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Research paper

A newly synthetic compound of Ibuprofen and Gabapentin as a novel analgesic and anti-inflammatory therapeutic agent: A pharmacological study in rats' experimental models

Manal Abdulkhaliq Ibrahim[1], Hiba N. Alsaad[2], Ahmed H. Al-Darraji[3]*, Monther F. Mahdi[4]

[1]Department of Pharmacology and Toxicology, University of Basrah, Basrah, Iraq
[2]Department of Pharmaceutical Chemistry, University of Basrah, Iraq
[3]College of Pharmacy, University of Basrah, Basrah, Iraq
[4]College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq
*Email: ahmedhamish313@gmail.com

ABSTRACT

Objective: Inflammation and pain are normally present concomitantly, which requires using a combination of anti-inflammatory and pain killer medications. This could potentially decrease patient adherence to such combinations. Therefore, there is an urgent need to develop combinations of anti-inflammatory and analgesic therapies. This study is designed to evaluate the analgesic and anti-inflammatory activities of a newly synthetic compound of ibuprofen and gabapentin.

Method: The study protocol includes two stages. The first stage: the evaluation of the analgesic effectiveness of tested compounds via using hot plate and acetic acid induced-writhing tests. The second stage: the investigation of the anti-inflammatory activity via using dextran induced- peritonitis, cotton pelt induced- granulomas, and formalin induced- paw edema analyses. Rats were randomly divided into four groups (six rats in each group): Group A (control): rats were orally treated with vehicle (propylene glycol 50 % v/v); Group B: rats were orally treated with ibuprofen (10 mg/ kg); Group C: rats were orally treated with gabapentin (200 mg/ kg); and Group D: rats were orally treated with the synthetic compound (ibuprofen-gabapentin) in dose equivalent to 10 mg/ kg ibuprofen and 200 mg/kg gabapentin.

Result: It was found that the newly synthesized compound of ibuprofen and gabapentin has significantly reduced the pain in comparison with control groups. Additionally, this compound has significant anti-inflammatory properties compared to medications admitted to the control group as well.

Conclusion: The newly synthesized compound (ibuprofen-gabapentin) demonstrates remarkable analgesic and anti-inflammatory activities in comparison with the conventional compounds.

Keywords: anti-inflammatory, gabapentin, ibuprofen, novel ibuprofen and gabapentin compound, analgesic

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INTRODUCTION

Ibuprofen is an archetype of non-steroidal anti-inflammatory drugs (NSAIDs) derived from propionic acid. It has antipyretic, analgesic, and anti-inflammatory properties. Ibuprofen is effectively used to manage moderate to severe inflammatory conditions such as rheumatoid arthritis and osteoarthritis. It is preferentially prescribed when the anti-inflammatory and painkiller effects are needed[1].

Gabapentin is a derivative of cyclohexane acetic acid. It has a chemical formula similar to γ-aminobutyric acid (GABA). Gabapentin was introduced to the markets in 1994 as an antiepileptic drug for partial seizures. Despite the fact that gabapentin is structurally related to the GABA neurotransmitter, there is no conclusive documentation yet that demonstrates that gabapentin prevents GABA uptake or metabolism, has GABA-analogue action, or attaches to GABAA/GABAB receptors[2]. In animal experimental models of thermal allodynia and over analgesic effect, it has been revealed that gabapentin possesses a potent pain management effect[3]. These effects include: decrease in tactile hypersensitivity and mechanical/cold hypersensitivity due to spinal cord compression or due to paclitaxel- and vincristine-administration[4]; attenuation of the second phase of nociceptive responses in formalin test[5]; attenuation of mechanical hypersensitivity induced by capsaicin[6]; and reduction in mechanical hypersensitivity in a model of varicella zoster virus-associated hypersensitivity[7].

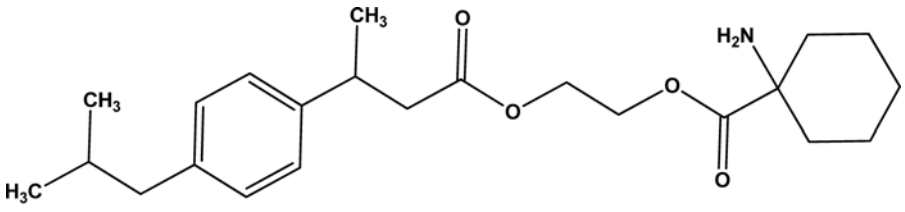
In humans, gabapentin has become a popular medication for chronic neuropathic pain. Clinical research has shown that gabapentin is an effectual analgesic for different types of neuropathic conditions such as diabetic mellitus[8], postherpetic neuralgia[9], trigeminal neuralgia[10], neuropathy pain caused by human immunodeficiency virus[11], pain due to malignancy[12], fibromyalgia[13], pain following burn injuries[14], and complex regional pain syndromes[15]. Although the fact that the exact molecular mechanism of action by which gabapentin alleviates pain is not yet known, evidence suggests that α2δ1 auxiliary subunit of voltage-gated calcium channels may be important for gabapentin activity[16]. Moreover, research indicates that gabapentin has gastric protective effects. Acute gastric mucosal irritation in rats induced by indomethacin is decreased as a result of concomitant administration of gabapentin. in addition, the drug raises gastric acid discharge in pylorus-part of colon[17].

