



Simultaneous determination of pethidine pharmacokinetics in rats: The impact of tramadol coadministration

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Abstract

The rats model has never thoroughly investigated the influence of tramadol on plasma pethidine concentration besides pethidine pharmacokinetics. Individually, analgesic ED₅₀s for pethidine and tramadol are estimated as 3.55 and 24.21 mg/kg, i.p. Subsequently, their measures decreased to 1.65 and 11.27 mg/kg, i.p., when both were given in combination at 1:1 from ED₅₀s. Tramadol and pethidine have a form of synergistic analgesic interaction, which is therefore classified as a pharmacodynamic interaction. Pethidine (7.1mg/kg, i.p.) reveals the plasma concentration of 369.00, 493.33, 373.33, 305.33, 306.33 and 247.67 µg/ml that was measured over distinctive times of 0.25, 0.5, 1, 2, 4, and 24 hours. At the same time, the concentration of plasma levels of tramadol and pethidine (48.42 and 7.1mg/kg, i.p., correspondingly) declined to 229.33, 268.33, 233.00, 198.33, 195.67 and 180.33 µg/ml by 38, 46, 38, 35, 36 and 27%, respectively. Tramadol affected the pethidine pharmacokinetics through an elevation in the area-under-curve (AUC_{0-∞}) 49%, area-under-moment-curve (AUMC_{0-∞}) 343%, mean-residence-time (MRT) 137%, half-life (t_{1/2β}) 136%, and the distribution volume (V_{ss}) 64%. Other estimated pharmacokinetic measures were reduced which included maximal concentration (C_{max}) 47% and elimination rate constant (K_{el}) 60%. In general, the findings revealed a synergism as a mode of pharmacological interaction between pethidine and tramadol, in addition to a change in pethidine pharmacokinetics, which could improve pethidine effectiveness in the rat's model.

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Introduction

Pethidine is a short-acting synthetic narcotic analgesic. It is known as meperidine in the United States because it is widely used to relieve severe and chronic pain, and reduce shivering induced by post anesthesia (1,2). The mechanism of action of pethidine is by working as a µ-agonist opioid (3-5). Like other opioid drugs, pethidine has several side effects such as pruritus, tolerance, vomiting, respiratory depression, or dependence (6). These signs have limited their clinical practice. Pethidine is metabolized significantly, forming a significant metabolite known as norpethidine through the hepatic enzyme cytochrome P₄₅₀ system. Furthermore,

compared to pethidine, the metabolite norpethidine has about half the analgesic effectiveness of pethidine and can cause agitation, hallucinations, tremulousness, and convulsions (7). Previous research has found that the adverse effects of pethidine were dose-dependent (8,9). Since tramadol is not categorized as a pure opioid, it acts on the central nervous system and has little binding capacity at the µ-opioid receptor. Besides, it affects the serotonergic and noradrenergic systems (3-5). Many European nations have recently approved tramadol as an analgesic (9). Tramadol works by inhibiting monoaminergic reuptake, which improves the analgesia mediated through the descendent inhibitory circuit of the spinal nerves. Since tramadol has the

less binding capacity to the μ -opioid receptor, it has been attributed not to cause respiratory suppression (10). Tramadol is converted to a bioactive metabolite called O-desmethyl tramadol, which has a more binding capacity at the μ -opioid receptor than tramadol itself, so, it considerably enhances tramadol's analgesic action (11).

The researchers aimed to assess how tramadol affected pethidine plasma concentrations and pharmacokinetics and how they interacted pharmacologically in the rats model.

Materials and methods

Ethical approval

The trials, as well as the use of experimental laboratory animals were approved according to the ethical code number UM.VET.2021.37 on November 1, 2021 from the Colleges of Veterinary Medicine, University of Mosul.

Laboratory animals and drugs preparation

Rats from both genders weighing between 250-450g were kept at 20 °C for 14 hours dark and 10 hours light routine besides consuming water and food were allowed freely. Experimental drugs involving pethidine (5%, Rotexmedica, Germany) and tramadol (5%, Pharmalife, Georgia) were prepared by dilution in normal saline to acquire the estimated dose, which will be injected into rats intraperitoneally (i.p.).

