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ASSESSMENT OF THE EFFECT OF EPITRIAZOLINE ON THE PHYSICAL AND PSYCHO-EMOTIONAL STATE OF EXPERIMENTAL ANIMALS WITH CHRONIC ADMINISTRATION

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ABSTRACT
This article shows that 4-(6-phenyl-7H - [1,2,4] triazolo [3,4-B] [1,3,4] thiadiazine-3-yl) - aniline is conditionally Epitriazoline in white rats 0.25, 2.5 and 25.0 mg/kg orally for 3 months, depending on body weight The body, skin color, coat condition, effects on motor and research activity in the "open field" method, and anti-anxiety activity have been confirmed by experimental data, and we can say that side effects do not appear with chronic administration.

ОЦЕНКА ВЛИЯНИЯ ЭПИТРИАЗОЛИНА НА ФИЗИЧЕСКОЕ И ПСИХОЭМОЦИОНАЛЬНОЕ СОСТОЯНИЕ ПОДОПЫТНЫХ ЖИВОТНЫХ ПРИ ХРОНИЧЕСКОМ ВВЕДЕНИИ

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ABSTRACT
В этой статье показано, что 4-(6-фенил-7H - [1,2,4] триазоло [3,4-B] [1,3,4] тиадиазин-3-ил) - анилин условно-Эпитриазолин у белых крыс 0,25; 2,5 и 25,0 мг/кг при пероральном приеме в течение 3 месяцев в зависимости от массы тела, цвета кожи, состояния шерсти, влияние на двигательную и исследовательскую активность в методе "открытое поле", противотревожную активность подтверждена экспериментальными данними, и мы можем сказать, что побочные эффекты не проявляются при хроническом введении.

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активность, хроническая токсичность.

EPITRIAZOLINNI SURUNKALI YUBORILGANDA TAJRIBA HAYVONLARINING FIZIK VA PSIXOEMOTSIONAL HOLATIGA TA'SIRINI BAHOLASH

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ABSTRACT

Ushbu maqolada 4-(6-fenil-7H-[1,2,4]triazolo[3,4-b][1,3,4]tiadiazin-3-il)-anilin shartli ravishda-Epitriazolin birikmasi oq kalamushlarda 0.25; 2.5 va 25.0 mg/kg dozalarda 3 oy davomida og'iz orqali berilganda tana massasi, teri rangi, jun holatiga, "ochiq maydon" usulida harakat va qidiruv faolligiga ta'siri, his-hayajonga qarshi faolligi eksperimental tajribalar asosida tasdiqlangan va surunkali berilganda nojo'ya ta'sirlar yuzaga chiqmaganligini ko'rishimiz mumkin.

Dolzarbligi. Epilepsiya bosh miyaning surunkali kasalligi bo'lib, yer yuzi aholisining 1%dan ko'prog'i ushbu dard bilan aziyat chekib kelmoqda [1]. Tutqanoq bilan kechadigan kasalliklarda qo'llaniladigan dori preparatlari uzoq vaqt davomida davolashni talab qiladi. Darhaqiqat antiepileptik davoning asosiy maqsadi kasallanishdagi xurujlar sonini kamaytirish, hayot sifatini yaxshilash va o'lim holatlarini oldini olishdan iborat. Shu sababdan yuqori faollikka ega bo'lgan, kam zaharli va surunkali terapiya davomida tajriba hayvonlarida kuzatilishi mumkin bo'lgan nojo'ya ta'sirlarni oldindan aniqlash muhim ahamiyat kasb etadi [2]. So'nggi yillarda 1,2,4-triazol hosilalarining umumiy farmakologik faolliklari, hayotiy muhim organlariga samarasi, neyrotrop samarasi, ta'sir mexanizmlari to'g'risida keng ko'lamli izlanishlar olib borilmoqda [3-6]. Xususan (arilalkil) triazollarga mansub loreklezol keng spektorli tutqanoqqa qarshi faolligi GAMK-retseptorlarining modulyatsiyasi bilan bog'liq [7]. Bir guruh olimlar olib borgan izlanishlarga ko'ra, 4-alkil-5-aril-1,2,4-triazol-3-tion birikmasi istiqbolli tutqanoqqa qarshi dori vositalari guruhiga kiritildi [8-11]. Bu birikmalarning tutqanoqqa qarshi faolligi natriy kanallari bilan o'zaro ta'sir qilish qobiliyatiga bog'liq [12]. Bundan tashqari, 4-alkil-5-aril-1,2,4-triazol-3-tion hosilalari yaxshi sifatli farmakologik va toksikologik ko'rsatkichlar: past neyrotoksiklik va kam zaharlilik inson hujayralariga nisbatan, genotoksik xususiyatni yuzaga keltirmasligi,