Many patients with inflammatory diseases also suffer from chronic pain[8-12]. Such patients are treated with polytherapy, which could potentially cause poor patient adherence. As such, there is an urgent need to find strategies that enhance the rate of adherence for this category of patients. Using combined preparations is an effective way to improve the rate of adherence. Therefore, the aim of this study is to investigate the pharmacological activity of a newly synthetic compound composed of a combination of ibuprofen and gabapentin. It is expected that such compound possesses both anti-inflammatory and analgesic activities. It was previously prepared by other groups of researchers via using specific and subsequent chemical reactions[18] (Scheme 1).

EXPERIMENTAL

General

Ibuprofen (*Bristel, UK*) was dissolved in propylene glycol 50% v/v to produce a stock solution of 2 mg/ml. This solution was used to give 10 mg/Kg of ibuprofen to the rats. Gabapentin (*actavis, UK)* was dissolved in propylene glycol 50% v/v to prepare a stock solution of 50 mg/ml. This solution was used to administer 200 mg/ Kg of the drug to the rats. These doses of ibuprofen and gabapentin are comparable to the commonly prescribed human dose and are effective in producing adequate distribution and tissue accumulation in animals[19, 20]. Gabapentin and ibuprofen were dissolved together in propylene glycol 50 % v/v to produce a stock solution of 50 and 10 mg/ mL; respectively.



2-((3-(4-isobutylphenyl)butanoyl)oxy)ethyl 1-aminocyclohexanecarboxylate

Scheme 1. Compound structure according to its references [18].

Then, doses were adjusted according to the body weight. *Sprague–Dawley* rats (180–220 g) of both genders were used in this work. They were kept at the animal house of Pharmacology and Toxicology Department, College of Pharmacy, University of Basra. Rats were feed standard pellet diet (25 ± 2 °C), and food was withdrawn 12 hours (hr) before the experiments, but water was let on *ad libitum*. All procedures were conducted under the approval of the University of Basra ethical instructions and instructions of laboratory animal's care (approval number: 2/1 in 1/3/2019). Rats were randomly divided into four groups (six rats in each group): **Group A** (control): rats were orally treated with vehicle (propylene glycol 50% vol/vol); **Group B**: rats were orally treated with ibuprofen (10 mg/ kg); **Group C**: rats were orally treated with gabapentin (200 mg/kg); **Group D**: rats were orally treated with the synthetic compound (ibuprofen-gabapentin) in dose equivalent to 10 mg/kg of ibuprofen and 200 mg/kg of gabapentin. A blinded investigator performed experimentation and analysis.

Analgesic tests

These tests are usually used to estimate the pain associated with inflammation. Pain is a net result of multiple complicated processes that comprise of central and peripheral nervous systems activity. Drugs that have anti-inflammatory effect are likely to possess analgesic properties. In this study, the peripheral analgesic effect was evaluated by the acetic-acid-induced writhing response. While the central analgesic effect was estimated by the hot plate assay.

Hot plate test

This test is used to examine centrally acting analgesics. These medications cause increase in duration times of response (jumping, withdrawal paws, and licking paws). The test was conducted by using an electronica hotplate (*Ugo Basile, Comerio, Italy)* that is heated to 53°C ± 0.1, as previously described[21]. Rats were put freely alone over the hot plate for baseline determination prior to propylene glycol 50% vol/vol or other treatments. The reaction time to the thermal stimulus was determined as the time duration between putting the animal over the hot plate and licking paw or jumping. This interval was calculated prior to the administration of all treatments (0 minutes (min)). The reaction time was measured also at 30 and 60 min after treatments. Cut-off time to the thermal stimulus was adjusted to 30 seconds to prevent tissue damage.

