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REPORTS OF ORIGINAL INVESTIGATIONS

Relative potency of pregabalin, gabapentin, and morphine in a mouse model of visceral pain

Puissance relative de la prégabaline, de la gabapentine et de la morphine dans un modèle de douleur viscérale chez la souris

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Abstract

Purpose *Pregabalin is probably more effective than prototype gabapentin in different kinds of pain treatments. This study was performed to compare the potency of gabapentin, pregabalin, and morphine in a well-established model of visceral pain.*

Methods *The number of abdominal contractions was counted for 30 min in adult male mice that received different doses of pregabalin, gabapentin, morphine, or placebo intraperitoneally 30 min before receiving 0.6% acetic acid 10 mL·kg^{-1}.The antinociceptive effect of each drug dose was determined as a percentage of the reduction in the number of acetic acid-induced writhes. The effective doses, for 20%, 50%, and 80% response (ED_{20}, ED_{50}, and ED_{80}, respectively), of each drug were calculated using least squares linear regression analysis, and then dose-response curves were compared.*

Results *Pregabalin, gabapentin, and morphine produced a linear dose-dependent antinociceptive effect (coefficient of determination [r^2] > 0.9). No difference was observed between slopes of dose-response curves. The ED_{50} estimates (95% confidence interval) for pregabalin, gabapentin, and morphine were 17.1 (12.9 to 22.1) mg·kg^{-1}, 87.1 (45.8 to 129.8) mg·kg^{-1}, and 0.2 (0.1 to 0.3) mg·kg^{-1}, respectively.*

Conclusion *In this animal model of visceral pain, all three drugs exhibited parallel dose-response curves. Pregabalin had five times the potency of gabapentin and 1/85th the potency of morphine. Similar potency ratios may apply in clinical practice. Despite some limitations of animal studies, this model could be useful for comparing new analgesics in visceral pain treatment.*

Résumé *ObjectifLa prégabaline est probablement plus efficace que son prototype, la gabapentine, dans divers traitements contre la douleur. Cette étude a été réalisée pour comparer la puissance de la gabapentine, de la prégabaline et de la morphine dans un modèle bien établi de douleur viscérale.*

Méthode *Le nombre de contractions abdominales a été compté pendant 30 min chez des souris mâles adultes recevant différentes doses de prégabaline, de gabapentine, de morphine ou de placebo par voie intrapéritonéale 30 min avant 0,6 % d'acide acétique (10 mL·kg^{-1}). L'effet antinociceptif de chaque dose de médicament a été déterminé en tant que pourcentage de réduction du nombre de contorsions induites par l'acide acétique. Les doses efficaces (DE) 20 %, 50 % et 80 % (DE_{20}, DE_{50} et DE_{80}) de chaque médicament ont été calculées à l'aide de l'analyse de régression linéaire des moindres carrés et les courbes de dose-réponse ont ensuite été comparées.*

Résultats *La prégabaline, la gabapentine et la morphine ont produit un effet antinociceptif dépendant linéairement de la dose (coefficient de détermination [r^2] > 0,9).*

Author contributions *Manzumeh Shamsi Meymandi* designed the study, wrote the protocol, contributed to the acquisition of data, and conducted the statistical analysis. *Fariborz Keyhanfar* interpreted the findings, contributed to the study design, provided summaries of previous research studies, and revised the intellectual content of the manuscript. *Manzumeh Shamsi Meymandi* and *Fariborz Keyhanfar* were responsible for the study's conception and were involved with manuscript preparation.

