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Pregabalin potentiates the analgesic effect of tramadol, diclofenac and paracetamol in chicks: Isobolographic analysis

Q.M. Bashar and Y.M. Albadrany

Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

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Correspondence:
Y.M. Albadrany
yasseralbadrany@yahoo.com

Abstract

The study aimed to reveal pregabalin's median effective analgesic dose (ED_{50}) and determine the type of analgesic interaction with tramadol, diclofenac, and paracetamol in chicks. The electrical stimulator device was used to detect pain before and after treatment, and through ascending and descending in doses and depending on the up and down method, the median effective analgesic doses were determined for all drugs used in the study, and then the interaction experiment was conducted at a fixed ratio 0.5:0.5 of pregabalin with each of tramadol, diclofenac and paracetamol of their individual ED_{50} values, the results were subjected to the isobolographic analysis to determine the type of interaction. Results showed that ED_{50s} for pregabalin, tramadol, diclofenac, and paracetamol in chicks were 156.5, 0.82, 5.65, and 10.74 mg/kg, respectively. Concomitant administration of drugs pregabalin: tramadol, pregabalin: diclofenac and pregabalin: paracetamol at a fixed ratio 0.5:0.5 of their individual ED_{50} values reduced their ED_{50s} to 36.2:0.18, 64.3:2.3 and 64.3:4.3 mg/kg respectively. Isobolographic analysis showed synergistic analgesic effects of both drugs interaction. The calculated interaction indexes were 0.45, 0.81, and 0.81, respectively. We conclude from the outcomes that the analgesic interaction was synergistic between pregabalin and tramadol significantly, while the analgesic interaction of pregabalin with both diclofenac and paracetamol was also synergistic, but to a lesser extent.

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Introduction

Adjuvant analgesics are a group of medications initially designed for a purpose other than pain relief. Many of these drugs are currently utilized to improve analgesia in specific situations. One of the cornerstones to good pain management is the proper use of adjuvant medications (1). In recent years, multimodal analgesia strategies have been proposed, combining additive and synergistic effects of different analgesics with fewer side effects and more effective capabilities (2). Multimodal analgesia is achieved by combining multiple analgesics that act on the nervous system through distinct processes and at different places, resulting in additive or synergistic analgesia (3). Pregabalin is a gamma-aminobutyric acid structural analog with a better pharmacodynamic and pharmacokinetic profile. Peripheral neuropathic pain, postherpetic neuralgia, partial seizures, and generalized anxiety disorder can all be treated with it (4). Pregabalin binding to the presynaptic alpha-2-delta (α2-δ) subunits of the voltage-activated calcium channels is significant and necessary for analgesic and anti-epileptic activities, affecting neurological pain reduction be explained by its anticonvulsant modes of action (5). Tramadol is a potent analgesic commonly used to treat moderate to severe pain. It is characterized as an atypical opioid with a low potency. Tramadol inhibits serotonin and norepinephrine reuptake in addition to activating the opioid receptor. Tramadol, unlike morphine, does not cause significant

respiratory depression and has a low risk of abuse and addiction (6). The phenylacetic acid derivative diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that treats pain and inflammation. It is commonly taken as a sodium salt. It is easily absorbed orally, rectally, and intramuscularly, and these are the primary routes of systemic delivery. NSAIDs' analgesic and anti-inflammatory effects are primarily due to cyclo-oxygenase inhibition; however, reduced leukotriene and arachidonic acid synthesis may also play a role. NSAIDs also have a central antinociceptive effect, albeit an unknown mechanism (7). Paracetamol does not appear to have the same ability to inhibit peripheral cyclo-oxygenase (COX) activity as non-steroidal anti-inflammatory medications. Currently, there is much evidence to back up the idea of a central antinociceptive impact. Although several biochemical studies suggest that central COX-2 activity is inhibited, the existence of a COX activity that is selectively responsive to paracetamol remains a mystery (8).

The study aimed to explore the analgesic effects of pregabalin on acute pain in chicks, as well as the possibility of pregabalin in activating the analgesic effect of tramadol (potent analgesic), diclofenac (moderate analgesic), and paracetamol (weak analgesic).

Materials and methods

Ethical approval

The birds were handled as directed by the College of Veterinary Medicine's animal ethics committee. The study's protocol (no.1396) was evaluated and approved by the Scientific Committee of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Mosul.