Acetic acid-induced writhing

After 60 min of treatments administration, rats were received intraperitoneal injection of 0.5 mL acetic acid (80%, v/v). The number of abdominal constrictions over 30 min following acetic acid injection was calculated for all groups of treatments and writhes number was determined[22].

Anti-inflammatory activity test

Dextran-induced peritonitis

Dextran motivated peritonitis was used to assess the anti-inflammatory action of all four treatments via using fluid extravasation and leukocyte immigration. Rats in each group were treated according to the protocol. After one hour, peritonitis was induced by using intraperitoneal injection of 100 mcg dextran, dissolved in 0.2 M physiologic solution 0.9%[23]. Then, after 4 hr of peritonitis induction, rats were sacrificed, and peritoneal fluid was collected for leukocyte analysis. The collected suspension was harvested and centrifuged x 2000 g for 10 min. Then, leukocytes were collected and resuspended in 2 mL of phosphate-buffered saline (PBS). After that, suspension was diluted to 1:20 to be ready for white blood cell counting via using *CELL-DYN RUBY* (automatically hematology analyzer, USA).

Cotton pellet granuloma

The anti-inflammatory activity of all treatments was estimated by using cotton pellet granuloma model[24]. Cotton pellets (10 ± 1 mg) were sterilized in an autoclave at 120 °C under 15 lb pressure for 30 min. Four pellets were placed subcutaneously into ventral region, two on each side under light ether anesthesia. Rats from each group were treated daily for seven days after cotton pellet insertion. Then, rats were anesthetized on day 8 and pellets with granuloma tissues were excised and was freed from connected tissues. The wet pellets were exsiccated in an incubator at 60°C for 18 hr until their weight became constant and their weight was determined again. The formation of granulation tissues (dry weight of granuloma) was determined by dedication of cotton pellet weight (10 mg) from the constant dry pellet weight.

Formalin-induced paw edema

min after treatment, inflammation was induced by sub planter injection (0.1 mL) of freshly prepared formalin (1% w/v) in the right hind paw of rats. Before formalin injection, the paw thickness of each paw was determined by using a digital calibrated Vernier caliper. Edema that was caused by formalin was measured at 0, 1, 2 and 3 hr. Increment in paw thickness induced by inflammation was calculated and compared with control groups according to the previously prescribed method[25].

STATISTICAL ASSAY

Data are expressed as mean ± standard error of mean (SEM). We used LSD and one-way analysis of variance (ANOVA) to estimate differences. Throughout the analyses "P- value", a value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS inversion for Windows.

RESULT

Ibuprofen-gabapentin has a rapid and potent analgesic activity

Since both ibuprofen and gabapentin have analgesic actions, it is important to determine whether the newly synthetic compound (ibuprofen-gabapentin) has similar characteristics to the parent drugs. We used hot plate test for this purpose and observed that there is no difference in the hot plate reaction time among groups of treatments at baseline (0 min) (Table 1 and Figure 1). However, we noticed that there is a significant increase ($p < 0.05$) in the hot plat reaction of the group treated with ibuprofen-gabapentin in comparison with the control group after 30 min. Interestingly, we never saw a similar effect induced by each treatment alone, ibuprofen and gabapentin, compared to controls (Table 1 and Figure 1). We also found that the reaction time in the newly synthetic compound group is

Table 1. Anti-nociceptive activity of ibuprofen, gabapentin and newly synthetic compound of ibuprofen and gabapentin in hot plate test in rats.

Latencies for nociceptive reaction after different time (sec)	Time (min)	Treatment group			
		Control (1 ml)	Ibuprofen (10 mg/kg)	Gabapentin (200 mg/kg)	Gabapentin + Ibuprofen (10,200 mg/kg)
	0	11 ± 0.428	11 ± 0.730	11.7 ± 0.505	11.4 ± 0.735
	30	12.1 ± 0.527	14 ± 0.930	15 ± 0.577	17.1 ± 0.945*[a]
	60	12.4 ± 0.663	15.8 ± 0.872*	15.6 ± 0.493*	17.6 ± 0.954*

Each value represents the mean ± standard error of means (SEM).
- * = Significantly different ($P < 0.05$) concerning the control group.
- Values with symbol superscript (a) are significantly different ($P < 0.05$) using unpaired Student t-test concerning group II.

