occurred in any dose of Ciprofloxacin (Table 1 and 2).

Table 1: Details of Cutaneous Drug reactions (CDRs) with Fluoroquinolones in Mice.

Groups of mice, n=6 (each group)	Name and dose of the drugs	CDRs Absent (number of Mice)	Cutaneous reactions present				
			Number of mice	Time to onset in hours	Type of reaction	Time to recovery in days	Outcome/ Death time to death
Group 01	Ciprofloxacin50mg/kg	6	Nil				
Group 02	Ciprofloxacin100mg/kg	5	1	96	Exfoliation	2days	-
Group 03	Ciprofloxacin150mg/kg	5	1	72	Exfoliation	4days	-
Group 04	Ciprofloxacin 200mg/kg	4	1	84	Exfoliation	10 days	
			1	60		10 days	
	Total of Ciprofloxacin	20	4	Mean±SD (84±9.80)		Mean - 6.5days	No Death
Group 05	Ofloxacin 50mg/kg	5	1	72	Dermatitis	10 days	-
Group 06	Ofloxacin 100mg/kg	4	2	48	Exfoliation	14 days	
				48	Exfoliation	16 days	
Group 07	Ofloxacin 150mg/kg	4	2	48	Exfoliation	Not recovered	Deathon10th day
				48	Exfoliation	16days	
Group 08	Ofloxacin 200mg/kg	3	3	48	Exfoliation	Not recovered	Death on 7th day
				48	Exfoliation	Not recovered	Death on 5th day
				36	Exfoliation	18 days	
	Total of Ofloxacin	16	8	Mean-49.5±10.01		Mean-14.8	Death of 3 rats
Group 09-12	Levofloxacin-50mg/100mg/150mg/& 200mg/kg	6 +6+6+6 =24	Nil	-		-	-
	Total of Levofloxacin	24	Nil	-		-	No death
Group 13	Moxifloxacin 50mg/kg	6	Nil				
Group 14	Moxifloxacin 100mg/kg	5	1	144	Stiffening of hairs	Recovered	
Group 15	Moxifloxacin 150mg/kg	4	1	96	Alopecia	No hair growth after two weeks	
			1	48			
Group 16	Moxifloxacin 200mg/kg	5	1	72	Alopecia	No hair growth after two weeks	
	Total of Moxifloxacin	20	4	Mean-90±40.99		No Death	

Treatment given injection Pheniramine Maleate (Avil) and injection Dexona

Ofloxacin produced maximum number of CDRs in experimental animals i.e. 33.3% (8 out of 24) mice treated with Ofloxacin developed serious CDRs. The incidence was 6.67% (1 out of 6 mice) in the dose of

50mg/kg, 33.3% (2 out of 6 mice) in the dose of 100mg/kg and 150mg/kg and 50% (3 out of 6 mice) with 200mg/kg dose. CDRs i.e. Dermatitis and skin exfoliation with Ofloxacin are demonstrated in (Figure 2 and 3).

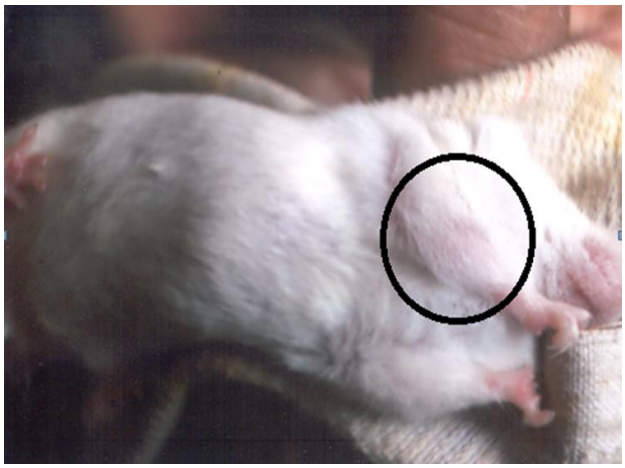

Figure 2: Ofloxacin induced skin rash.

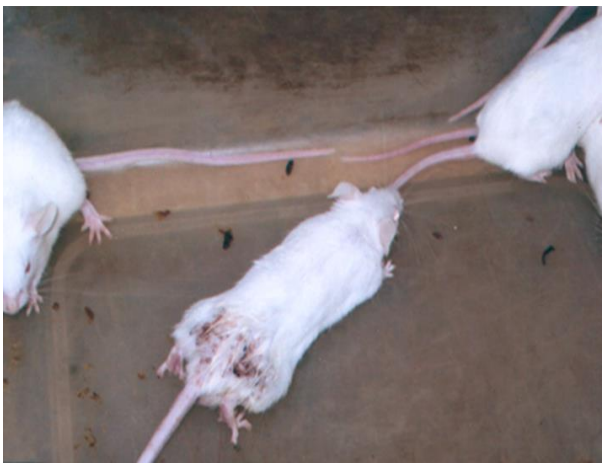

Figure 3: Ofloxacin induced skin exfoliation.

