Indian Journal of Animal Sciences **89**(10): 1086–1090, October 2019/Article
https://doi.org/10.56093/ijans.v89i10.95003

Analgesic, antipyretic and anti-inflammatory efficacy of ketorolac in the chicks

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Received: 9 November 2018; Accepted: 20 March 2019

ABSTRACT

Now-a-days, there is a need for newly, non-addicted and effective analgesics with less side effects. Therefore, the present study evaluated the analgesic, antipyretic and anti-inflammatory efficacy of ketorolac in 7–21 days old broiler chicks and its possible application in the related field. The analgesic median effective dose (ED_{50}) of ketorolac that caused analgesia in 50% of the chicks was 9.1 mg/kg, intramuscular (IM). Ketorolac caused analgesic and antipyretic effects at multiple doses (5, 10 and 20 mg/kg, IM) in a dose dependent manner, whereas these percentages were significantly higher when ketorolac was injected @ 10 and 20 mg/kg, IM. All times recorded (15, 30, 60 and 120 min) for evaluating the analgesic effect of ketorolac produced analgesia while the higher and better analgesic efficacy was observed at 15 min after ketorolac injection. The injection of ketorolac @ 20 mg/kg, IM exerted anti-inflammatory activity by significantly reducing the right paw thickness of the chicks as a result of formaldehyde injection in comparison to control. There was no liver damage, impaired metabolism and function may be attributed to the ketorolac treatment in the chicks which was evaluated through estimation of serum AST and ALT concentrations. The study suggests the benefit of using ketorolac as an analgesic, antipyretic and anti-inflammatory drug in the field of veterinary medicine due to its good, reliable and efficient efficacy.

Key words: Analgesia, Anti-inflammation, Antipyresis, Chicks, Ketorolac

Ketorolac is considered as one of the most famous agents that belongs to the first generation of the non-steroidal anti-inflammatory Drugs (NSAIDs) which have a therapeutic benefit for preventing nociception thus producing analgesia as well as its effect on lowering the pyresis and its anti-inflammatory action (Resman-Targoff 1990, Finkel *et al.* 2009, Smyth and FitzGerald 2009, Hilal-Dandan and Brunton 2014, Soleimanpour *et al.* 2016). Ketorolac's action in the body are achieved by the reversible non-selective inhibition of the cyclooxygenase (COX) (COX1 and COX2 isoform) enzyme, thus interrupting arachidonic acid from converting to prostaglandins and relieving the pain, fever and inflammation produced (Botting 2006, Finkel *et al.* 2009, Smyth and Fitz Gerald 2009, Hilal-Dandan and Brunton 2014). Ketorolac benefits as peripheral analgesics to manage moderate to severe pain and have few side effects only and considered a good approved, effective parenteral drug, cheaper and economic analgesics unlike other central opioids analgesic like tramadol and morphine which causes a serious side effects like respiratory depression and drug abuse (Jelinek 2000, Ollé *et al.* 2000, Rainer *et al.* 2000, Shankariah *et al.* 2012, Hendarman *et al.* 2014). The ketorolac's effect on non-opioid receptors lessens the risk of potentially additive side effects such as hemodynamic changes, central nervous system changes, or respiratory depression (Shankariah *et al.* 2012, Rai and Kiran 2013). Ketorolac is useful for the postoperative nociceptive cure due to both pain and inflammation caused by surgery while opioids, in contrast, do not provide anti-inflammatory activity in this setting and have also a narrow therapeutic index (O'Hanlon *et al.* 1996, Macario and Lipman 2001, Gupta *et al.* 2001).

The previous studies on ketorolac did not deal with the benefit of using it as a first choice drug for relieving pain, fever and inflammation in the chicken and other animals. The goal of this study was to evaluate the analgesic, antipyretic and anti-inflammatory actions of ketorolac for the first time in chicken species and its possible applicability in the related field.

MATERIALS AND METHODS

Animals: Broiler chicks (Ross species) 7–21 days old weighing between 48–125 g were used in this study. They were kept in cages at a constant temperature of 32–35°C with continuous lighting and the litter consisted of wood shavings. The chicks had free access to drinking water and feed *ad lib*. Ketorolac (3% as ketorolac, Normon, Spain) was diluted in physiological normal saline to prepare the doses at a volume of injection of 5 ml/kg body weight, IM.