Animals

Ross broiler chicks of both sexes were obtained from the Bashiqa hatchery. The one-day-old chicks were reared in cages (dimensions: 107 x 64 x 50 cm) under standard conditions of temperature (32-35°C), ventilation, lighting (23 hours of light / 1 hour of darkness). Water and feed were given *ad libitum*. The experiments were conducted on them at 7-15 days.

Drugs

Pregabalin was a gift from Pioneer Pharmaceutical Company, Iraq. Tramadol hydrochloride (Trabilin™ 100mg/2ml), acino, Switzerland. Diclofenac sodium (CLOFEN® 75mg/3ml), Gulf Pharmaceutical Industries, United Arab Emirates. Paracetamol (Paracetamol NORMON® 10mg/ml), NORMON, Spain. All drugs were diluted with normal physiological saline to obtain the required concentrations. Pregabalin was administered orally, while Tramadol, Diclofenac, and Paracetamol were administered intraperitoneally.

Determination of the median effective analgesic doses (ED_{50s}) for pregabalin, tramadol, diclofenac, and paracetamol in chicks using an electro-stimulator device by adopting the up and down method.

An electro-stimulator device was used (SRI, Scientific and Research Instruments Ltd, UK) to stimulate the pain. The device was adjusted to suit the conditions of the current experiment, considering that the highest voltage was ten volts, and the width of the electrical pulse was five milliseconds. The degree of frequency was 50 Hz with continuous electrical current. Electrodes connected to the device were put on the chick's skin in the free-feather region under the wing (this region is more sensitive to the electrical stimulus generated by the stimulus device). The skin was moistened with physiological saline to facilitate the passage of electric current through the skin. The responses to the pain induced by the device were recorded before and after administration of the drugs (The chick's response to pain after electric stimulation was revealed as wing jiggling (9).

In the beginning, the voltage that led to response as a result of pain was determined for each chick before treatment, and the dose of the drug was adopted as the initial dose. Analgesia or failure one hour after the treatment was also recorded. To determine the final result, the analgesia was symbolized by X, or lack of analgesia was symbolized by O, and by repeating this method up and down for three chicks after the change (the change is the occurrence to non-occurrence of analgesia or vice versa) and the result was compared with the table of measuring the median analgesic effective dose with the use of the law of the method (10) (11) for obtaining the median effective dose; ED50=Xf + Kd. Xf: The last dose used in the experiment. K: tabular value. d: The constant increase or decrease in the given dose.

Determination of the type of analgesic interaction between pregabalin and each of tramadol, diclofenac and paracetamol

The median analgesic effective doses of the drugs used were determined based on previous experiments. Pain-inducing voltage was determined for each chick before the treatment. Then the first chick was treated with pregabalin (*p.o.*), tramadol (*i.p.*), diclofenac (*i.p.*), and paracetamol (*i.p.*) at a ratio of 0.5:0.5 of the median analgesic effective dose of each drug alone in three different treatments. The same chick was re-stimulated by electro-stimulators an hour after treatment to measure the pain-inducing voltages and record the final result, represented by analgesia or lack of analgesia from the pain. The decrease or increase in the doses was in a fixed percentage and represented a quarter of the first dose. Finally, according to the law as in the previous experiments, the median effective analgesic dose for both drugs was determined. To find out the type of drug interaction between the two drugs, isobolographic analysis (12) was used, and to confirm the result, the Interaction Index

equation (13) was applied; Y=da/Da+db/Db. Da: ED_{50} for pregabalin alone. Db: ED_{50} for tramadol or diclofenac or paracetamol alone. da, db: ED_{50} for both drugs when given together. The value of ED50 was obtained for each drug alone or when giving the two drugs together by up and down method (calculating the value of ED50), so if the value of Y; Y = 1 There is no interaction between the two drugs (Additive). Y < 1, the interaction between the two drugs is synergistic. Y > 1 the interaction between the two drugs is antagonism.

