THE EFFECT OF HIGH CONCENTRATIONS OF FENTANYL ON AN ISOLATED HEART OF RAT

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Synthetic short-acting opioids are commonly used in anesthesiology as painkillers because their effect is more pronounced compared to that of natural substances. However, they have a number of side effects that, when fentanyl is used in doses larger than therapeutic, can lead to a lethal outcome. This study aimed to assess the cardiotropic effects of high doses of fentanyl using a rat heart isolated in a Langendorff perfusion system. Parameters of the heart's contractile activity were recorded with the help of PowerLab Data acquisition system 8/30 (ADInstruments, USA) and processed in the LabChartProUpgrade 7.0 program. At the concentration of 3.7×10^{-6} M, which corresponds to the opioid content in blood after administration of a 5 ED_{50} dose, fentanyl caused the QT interval duration to grow by 22%, as registered on an ECG, and a 256% spike of T wave (compared to control; $p < 0.05$). At the concentration of 7.4×10^{-6} M (10 ED_{50}), the drug decreased heart rate by 20.4% ($p < 0.05$) and triggered a coronary constrictor effect that raised the perfusion pressure by 18.6% ($p < 0.05$). Further increase of fentanyl concentration to 1.5×10^{-5} M (20 ED_{50}) was accompanied by an 83.5% growth of the end diastolic pressure ($p < 0.05$). Administration of nalmefene, non-selective opioid receptor blocker, did not cancel the cardiovasotropic action of fentanyl. Thus, fentanyl has a dose-dependent cardiotoxic effect. Despite the drop in the registered values of isolated heart's parameters, the results of this experiment confirm that cardiac activity persists under the influence of high doses of the opioid.

Keywords: opioid analgesics, isolated heart, fentanyl

Author contributions: Nechaykina OV — study conceptualization and design, data collection, data processing, article authoring; Laptev DS — study conceptualization and design, data collection, data processing, article editing; Bobkov DV — data processing, article editing; Petunov SG — data processing and interpretation, general guidance; Radilov AD — data processing and interpretation.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Research Institute of Hygiene, Occupational Pathology and Human Ecology (Minutes #3 of July 21, 2022), and executed in compliance with the bioethics rules approved by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. The animals were kept in accordance with GOST 33215-2014 Laboratory Animals Keeping Guidelines (edition of 2016).

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Received: 06.03.2024 **Accepted:** 08.06.2024 **Published online:** 26.06.2024

DOI: 10.47183/mes.2024.021

ДЕЙСТВИЕ ВЫСОКИХ КОНЦЕНТРАЦИЙ ФЕНТАНИЛА НА ИЗОЛИРОВАННОЕ СЕРДЦЕ КРЫСЫ

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Синтетические опиоиды короткого действия получили широкое распространение в анестезиологии в качестве обезболивающих средств за счет более выраженного эффекта в сравнении с природными веществами. Однако они обладают рядом побочных эффектов, которые при использовании фентанила в дозах, превышающих терапевтические, могут приводить к смертельным исходам. Целью работы было оценить кардиотропные эффекты высоких доз фентанила на модели изолированного по Лангендорфу сердца крысы. Параметры сократительной активности изолированного сердца крысы регистрировали с помощью системы PowerLab Data acquisition system 8/30 (ADInstruments, USA) с последующей обработкой в программе LabChartProUpgrade 7.0. При действии фентанила в концентрации $3,7 \times 10^{-6}$ М, что соответствует содержанию опиоида в крови при его внутривенном введении в дозе 5 ED_{50}, зарегистрировано увеличение продолжительности QT-интервала на ЭКГ на 22% и рост амплитуды зубца Т на 256% по сравнению с контролем ($p < 0,05$). При действии фентанила в концентрации $7,4 \times 10^{-6}$ М (10 ED_{50}) зарегистрированы снижение ЧСС на 20,4% ($p < 0,05$) и коронароконстрикторное действие, выражающееся в увеличении давления перфузии на 18,6% ($p < 0,05$) по сравнению с контролем. Увеличение концентрации фентанила до $1,5 \times 10^{-5}$ М (20 ED_{50}) сопровождалось ростом конечного диастолического давления на 83,5% ($p < 0,05$). Использование неселективного блокатора опиоидных рецепторов налмефена не приводило к отмене кардиовазотропных эффектов фентанила. Таким образом, фентанил обладает дозозависимым кардиотоксическим влиянием. Несмотря на снижение регистрируемых показателей изолированного сердца, полученные результаты свидетельствуют о сохранении сердечной деятельности миокарда при влиянии высоких доз опиоида.