Ethics: Ethical considerations related to this study were approved by the scientific committee of the College of

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Veterinary Medicine, University of Mosul and all necessary procedures were applied regarding the euthanasia of the chicks at the end of all experiments.

Analgesic ED_{50} of ketorolac in the chicks: The ED_{50} value of ketorolac that causes analgesia in 50% of the chicks was measured as the first step as per the up-and-down method described by Dixon (1980) to extrapolate the dose of ketorolac that would be used in this study. The initial dose of ketorolac was chosen to be 10 mg/kg, IM depending on a preliminary study with an increase or decrease in the dose that is about 30% of the initial dose (3 mg represented as d). Ketorolac's antinociceptive effect was measured by the use of an electrostimulator apparatus (Scientific and Research Ltd., United Kingdom) for induction of nociception through its electrostimulation in the chicks (Mousa and Mohammad 2012, Mousa 2014, Mousa and Al-Zubaidy 2019). The distress call in the chicks due to pain stimulation was recorded as voltage for each chick in the experiment before and after 15 min of ketorolac injection (Mousa and Mohammad 2012, Mousa 2014, Mousa and Al-Zubaidy 2019). Ketorolac was considered having an antinociceptive effect if the measured voltage after injection increased in comparison to the voltage recorded before ketorolac injection (chick marked as X), if not the chick was marked as O. Table value (K) was obtained from Dixon's table depending on X–O consequences (which last for 3 recorded chicks after changing of the effect) and ED_{50} value was measured according to the following equation:

$ED_{50} = xf + Kd$ (xf, last dose used in the experiment)

Analgesic effect of multiple doses of ketorolac in the chicks: According to the ED_{50} value (9.1 mg/kg, IM) measured in the previous experiment, three groups (6 chicks/group) were treated with multiple doses of ketorolac @ 5, 10, 20 mg/kg, IM (which represented ED_{25}, ED_{50} and ED_{100} of ketorolac, respectively) for examining the dose dependency. The voltage (volt) induced by electro-stimulation for each chick was recorded before and after 15 min of ketorolac injection. Later, the percentage of analgesia occurred in each group of the chicks in addition to the delta voltage (the difference between voltage before and after injection of ketorolac) were also recorded.

Analgesia of ketorolac at different times in the chicks: Ketorolac was injected @ 20 mg/kg, IM which represented the dose that causes analgesia in 100% of the chicks (ED_{100}) and the voltage was obtained from one group of 6 chicks. The voltage for every individual chick was recorded before and after 15, 30, 60 and 120 min of ketorolac treatment to measure the change in the efficacy of ketorolac analgesia at different times after injection.

Antipyretic effect of multiple doses of ketorolac in the chicks: The antipyretic effect of ketorolac was recorded by using the digital thermometer for obtaining the temperature via the rectum. Three groups (6 chicks/each) were treated with 5, 10 and 20 mg/kg, IM of ketorolac. The temperature for each chick was recorded before and after 30 min of ketorolac injection and the delta change in temperature for each chick was measured at acquisition.

Anti-inflammatory effect of ketorolac in the chicks: Two groups (6 chicks/group) namely control (normal saline injection) and treated (ketorolac injection) were selected. Ketorolac was injected @ 20 mg/kg, 30 min prior to 0.05 ml (1%) formaldehyde injection (May & Baker Ltd, Dagenham, UK) in the right paw for inducing inflammation (Sufka *et al.* 2001). The right paw thickness was measured with the digital caliber in millimeter (mm) both before and after 60 min of formaldehyde injection. The delta change in paw thickness, which reveals the inflammation (Collin *et al.* 2001, Sondhi *et al.* 2009) caused by ketorolac for both groups of chicks was measured and its alteration percentage was recorded regarding the anti-inflammatory action of ketorolac.

Measurement of the liver function as indicated by serum alanine transaminase (ALT) and aspartate transaminase (AST): After 2 h of ketorolac injection @ 20 mg/kg IM, the blood samples were obtained from the jugular vein from both the control (normal saline injection) and treated chicks with ketorolac (6 chicks/group). Serum ALT (Reitman and Frankel 1957) and serum AST (Plummer 1987) levels (expressed in IU/L) were obtained using the specified kit (BIOLABO SA, France) by using the spectrophotometric analysis at 505 nm.

