ЕКСПЕРИМЕНТАЛЬНА ТА КЛІНІЧНА ФАРМАКОЛОГІЯ

Recommended by Doctor of Pharmacy, Professor B.A.Samura

UDC 615.015.35:547.472.2

DETERMINATION OF TOXICITY OF NEW BENZILIC ACID DERIVATIVES

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Key words: acute toxicity; derivatives of benzilic acid; low-toxic compounds

The acute toxicity of 17 new derivatives of benzilic acid in outbred mice weighing 20-26 g has been determined. Animals were divided into 68 groups of 5 mice each. Each group of animals received the aqueous solution of the substance under study once orally by gavage in the doses of 100, 250, 750, 1000 mg/kg. The total duration of follow-up of the animals after administration of the test substance was 14 days. Administration of substances under the codes of KMS-10, KMS-19, KMS-49, KMS-68, KMS-70, KMS-71, KMS-73, KMS-228, KMS-230, KMS-284 in the dose of 1000 mg/kg caused no deaths of mice. It suggests that these substances are non-toxic in the selected doses. Since the dose of 1000 mg/kg did not result in the death of animals in these groups, the conclusion can be made that LD_{50}>1000 mg/kg. According to the classification of K.K. Sidorov the substances under study can be referred to Class IV toxicity (low-toxic compounds).

Modern drugs should be characterized by low toxicity and high efficiency [4]. Determination of the acute toxicity of substances is the first stage when considering toxicological characteristics; its aim is to obtain information concerning the substance danger to health in terms of the short-term action. These data can be taken as a basis for toxicity class determination. Taking into account the possibility of random situations that cause accidents, suicide and criminal poisonings it is expedient to determine the acute toxicity for the oral route of administration [1]. To study the toxicity of substances the pharmacological model, which makes possible to study the effects on the experimental animals, is created.

The aim of this study was to determine the acute toxicity of new pharmacologically active derivatives of benzilic acid.

Materials and Methods

The study objects included 17 new derivatives of benzilic acid synthesized at the Department of Organic Chemistry of the National University of Pharmacy. Determination of the acute toxicity was conducted according to the guidelines "Preclinical studies of drugs" edited by O.Stefanov in outbred mice weighing 20-26 g. They were kept in the vivarium of the Central Research Laboratory of the National University of Pharmacy in standard conditions on a normal diet with a free access to food and water [1]. Animals were divided into 68 groups of 5 mice each. Each group of animals received the aqueous solution of the substance under study once orally by gavage in the doses of 100, 250, 750, 1000 mg/kg [2]. The total duration of follow-up of the animals after administration of the test substance was 14 days. The following parameters were taken into account: appearance, behaviour of animals, condition of hair, visible mucous membranes, attitude to food, rhythm, respiratory rate, time of occurrence and nature of intoxication, its severity, course, and time of the animals' death or recovery [5]. The experiment was carried out in strict compliance with the requirements of the European Convention "On protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 1986) [3].

Results and Discussion

The results obtained within 14 days of observation of the laboratory animals received the test compounds in the dose of 1000 mg/kg are given in Tab. 1. In the early days of the experiment the animals remained active, agile, had normal motor coordination, standard response to external stimuli, normal appearance, and that was similar to the group of control animals. On the third and eighth days of the study one animal died from each group receiving the aqueous solutions of products of cyclization of benzilic acid amides containing the fragment of 2-oxo-3,3-diphenyl-2,3-dihydro-1H-thieno[3, 4-b]pyrrole-6-carboxylic acid – KMS-72 and KMS-69, respectively. On the eighth day of the experiment one animal also died from each group receiving the dose of 3-indolilamid of benzilic acid (KMS-283) and thienolactams with six-membered (KMS-303) and seven-membered (KMS-258) cycles. Animals receiving the substance KMS-72 (1 mouse), KMS-282 (2 mice) had wounds on their back, and mice from groups receiving KMS-229, KMS-230, KMS-282 KMS-303 had problems with their eyes. On the background of all experimental animals the mouse receiving the substance KMS-282 was very weak and

Table 1

The acute toxicity of benzilic acid derivatives in the dose of 1000 mg/kg with the oral route of administration

Substance	The number of dead animals/ the total number of animals in the group	Substance	The number of dead animals/ the total number of animals in the group
KMS-10	0/5	KMS-228	0/5
KMS-19	0/5	KMS-229	3/5
KMS-49	0/5	KMS-230	0/5
KMS-68	0/5	KMS-258	1/5
KMS-69	1/5	KMS-282	2/5
KMS-70	0/5	KMS-283	1/5
KMS-71	0/5	KMS-284	0/5
KMS-72	1/5	KMS-303	1/5
KMS-73	0/5		

Table 2

The acute toxicity of benzilic acid derivatives in the dose up to 1000 mg/kg with the oral route of administration

Substance	The number of dead animals/ the total number of animals in the group	Substance	The number of dead animals/ the total number of animals in the group
KMS-10	0/5	KMS-228	0/5
KMS-19	0/5	KMS-229	0/5
KMS-49	0/5	KMS-230	0/5
KMS-68	0/5	KMS-258	0/5
KMS-69	0/5	KMS-282	0/5
KMS-70	0/5	KMS-283	0/5
KMS-71	0/5	KMS-284	0/5
KMS-72	0/5	KMS-303	0/5
KMS-73	0/5		

died the next day, and the animal from another group of thienolactam studied with seven-membered cycle (KMS-229) also died. On the eleventh day of the study we lost another 3 animals: one mouse from KMS-282 group and two mice receiving the substance KMS-229. Introduction of this substance resulted in death of 3 animals due to its toxic effects; there were no visible changes in behaviour or appearance of the experimental animals. In the group of animals receiving dimethyl-substituted 3-indolilamid (KMS-282) two animals died: one mouse, as mentioned above, had wounds on its back, another mouse experienced disorientation in space and the motor activity impairment on the background of eye lesions.