Results

The ED_{50s} for pregabalin (*p.o.*), tramadol (*i.p.*), diclofenac (*i.p.*) and paracetamol (*i.p.*) administered alone for induction of analgesia in chicks were 156.5 mg/kg (Table 1), 0.82 mg/kg (Table 2), 5.65 mg/kg (Table 3) and 10.74 mg/kg (Table 4) respectively. Isobolographic analysis of the ED_{50s} for pregabalin and tramadol administered concomitantly for induction of analgesia in chicks at a fixed ratio (0.5:0.5) of their individual ED_{50} values were 36.2 mg/kg, and 0.18 mg/kg (Figure 1), the percentage of decrease in the ED_{50s} were 53.84% and 55% respectively, the calculated interaction index was 0.45 (Table 5). Isobolographic analysis of the ED_{50s} for pregabalin and diclofenac administered concomitantly for induction of analgesia in chicks at a fixed ratio (0.5:0.5) of their individual ED_{50} values were 64.3 mg/kg and 2.3 mg/kg (Figure 2), the percentage of decrease in the ED_{50s} were 17.5% and 17.8% respectively, the calculated interaction index was 0.81 (Table 6). Isobolographic analysis ED_{50s} for pregabalin and paracetamol administered concomitantly for induction of analgesia in chicks at a fixed ratio (0.5:0.5) of their individual ED_{50} values were 64.3 mg/kg and 4.3 mg/kg (Figure 3), the percentage of decrease in the ED_{50s} were 17.5% and 18.8% respectively, the calculated interaction index was 0.81 (Table 7).

Table 1: Median effective dose (ED_{50}) of Pregabalin in chicks by the up-and-down method after 60 min

Variable	Result
ED_{50} (mg/kg) (*p.o.*)	156.5
Doses range (mg/kg)	150-200
Early dose (mg/kg)	200
Latest dose (mg/kg)	175
Increase or decrease in dose (mg/kg)	25
Total of chicks used, Symbols and their corresponding dose	6 (xxoxox)[a] (200-175-150-175-150-175)
Equation application	ED_{50}=Xf + Kd ED_{50}=175+ (-0.737)25= 156.575

[a]X- analgesia; O-no analgesia.

Table 2: ED_{50} of tramadol in chicks by the up-and-down method after 60 min

Variable	Result
ED_{50} (mg/kg) (*i.p.*)	0.82
Doses range (mg/kg)	0.75-1
Early dose (mg/kg)	1
Latest dose (mg/kg)	0.75
Increase or decrease in dose (mg/kg)	0.25
Total of chicks used, Symbols and their corresponding dose	5 (xoxox)[a] (1-0.75-1-0.75-1)
Equation application	ED_{50}=Xf + Kd ED_{50}=1+ (-0.701)0.25= 0.824

[a]X- analgesia; O-no analgesia.

Table 3: ED_{50} of diclofenac in chicks by the up-and-down method after 60 min

Variable	Result
ED_{50} (mg/kg) (*i.p.*)	5.65
Doses range (mg/kg)	5-10
Early dose (mg/kg)	10
Latest dose (mg/kg)	0.75
Increase or decrease in dose (mg/kg)	2.5
Total of chicks used, Symbols and their corresponding dose	6 (xxoxox)[a] (10-7.5-5-7.5-5-7.5)
Equation application	ED_{50}=Xf + Kd ED_{50}=7.5+ (-0.737)2.5= 5.657

[a]X- analgesia; O-no analgesia.

Table 4: ED_{50} of paracetamol in chicks by the up-and-down method after 60 min

Variable	Result
ED_{50} (mg/kg) (*i.p.*)	10.74
Doses range (mg/kg)	10-12.5
Early dose (mg/kg)	12.5
Latest dose (mg/kg)	12.5
Increase or decrease in dose (mg/kg)	2.5
Total of chicks used, Symbols and their corresponding dose	5 (xoxox)[a] (12.5-10-12.5-10-12.5)
Equation application	ED_{50}=Xf + Kd ED_{50}=12.5+ (-0.701)2.5= 10.747

[a]X- analgesia; O-no analgesia.

Table 5: ED_{50} of Pregabalin and Tramadol administered concomitantly for induction of analgesia in chicks at fixed ratio (0.5:0.5) of their individual ED_{50} values after 60 min

Variable	Pregabalin (*p.o.*) + Tramadol (*i.p.*)	
ED_{50} (mg/kg)	36.2	0.18
Doses range (mg/kg)	19.5-78	0.1-0.4
Early dose (mg/kg)	78	0.4
Latest dose (mg/kg)	19.5	0.1
Change in dose (mg/kg)	19.5	0.1
Total of chicks used	6 (xxoxxo)[a] (78-58.5-39-58.5-39-19.5)	6 (xxoxxo)[a] (0.4-0.3-0.2-0.3-0.2-0.1)
Equation application	ED_{50}=Xf+Kd ED_{50}=19.5+ (+0.861)19.5=36.289	ED_{50}=Xf + Kd ED_{50}=0.1+ (+0.861)0.1=0.186
% Decrease in ED_{50}	53.5%	55%
Y	0.45	

[a]X- analgesia; O-no analgesia. The ED_{50} was determined by the up-and-down method. Y= calculated interaction index.