Statistical analysis: Parametric data for more than three groups were statistically analyzed by one way analysis of variance, and then submitted to the least significant difference while paired and unpaired student T-test was used to compare the means of two parametric groups (Petrie and Watson 1999, Katz 1999). On the other hand, Fisher exact probability test and Mann-Whitney U-test were applied to the non-parametric data of the two groups (Runyon 1977, Katz 1999). The level of significance was at $P<0.05$.

RESULTS AND DISCUSSION

Analgesic ED_{50} of ketorolac in the chicks: The dose of ketorolac that caused analgesia in 50% of the chicks (ED_{50}) was 9.1 mg/kg, IM (Table 1) conducted in the chicks for the first time. The analgesic ED_{50} value of ketorolac was near the value reported in the rat model (Javier Lopez-Munoz *et al.* 2004, Medina-Santillan *et al.* 2004).

Analgesic effect of multiple doses of ketorolac in the chicks: Analgesic percentages of ketorolac injection @ 10 and 20 mg/kg, IM were significantly different from the group of chicks that received 5 mg/kg, IM of ketorolac (Table 2). The voltage recorded after 15 min of ketorolac injection for all the above mentioned groups was significantly different from the voltage recorded before injection which means that ketorolac causes analgesia at different doses. Meanwhile, the doses of ketorolac @ 10 and 20 mg/kg, IM had more analgesic efficacy and differed significantly from the ketorolac dose @ 5 mg/kg, IM based on the voltage after 15 min of ketorolac injection in addition to the delta voltage estimated. Ketorolac produced analgesic and antipyretic effects in a dose dependent when injected at different multiple doses (5, 10 and 20 mg/kg, IM) which represented its ED_{25}, ED_{50} and ED_{100} respectively, which

Table 1. Analgesic ED_{50} value of ketorolac in the chicks

Parameter	Results
Range of the doses	7–13 mg
Initial dose used	10 mg/kg
Last dose used (xf)	10 mg/kg
Number of chicks	5 (XOOXX)
K (The table value) (Dixon 1980)	– 0.305
±in doses (d)	3 mg
ED_{50} = xf + Kd	9.1 mg/kg, IM

X, effect (antinociception); O, no effect (nociception).

Table 2. Analgesic effect of ketorolac in the chicks for multiple doses (Mean±SE)

Ketorolac mg/kg, IM	Analgesia %	Voltage (volt) before injection	Voltage (volt) after 15 min of injection	Delta voltage
5	83.33	6.67±0.21	8.83±0.65[a]	2.17±0.60
10	100[*]	6.17±0.31	11.83±0.79[*a]	5.67±0.84[*]
20	100[*]	5.83±0.31	13.33±0.49[*a]	7.50±0.67[*]

Electrostimulation for pain induction was recorded before and after 15 min. of ketorolac injection. *Significantly different from ketorolac 5 mg/kg, IM at P<0.05. +Significantly different from the ketorolac 10 mg/kg, IM at P<0.05. [a]Significantly different from voltage before injection of ketorolac in the same group at P<0.05

is in accordance with previous studies (Vargas *et al.* 1994, Soleimanpour *et al.* 2016). The findings reveal that the better and higher analgesic effect of ketorolac was at 15 min after injection of 20 mg/kg, IM in the chicks which may be due to the higher dose injected of ketorolac and its parenteral route which reaches the blood circulation faster and exert its effect (Smyth and Fitz Gerald 2009, Hilal-Dandan and Brunton 2014).

Analgesia of ketorolac at different times in the chicks: Ketorolac analgesic efficacy increased significantly through times estimated at 15, 30, 60 and 120 min after ketorolac injection @ 20 mg/kg, IM (Table 3). All times recorded produces analgesia while the higher and better analgesic efficacy was at 15 min after ketorolac injection.