Analgesic ED_{50s} determination for pethidine and tramadol

The analgesic ED_{50s} of each pethidine or tramadol were assessed by using the thermal method (hot plate) for each drug alone. The procedure is illustrated by injecting an initial dose of pethidine or tramadol at 20 and 20 mg/kg given i.p. (12-14). Meanwhile, both medications' dosages were lowered or increased by 30% (6 mg/kg, i.p. for both drugs) (15). The thermal method was applied using the hot plate (Panlab, Spain) to evaluate the two drugs' analgesic responses. The hot plate was fixed at 56 °C of temperature then, rats were separately placed at the center of hot plate and recorded for the pre-injection response time of pain, which was hind paw drawing, licking, or jumping. Then, after 30 minutes of pethidine or tramadol treatment, the post-injection time response of pain was also documented. The induction of analgesic effect was then predicted if the post-injection time was beyond the pre-injection time. Rats were left on a hot plate for less than 20 seconds to avoid skin injury to paws (16,17).

Isobolographic inspection of the analgesic pharmacological interaction

The analgesic ED_{50s} for pethidine and tramadol jointly as 1:1 of their ED_{50s} were specified via the up-and-down procedure stated previously by (15). The initial dose for

pethidine and tramadol has been 3.55 and 24.21 mg/kg, i.p., respectively, equal to their ED_{50s} found in the previous experiment. Rats are estimated separately after 30 min of both drugs administration using the hot plate of the thermal method illustrated above. Later, dosages of the two drugs are decreased or elevated by 25% (i.e. 0.89 and 6.05 mg/kg, respectively) from the initial dosage injected before conferring to the occurrence or absence of analgesia (18-20). To estimate the mode of analgesic interaction concerning pethidine and tramadol administration in rats, pethidine, and tramadol resembling the analgesic ED_{50s} were positioned onto x and y-axes (21-23). The upstanding line to be displayed isobolographic analysis amid the ED_{50s} doses for pethidine besides tramadol given separately, producing an analgesic effect in rats. A triangular point beneath the straight line is a synergism, while a triangular point over the straight line means an antagonism. The equation interpreting the interaction index to be then produced as a Y character that is predicted as stated below:

$da/Da + db/Db$. The analgesic ED_{50s} for pethidine and tramadol are denoted by Da and Db, correspondingly. The da and db approximate the united ED_{50s} that are seen in Table 2 along with Figure 2. If Y value equal to 1, it suggests additive; if it is less than 1, it shows synergism; and if it is greater than 1, it implies antagonism (24-26).

Pethidine plasma concentration and the impact of tramadol administration

Pethidine was given at 7.1 mg/kg, i.p. for one rat's group, whereas the other group was given pethidine at 7.1 mg/kg, i.p. with tramadol at 48.42 mg/kg, i.p. Blood samples were taken from three rats at 0.25, 0.5, 1, 2, 4, and 24 hours for the pethidine alone and the pethidine + tramadol groups. The plasma was then collected using heparinized test tubes (B. Braun Medical Inc, USA). The heparin ratio to the blood samples was (at a ratio of 1:10 v/v) and centrifuging (at 3000 rpm / 15 min). Finally, the samples were stored at -18 °C for 72 hours before being analyzed using a spectrophotometer (Lovbond, Germany) containing UV detector (13,14).

Preparing of pethidine standards

Pethidine standards of 7.5, 15, 30, 60, 120, and 240 μ g/ml were made through dilution of pethidine with methanol previously defined (13,14). Filtration was performed on the solution using filter paper. Finally, the net solution was compared to a methanol blank using a spectrophotometer 248.1 nm. The pethidine concentration in the samples of the two groups of rats can be determined using the regression formula for pethidine standards as $R^2 = 0.9657$ (Figure 1). $y = bx + a$, where y= plasma sample absorbance (measured by spectrophotometer at 248.1 nm, b= slope 0.0008, x= plasma pethidine content (unknown), and a= intercept 0.007.