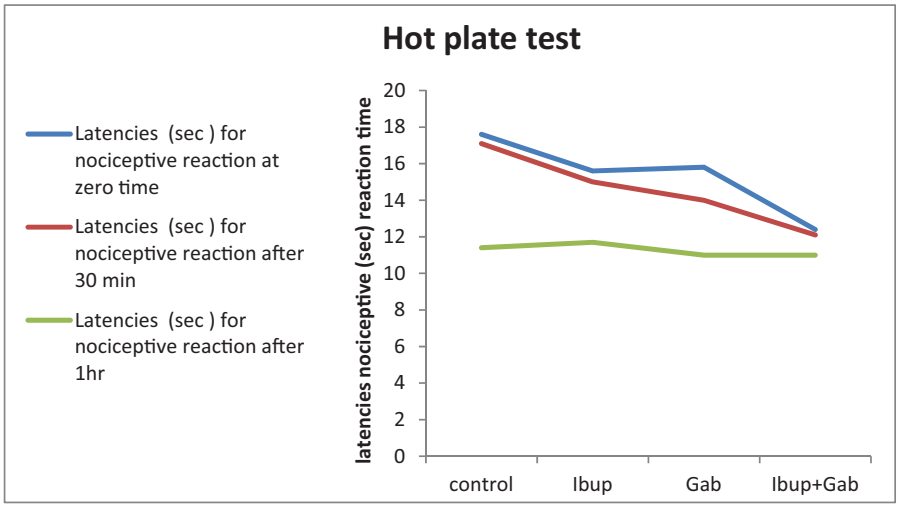


Figure 1. Bar chart showing Anti-nociceptive activity of ibuprofen (10 mg/ kg), gabapentin (200mg/ kg) and newly synthetic compound of ibuprofen and gabapentin (10,200mg/ kg) in hot plate test in rats.

significantly different ($p < 0.05$) from that of the group that was treated with ibuprofen only (Table 1 and Figure 1). After 60 min, the reaction time in the ibuprofen-gabapentin group remained significantly different ($p < 0.05$) from the control group which proved it to be more powerful than other treatments (Table 1 and Figure 1). Taken together, these data suggest that the newly synthetic compound (ibuprofen-gabapentin) has a more rapid onset of action and more potent analgesic effect in comparison with the controls.

4.2 Ibuprofen-gabapentin remarkably reduces the number of writhes

In order to demonstrate the analgesic activity of the newly synthetic compound (ibuprofen-gabapentin), acetic acid-induced writhing assay was performed in addition to the hot plate test (above). It was found that the number of writhes on acetic acid-induced abdominal writhing in rats treated with the newly synthesized compound (ibuprofen-gabapentin) has significantly reduced ($p < 0.05$) compared to rats treated with vehicle (Table 2 and Figure 2). Importantly, there was a significant decline in the number of writhes ($p > 0.05$) in ibuprofen-gabapentin treated group in comparison with the group that received ibuprofen only (Table 2 and Figure 2). These data also support that ibuprofen-gabapentin combined formula synergizes the analgesic effects of each compound alone with more powerful and rapid onset of action.

Ibuprofen-gabapentin has a potent anti-inflammatory activity

Ibuprofen is well known to exhibit anti-inflammatory in addition to its analgesic and antipyretic effects[1]. Gabapentin could have an anti-inflammatory activity as well[8-17]. Therefore, the anti-inflammatory effectiveness of the newly formulated compound (ibuprofen-gabapentin) via using dextran-induced peritonitis was examined. It was noted that there was a significant reduction ($p < 0.05$) in white blood cell (WBC) counts with ibuprofen-gabapentin treatment in comparison with controls (Table 3 and Figure 3). Moreover, the WBC counts were significantly different ($p < 0.05$) in rats that have received ibuprofen-gabapentin from those that only received gabapentin (Table 3 and Figure 3). However, no remarkable differences between ibuprofen-gabapentin and ibuprofen only treated groups was

Table 2. The effect of ibuprofen, gabapentin, and newly synthetic compound of ibuprofen with gabapentin on the number of writhes in acetic acid test in rats.

Treatment group	Mean number of abdominal constriction /30 min
Control	69.1 ± 3.4
Ibuprofen (10 mg/ kg)	55 ± 2.8*
Gabapentin (200 mg/ kg)	47.5 ± 3*
Gabapentin + Ibuprofen (10,200 mg/ kg)	36.6 ± 2.7*[a]

Each value represents the mean ± standard error of means (SEM).
- * = Significantly different ($P < 0.05$) concerning the control group.
- Values with symbol superscript (a) are significantly different ($P < 0.05$) using unpaired Student t-test concerning group II.