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Aucune différence n'a été observée entre les pentes des courbes de dose-réponse. La DE_{50} avec des intervalles de confiance de 95 % était de 17,1 mg·kg^{-1} (12,9 à 22,1) pour la prégabaline, 87,1 mg·kg^{-1} (45,8 à 129,8) pour la gabapentine et 0,2 mg·kg^{-1} (0,1 à 0,3) pour la morphine.
Conclusion *Dans ce modèle animal de douleur viscérale, les trois médicaments ont montré des courbes de dose-réponse parallèles. La prégabaline était cinq fois plus puissante que la gabapentine et 85 fois moins puissante que la morphine. Des ratios de puissance semblables pourraient s'appliquer dans la pratique clinique. Malgré certaines des limites des études animales, ce modèle pourrait être utile pour comparer de nouveaux analgésiques pour le traitement de la douleur viscérale.*

The anticonvulsants, pregabalin and gabapentin, are effective in pain treatment. Their anticonvulsant and analgesic effects are attributed to their binding to the alpha-2-delta-1 subunit of voltage-dependent Ca-channels that decrease calcium influx and consequently decrease the release of the neurotransmitters norepinephrine, serotonin, and dopamine.[1] Pregabalin and gabapentin are prescribed in chronic pain states, such as post-herpetic neuralgia and diabetic peripheral neuropathy,[2] and they are used in complex pain syndromes such as fibromyalgia.[3] In addition, animal studies have shown that these drugs could have an analgesic effect in acute pain treatment.[4-6]

Like most anticonvulsants, gabapentinoids have also been found to have an antinociceptive effect in visceral pain.[7] Previous reports have shown that pregabalin inhibits trinitrobenzene sulfonic acid-induced allodynia in rats, and gabapentin inhibits acetic acid-induced irritation in rats.[8,9] Both pregabalin and gabapentin are recognized to reduce pain behaviour in colorectal distension and stress-induced visceral pain in rats.[10,11]

Visceral pain still constitutes a large portion of clinically treated pain. It is caused by intense activation of nociceptive primary afferent fibres and is characterized by referral hyperalgesia.[12] Contrary to conventional belief, it is not a variant of somatic pain; it has an inflammatory component and differs in neurological mechanisms and transmission pathways.[12] The acetic acid-induced writhing response in rodents is probably the best model of visceral pain, and it is considered to predict human response to pain.[7,13] Consequently, this model is widely used as a test to evaluate and compare efficacy of new drugs in visceral pain treatment.[7,9,13-18] The writhing responses reflect peritoneovisceral pain, because acetic acid directly activates both visceral and somatic nociceptors that innervate the peritoneum. This model also induces inflammation in the subcutaneous and muscular layers of the abdominal wall as well as in the subdiaphragmatic visceral organs.[17]

Gabapentin has been shown to be less potent than pregabalin in many pain models. The purpose of the present study is to quantify this potency ratio in a simple well-established visceral pain model. Therefore, our main objective was to establish dose-response relationships for pregabalin and gabapentin, compare them to morphine, a reference drug, using an acetic acid-induced writhing model of visceral pain.

Methods

Animals

The study protocol (Ka-90/123) was approved in March 2011 by the Animal Research Ethics Committee of Kerman University of Medical Sciences (Deputy of Research, Kerman, Iran) in accordance with internationally accepted principles for laboratory animal use and care (European Economic Community Directive of 1986; 86/609/EEC).

Male NMRI (Naval Medical Research Institute) mice weighing 25-35 g were used in the study. They were housed four or five per cage at a mean (standard deviation) controlled temperature of 22 (2)°C and on a 12-hr light-dark cycle with free access to food and water. The animals were used for one procedure only and were humanely killed under anesthesia with diethyl-ether after the observation period. The experiments were performed on light cycle from 8 a.m.-12 p.m.

Acetic acid-induced writhing

The animal model considered clinically relevant to intestinal pain in humans is acetic acid-induced visceral contractions in mice.[15,19] In our study, the animals were placed in individual polypropylene transparent boxes and allowed to habituate to laboratory surroundings for 30 min. The mice were restrained for intraperitoneal injection and held with their ventrum exposed. At that point, 0.6% acetic acid 10 mL·kg^{-1} was injected intraperitoneally (*ip*) into the lower right quadrant of the abdominal cavity at an angle of 30° and inserted to an approximate depth of 5 mm. Immediately after injection, the mice were observed for writhing behaviour. The writhing reflex is characterized by the presence of abdominal muscle contractions associated with inward outstretching of the hind limbs, a hind paw reflex, or whole body extension.[7,9,14,17,20] The number of writhing reflexes, a measure of visceral pain, were recorded for a 30-min period.[20]

Drugs and experimental protocol

The drugs used in the study were pregabalin (Hetero Drugs Limited, India), gabapentin (Park Davis Company, Italy), and morphine sulfate (Temad, Iran).