Antipyretic effect of multiple doses of ketorolac in the chicks: Ketorolac treatment at doses of 5, 10 and 20 mg/kg, IM produces antipyretic efficacy in a dose dependent manner which was significant at doses 10 and 20 mg/kg, IM. The delta temperature (temperature difference before and after injection of ketorolac) was higher at a dose of 20 mg/kg, IM (Table 4). Ketorolac produces analgesia, antipyretic and anti-inflammatory effect because it belongs to the agents of the first generation of NSAIDs (Finkel *et al.* 2009, Smyth and Fitz Gerald 2009, Hilal-Dandan and Brunton 2014, Soleimanpour *et al.* 2016) by reversible non-selective inhibition of the enzyme cyclo-oxygenases, therefore preventing arachidonic acid from converting to prostaglandins and relieving the pain, fever and

Table 3. Analgesic effect of ketorolac in the chicks at different times (Mean±SE)

Voltage before injection (V)	Voltage after 15 min of injection (V)	Voltage after 30 min of injection (V)	Voltage after 60 min of injection (V)	Voltage after 120 min of injection (V)
5.83±0.31	14.00± 0.45[*]	11.17± 0.3[*a]	9.00± 0.68[*a,b]	7.50± 0.34[*a,b,c]

Values represent Mean±SE for 6 chicks/group. Pain–induced by electrostimulation was recorded before and after 15, 30 and 60 min. of ketorolac injection at 20 mg/kg, IM. *Significantly different from voltage before injection of ketorolac at P<0.05. [a]Significantly different from voltage after 15 min of ketorolac injection at P<0.05. [b]Significantly different from voltage after 30 min of ketorolac injection at P<0.05. [c,b]Significantly different from voltage after 60 min. of ketorolac injection at P<0.05.

inflammation elicited (Botting 2006, Finkel *et al.* 2009, Smyth and Fitz Gerald 2009, Hilal-Dandan and Brunton 2014).

Anti-inflammatory effect of ketorolac in the chicks: Anti-inflammatory effect due to ketorolac injection @ 20 mg/kg, IM increased in the treated group evidenced by significant decrease in the paw thickness in comparison to the control group. Ketorolac anti-inflammatory effect was elevated by 62% in the treated group as well as, there was a significant decrease in the delta change in paw thickness of the treated group in comparison to control group of the chicks (Table 5). In this study, the efficacy of ketorolac was measured using the formalin test. The injection of ketorolac exerts anti-inflammatory activity by reducing the right paw thickness of the chicks as a result of formaldehyde injection. The mechanism by which ketorolac reduce inflammation is thought to be the stimulation of the L-arginine/nitric oxide/cGMP pathway as well as reducing the production of inflammatory prostaglandin within the body (Alves and Duarte 2002, Alves *et al.* 2004).

Liver function in the chicks estimated through ALT and AST levels: Ketorolac (20 mg/kg, IM) in the treated groups did not significantly alter the concentrations of both serum AST and ALT levels compared control group of the chicks that injected with physiological normal saline (Table 6).

Table 4. Antipyretic effect of ketorolac in the chicks

Ketorolac mg/kg, IM	Temperature (°C) before injection	Temperature (°C) after injection	Delta temperature
5	41.47±0.02	41.38±0.03	0.08±0.03
10	41.43±0.02	41.20±0.05[*a]	0.23±0.04[*]
20	41.35±0.02	40.78±0.04[*+a]	0.57±0.06[*+]

Values represent Mean±SE for 6 chicks/group. Digital thermometer was used to measure the temperature through the rectum before and after 30 min of ketorolac injection. *Significantly different from the ketorolac 5 mg/kg, IM at P<0.05. +Significantly different from the ketorolac 10 mg/kg, IM at P<0.05. [a]Significantly different from temperature before injection of ketorolac in the same group at P<0.05.

Table 5. Anti–inflammatory effect of ketorolac in the chicks

Group	Paw thickness (mm) before injection	Paw thickness (mm) after injection	Delta change in paw thickness
Control	10.11±0.31	10.81±0.25 [a]	0.71±0.12
Treated	10.13±0.19	10.40±0.18 [a,*]	0.27±0.06 [*]

Anti-inflammatory action of Ketorolac = Control–Treated/ Control*100 = 62%

Values represent Mean±S.E. for 6 chicks/group. Ketorolac was injected at 20 mg/kg, IM before 30 min. of formaldehyde injection in the right paw. Paw thickness was calibrated with the digital caliber before and after 60 min. of 0.05 ml (1%) formaldehyde injection in the right paw of the chicks. *Significantly different from the control group at P<0.05. [a]Significantly different from paw thickness (mm) before injection of ketorolac in the same group at P<0.05

Table 6. Effect of ketorolac on serum ALT and AST levels in the chicks

Group	ALT (IU/L)	AST (IU/L)
Control (Normal saline)	23.33±1.17	69.00±2.27
Treated (Ketorolac)	27.83±1.90	75.17±2.93

Values represented Mean±S.E. for 6 chicks/group. Blood samples were collected after 2 h of normal saline or ketorolac injection at 20 mg/kg, IM.