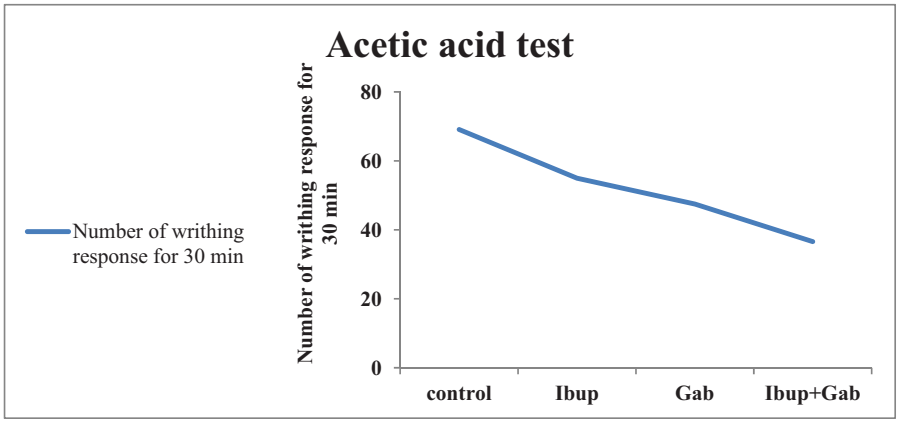


Figure 2. Bar chart showing Effect of ibuprofen (10 mg/kg), gabapentin (200 mg/ kg), and newly synthetic compound of ibuprofen and gabapentin (10,200 mg/ kg) on number of writhes in acetic acid test in rats.

Table 3. The effect of ibuprofen, gabapentin, and newly synthetic compound of ibuprofen with gabapentin on white blood cell by dextran induced peritonitis test in rats.

Treatment group	Mean WBC X10^3/μL by dextran induced peritonitis
Control	0.474 ± 0.026
Ibuprofen(10 mg/kg)	0.344 ± 0.013*
Gabapentin(200 mg/kg)	0.366 ± 0.005*
Gabapentin + Ibuprofen (10,200 mg/kg)	0.284 ± 0.004*[b]

Each value represents the mean ± standard error of means (SEM).
- * = Significantly different ($P < 0.05$) concerning the control group.
- Values with symbol superscript (b) are significantly different ($P < 0.05$) using unpaired Student t-test concerning group III.

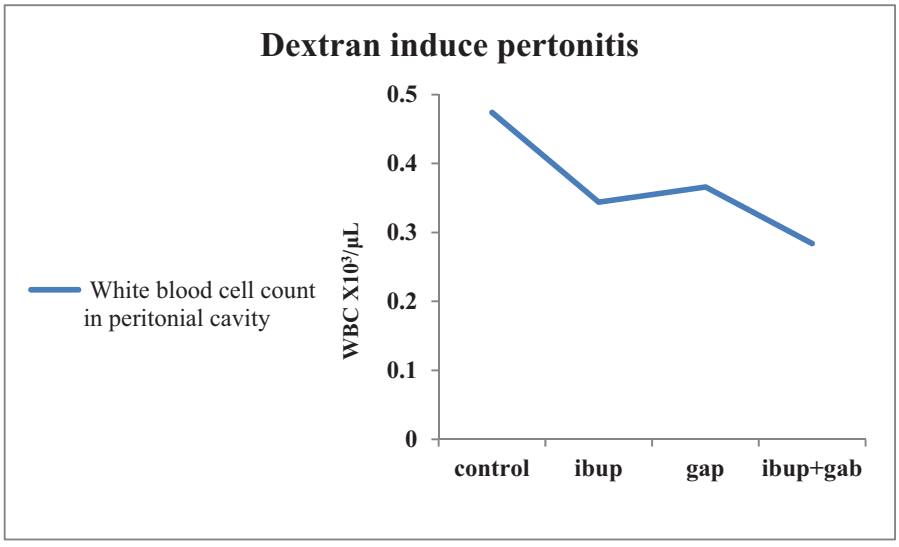


Figure 3. Bar chart showing Effect of ibuprofen (200 mg/kg), gabapentin (10,200 mg/ kg), and newly synthetic compound of ibuprofen with gabapentin on white blood cell by dextran induced peritonitis test in rats.

observed (Table 3 and Figure 3). Moreover, a cotton-pellet granuloma test was performed. It was noticed that there was a significant decline ($p < 0.05$) in the inflammatory exudates with ibuprofen-gabapentin treatment compared to the vehicle treatment (Table 4 and Figure 4). Collectively, these findings imply that the newly formulated compound (ibuprofen-gabapentin) has a potent anti-inflammatory activity, which can be harnessed to reduce the complications of many inflammatory pathologies.