tez ta’sirini boshlanishi hamda davomli bo‘lishi, valproatning tutqanoqqa qarshi faolligini kuchayishi bilan namoyon bo‘ladi [13]. Zamonaviy tadqiqotlarga ko‘ra, hissiy-qo‘rquv, vahima, somatoform va gipoxondriya kasalliklarining tashxis qo'yilgan, boshlang'ich yoki klinik jihatdan aniqlangan belgilarining yomonlashishiga yordam beradi yurak-qon tomir tizimi bilan bog'liq kasalliklarning oldini olish, shuning uchun stress va stressni keltirib chiqaradigan jarayonlarning oldini olish jamiyatning muhim vazifasi bo'lib, nafaqat aqliy, balki yurak-qon tomir patologiyasining kuchayishi yoki rivojlanishi xavfini kamaytirishga yordam beradi [14-17].

Psixotrop faollikka эga bo‘lgan dori vositalari O‘zbekiston hududida asosan chet mamlakatlardan olib kelinadi. Ushbu dori vositalarining o‘rnini mahalliy preparatlar bilan to‘ldirish hozirgi kunda dolzarb hisoblanadi. Nafaqat O‘zbekistonda, balki butun dunyo olimlari izoxinolin alkaloidlari asosida olingan birikmalarda Shizofreniya [18], Parkinson [19], neyroprotektor [20], antidepressant [21-22] va shunga o‘xshash markaziy nerv tizimi kasalliklari bo‘yicha eksperimental tajribalar olib bormoqda. Shu sababli O‘simlik moddalari kimyosi instituti olimlari tomonidan asosida yangi birikmalarning sintezi amalga oshirilmoqda. Ushbu sintez qilingan birikmalar orasidan atipik neyroleptik [23-24], sedativ anksiolitik [25-26] faollikka эga bo‘lgan moddalar aniqlandi. Shu maqsadda 4-(6-fenil-7H-[1,2,4]triazolo[3,4-b][1,3,4]tiadiazin-3-il)-anilin birikmasi shartli ravishda – epitriazolin deb nomlangan farmakologik vositasida surunkali yuborilganda tajriba hayvonlarida fizik va psixoemotsional holatiga ta’siri o‘rganildi.

TADQIQOT UCHUN ISHLATILGAN MATERIAL VA METODLAR. Farmakologik tadqiqotlar vivariy sharoitida 14 kun karantinda saqlangan massasi 120-240 g. bo‘lgan oq kalamushlarda olib borildi. Hayvonlar bilan o‘tkazilgan barcha tajribalar umurtqali hayvonlarni himoya qilish bo‘yicha Yevropa konvensiyasining xalqaro tavsiyalari talablariga muvofiq amalga oshirildi [27]. Har bir guruh 8-10 tadan tajriba hayvonlari joylashtirildi. O‘rganiluvchi modda suvda yaxshi erimaganligi sababli, Epitriazolin TVIN-80 moddasida eritilib tajribalar olib borildi. Tadqiqotlar uchun metodik qo‘llanmada ko‘rsatilgan [28] tajriba modellarida amalga oshirildi. Surunkali zaharlilikni 0.25; 2.5 va 25 mg/kg dozada tana massasiga ta’sirini, harakatlanish aktivligi, “ochiq maydon” usulida harakat va qidiruv faolligiga ta’sirni, his-hayajonga qarshi faolligi o‘rganib chiqildi. Tajribalardan olingan natijalar statistik tahlil usullari [29] yordamida qayta ishlandi. O‘zgarishlar aniqligi p≤0,05 ko‘rsatkichi bo‘yicha hisoblandi.