There was no liver damage, and impaired metabolism and function may be attributed to the ketorolac treatment in the chicks which is in accordance with another study in the animals (Aly 2015).

The study suggests the benefit of using ketorolac as an analgesic, antipyretic and anti-inflammatory drug in the field of veterinary medicine due to its good, reliable and efficient efficacy.

ACKNOWLEDGEMENTS

The author is grateful to the University of Mosul/College of Veterinary Medicine for the support.

REFERENCES

Alves D P and Duarte I D G. 2002. Involvement of ATP-sensitive K+ channels in the peripheral antinociceptive effect induced by dipyrone. *European Journal of Pharmacology* **444**: 47–52.

Alves D P, Soares A C, Francischi J N, Castro M S A, Perez A C and Duarte I D G. 2004. Additive antinociceptive—effect of combination of diazoxide, an activator of ATP-sensitive K+ channels, and sodium nitroprusside and dibutyryl-cGMP. *European Journal of Pharmacology* **489**: 59–65.

Aly S, Mahmoud M F, Hassan S H M and Fahmy A. 2015. Evaluation of the analgesic activity and safety of ketorolac in whole body fractionated gamma irradiated animals. *Future Journal of Pharmaceutical Sciences* **1**: 8–15.

Botting R M. 2006. Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. *Journal of Physiology and Pharmacology* **57**:113–124.

Collin X, Robert J M, Duflos M, Wielgosz G, Le Baut G, Robin-Dubigeon C, Grimaud N, Lang F and Petit J Y. 2001. Synthesis of N–Pyridinyl (methyl)1, 2-dihydro-4-hydroxyl-2-oxoquinolone-3-carboxamides and analogues and their anti-inflammatory activity in mice and rats. *Journal of Physiology and Pharmacology* **53**: 417–23.

Dixon W J. 1980. Efficient analysis of experimental observations. *Annual Review of Pharmacology and Toxicology* **20**: 441–62.

Finkel R, Clark M A, Cubeddu L X, Harvey R A and Champe P C. 2009. Anti-inflammatory drugs, pp. 500–18. *Lippincott's Illustrated Reviews: Pharmacology*. (Eds) Williams and Wilkins. Philadelphia, USA.

Gupta A, Cheng J, Wang S and Barr G A. 2001. Analgesic efficacy of ketorolac and morphine in neonatal rats. *Pharmacology Biochemistry and Behavior* **68**: 635–40.

Hendarman I, Triratna S and Kamaludin M T. 2014. Ketorolac vs. tramadol for pain management after abdominal surgery in children. *Paediatrica Indonesiana* **54**: 118–21.

Hilal-Dandan R and Brunton L L. 2014. Pharmacotherapy of inflammation, fever, pain, and gout. *Goodman and Gilman's Manual of Pharmacology and Therapeutics*. McGraw-Hill Companies Inc., USA.

Javier Lopez-Munoz F, Dýiaz-Revalb I, Terronc J A and Camposa M D. 2004. Analysis of the analgesic interactions between ketorolac and tramadol during arthritic nociception in rat. *European Journal of Pharmacology* **484**: 157–65.

Jelinek G A. 2000. Ketorolac versus morphine for severe pain. *British Medical Journal* **321**: 1236–37.

Katz M H. 2006. Bivariate statistics. Study design and statistical analysis, pp. 66–119. Cambridge University Press, New York, USA.

Macario A and Lipman A G. 2001. Ketorolac in the era of cyclo-oxygenase-2 selective nonsteroidal anti-inflammatory drugs: A systematic review of efficacy, side effects, and regulatory issue. *Pain Medicine* **2**: 336–51.