Table 6: ED_{50} of Pregabalin and Diclofenac administered concomitantly for induction of analgesia in chicks at a fixed ratio (0.5:0.5) of their individual ED_{50} values after 60 min

Variable	Pregabalin (*p.o.*) + Diclofenac (*i.p.*)	
ED_{50} (mg/kg)	64.3	2.3
Doses range (mg/kg)	58.5-78	2.1-2.8
Early dose (mg/kg)	78	2.8
Latest dose (mg/kg)	78	2.8
Change in dose (mg/kg)	19.5	0.7
Total of chicks used	5 (xoxox)[a] (78-58.5-78-58.5-78)	5 (xoxox)[a] (2.8-2.1-2.8-2.1-2.8)
Equation application	ED_{50}=Xf + Kd ED_{50}=78+ (-0.701)19.5=64.330	ED_{50}=Xf + Kd ED_{50}=2.8+ (-0.701)0.7=2.309
% Decrease in ED_{50}	17.5%	17.8%
Y	0.81	

[a]X- analgesia; O-no analgesia. The ED_{50} was determined by the up-and-down method. Y= calculated interaction index.

Table 7: ED_{50} of Pregabalin and Paracetamol administered concomitantly for induction of analgesia in chicks at a fixed ratio (0.5:0.5) of their individual ED_{50} values after 60 min

Variable	Pregabalin (*p.o.*) + Paracetamol (*i.p.*)	
ED_{50} (mg/kg)	64.3	4.3
Doses range (mg/kg)	58.5-78	4-5.3
Early dose (mg/kg)	78	5.3
Latest dose (mg/kg)	78	5.3
Change in dose (mg/kg)	19.5	1.3
Total of chicks used	5 (xoxox)[a] (78-58.5-78-58.5-78)	5 (xoxox)[a] (5.3-4-5.3-4-5.3)
Equation application	ED_{50}=Xf + Kd ED_{50}=78+ (-0.701)19.5=64.330	ED_{50}=Xf + Kd ED_{50}=5.3+ (-0.701)1.3=4.388
% Decrease in ED_{50}	17.5%	18.8%
Y	0.81	

[a]X- analgesia; O-no analgesia. The ED_{50} was determined by the up-and-down method. Y= calculated interaction index.

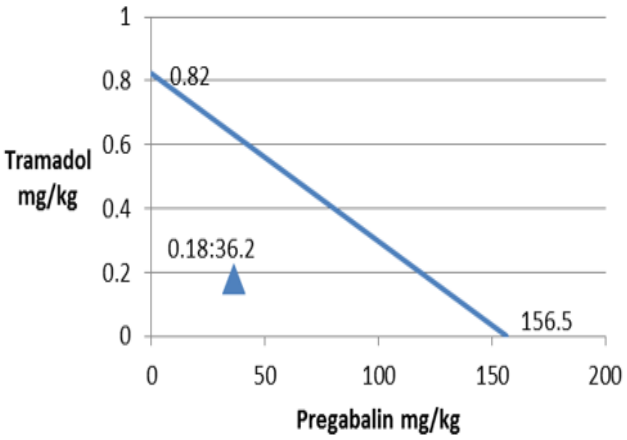

Figure 1: Isobolographic analysis of Pregabalin and Tramadol analgesic interactions in chicks. The points on axes x and y represent the median analgesic doses (ED50s, mg/kg) of drugs administered alone, whereas the triangular point represents a 0.5:0.5 ED50 combination of both drugs. The diagonal line connecting the individual ED50s of Pregabalin and Tramadol is synergistic, and thus the triangular point reveals a synergistic relationship.