All drugs were freshly dissolved in normal saline and injected 30 min before injecting the acetic acid. The pH of all drug solutions was controlled and did not differ from that of normal saline. The acetic acid (Sigma) was dissolved in distilled water. The treated groups received pregabalin (2-200 $mg{\cdot}kg^{-1}$), gabapentin (5-200 $mg{\cdot}kg^{-1}$), and morphine (0.1-5 $mg{\cdot}kg^{-1}$) *ip*.

Initially, a control group ($n = 8$) received normal saline before the acetic acid test, and then dose-response curves were obtained using five to seven different doses of gabapentin, pregabalin, and morphine, given sequentially. The maximum doses of gabapentin and morphine selected were 200 and 5 $mg{\cdot}kg^{-1}$, respectively, based on similar studies,[4,9,14,16] while the maximum dose for pregabalin, which was novel in this model, was presumed to be 200 $mg{\cdot}kg^{-1}$.[8] The dose used for the dose-response data was the maximum dose and simple divisions (½, ¼ …) of that dose. Dilutions were made in normal saline so that a volume of 1/100 of mouse body weight would be injected. For example, the volume required for a 32-g mouse was 0.32 mL. Data collection was continued until six mice received each dose. In an earlier part of our protocol, a preliminary experiment revealed that the injection of gabapentin 300 $mg{\cdot}kg^{-1}$ produced the same effect as 200 $mg{\cdot}kg^{-1}$, while 400 $mg{\cdot}kg^{-1}$ was toxic. Accordingly, the dose-response curve for gabapentin was obtained by using doses ranging from 5-200 $mg{\cdot}kg^{-1}$. The same procedure was implemented for pregabalin and morphine. The dose ranges used for pregabalin and for morphine were 2-200 $mg{\cdot}kg^{-1}$ and 0.1-5 $mg{\cdot}kg^{-1}$, respectively. Constructing an adequate dose-response curve requires a coefficient of determination $r^2 \geq 0.9$; therefore, the doses occasionally needed additional subdivisions to achieve the best fit. A laboratory collaborator, who was unaware of the dose given to the animal, counted the number of writhes. The collaborator could not possibly predict or expect the number of writhes because all dilutions were prepared daily, and he did not know which dilutions were given to which specific mouse.

Analgesic effect was quantified as the percent reduction in the number of writhes produced by each drug dose. For a given dose, the percent effect (%E) was calculated as follows: %E = [(number of writhes in control − number of writhes with that dose) / number of writhes in control] × 100.

The %E was used to establish a dose-response relationship. The drug doses were first transformed into base 10 logarithms and plotted on the x-axis of a Cartesian system, while the corresponding %E of each dose was plotted on the y-axis.[A] The number of mice for each dose was set at six according to similar isobolographic studies.[5,6,17]

Statistical analysis

The results of the six mice were shown as mean [standard error of the mean (SEM)], and the slopes of dose-response lines were compared by analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons *post hoc* test. A least-square linear regression analysis of the log dose-response curves allowed the calculation of the dose that produced 20, 50, and 80% of effect (ED_{20}, ED_{50}, and ED_{80}, respectively) with 95% confidence interval (CI) and respective equation, according to Motulsky's method.[1] Statistical analyses were done using the specialized software, GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). A P value < 0.05 was considered to indicate a statistically significant difference.

Results

Data from 110 mice were analyzed. The injection of *ip* acetic acid produced evident writhing behaviour in the control group with 60 (4) contractions during 30 min of the experiment. The linear regression showed a dose-dependent effect with an adequate coefficient of determination (r^2) for all three drugs. The dose-response equations for the three drugs were as follows:

pregabalin: %E = 37.45.log(dose) + 3.83; $r^2 = 0.98$;
gabapentin: %E = 42.69.log(dose) − 32.80; $r^2 = 0.93$;
morphine: %E = 39.85.log(dose) + 75.05; $r^2 = 0.98$,

where log(dose) is the base 10 logarithm of the dose expressed in log(dose).