Ibuprofen-gabapentin reduces inflammatory edema

To confirm the anti-inflammatory effects of the newly synthesized compound (ibuprofen-gabapentin), a formalin-induced paw edema assay was performed. The paw thickness was measured at 0, 1 hr, 2 hr

Table 4. The effect of ibuprofen, gabapentin, and newly synthetic compound of ibuprofen with gabapentin on exudate weight by cotton pellet induced granuloma test in rats.

Treatment group	Mean exudate weight (mg) by cotton pellet induced granuloma
Control	100.4 ± 5.9
Ibuprofen (10 mg/ kg)	83.3 ± 3.7*
Gabapentin (200 mg/ kg)	83.6 ± 6*
Gabapentin + Ibuprofen (10,200 mg/kg)	80.4 ± 4.8*

Each value represents the mean ± standard error of means (SEM).
- * = Significantly different ($P < 0.05$) concerning the control group.

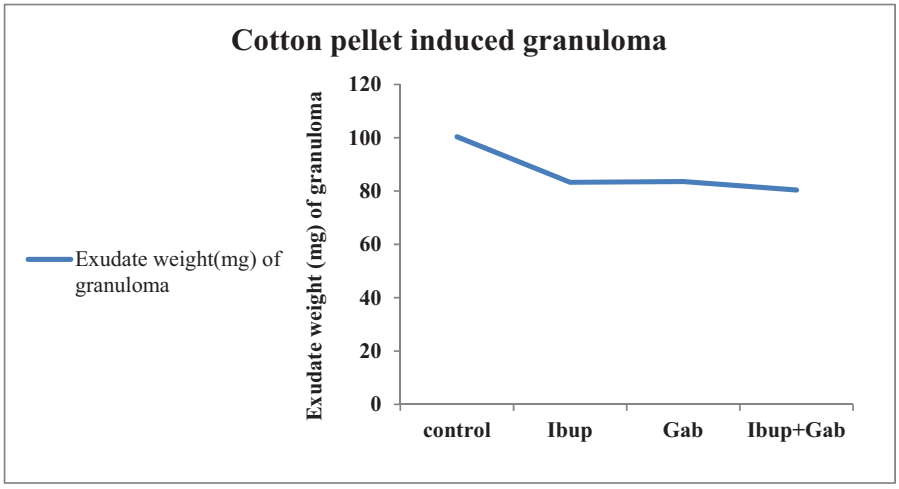


Figure 4. Bar chart showing Effect of ibuprofen (10mg/kg), gabapentin (200 mg/kg), and newly synthetic compound of ibuprofen with gabapentin (10,200 mg/kg) on exudate weight(mg) of granuloma in cotton pellet test in rats.

and 3 hr after formalin treatment. In the first three time points, there was profound reduction in the paw thickness among the groups of treatments (Table 5 and Figure 5). Nevertheless, it was observed that after 3 hr, the paw thickness was significantly reduced ($p < 0.05$) with ibuprofen-gabapentin treatment in comparison with the control group (Table 5 and Figure 5). Interestingly, it was also found that there was a significant reduction ($p > 0.05$) in paw thickness in rats that received ibuprofen-gabapentin compared to the rats that received gabapentin only (Table 5 and Figure 5). These findings represent a supporting piece of information that demonstrates a momentous anti-inflammatory effectiveness of the newly synthesized compound (ibuprofen-gabapentin).

DISCUSSION

Inflammation is always linked to pain, which requires prescribing multiple medications to the patients. This practice profoundly decreases the patient's adherence to their prescriptions. Using combined formulations is an attractive solution to minimize patient's non-adherence. In this work, the analgesic and anti-inflammatory effectiveness of a newly synthetic compound composed of ibuprofen and gabapentin was investigated. It was found that ibuprofen-gabapentin exerts analgesic and anti-inflammatory activities, as demonstrated by pain and inflammation models in rats. Our data show that ibuprofen-gabapentin has a more rapid onset of action and more powerful analgesic effect in comparison with traditional pain killers, as evidenced by hot plate and acetic acid-induced writhing tests. On the other hand, the anti-inflammatory efficacy of the new compound was also demonstrated in inflammatory models such as formalin-induced paw edema, cotton pellet granuloma, and dextran-induced peritonitis. Taken together, ibuprofen-gabapentin combined formulation represents a novel and clinically available target for reducing pain and inflammation in various inflammatory pathologies.

Table 5. The effect of ibuprofen, gabapentin, and newly synthetic compound of ibuprofen with gabapentin on paw thickness in formaldehyde test in rats.