Medina-Santillán R, Reyes-García G, Rocha-González H I and Granados-Soto V. 2004. B vitamins increase the analgesic effect of ketorolac in the formalin test in rat. *Proceedings of the Western Pharmacology Society* **47**: 95–99.

Mousa Y J. 2014. Anaesthetic properties of ketamine in chicks stressed with hydrogen peroxide. *Veterinarni Medicina* **59**: 369–75.

Mousa Y J and Mohammad F K. 2012. The analgesic efficacy of xylazine and dipyrone in hydrogen peroxide–induced oxidative stress in chicks. *Iraqi Journal of Veterinary Sciences* **26**: 69–76.

Mousa Y J and Al-Zubaidy M H I. 2019. Anesthetic efficacy of ketamine, ketamine/tramadol and ketamine/ketorolac in the chicks. *Iranian Journal of Veterinary Research* **20**: 33–38.

O'Hanlon J J, Beers H, Huss B K D and Milligan K R. 1996. A comparison of the effect of intramuscular diclofenac, ketorolac or piroxicam on post-operative pain following laparoscopy. *European Journal of Anaesthesiology* **13**: 404–07.

Ollé F G, Opisso J L, Oferil R F, Sánchez P M, Calatayud M R and Cabré R I. 2000. Ketorolac versus tramadol: comparative study of analgesic efficacy in the postoperative pain in abdominal hysterectomy. *Revista Española de Anestesiologíay Reanimación* **47**: 162–67.

Petrie A and Watson P. 1999. *Statistics for Veterinary and Animal Sciences*, pp. 90–140. Blackwell Science, Oxford, USA.

Plummer D T. 1987. *An Introduction to Practical Biochemistry*. 3rd edn, pp.182–88. McGrew-Hill Co. Inc., New York, USA.

Rai A and Kiran U. 2013. Patient controlled analgesia using

ketorolac prevented respiratory failure in a child after cardiac surgery. *Annals of Cardiac Anaesthesia* **16**: 68–69.

Rainer T H, Jacobs P, Ng Y C, Cheung N K, Tam M, Lam P K W, Wong R and Cocks R A. 2000. Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial. *British Medical Journal* **321**: 1247–51.

Reitman S and Frankel S. 1957. A colorimetric method for the determination of serum glutamic oxaloacetic and glutamic pyruric transaminase. *American Journal of Clinical Pathology* **28**: 56–63.

Resman-Targoff B H. 1990. Ketorolac: a parenteral nonsteroidal anti-inflammatory drug. *Annals of Pharmacotherapy* **24**: 1098–1104.

Runyon R P. 1977. *Non-parametric Statistics: A Contemporary Approach,* pp. 2–217. Addison-Wesley Publishing Co. Reading, Massachusetts, USA.

Shankariah M, Mishra M and Kamath R A. 2012. Tramadol versus ketorolac in the treatment of postoperative pain following maxillofacial surgery. *Journal of Maxillofacial and Oral Surgery* **11**: 264–70.

Smyth E M and Fitz Gerald G A. 2009. The eicosanoids: prostaglandins, thromboxanes, leukotrienes, and related compounds, pp. 313–29. *Basic and Clinical Pharmacology*. McGrew-Hill Co. Inc., New York, USA.

Soleimanpour M, Imani F, Safari S, Sanaie S, Soleimanpour H, Ameli H and Alavian S M. 2016. The role of non-steroidal anti-inflammatory drugs (NSAIDS) in the treatment of patients with hepatic disease: a review article. *Anesthesiology and Pain Medicine* **6**: e37822.

Sondhi S M, Dinodia M, Rani R, Shukla R and Raghubir R. 2009. Synthesis, anti-inflammatory and analgesic activity evaluation of some pyrimidine derivatives. *Indian Journal of Chemistry* **49**: 273–81.

Sufka K J, Roach J T, Chambliss Jr. W G, Broom S L, Feltenstein M W, Wyandt C M and Zeng L. 2001. Anxiolytic properties of botanical extracts in the chick social separation-stress procedure. *Psycopharmacology* **153**: 219–24.

Vargas R, Maneatis T, Bynum L, Peterson C and McMahon F G. 1994. Evaluation of the antipyretic effect of ketorolac, acetaminophen, and placebo in endotoxin induced fever. *Journal of Clinical Pharmacology* **34**: 848–53.