Ключевые слова: опиоидные анальгетики, изолированное сердце, фентанил

Вклад авторов: О. В. Нечайкина — концепция и дизайн исследования, сбор информации, обработка данных, написание текста; Д. С. Лаптев — концепция и дизайн исследования, сбор информации, обработка данных, редактирование; Д. В. Бобков — обработка данных, редактирование; С. Г. Петунов — обработка и интерпретация данных, общее руководство; А. Д. Радилов — обработка и интерпретация данных.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГУП НИИ «ГПЭЧ» ФМБА России (протокол № 3 от 21 июля 2022 г.), выполнено с соблюдением правил биоэтики, утвержденных Европейской конвенцией о защите позвоночных животных, используемых для экспериментальных и других целей. Животных содержали в соответствии с ГОСТ 33215–2014 «Руководство по содержанию и уходу за лабораторными животными» от 2016 г.

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Статья получена: 06.03.2024 **Статья принята к печати:** 08.06.2024 **Опубликована онлайн:** 26.06.2024

DOI: 10.47183/mes.2024.021

Synthetic opioids are widely used in medicine as powerful painkillers (opioid analgesics) or as an adjunct to non-narcotic anesthetics. At the same time, abuse of narcotic substances and the associated growth of the number of acute poisoning cases remain a serious social problem. According to the State Antidrug Committee, in 2022, there has been registered 22,000 cases of acute poisoning with narcotic substances and psychodisleptics in Russia, 10,000 of which had a lethal

outcome. Fentanyl, an agonist mainly of the μ-opioid receptors found in the central nervous system, heart, lungs, blood vessels and intestines, is one of the commonly abused drugs [1]. The main side effects of opioid analgesics are well known: respiratory depression and an increased risk of lethal apnea, hemodynamic changes, histamine release, hypersensitivity reactions, and serotonin syndrome [2]. Among the most significant causes of death associated with fentanyl overdose are respiratory depression, pulmonary edema, respiratory arrest, bradycardia, and cardiac arrest.

There is only a limited number of published papers that touch upon the subject of effect of deliberately high doses of fentanyl on the myocardium in the context of an overdose. This study aimed to assess the cardiotropic effects of toxic doses of fentanyl using a rat's heart isolated in a Langendorff perfusion system.

METHODS

An isolated heart model is the most informative and adequate solution for the task of gauging direct effects of opioids on the myocardium: it removes the influence of systemic regulatory factors, provides the most objective information about how xenobiotics affect the functional activity parameters, allows determining the degree of dysfunction caused by xenobiotics at the level of organs, and enables assessment of the possibility of pharmacological adjustment of the identified changes.

For the experiment, we made isolated heart models using the myocardium of male white mongrel rats weighing 300–350 g (branch of the Kurchatov Institute – PNPI – Rappolovo Laboratory Animal Nursery; Leningrad region).

The rooms where the animals were kept had the following parameters: temperature 20 ± 1 °C, relative humidity 60 ± 5%, 12 hours of daylight and 12 hours of night. The animals had unrestricted access to water and food.

The choice of the active substance concentrations for the study was based on the data found in scientific literature, according to which injection of a 5 ED_{50} dose of fentanyl into the rat's tail vein induced a superficial coma with a 100% survival rate [3, 4]. Hot plate test allowed establishing the ED_{50} of fentanyl for white rats: 0.01 mg/kg [5].

For the purpose of evaluating the resistance of myocardium to the effects of high doses of fentanyl, we selected three concentrations: 3.7×10^{-6} M, 7.4×10^{-6} M, and 1.5×10^{-5} M, which, in terms of fentanyl content in blood after an IV injection, are equivalent to doses 5 ED_{50}, 10 ED_{50}, 20 ED_{50}, respectively.