Paw thickness (mm) after formalin injection	Time	Treatment group			
		Control	Ibuprofen (10 mg/kg)	Gabapentin (200 mg/kg)	Gabapentin + Ibuprofen (10,200 mg/kg)
	0	4.8 ± 0.243	4.5 ± 0.235	4.7 ± 0.203	4.3 ± 0.198
	1hr	5.3 ± 0.321	4.1 ± 0.264	4.2 ± 0.203	4 ± 0.340
	2hr	5.7 ± 0.381	3.5 ± 0.173	4 ± 0.298	3.8 ± 0.310
	3hr	6.3 ± 0.508	3.2 ± 0.193*[b]	4.2 ± 0.289*[a]	3 ± 0.222*[b]

Each value represents the mean ± standard error of means (SEM).
- * = Significantly different ($P < 0.05$) concerning the control group.
- Values with symbol superscript (a) are significantly different ($P < 0.05$) using unpaired Student t-test concerning group II.
- Values with symbol superscript (b) are significantly different ($P < 0.05$) using unpaired Student t-test concerning group III.

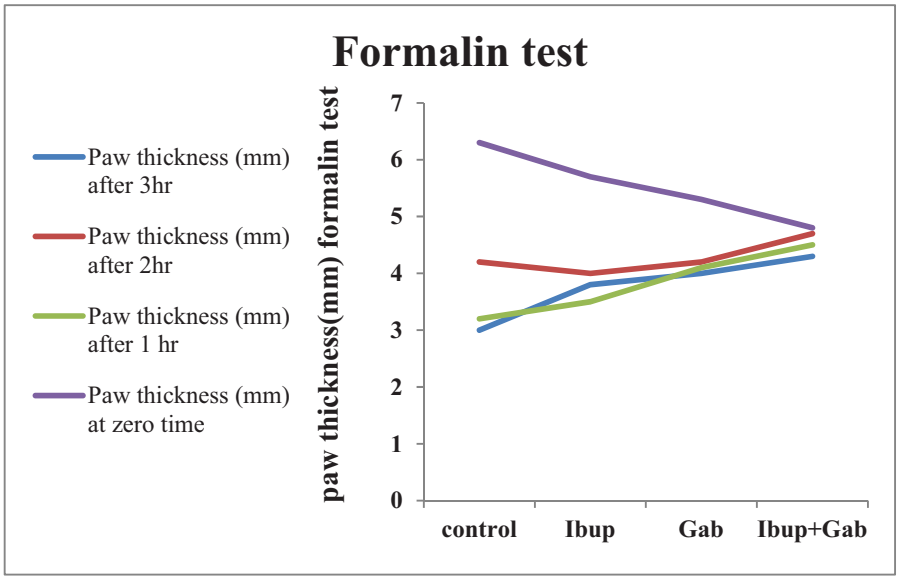


Figure 5. Bar chart showing Effect of ibuprofen (10 mg/kg), gabapentin (200 mg/kg), and newly synthetic compound of ibuprofen with gabapentin (10,200 mg/ kg) on paw thickness in formaldehyde test in rats.

The pharmacological activity of the newly synthesized compound (ibuprofen-gabapentin) is most likely related to the effect of parent drugs, ibuprofen and gabapentin. Previous research has demonstrated that this newly synthetic compound is hydrolyzed to the parent compounds, ibuprofen and gabapentin[18]. Apparently, the hydrolysis happens in the blood stream, not gastrointestinal tract, which provides a protective mechanism against the gastrointestinal adverse effects that could be produced by ibuprofen and gabapentin. Moreover, this compound is less likely to induce gastritis due to the blockage of hydroxyl groups in the parent compounds, as previously shown[18].

It is known that ibuprofen has a marked analgesic activity in different painful pathologies such as hyperalgesia[26] and rheumatoid arthritis[27]. Ibuprofen exerts its pharmacological action through inhibition the activity of COX-2 isoenzyme and the generation of prostaglandins (PGs), mainly PGE2, like other NSAIDs[28]. On the other hand, the painkiller mechanism of gabapentin is not entirely clear. However, evidence suggests that voltage-gated calcium channels ($\alpha 2\delta 1$ auxilliary subunit) could be essential for gabapentin actions[29], with minor or absent effect on acute prevention of calcium currents[30]. The analgesic effect of gabapentin is probably due to inhibition substance P, calcitonin gene-related peptide (CGRP)[28-31], and glutamate[32]. Evidence also shows that analgesic and antiallodynic activities of gabapentin are primarily mediated by activation of spinal $\alpha 2$-adrenergic receptor[33]. Here, the newly synthetic compound of ibuprofen and gabapentin exhibits was shown to have more powerful analgesic actions than the parent compounds (Table 1 and 2; Figure 1 and 2).