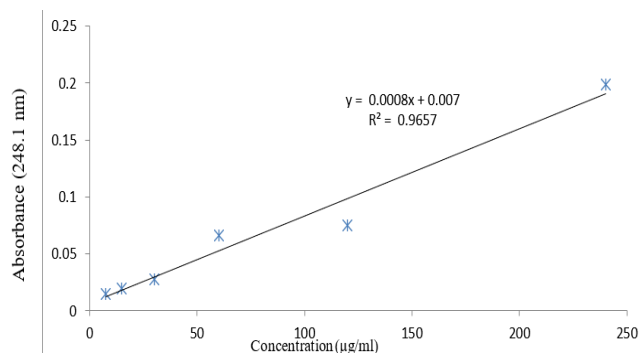


Figure 1: A simple linear regression of the absorbance (248.1 nm) and the calibration curve of pethidine's standards (7.5, 15, 30, 60, 120, and 240 µg/ml).

Extraction of pethidine from the plasma samples

We applied a simple, approved, and exact approach to liquid-liquid extraction of pethidine in the samples (13,14). The technique was demonstrated by mixing 50 µL (of 0.1 mol/L) of sodium carbonate (prepared by dissolving 10.6-gram sodium carbonate in 1 liter distilled water) with 100µL of plasma in a glass test tube, followed by 1.5 µL of ethyl acetate, and then vortexed for 4 min and then centrifugation (3000 rpm for 5 min). The supernatant was then transferred into another tube and allowed to dry. The aliquot was identified using a spectrophotometer and a UV-chromatographic detection at 248.1 nm. The absorbance of various dilutions was measured compared to a blank made of sodium carbonate and ethyl acetate.

Pethidine pharmacokinetic parameters determination and its alteration with tramadol administration

A PKSolver tool was used to derive the pethidine pharmacokinetics and its alteration with tramadol combination by using a non-compartmental model of pharmacokinetics (27). $AUC_{0-\infty}$, $AUMC_{0-\infty}$, MRT, $t_{1/2\beta}$, V_{ss} , C_{max} , K_{el} , T_{max} , and CI were among the parameters. The percentages obtained for these parameters were increased or decreased in the two clusters injected with pethidine alone or in combination with tramadol.

Statistical analysis

The unpaired student T-test helps compare the mean of both groups of rats, while the analysis of variance is used to compare the means of more than three groups in the parametric statistical analysis (28,29), when $P < 0.05$, the level is considered significant.

Results

Analgesic Median Effective Doses (ED_{50} s) determination for pethidine and tramadol

The amount of pethidine required to an induce analgesic effect in half of the populated rats was 3.55 mg/kg, i.p. The

dose of tramadol that caused antinociception in half of the populated rats was 24.21 mg/kg, i.p (Table 1).

Table 1: Analgesic ED_{50} s for pethidine and tramadol in rats

Parameters	Pethidine alone	Tramadol alone
ED_{50} value*	3.55 mg/kg, i.p.	24.21 mg/kg, i.p.
Initial dosage	20 mg/kg	20 mg/kg
Last dose (xf)	8 mg/kg	20 mg/kg
Table value (k)	- 0.741	0.701
± dosage (d)	6 mg/kg	6 mg/kg
Range of the dosages	20-2= 18 mg/kg	26-20= 6 mg/kg
Rats used	7 (XXXOXOX)	5 (OXOXO)

* $ED_{50} = xf + (k.d)$. X denoted analgesia, whereas O represented no effect. Analgesia estimated pre and post 30 min of the injection of the drugs

Isobolographic investigation of the pharmacological interaction

The analgesic ED_{50} value of pethidine and tramadol was 3.55 and 24.21 mg/kg, i.p., respectively. After that, pethidine and tramadol were given together (at a ratio of 1:1 from their ED_{50}), and the analgesic ED_{50} for them was reduced to 1.65 and 11.27 mg/kg, i.p., respectively. The interaction index, denoted by the Y, has a value of 0.93, less than one. The nature of the pharmacological interaction between pethidine and tramadol was synergistic, according to the value measured (Table 2 and Figure 2).