As a whole there was significant difference in the incidence of CDRs among the four Fluoroquinolones (p=0.048*). On Individual comparison, Incidence of CDRs with Ofloxacin was significantly higher than levofloxacin (p=0.006*). Though the incidence of CDRs with Ofloxacin is higher than that with Ciprofloxacin and Moxifloxacin and the incidence of CDRs with Ciprofloxacin and Moxifloxacin are higher than Levofloxacin but there was no statistically significant difference (p=0.317 and 0.117 respectively). The mean duration of exposure of Ofloxacin before development of CDRs was 49.5±10.01 hours which was significantly earlier among the Fluoroquinolones (P=0.013) (Table 1 and 2).

Levofloxacin administration in the dose range of 50mg/kg to 200mg/kg over duration of 10 days did not produce any CDR in any of the 24 mice (Table 1 and 2).

Moxifloxacin 50mg/kg did not produce any CDRs. 16.6% mice in dose of 100mg/kg developed stiffening of hairs (Figure 4) and 3 (25%) of total 12 mice receiving Moxifloxacin 150 and 200mg/kg developed patchy alopecia (Figure 5). None of the mice developed skin exfoliation. The Mean duration of exposure before development of CDRs was 90± 40.99 hours. No death had occurred in mice treated with Moxifloxacin (Table 1 and 2).

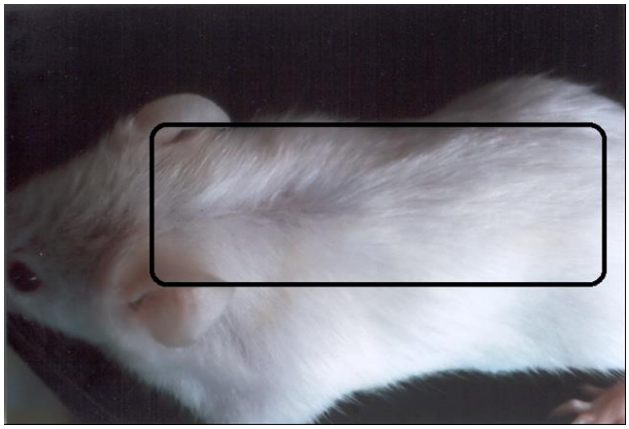

Figure 4: Moxifloxacin induced stiffening of hair.

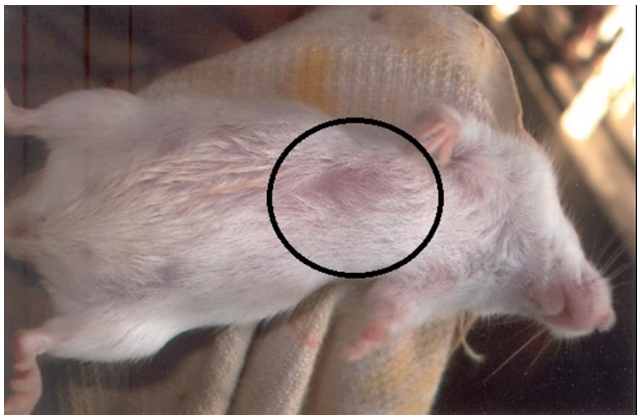

Figure 5: Moxifloxacin induced patchy alopecia.

Comparison of incidence of CDRs by chi square Test with Yates correction:

- Among the 4 Fluoroquinolones by χ^2 analysis: χ^2 = 9.6, p=0.02, Yates=7.5, corrected- p=0.048*
- Between Ofloxacin and levofloxacin: χ^2=9.6, p=0.0019, (Yates=7.35), corrected- p=0.006*
- Between Ofloxacin and Cipro /moxi floxacin: χ^2 =1.778, p=0.182, (Yates=1), corrected- p=0.317
- Between Ciprofloxacin and levofloxacin: χ^2 =4.3, p=0.036, (Yates=2.4), corrected- p=0.117

Comparison of time for onset of CDRs by ANOVA

The Table 2 and the statistical analysis showed that as a whole there was significant difference in the incidence of CDRs among the four Fluoroquinolones (p=0.048*). On

Individual comparison, Incidence of CDRs with Ofloxacin was significantly higher than levofloxacin (p=0.006*). Though the incidence of CDRs with Ofloxacin is higher than that with Ciprofloxacin & Moxifloxacin and the incidence of CDRs with Ciprofloxacin and Moxifloxacin are higher than Levofloxacin but there was no statistically significant difference. The onset for CDRs was significantly earlier with Ofloxacin among the Fluoroquinolones (P =0.013*).