NATIJALAR

Farmakologik vositalarni tirik organizmlarga ta’sirini baholashda surunkali yuborilganda amaliyotga tatbiq etilishi kutilayotgan dori vositasini xavfsizligini, kumulyativ xossaga ega emasligi, tajriba hayvonlarining jun holatiga ta’sirini, ozuqa hamda suvga bo‘lgan munosabtini qabul qilishga ta’sirini, fizik va psixoemotsional holatiga ta’sirini baholab chiqildi. Epitriazolin birikmasini yuborishdan oldin tajriba hayvonlari nazorat va uch guruhga bo‘lingan holda 90 kun davomida berilganda oq kalamushlarning ozuqa va suv iste’moliga, tashqi ko‘rinishi, umumiy hamda jun holatiga nojo‘ya ta’sirlarni yuzaga keltirmadi. Dori vositalarini surunkali yuborilganda tana massasining me’yoridan ortiq ortishi yoki kamayishi turli patologik holatlarga sabab

bo‘lishi mumkin. Dastlab barcha tajriba hayvonlarining tana massasi o‘lchab chiqilgandan so‘ng, 0.25; 2.5 va 25 mg/kg dozalarda og‘iz orqli kuniga bir mahaldan berilganda, 7; 15; 21; 28; 35; 42; 50; 60; 70; 80 va 90 kunlar davomida tana massasi nazoratga olib borildi. Har bir guruhda 8 tadan hayvonlarda o‘rtacha tana massasi statistik usullar yordamida hisoblab chiqildi. Olingan natijalar 1-jadvalda keltirilgan.

1-jadval

Epitriazolinni 3 oy davomida oq kalamushlar turli dozalarda og‘iz orqali berilganda tana massasiga ta’sirini baholash (n=8)

Guruhlar / Kunlar	Nazorat	Epitriazolin 0.25 mg/kg	Epitriazolin 2.5 mg/kg	Epitriazolin 25.0 mg/kg
Dastlabki kun	236.38±23.56	189.88±27.28	178.13±12.09	125.38±4.03
7 kun	240.63±23.25	195.00±26.66	183.50±12.40	130.38±4.65
15 kun	245.63±23.56	199.63±26.35	188.13±12.40	134.50±4.96
21 kun	250.50±23.25	205.13±26.04	192.00±12.71	138.88±5.89
28 kun	254.63±23.25	209.63±25.42	197.38±12.40	142.75±4.65
35 kun	259.50±23.87	214.75±24.80	201.13±13.64	146.75±4.96
42 kun	264.13±23.56	220.00±25.42	205.25±14.26	151.75±6.20
50 kun	268.25±23.56	224.63±24.80	210.38±16.12	157.25±6.20
60 kun	273.63±24.18	230.38±25.42	214.50±15.81	162.00±6.82
70 kun	278.38±24.18	236.88±27.59	219.25±17.05	167.88±8.06
80 kun	285.38±26.04	243.63±30.69	226.25±17.05	177.00±10.54
90 kun	291.13±31.62	250.00±32.24	230.75±17.67	185.75±12.4

Eslatma. p≤0,05 nazorat guruhiga nisbatan

Olingan natijalarga ko‘ra, tajriba hayvonlarining tana massasiga nazorat guruhiga nisbatan statistik jihatda deyarli farq qilmadi. Epitriazolinning turli dozalarida nazorat guruhiga nisbatan 3-5% tana massasining o‘zgarishi davolash paytida surunkali berilganda nojo‘ya ta’sirlarni keltirib chiqarmasligi asoslandi.

Epitriazolinning surunkali yuborilganda harakatlanish faolligini ta’sirini baholash. Harakat faolligi oq kalamushlarda 0.25; 2.5 va 25 mg/kg dozalarda og‘iz orqali yuborib, dastlabki holatda, 15; 30; 60 va 90 kunlar davomida kuzatildi. Tutqanoqqa qarshi faollikka ega bo‘lgan birikmalarda odatda harakat faolligi nisbatan kamayishi va sedativ xossani namoyon qilishi muhim ahamiyat kasb etadi. Tutqanoq yuzaga kelishida qo‘zg‘atuvchi glutaminergik mediatorlar faolligini ortishi, tormozlovchi GAMKergik mediatorlarning faolligini kamayishi toniko-klonik tutqanoqlar yuzaga kelishida muhim ahamiyat kasb etadi. Sedativ xossaga ega bo‘lgan birikmalar ushbu xurujlarni yuzaga kelish ehtimolligini kamayishiga sabab bo‘ladi. Sedativ xossa bosh miya yarim sharlarining xarakat markazidagi qo‘zg‘alish impulsini kamayishiga olib kelish ehtimoli yuqori. Ushbu xossalarni inobatga olgan holda surunkali yuborish davomiyligi asosida tajriba hayvonlarining harakatlanish aktivligiga ta’sirini o‘rganib chiqish va kerakli natijalarni olish zarur hisoblanadi. Olingan natijalar quyidagi 2-jadvalda keltirilgan.