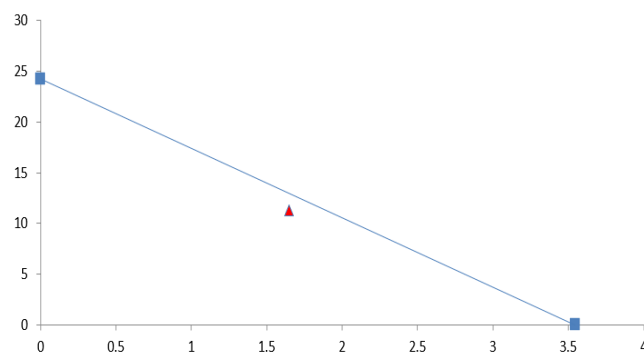


Figure 2: Analgesic interaction measured by isobolographic analysis between pethidine and tramadol.

The blue point on the x-axis represents the ED_{50} s value of pethidine 3.55 mg/kg, i.p., while the ED_{50} s of tramadol 24.21 mg/kg, i.p. point on the y-axis. The red triangular point below the straight line represents the value of 1:1 of ED_{50} s combinations for both pharmaceuticals 1.65 and 11.27 mg/kg, i.p. for pethidine and tramadol, respectively. This indicates that the pharmacological interaction between pethidine and tramadol is synergistic.

Plasma concentration of pethidine given alone: its alteration with tramadol injection

When pethidine is combined with tramadol, the plasma concentration of pethidine is significantly lower than when pethidine is given alone. Pethidine alone (7.1 mg/kg, i.p.) plasma concentrations were 369.00, 493.33, 373.33, 305.33,

306.33, and 247.67 µg/ml at different periods (0.25, 0.5, 1, 2, 4, and 24 hours). Pethidine and tramadol plasma concentrations (7.1 and 48.42 mg/kg, i.p., respectively) were reduced by 38, 46, 38, 35, 36, and 27 percent, respectively, to 229.33, 268.33, 233.00, 198.33, 195.67, and 180.33 µg/ml (Table 3 and Figure 3).

Table 2: Isobolographic analysis of the pharmacological interaction

Variables	Pethidine + Tramadol (1:1)	
	Pethidine	Tramadol
ED ₅₀ = xf + (k × d)	1.65 mg/kg, i.p.	11.27 mg/kg, i.p.
The first dose	3.55 mg/kg	24.21 mg/kg
The last dose (xf)	0.88 mg/kg	6.06 mg/kg
The table value (k)	0.861	0.861
± dosage (d)	0.89 mg/kg	6.05 mg/kg
Range of the dosages	3.55-0.88= 2.67 mg/kg	24.21-6.06= 18.15 mg/kg
Rats used	6 (XXOXXO)*	
Interaction index (Y)= da/Da + db/Db = 0.46 + 0.47= 0.93		

*X means analgesia while O indicates no analgesia. Da and Db indicate the analgesic values of ED₅₀s for pethidine and tramadol given separately, while da and db mean the analgesic ED₅₀ values when pethidine and tramadol are given together.

Table 3: Pethidine plasma concentrations alone or in combination with tramadol

Time (Hour)	Groups		Effect of tramadol on plasma concentration of pethidine (%)
	Pethidine alone	Pethidine and tramadol	
0.25	369.00 ± 139.24 ^a	229.33 ± 36.89 ^{*,a}	38
0.5	493.33 ± 115.70 ^b	268.33 ± 59.18 ^{*,b}	46
1	373.33 ± 55.53 ^a	233.00 ± 13.32 ^{*,a}	38
2	305.33 ± 64.85 ^c	198.33 ± 50.13 ^{*,c}	35
4	306.33 ± 80.08 ^c	195.67 ± 48.45 ^{*,c}	36
24	247.67 ± 60.68 ^d	180.33 ± 30.33 ^{*,d}	27

Numbers are mean ± Std. Err. (3 rats/ time) in µg/ml. *differ significantly from pethidine group (P<0.05). Different letters indicate a significant difference within the same column. Pethidine gave alone at 7.1 mg/kg, i.p. or with tramadol (48.42 mg/kg, i.p.). % tramadol's effect on pethidine plasma concentration= pethidine alone - pethidine plus tramadol / pethidine alone × 100.