Table 2: Comparative analysis of cutaneous drug reactions among different fluoroquinolones number of mice in each drug (n=24) total number of mice (n=96).

Name of drugs	CDRs appeared number of mice	CDRs did not appear number of mice	% of mice developed CDRs with each drug (n=24)	% of mice developed CDRs within total number of Mice (n=96)	Time for onset of CDRs in hours Mean±SD	Mean time to recovery in days	% of death
Ciprofloxacin	4	20	16.67 %	4.16%	(84±9.80)	6.5	Nil
Ofloxacin	8	16	33.33%	8.33%	49.5±10.01	14.8	12.5%
Levofloxacin	0	24	Nil	Nil	-	-	Nil
Moxifloxacin	4	20	16.67%	4.16%	90±41.96	Alopecia persisted even after 2-weeks	Nil

Analysis of death

Ofloxacin produced death in 12.5% (3 out of 24) mice. Ofloxacin was withdrawn immediately after appearance of exfoliation and the mice were treated with adequate anti-histaminic, steroids and antibiotics creams by the veterinary surgeon. Still there was death of the animals with exfoliation. But in contrast there was no death with other three Fluoroquinolones i.e. ciprofloxacin, levofloxacin, moxifloxacin in the dose range of 50-200mg/kg (Table 1 and 2).

DISCUSSION

Fluoroquinolones are commonly used anti-microbial agent, as a class they are generally well tolerated; most adverse effects are mild in severity, self-limiting and rarely result in treatment discontinuation.[2] The most commonly occurring effects are GI upset (nausea, vomiting, diarrhea, constipation and abdominal pain; less than 7% of the total). Less common effects may include central nervous system (CNS) events (less than 5%), blood disorders (approximately 5%) and skin hypersensitivity and photosensitivity effects (approximately 2%).[3] But recently there is a paradigm shift on the statement regarding safety of Fluoroquinolones. The U.S. Food and Drug Administration (FDA) in its safety communication on May12, 2016 approved changes to the labels of Fluoroquinolones antibacterial drugs for systemic use and states that these medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, they have revised the boxed warning and have determined that Fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis (AECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections, the benefits of Fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.[11] At this juncture we have tried to focus on cutaneous drug reactions (CDRs) of Fluoroquinolones. Though there are some large studies on adverse reactions related to Fluoroquinolones, but till date there is lack of comprehensive study focusing on relative incidence of cutaneous adverse drug reactions among different Fluoroquinolones. Hence initially we have taken up this animal study to focus on this issue. The photosensitive and phototoxic reactions to Fluoroquinolones are already highlighted.[8] So we have conducted our study in mice model without exposing them to direct Ultra-Violet irradiation or direct Sun ray exposure, to study the direct effect of Fluoroquinolones on the skin by minimizing risk of photosensitive and phototoxic reactions.[10] Again many studies on mice is done on hairless skin to see the effect on epidermis and dermis. But we have used the mice with intact hairs to see the effect both on the hairs and the skin.

In our systematic comparative study, we found that among the commonly used Fluoroquinolones, Ofloxacin produced maximum number of cutaneous drug reactions (CDRs) i.e. in 33.3% mice which was significantly higher than Incidence of CDRs with levofloxacin (p=0.006*). Though the incidence of CDRs with Ofloxacin is higher than that with Ciprofloxacin and Moxifloxacin and the

incidence of CDRs with Ciprofloxacin and Moxifloxacin are higher than Levofloxacin but there was no statistically significant difference with the present number mice (Table 2). The onset for CDRs was significantly earlier with Ofloxacin among the Fluoroquinolones (P =0.013*). The reactions varied from severe dermatitis to serious exfoliation (resembling Epidermal Necrolysis) of the skin with ofloxacin and Ciprofloxacin. There were various grades of Alopecia with Moxifloxacin. There were no cutaneous reactions to Levofloxacin. These reactions are possibly direct cutaneous reactions to Fluoroquinolones rather than photosensitive or phototoxic reactions as we have minimized the risk of these reactions in our study methodology. The onset of these reactions was earliest i.e. (49.5±10.01 hours) with Ofloxacin which was significantly earlier among the Fluoroquinolones (P =0.013*).