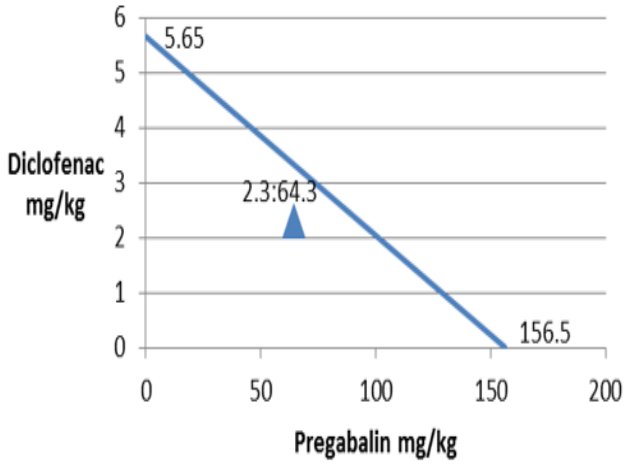

Figure 2: Isobolographic analysis of Pregabalin and Diclofenac analgesic interactions in chicks. The points on axes x and y represent the median analgesic doses (ED50s, mg/kg) of drugs administered alone, whereas the triangular point represents a 0.5:0.5 ED50 combination of both drugs. The diagonal line connecting the individual ED50s of Pregabalin and Diclofenac is synergistic, and thus the triangular point reveals a synergistic relationship.

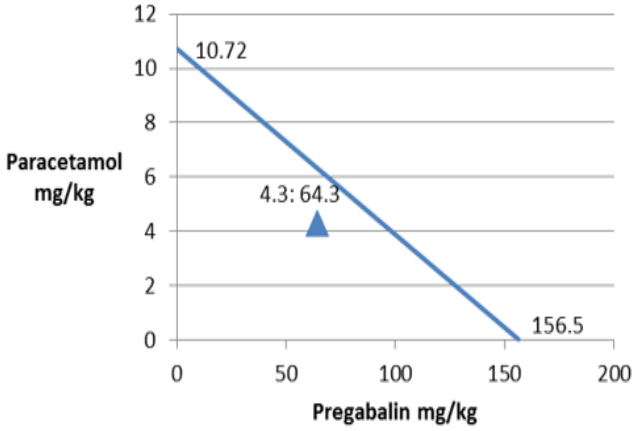

Figure 3: Isobolographic analysis of Pregabalin and Paracetamol analgesic interactions in chicks. The points on axes x and y represent the median analgesic doses (ED50s, mg/kg) of drugs administered alone, whereas the triangular point represents a 0.5:0.5 ED50 combination of both drugs. The diagonal line connecting the individual ED50s of Pregabalin and Paracetamol is synergistic, and thus the triangular point reveals a synergistic relationship.

Discussion

Drugs have side effects, which are often undesirable (14). So we may have to do drug interaction experiments between two types of drugs. The aim is to reduce the side effects of both drugs by reducing the dose of both and increasing the therapeutic effect (15). In recent years, multiple analgesic techniques have been proposed, combining the additive and synergistic effects of multiple analgesics with fewer adverse effects and offering more effective properties in terms of the potential advantages of using two drugs, improving patient compliance, increasing efficacy while reducing the likelihood of side effects (16).

The pain arising from the body wall is called superficial pain, which is generated from the skin or superficial tissues; As the cutaneous pain receptors terminate directly under the skin and generate particular and localized pain for a short period due to the high concentration of nerve endings, and this pain is described as sharp, tingling-like pain and well-defined (17). Holloway observed similarities in fibers and neurotransmitters when comparing the physiological response to pain receptors in chickens and mammals (18). The electric stimulus induces pain in chicks and avoidance that includes attempts to escape forcefully, represented by jumping and flapping wings (19). Electrical stimulation is used to generate pain and measure the occurrence of analgesia in chicks as a qualitative and quantitative method for measuring analgesia (20,21).

From the results of our study, it was observed that pregabalin has an analgesic effect for acute pain induced by electrical stimulation. The literature shows that pregabalin can help with thermal hyperalgesia, chemical-induced nociception, and carrageenan or formalin-induced peripheral inflammation (1). Pregabalin reduces hyperalgesia and central sensitization by inhibiting the release of excitatory pronociceptive neurotransmitters (22). Pregabalin binding to the presynaptic alpha-2-delta (α2-δ) subunits of the voltage-activated calcium channels is significant and necessary for analgesic and anti-epileptic activities, affecting neurological pain reduction be explained by its anticonvulsant modes of action (5).