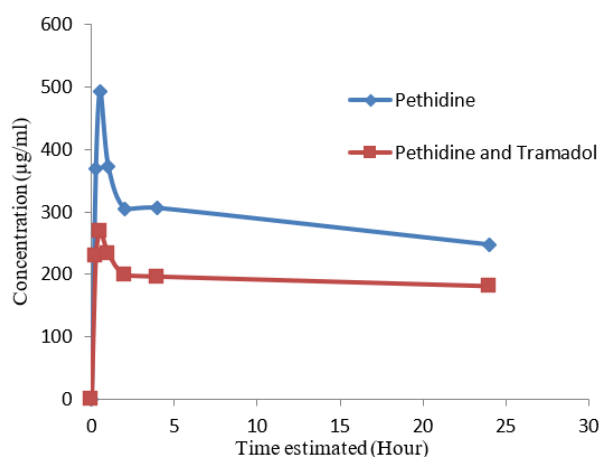


Figure 3: Pethidine plasma concentration is given alone or in combination with tramadol in rats

Pethidine pharmacokinetics in rats given alone or with tramadol

The pharmacokinetics represented as AUC_{0-∞} 31714.53 µg.h/ml, AUMC_{0-∞} 3164624.02 µg.h²/ml, MRT 99.78 h, t_{1/2β} 69.55 h, V_{ss} 0.022 L/kg, C_{max} 493.33µg/ml, K_{el} 0.010 h⁻¹, T_{max} 0.5 h with Cl of 0.0002 L/h/kg when pethidine was given alone. In the rats given pethidine plus tramadol the values of AUC_{0-∞}, AUMC_{0-∞}, MRT, t_{1/2β} and V_{ss} were increased by 49, 343,137, 136, and 64 percent to become 47253.99, 11172517.66, 236.44, 164.01 and by 0.036 respectively. In contrast, other pharmacokinetic parameters such as C_{max} and K_{el} were reduced by 47 and 60% to 268.33, and 0.004, correspondingly compared to the group of rats injected with pethidine (Table 4).

Table 4: Pharmacokinetics of pethidine alone in rats or with tramadol administration

Pharmacokinetic parameters	Units	Treated groups		Effect of tramadol (%)
		Pethidine alone	Pethidine plus tramadol	
AUC _{0-∞}	µg.h/ml	31714.53	47253.99	49 (+)
AUMC _{0-∞}	µg.h ² /ml	3164624.02	11172517.66	343 (+)
MRT	h	99.78	236.44	137 (+)
t _{1/2β}	h	69.55	164.01	136 (+)
V _{ss}	L / kg	0.022	0.036	64 (+)
C _{max}	µg/ml	493.33	268.33	47 (-)
K _{el}	h ⁻¹	0.010	0.004	60 (-)
T _{max}	h	0.5	0.5	0
Cl	L / h / kg	0.0002	0.0002	0

Pethidine given at 7.1 mg/kg, i.p. or injected with tramadol at 48.42 mg/kg, i.p. Pharmacokinetics gained with the application of the non-compartment measurement with the PKSolver tool. % tramadol's impact on pethidine pharmacokinetics= pethidine and tramadol - pethidine / pethidine ×100.

Discussion

This study aimed to combine intraperitoneal pethidine with tramadol to use these mixtures with various mechanisms of action and thus boosting the analgesic activity of pethidine with the most negligible side effects. The study also aimed to identify how tramadol affects the plasma concentration of pethidine alongside the pharmacokinetic features, acknowledging their recognized pharmacological interaction in the rats model, as presented through the isobolographic study.

In this study, the ED₅₀ values of pethidine alone and with tramadol in combination were lower than their distinct values separately. This gives the meaning of a rise in the efficiency of the analgesia essential to produce the pharmacological effect in half of the experimental laboratory rats. The use of the isobolographic analysis in each dual medicine is a convenient design for the detection of analgesic interaction nature (24-26). The study has disclosed a pharmacological synergism interaction when measuring their interaction index shown among pethidine and tramadol as settled over assessing the interaction index assembled as Y symbol.

In comparison to the level of plasma concentration of pethidine alone, tramadol treatment with pethidine resulted in a considerable drop in pethidine plasma concentration levels, which was first discovered in the current investigation. The distinctions between the several pharmacokinetic characteristics go to the pethidine administration when given along with tramadol. Besides, the synergistic effect and the effectiveness of the two medications when given together were markedly significant.

Tramadol has an analgesic with a different spectrum of activity (30,31). Inhibition in pain is primarily involved in activating both opioid and non-opioid systems. In addition, tramadol is believed to produce its analgesic and antinociceptive effects across supraspinal and spinal spots rather than through a local anesthetic action (32,33).