Experimental animals were euthanized by stunning and bilateral transabdominal thoracotomy, the latter performed after securing the bodies in the preparation pans. This method of euthanasia was chosen because of the need to have an intact contracting heart, which disallows narcotization of experimental animals or inducing systemic hypoxia. The heart, once exposed, was taken by the base with thumb and forefinger of the left hand, carefully pulled ventrally and downward, then the great vessels were cut with scissors. Immediately after the heart was removed from the chest cavity, it was placed in Krebs-Henseleit saline solution of the following composition (in mM): NaCl — 118.99; KCl — 4.69; $NaHCO_3$ — 25; KH_2PO_4 — 1.18; $MgSO_4 \times 7\ H_2O$ — 1.17; $CaCl_2 \times 2\ H_2O$ — 2.5; EDTA — 0.03; $C_6H_{12}O_6$ — 5.5. The aorta was fixed to the cannula of the Langendorff System perfusion rig (Panlab; Spain) with a crocodile clamp and then with sutures. The heart was perfused through the cannula, with the perfusate retrogradely delivered to the left ventricle. The perfusate was Krebs-Henseleit solution warmed to 37 °C. To bring its pH to the physiological level (7.39–7.41) and to ensure adequate oxygenation of the heart, the solution was continuously aerated with carbogen (95% oxygen and 5% carbon dioxide). The feeding rate of the perfusate (delivered by a peristaltic pump) was 10 ml per minute per 1 g of heart wet weight. The adequacy of perfusion was judged by the pressure in the "pump – aortic cannula" circuit (at least 50 mmHg). Contractile activity of the heart stabilized within 30 minutes from its locking in the system; after that, the contractility baseline value was registered [6]. We used a catheter with a polyethylene balloon to measure pressure in the left ventricle. The parameters of cardiac contractile activity were recorded using the PowerLab Data acquisition system 8/30 (ADInstruments; USA) and subsequently processed in the LabChartProUpgrade 7.0 software (ADInstruments; USA). The recorded parameters were perfusion pressure (PerP; reflects coronary flow); pressure in the left ventricle (systolic, diastolic); heart rate (HR; beats/minute); end diastolic pressure (EDP, mmHg; reflects the left ventricle's relaxation capacity). Simultaneously with registration of the parameters of myocardial contractile activity, we recorded ECG.

At the end of stabilization, we added fentanyl to the perfusate in one of the studied concentrations, seeking to identify the dose — effect relationship. For each concentration, the exposure time was 10 minutes. Nalmefene, a non-selective opioid receptor antagonist, was used at a concentration of 1×10^{-6} M to evaluate fentanyl's receptor activation capacity.

After the experiment, we calculated pulse pressure (PP, mmHg), the integral cardiac contractility index per minute (Int_{1min}, c.u.), and the first time derivative of pressure (+dP/dt and –dP/dt, mmHg/s) that describes the rate of left ventricle's contraction and relaxation.

For the analysis part, we compared the dynamics of parameters of the cardiac contractile and electrical activity in treatment and control groups. GraphPad Prism 5.04 software (USA) was used for statistical processing. To establish the significance of differences in the values intragroup, we applied the Wilcoxon T-test for related samples, and for intergroup differences we used the Mann–Whitney *U*-test. The differences were considered significant at $p \leq 0.05$.

RESULTS

The study has shown that the action of fentanyl on an isolated heart depends on the concentration, and the drug can have opposite effects. Minimal and medium concentrations yielded potentiating effect: left ventricular contraction rate increased by 9.7 and 8.4%, respectively (Table 1).

Medium (7.4×10^{-6} M) and high (1.5×10^{-5} M) concentrations trigger vasoconstriction, wuth perfusion pressure growing by 18.6 and 46.5%, respectively. A negative lusitropic effect, when the heart's diastolic relaxation capability deteriorates, was registered only after administration of the maximum studied concentration, with the said effect confirmed by the growth of end diastolic pressure by 83.5% compared to the values recorded in the control group.