It should be also noted that when introducing substances KMS-69 and KMS-303 the inhibition of the visual analyzer response was observed in the experimental animals.

When studying toxicity of the test compounds administered to laboratory animals in the doses of 100, 250, 750 mg/kg no animals died, their appearance and behaviour did not change within the entire observation period (Tab. 2).

Thus, within 14 days of observation in groups of animals received the new derivatives of benzilic acid under the codes KMS-10, KMS-19, KMS-49, KMS-68, MS-70, KMS-71, KMS-73, KMS-228, KMS-230, KMS-284 in the dose of 1000 mg/kg no deaths of mice were observed. It suggests that these substances are non-toxic in the selected doses. Since the dose of 1000 mg/kg did not result in the death of animals in these groups, the conclusion can be made that LD_{50}>1000 mg/kg. According to the classification of Sidorov K.K. the test substances can be referred to Class IV toxicity (low-toxic compounds) [2].

CONCLUSIONS

The acute toxicity of new derivatives of benzilic acid has been determined. Substances KMS-10, KMS-19, KMS-49, KMS-68, KMS-70, KMS-71, KMS-73, KMS-228, KMS-230, KMS-284 are non-toxic in the dose of 1000 mg/kg according to the classification of K.K. Sidorov. Therefore, these substances can be referred to Class IV toxicity (low-toxic compounds).

REFERENCES

1. *Доклінічні дослідження лікарських засобів: Метод. рекоменд. / За ред. О.В.Стефанова. – К.: Авіценна, 2001. – 528 с.*
2. *Патерега І. П. // Наук.-техн. бюл. Інституту біології тварин і Державного науково-дослідного контрольного інституту ветпрепаратів та кормових добавок. – 2013. – Вип. 14, №3-4. – С. 189-192. – Режим доступу: http://nbuv.gov.ua/j-pdf/Ntbibt_2013_14_3-4_37.pdf*
3. *Саліонов В.О. // Актуальні питання фар мац. і мед. науки та практики. – 2015. – №3(19). – С. 19-24.*
4. *Сидоров К.К. Токсикология новых промышленных химических веществ. – М.: Медицина, 1973. – Вып. 3. – 47 с.*
5. *European convention for the protection of vertebrate animals used for experimental and other scientific purposes. – Council of Europe, Strasbourg, 1986. – 53 p.*

ВИЗНАЧЕННЯ ТОКСИЧНОСТІ НОВИХ ПОХІДНИХ БЕНЗИЛОВОЇ КИСЛОТИ

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Ключові слова: *гостра токсичність; похідні бензилової кислоти; малотоксичні сполуки*

Досліджено гостру токсичність 17 нових похідних бензилової кислоти на безпородних мишах масою 20-26 г. Тварини були розділені на 68 груп по 5 мишей в кожній. Кожна група тварин отримувала перорально через шлунковий зонд одноразово водний розчин досліджуваної речовини в дозах 100, 250, 750, 1000 мг/кг. Загальна тривалість нагляду за тваринами після введення досліджуваної речовини складала 14 днів. Введення речовин під шифрами KMS-10, KMS-19, KMS-49, KMS-68, KMS-70, KMS-71, KMS-73, KMS-228, KMS-230, KMS-284 в дозі 1000 мг/кг не викликало загибелі мишей, що дозволяє вважати досліджувані речовини нетоксичними в обраній дозі. Оскільки доза 1000 мг/кг не призвела до смерті тварин у даних групах, можна зробити висновок, що LD_{50}>1000 мг/кг і згідно з класифікацією Сидорова К.К. досліджувані речовини можна віднести до IV класу токсичності (малотоксичні сполуки).

ОПРЕДЕЛЕНИЕ ТОКСИЧНОСТИ НОВЫХ ПРОИЗВОДНЫХ БЕНЗИЛОВОЙ КИСЛОТЫ

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Ключевые слова*: острая токсичность; производные бензиловой кислоты; малотоксичные соединения*

Установлена острая токсичность 17 новых производных бензиловой кислоты на беспородных мышах массой 20-26 г. Животные были разделены на 68 групп по 5 мышей в каждой. Каждая группа животных получала перорально через желудочный зонд однократно водный раствор исследуемого вещества в дозах 100, 250, 750, 1000 мг/кг. Общее время наблюдения за животными после введения исследуемого вещества составляло 14 дней. Введение веществ под шифрами KMS-10, KMS-19, KMS-49, KMS-68, KMS-70, KMS-71, KMS-73, KMS-228, KMS-230, KMS-284 в дозе 1000 мг/кг не вызывало гибели мышей, что позволяет считать данные соединения нетоксичными в выбранной дозе. Поскольку доза 1000 мг/кг не приводила к смерти животных в данных группах, можно сделать взвод, что LD_{50}>1000 мг/кг и согласно классификации Сидорова К.К. исследуемые вещества можно отнести к IV классу токсичности (малотоксичные соединения).