In a study by K. Owen, in 1998, mice were given different Fluoroquinolones at an oral dose of 200mg/kg followed by exposure to 20j/cm^2 long wave UV irradiation and showed that Lomefloxacin and Sparfloxacin caused erythema and oedema which were severe and lasted for 7-10 days, in contrast erythema with Grepafloxacin, Ciprofloxacin and Ofloxacin was relatively mild and short lived.[12] However in our study Ofloxacin has highest and severe CDRs with earliest onset of reactions followed by Ciprofloxacin. This difference may possibly be due to more direct cutaneous reactions of Ofloxacin and ciprofloxacin than photosensitive reactions. Moxifloxacin induced Alopecia found in our study was not reported earlier.

Though text books comments that most common adverse reactions to Fluoroquinolones involve GI Tract (3-17%), followed by CNS (0.9-11%) followed by Musculoskeletal and cutaneous reactions, but in a clinical study on adverse drug reactions related to the use of Fluoroquinolones Antimicrobials in Italy in 2003, the most frequently reported reactions to Fluoroquinolones, involved the skin, but their percentage (25%) was significantly lower (p <0.01) than those of other systemic antimicrobials (58.5%).[13] They found some significant differences in the safety profiles of individual Fluoroquinolones: ciprofloxacin was more frequently associated with skin reactions (p <0.01), levofloxacin and pefloxacin with musculoskeletal (p <0.01), Stevens-Johnson syndrome were seen only with ciprofloxacin.[14] In another study in 2011, it was found that among 166,736 patients who had been treated with Fluoroquinolones, the prevalence of adverse reaction and cutaneous adverse reaction were 0.13% and 0.09%, respectively. The prevalence of cutaneous reaction to individual Fluoroquinolones varies between 0.04% and 0.37%. Out of hundred fifty-one subjects with adverse reaction, most of the cutaneous reactions were attributed to ciprofloxacin (n = 93), and the most frequent adverse cutaneous reaction seen was maculo papular rash 39.7%.[15]

Justifiably we have focused on Cutaneous Drug Reactions (CDRs) of Fluoroquinolones in this animal study. We have found high incidence of CDRs with Fluoroquinolones i.e. highest (33.3%) with Ofloxacin followed by 16.67% with Ciprofloxacin and Moxifloxacin and no CDRs with Levofloxacin. In our study there was 12.5% mortality in the mice with ofloxacin in dose range of 150-200mg/kg. No mortality with other three commonly used Fluoroquinolones. Our animal study has pertinent clinical significance. Though various clinical studies mentioned above have shown ciprofloxacin as most common Fluoroquinolone for (CDRs) and some study have commented that Stevens-Johnson syndrome were seen only with ciprofloxacin, and had no mention about CDRs with Ofloxacin.[14] our study have shown that among Fluoroquinolones i.e. highest CDRs found with Ofloxacin without significant difference from Ciprofloxacin and Moxifloxacin.[14] Our recent search in Vigi- Access (the website of Pharmacovigilance of WHO UMC) have shown 6,288 skin reactions with ofloxacin though very high numbers (i.e.30372) of skin reactions also found with Ciprofloxacin.[16] But it needs to be analyzed whether this difference is due to more use and better spontaneous reporting with ciprofloxacin.

From the present study in mice model we conclude that cutaneous Drug reactions (CDRs) with Fluoroquinolones are common, they may present as severe dermatitis, Skin Exfoliation with Ofloxacin and ciprofloxacin or Alopecia with Moxifloxacin. The incidences of CDRs are Maximum with Ofloxacin without significant difference from ciprofloxacin but significantly higher than levofloxacin which has least potential for CDRs. These CDRs may be direct cutaneous reactions of the drugs rather than Photosensitive and phototoxic reactions.

ACKNOWLEDGMENTS

Authors would like to acknowledge the Morale support of Pharmacovigilance Programme of India (PvPI), Indian Pharmacopoeia Commission, Ghaziabad for inspiring them to do basic research on adverse drug reactions. Authors are thankful to present Professor and HOD, Pharmacology Dr. Srikanta Mohanty, Professor and HOD, Dermatology Dr. Prasanjeet Mohanty for their inspiration and support and Mr. Bikash Ch. Naik, PG Lab Assistant Pharmacology for assisting the animal experiment during this research.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of SCB Medical College Cuttack

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Cite this article as: Devadarshini S, Pattnaik KP, Samal R, Mohapatra J, Sahoo SS. Comparative analysis of cutaneous drug reactions among different fluoroquinolones: an experimental study. Int J Basic Clin Pharmacol 2017;6:1254-60.