Medium and high concentrations of fentanyl provoked a significant drop in the heart rate: by 20.4 and 28.3%, respectively, compared to the control. The negative chronotropic effect of the drug pushed the integral myocardial contractility index down while the pulse pressure did not change (Table 1).

The vasotropic effects of fentanyl at the concentration of 1.5×10^{-5} M were almost unaffected by nalmefene injected at the concentration of 1×10^{-6} M (Table 1).

The effect of fentanyl at concentrations of 3.7×10^{-6} M, 7.4×10^{-6} M, 1.5×10^{-5} M on the isolated heart's electrical activity manifested in the growth of the QT interval (compared

Table 1. Parameters of contractile activity of the isolated heart of white rats under the action of fentanyl. The data are percentage relative to the background (M ± SE)

Perfusate	*n*	PerP	Int $_{1min}$	Heart rate	PP	+dP/dt	–dP/dt	EDP
Control (saline solution)	20	99.3 ± 1.8	99.4 ± 2.2	98.7 ± 4.1	103 ± 4.1	100.9 ± 1.5	101.5 ± 2.9	100.1 ± 3.2
Fentanyl 3.7×10^{-6} M	6	110.4 ± 7.8	95.1 ± 5.2	100.3 ± 6.0	102.4 ± 7.1	110.6 ± 4.4*	110.2 ± 2.8	78.9 ± 12.3
Fentanyl 7.4×10^{-6} M	6	118.6 ± 7.1*	93.3 ± 3.4	78.3 ± 5.5*	105.2 ± 2.4	109.3 ± 1.5*	104.8 ± 2.3	90.3 ± 8.3
Фентанил 1.5×10^{-5} M	6	146.5 ± 6.1*	93.9 ± 2.2	70.4 ± 7.1*	94.5 ± 2.6	97.0 ± 0.7	94.0 ± 4.5	183.6 ± 18.8*
Fentanyl 1.5×10^{-5} M + nalmefene 1×10^{-6} M	6	125.8 ± 13.6*	81.6 ± 4.7*	68.7 ± 15.2*	91.3 ± 6.9	92.9 ± 3.3	90.6 ± 1.7	195.8 ± 23.5*

Note: * — statistically significant difference from the control at $p < 0.05$; *n* — number of observations; PerP — perfusion pressure; Int $_{1min}$ — integral indicator of heart contractility per minute; PP — pulse pressure; +dP/dt and –dP/dt — first time derivative of pressure; EDP — end diastolic pressure.

to the control) by 22%, 24% and 53%, and T-wave amplitude of 256%, 307% and 245%, respectively (Table 2).

The increase in the rate of myocardial contraction (+dP/dt) associated with administration of fentanyl at the concentrations of 3.7×10^{-6} M and 7.4×10^{-6} M was accompanied by an increase amplitude of the R-wave.

DISCUSSION

The effects of fentanyl on the cardiovascular system in general and on the myocardium in particular have been investigated for a long period of time. The respective studies yielded large amount of evidence from experiments with models based on objects of various levels of organization. An ex vivo isolated heart model that excludes modulation from the central nervous system allowed documenting the most complete and objective description of the cardiotropic effect of fentanyl, with some points thereof confirmed by numerous works by Russian and foreign authors [7–9].

This study looked into the direct effects fentanyl has on the heart. For the minimal considered concentration of the drug (3.7×10^{-6} M), we learned that it raises the rate of contraction of the left ventricle, which is a sensitive marker of its systolic function, and does not affect heart rate and PP. As a trend, we have also registered faster relaxation of the left ventricle and a drop of the end diastolic pressure associated therewith, which signal a positive lusitropic effect of fentanyl on the isolated rat heart. This effect is likely mediated by catecholamines that induce calcium uptake in the sarcoplasmic reticulum and, consequently, trigger a rapid depletion thereof in the cytosol.

A higher concentration of fentanyl in the perfusate (7.4×10^{-6} M) raises perfusion pressure by inducing vasoconstriction of the coronary artery and heart rate slowdown (a negative chronotropic effect). The rate of contraction of the left ventricle grows further, but the positive lusitropic effect is offset almost completely.