It is a well-established fact that increment of membrane phospholipase activity and production of pain/inflammatory mediators is promoted by acetic acid. Therefore, protection against acetic acid effect is an indicator of blockage pain mediators[31,34]. On the other hand, tail-flick response is used to investigate the neuronal action of opioid and other centrally acting painkillers. Although thermal stimuli are used in both assays, the tail-flick response is mainly used for spinal reflex[32-35]. In this work, the analgesic effect of the newly synthetic compound (ibuprofen-gabapentin) by both hot plate and acetic acid induce writhing tests was examined. Our results indicate that ibuprofen-gabapentin has a very potent analgesic action in comparison with controls, including ibuprofen and gabapentin. Moreover, it was observed, in both tests, that this compound is more efficacious than ibuprofen in reducing pain at certain time points (please see results section). It is possible that ibuprofen-gabapentin was able to suppress pain through inhibition central reflexes and peripheral mediators, which needs more investigations in the upcoming studies.

Inflammation is a complicated process that involves multiple mediators and cellular players. It has been noticed that ibuprofen exerts its anti-inflammatory effects through regulation of various inflammatory pathways in both acute and chronic inflammation[27]. These effects are not only explaining the drug anti-inflammatory activity, but also its hyper painkiller activity[34]. Gabapentin is thought to act

at supraspinal and intraspinal sites via inducing antinociceptive responses[36]. It has been suggested that Gabapentin modifies brain c-Fos expression in surgical paw incision and weakens acute morphine-induced c-Fos expression in the rat striatum[37]. Stimulation of brain areas, involved in nociceptive process, implies a supraspinal site of action for gabapentin[38]. Research shows also that gabapentin reduces the inflammatory edematogenic response to subplantar carrageenan injection. Gabapentin at high doses is unlikely to interfere with the anti-inflammatory actions of NSAIDs e.g., indomethacin[17].

Formalin and cotton pellet-induced inflammation assays have a similar pathophysiology to what takes place during inflammation. These animal models are standard to evaluate the activity of a predicted anti-inflammatory therapy[39]. Multiple cellular reactions are triggered by the inflammatory response in the injured area, which results in releasing pro-inflammatory cytokines such as TNF-a, interleukin (IL)-1b, IL-6, IL8, and other inflammatory mediators[40]. Prostaglandins, like PGE1 and PGE2, are also induced by inflammation in the injured tissues. These mediators work through several mechanisms, leading to raise local blood stream and enhance the activity of other endogenous compounds such as bradykinin, which motivates vasopermeability [41].

In this work, it was found that the newly synthetic compound (ibuprofen-gabapentin) is a potent anti-inflammatory therapy, and is even more potent than ibuprofen and gabapentin (Table 3, 4 and 5; Figure 3,4 and 5), as evidenced with formalin and dextran-induced inflammation assays. Additionally, with cotton pellet granuloma model, it was noted that ibuprofen-gabapentin causes dramatic decrease in paw thickness compared to control and indeed more than that of gabapentin alone after 3 hrs of inflammation induction. This compound was also very efficacious in reducing the weight of exudate in granuloma model, suggesting a less recruitment of the inflammatory mediators to the injured zone. This remarkable anti-inflammatory effect is very likely related to multiple mechanisms. More studies are needed to provide a comprehensive examination of the effect of ibuprofen-gabapentin on the various inflammatory pathways.

In conclusion, poor drug tolerability is a common issue in clinical practices, especially for patients with multiple medications prescription. Patients with inflammatory and pain are commonly experiencing this phenomenon. Using combined formulations could represent an attractive strategy to solve such a dilemma. This study is the first to introduce a newly synthetic compound (ibuprofen-gabapentin) that exerts a potent analgesic and anti-inflammatory activity and indeed more than that of parent drugs. Our data demonstrate that this has a more rapid onset of action and more potent analgesic activity in comparison with the parent drugs. Additionally, this work indicates that this compound has a potent anti-inflammatory activity, which can be harnessed to reduce the complications of many inflammatory pathologies. Our prepared compound could represent as an ideal option for patients with poor adherence due to polytherapy for pain and inflammation.

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Competing interests

There are no competing interests to declare.

Author contributions

Manal performed the experiments and data analysis; explicate the results; plotted the gures; wrote the manuscript; edited and revised the manuscript; as well as contributed to the study conception and design. Manal approved the nal version of the manuscript. Hiba and Monther participated in chemical perpetration of newly synthesized gabapentin and ibuprofen. Ahmed re-wrote the manuscript according to the reviewer's recommendations.

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