In the dose range used, the effects (%E) produced by the three drugs were: pregabalin 20-95%; gabapentin 2-65%; and morphine 35-99% (Figure). All effective doses of pregabalin (ED_{20}, ED_{50}, and ED_{80}) were significantly more than the respective effective doses of gabapentin and less than the respective effective doses of morphine ($P < 0.05$) (Table). The dose-response curves did not deviate significantly from parallelism, and the slopes for pregabalin, gabapentin, and morphine with 95% CI were: 37.4 (30.9 to 43.9), 42.7 (23.1 to 64.2), and 39.8 (30.5 to 49.2), respectively (Figure).

Discussion

Pregabalin, gabapentin, and morphine produced a dose-dependent analgesic effect in an acetic acid-induced visceral pain model in mice. The order of analgesic potency in terms of ED_{50} was morphine > pregabalin > gabapentin.

[A] *Motulsky H, Christopoulos A.* Fitting Models to Biological Data using Linear and Nonlinear Regression. A Practical Guide to Curve Fitting. San Diego, CA: Graphpad Software Inc., 2003, www.graphpad.com.

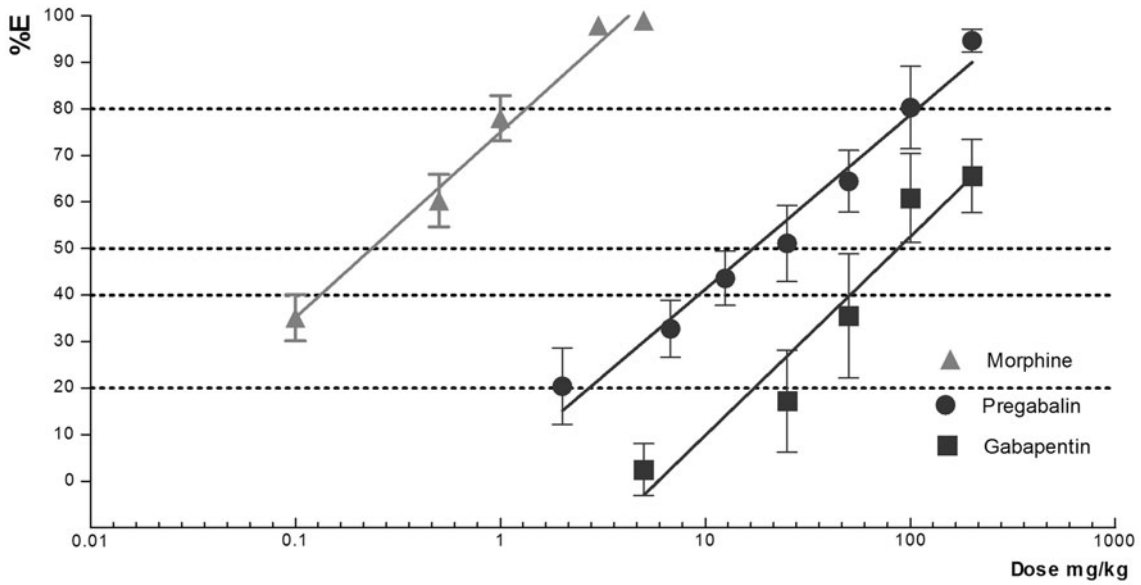

Figure Dose-response relationship for morphine, pregabalin, and gabapentin in the acetic acid-induced writhing test in mice. Analgesic effect is defined as the percent reduction in the number of writhes (%E) produced after each dose compared with control. Least square linear regression analysis determined the equation of each drug. Each point represents the standard error of the mean (SEM) of the %E of six mice

Table Effective dose (ED) values in $mg \cdot kg^{-1}$ with 95% confidence intervals (95% CI) for the analgesic effects of pregabalin, gabapentin, and morphine in acetic acid-induced writhing in mice