One of the distinguishing results in our study is that the concomitant administration of Pregabalin and Tramadol decrease the median analgesic dose by fifty percent for both drugs with synergistic analgesia. In an acute model of pain, pregabalin showed a comparable antinociceptive effect to tramadol, although the interaction between these two medications is highly dependent on their proportion in the combination. Although analgesia may rise, adverse effects such as tramadol's seizurogenic impact can be decreased in a clinical environment if the proper proportion is administered (6). Pregabalin lowers substance P after inflammation in spinal cord slices and formalin-induced glutamate release in the dorsal horn of the spinal cord. On the other hand, tramadol blocks both ionotropic and metabotropic glutaminergic receptors, reducing the effects of glutamate and substance P (23).

On the other hand, pregabalin reduced the analgesic dose of Diclofenac and Paracetamol by approximately 20 percent, synergistically.

Diclofenac has numerous ways for decreasing acute pain, according to researchers. In mammals, the prolonged firing of C-fiber nociceptors causes glutamate release; it is assumed that this is similar in birds. Glutamate acts on N-methyl-D-aspartate receptors in the spinal cord, leading to central sensitization. Diclofenac reduces NMDA-mediated hyperalgesia in rats via the L-arginine/NO/cGMP pathway (24). As we mentioned at the beginning of the discussion, pregabalin inhibits the release of excitatory pronociceptive neurotransmitters like glutamate. It is possible to assume a synergistic action in inhibiting the excitatory neurotransmitters.

The exact mechanism of paracetamol action is yet unknown. Paracetamol may enhance the activity of descending 5-HT pathways in the spinal cord, which reduces nociceptive signal transmission (8). In another study by Björkman, he is indicated that paracetamol interacts with the central nervous system's L-arginine-NO pathway (25), Which enables us to build the same hypothesis regarding the mechanism of interaction between pregabalin and diclofenac.

Conclusion

It can be concluded from the results that we obtained that pregabalin has analgesic effects for the acute induced pain by electrical stimulator and the ability to increase the analgesic effect of each of tramadol, diclofenac, and paracetamol in a clear synergistic manner.

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Conflict of Interest

The authors state no competing interests.

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البريكابالين يعزز التأثير المسكن للترامادول والديكلوفيناك والباراسيتامول في افراخ الدجاج: تحليل ايزوبالوكرافي

قتيبة محمد بشار وياسر محمدامين البدراني

فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

هدفت الدراسة إلى الكشف عن الجرعة المسكنة الفاعلة الوسطية للبريكابالين وتحديد نوع التداخل المسكن مع كل من الترامادول والديكلوفيناك والباراسيتامول في الكتاكيت. تم استخدام جهاز التحفيز الكهربائي للكشف عن الألم قبل وبعد العلاج ومن خلال الصعود والنزول بالجرع واعتمادًا على طريقة الصعود والنزول، تم تحديد الجرعة المسكنة الفاعلة الوسطية لجميع الأدوية المستخدمة في الدراسة، ثم أجريت تجربة التداخل بنسبة ثابتة ١:٠,٥ من البريكابالين مع كل من الترامادول والديكلوفيناك والباراسيتامول من قيم الجرعة المسكنة الفاعلة الوسطية الفردية، ومن ثم خضعت النتائج للتحليل الايزوبالوكرافي لتحديد نوع التداخل. أظهرت النتائج ان الجرعة المسكنة الفاعلة الوسطية للبريكابالين والترامادول والديكلوفيناك والباراسيتامول في الكتاكيت ١٥٦,٥ و ٠,٨٢ و ٥,٦٥ و ١٠,٧٤ ملغم/ كغم على التوالي. أدى اعطاء الأدوية المترافقة بريكابالين: ترامادول وبريكابالين: ديكلوفيناك وبريكابالين: باراسيتامول بنسبة ثابتة ١:٠,٥ من قيم الجرعة المسكنة الفاعلة الوسطية الفردية إلى خفض الجرعة المسكنة الفاعلة الوسطية إلى ٣٦,٢: ٠,١٨ و ٦٤,٣: ٢,٣ و (٦٤,٣: ٤,٣ ملغم/ كغم على التوالي. أظهر التحليل الايزوبالوكرافي تأثيرات مسكنة تآزرية لاعطاء كلا الدوائين معا. وكانت مؤشرات التداخل المحسوبة ٠,٤٥ و ٠,٨١ و ٠,٨١ على التواليز الاستنتاج: نستنتج من الدراسة أن التسكين كان تآزرياً بين البريكابالين والترامادول وبصورة قوية، بينما كان التسكين بين البريكابالين مع كل من الديكلوفيناك والباراسيتامول تآزريا أيضاً ولكن بدرجة أقل.