The change in the pethidine pharmacokinetic profile gave an escalation of the plasma levels of the free drug due to competition at the protein binding sites which are available at albumins, and this directly affects the apparent volume of distribution of pethidine and tramadol, which could be ascribed to the assertion at the protein binding sites on albumins as one of the characteristic of pethidine that is extensively protein-bound 65-75 % (34,35). At the same time, tramadol is considered relatively low protein-bound at 20% (36-38). This leads to a rise in the amount of available pethidine-free medicaments at the sites of action.

Furthermore, both pethidine and tramadol affect the essential pharmacokinetic variables such as absorption, metabolism, and excretion, including other aspects like mean residence time, elimination rate constant, the clearance of the medication, and half-life as illustrated in the findings. Former studies discovered that pethidine and tramadol are effective in postoperative analgesia, obstetric pain, and pain duo to various other origins (9,39,40).

Conclusion

In general, the findings disclosed a synergism as a mode of pharmacological interaction between pethidine and tramadol and an alteration in pethidine pharmacokinetics that could improve pethidine effectiveness in the rats.

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Conflict of interest

There are no conflicts of interest declared by the authors.

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نوع التداخل الدوائي بين البيثيدين والترامادول هو تداخل تآزري كنوع من أنواع التداخل الدوائي-الديناميكي بينهما. كان تركيز البيثيدين في بلازما الدم (عند إعطائه حقنه بجرعة ١,٧ ملغم/كغم، في البريتون) خلال أوقات القياس المختلفة وهي ٥,٠، ١، ٢، ٤، ٢٤ ساعة هي ٣٦٩,٠٠، ٤٩٣,٣٣، ٣٧٣,٣٣، ٣٠٥,٣٣، ٣٠٦,٣٣ و ٢٤٧,٦٧ ميكروغرام/مل وسبب إعطاء الترامادول (٤٨,٤٢ ملغم/كغم، في البريتون) مع البيثيدين انخفاضا معنويا في تركيزه على التوالي بنسبة ٣٨، ٤٦، ٣٨، ٣٥، ٣٦ و ٢٧% إذ اصبح تركيزه ٢٢٩,٣٣، ٢٦٨,٣٣، ٢٣٣,٠٠، ١٩٨,٣٣، ١٩٥,٦٧ و ١٨٠,٣٣ ميكروغرام/مل. تكونت الحركية الدوائية للبيثيدين من معايير المنطقة الواقعة تحت المنحنى، المنطقة الواقعة تحت منحنى اللحظة، متوسط وقت البقاء، عمر النصف وحجم التوزيع إذ زادت هذه المعايير عند حقن الترامادول مع البيثيدين على التوالي بنسبة ٤٩، ٤٣، ٣٧، ١٣٦ و ٦٤% وقلت معايير التركيز الأعلى وثابت معدل الطرح على التوالي بنسبة ٤٧ و ٦٠%. تدل النتائج على العموم أن هناك تداخلا تآزريا بين البيثيدين والترامادول فضلا عن التحوير في قياسات الحركية الدوائية للبيثيدين عند الإعطاء المترافق للترامادول مما قد تزيد من الفعالية الدوائية للبيثيدين في نموذج الجرذان.

تحديد الحركية الدوائية المتزامن للبيثيدين في الجرذان: تأثير الإعطاء المترافق للترامادول

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الخلاصة

لم يتم التطرق في دراسات سابقة الى تداخل وتأثير الترامادول على تركيز البيثيدين في بلازما الدم فضلا عن التغير في حركيته الدوائية في الجرذان. قدرت الجرعة الفعالة الوسطية (الجف٥٠) للبيثيدين والترامادول المسكنة للألم بحيث كانت على التوالي ٣,٥٥ و ٢٤,٢١ ملغم/كغم، في الخلب. بعد هذا، تم حدد التداخل الدوائي ونوعه بين البيثيدين والترامادول عن طريق الاستعانة بتحليل الايزوبولوكرافيك إذ أصبحت على التوالي ١,٦٥ و ١١,٢٧ ملغم/كغم، في الخلب وتبين أن