Drugs	ED_{20} (95% CI)	ED_{50} (95% CI)	ED_{80} (95% CI)
Pregabalin	2.7 (1.6 to 4.0)	17.1 (12.9 to 22.1)	108.1 (77.6 to 165.5)
Gabapentin	17.2 (4.9 to 33.0)	87.1 (45.8 to 129.8)	438.5 (188.8 to 782.0)
Morphine	0.04 (0.01 to 0.08)	0.2 (0.1 to 0.3)	1.3 (1.0 to 2.8)

The ED_{20}, ED_{50}, and ED_{80} (doses for 20, 50, and 80% analgesic effect, respectively) were calculated based on equations of dose-response curves using least squares linear regression analysis

Morphine had 85 times the potency of pregabalin, and pregabalin was five times more potent than gabapentin. Previously, pregabalin has been reported as being three times more potent than gabapentin, specifically, in a hot-plate acute model of pain, in allodynia after spinal cord injury, and also in a carrageenan model of peripheral inflammation.[6,21,22] Similar results were obtained in clinical treatment of pain after acute spinal cord injury and in treatment of irritable bowel syndrome where pregabalin was two to ten times more potent than gabapentin.[23] It is well accepted that the efficacy and relative potency of drugs depend on the nature of pain. Indeed, the dose of gabapentin was four times greater than pregabalin in the treatment of fibromyalgia, whereas it was six times greater in neuropathic pain.[24]

Similar slopes of dose-response curves do not necessarily indicate the existence of the same mechanisms of action, but it is already established that pregabalin and gabapentin exert their analgesic effect through the same site of action.[1,23] Although different slopes point to different mechanisms, the opposite is not true. Morphine has a different mechanism of action than gabapentinoids, but in the model studies, the dose-response relationships were parallel. The higher maximum effect achieved by pregabalin and the difference in potency can be attributed to a higher availability and affinity of pregabalin for alpha-2-delta-1 subunits of calcium channels involved in visceral pain transmission[1] or due to a wider distribution of these channels in the central nervous system.[25] Nevertheless, two substances can have a combination of different availabilities and different sites of action that result in similar slopes on the dose-response curves. This is the case with morphine, since the slope of the morphine dose-response curve does not appear to be significantly different from the other two agents.

The acetic acid-induced writhing test indicates utility[7] for clinically relevant intestinal pain in humans, especially because of the correlation found between the ED_{50} values in this test and analgesic doses in humans.[19,26,27] This test is a highly sensitive visceral model in pain assessment

because it also works for weak analgesics,[19] and therefore, it is suitable for comparison of new drugs and sifting molecules, the pharmacodynamics of which are unknown.[19] Viscerosomatic responses can also be evoked by colorectal distension, but we chose a writhing test since colonic distension has a lower degree of inflammation and is more conducive for specific abdominal pain associated with altered colonic sensitivity such as in irritable bowel syndrome.[10,11,23,28]

Availability and ease of management were the main reasons for using mice instead of rats[7,14-18] and intraperitoneal injection instead of other routes of administration. The duration of the test was set at 30 min to reduce variability and obtain a rapid result. Although this procedure is a well-established visceral pain model, the intraperitoneal injection of drugs does not exactly simulate the clinical reality of drug administration. Considering the objective of the study, we preferred all these limitations over performing a difficult model. The ED_{50} of morphine found in this study ($ED_{50} = 0.23$ mg·kg^{-1}) was nearly equal to that ($ED_{50} = 0.25$ mg·kg^{-1}) found in the previous study by Romero *et al*. who adopted the same method and dose range.[16]

In conclusion, in this simple well-established model, ED ratios determine the relative potency that may be useful to quantify the proportion of clinically required drug dose for visceral pain. Therefore, despite the limitations of animal studies, including route of administration, species differences, duration of test, and dosage, in our view, this model could be used to characterize and define the effect of new analgesics in visceral pain treatment and could help in the development of drug selection strategies in clinical practice.

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Conflicts of interest None declared.

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