Addition of fentanyl to the perfusate to the concentration of 1.5×10^{-5} M causes heart rate drop and perfusion pressure growth. Coronary vessels narrow significantly, which limits inflow of oxygen and energy substrates and, consequently, disrupts transportation of calcium ions from the cytosol to intracellular depots of cardiomyocytes. The ultimate outcome is the significant increase of EDP, which reflects deterioration of the myocardium's relaxation capacity.

Pretreatment of isolated heart preparations with nalmefene (1×10^{-6} M) did not yield cancellation of the cardiovasotropic effects of fentanyl administered at the concentration of 1.5×10^{-5} M. Moreover, with nalmefene in the background, we registered a progressive inhibition of the heart's contractile function, which was seen in all its parameters except the perfusion pressure. Continued depression of the myocardium's functional activity under the action of fentanyl when opioid receptors are blocked can indicate that the drug's cardiotropic effects are realized, inter alia, through the activation of non-opioid receptors [10].

Studying the effect of fentanyl on the electrical activity of an isolated rat heart, we registered a dose-dependent elongation of the QT interval, which reflects the longer time of excitation of the ventricles. Such changes are possible when the electrolyte balance is disrupted, or in case of a myocardial ischemia, which are unfavorable prognostic signs. This fact was confirmed by an experimental study that reported a significant increase of duration of action potential of dog's cardiomyocytes under the influence of fentanyl (1.9×10^{-7} M) [11]. In addition, the negative effect of the studied concentrations of the drug on the myocardium are evidenced by an increase amplitude T-wave that reflects repolarization of the ventricular myocardium, which may indicate myocardial ischemia caused by increased coronary artery tone and decreased oxygen flow.

CONCLUSIONS

In the course of the study, we analyzed the effect of fentanyl on an isolated rat heart in concentrations significantly higher than

Table 2. Parameters of ECG of the isolated heart of white rats under the action of fentanyl. The data are in absolute values (M ± SE)

Group of animals	RR interval, s	PR interval, s	Duration P, s	QRS interval, s	QT interval, s	Amplitude R, mV	Amplitude T, mV
Control	0.265 ± 0.020	0.061 ± 0.011	0.032 ± 0.010	0.022 ± 0.001	0.078 ± 0.007	4.016 ± 0.570	0.749 ± 0.152
Fentanyl $3{,}7 \times 10^{-6}$ M	0.309 ± 0.270	0.064 ± 0.003	0.019 ± 0.002	0.024 ± 0.001	0.095 ± 0.004*	11.150 ± 1.852*	2.667 ± 0.942*
Fentanyl $7{,}4 \times 10^{-6}$ M	0.373 ± 0.047	0.064 ± 0.005	0.019 ± 0.002	0.020 ± 0.002	0.097 ± 0.007*	10.790 ± 1.539*	3.047 ± 0.928*
Fentanyl $1{,}5 \times 10^{-5}$ M	0.381 ± 0.063	0.069 ± 0.009	0.023 ± 0.002	0.025 ± 0.001	0.119 ± 0.003*	8.167 ± 0.905*	2.883 ± 0.450*

Note: * — statistically significant difference from control at $p < 0.05$.

those achieved when the drug is used for therapeutic purposes. For the minimal studied concentration (3.7×10^{-6} M), the effects were visible mostly on ECG. The parameters describing myocardium's contractile activity practically remained unchanged, with the exception of the rate of contraction of the left ventricle (it increased), which is a sensitive indicator of the cardiotropic effect of the drug. Higher concentrations of fentanyl in the perfusate (7.4×10^{-6} M and 1.5×10^{-5} M) supported changes in the electrical activity and triggered further negative changes: heart rate depression, vasoconstriction and subsequent drop in the coronary flow, disruption of the heart's diastolic function, which indirectly points to hindered energy supply. Thus, fentanyl has a dose-dependent cardiotoxic effect. Our results indicate that under the influence of high (sublethal) doses of the opioid, cardiac activity persists. Fentanyl's cardiotoxic effects are realized through activation of both opioid and non-opioid receptors, which should be factored in when planning pharmacological measures to counter its negative effects.

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