2-jadval

Epitriazolin surunkali yuborilgandagi harakatlanish aktivligiga ta’siri (n=8)

Modda	Dastlabki holat	15 kun	30 kun	60 kun	90 kun
Nazorat guruhi	16.0±1.44 (100%)	10.0±0.96 (62.5%)	5.0±0.72 (31%)	3.5±0.24 (22%)	5.0±0.48 (31%)
0.25 mg/kg p.o.	19.0±1.92 (100%)	14.0±1.2* (74%)	12.0±0.96* (63%)	5.0±0.48* (26%)	4.0±0.48* (21%)
2.5 mg/kg p.o.	18.0±2.16 (100%)	12.0±1.92* (67%)	10.0±0.96* (56%)	7.0±0.72* (39%)	3.5±0.48* (19%)
25.0 mg/kg p.o.	18.6±1.44 (100%)	11.2±1.2* (60%)	8.8±0.96* (47%)	6.2±0.72* (33%)	3.2±0.48* (17%)

Eslatma.*P≤0.05 dastlabki holatiga nisbatan

Olingan natijalarga ko‘ra, har uchala dozada harakat aktivligini nazorat guruhiga nisbatan susaytirdi. Kuzatishlar natijasi bo‘yicha moddaning doza oshib borish tartibida harakatlanish aktivligi pasayishi, ya’ni sedativ xossasi mavjudligi to‘g‘risida xulosaga kelish mumkin.

Epitriazolinning “ochiq maydon” usulida harakat va qidiruv faolligini ta’sirini aniqlash. Ushbu usulda tekshirishdan maqsad, yuqorida o‘rganilgan usullardan ko‘rinib turibdiki, *Epitriazolin* nisbatan sedativ faollikka ega ekanligi aniqlandi. “Ochiq maydon” usulida tekshirilganda ko‘pchilik sedativ faollikka ega bo‘lgan preparatlar garchi organizm tinch turgan holatda bo‘lsa ham aqliy faoliyatni yuqori darajada saqlanganligi tajribalarda asoslangan. Shunga asoslanib, ushbu moddani 0.25; 2.5 va 25 mg/kg dozalarda oq kalamushlarda og‘iz orqali surunkali yuborilganda tajribaning 30 kunida yuzaga keladigan o‘zgarishlar o‘rganildi. Harakat va qidiruv faolligi oshishi aqliy kognitiv faoliyatni rivojlanishiga, tik turishlar sonini oshishi dofaminergik mediatorlar miqdorini ortishiga, axlat ajratishlar sonini oshishi esa his-hayajonni oshishiga olib keladi. Tajribadan olingan natijalar 3-jadvalda keltirilgan.

3-jadval

Epitriazolinni surunkali yuborilganda tajribaning 30 kundagi “ochiq maydon” usulida o‘rganish

Modda	Harakat faolligi	Qidiruv faolligi	Tik turishi	Axlat ajratish soni
Nazorat guruhi	8.7±1.3	9.2±1.5	0	2.5±0.9
Epitriazolin 0.25 mg/kg p.o.	12.4±2.8*	11.4±2.4*	2.1±0.6*	1±0.05*
Epitriazolin 2.5 mg/kg p.o.	14.8±3.7*	13.2±3.2*	1.6±0.2*	0*
Epitriazolin 25 mg/kg p.o.	15,9±4.2*	13.8±2.7*	1.2±0.2*	1±0.06*

Eslatma.*p≤0,05 nazorat guruhiga nisbatan

Yuqorida o‘tkazilgan tajribalarga asoslanib, Epitriazolin nisbatan sedativ faollikni namoyon etganligiga qaramay barcha dozalarda tajriba hayvonlarda kognitiv faoliyatni

yaxshilaganligi, tik turishlar sonining nazorat guruhiga nisbatan yuqoriligi dofaminergik mediatorlarning ajralishi bilan bog‘liq bo‘lishi mumkinligi hamda barcha dozalarda axlat ajratishlar soni nazorat guruhiga nisbatan kamligi, serotonin mediatorlarining ko‘p miqdorda ajralishi hisobiga anksiolitik faollikni namoyon qilganligini ko‘rish mumkin.

Epitriazolinni surunkali yuborilganda his-hayajonga qarshi faolligini o‘rganish. Epitriazolinni surunkali yuborilganda tajribaning 30 kunida oq kalamushlarda “ochiq maydon” usulida tekshirilganda axlat ajratish sonining kamligi yaqqol his-hayajonga qarshi xossasi mavjud ekanligi asoslangandan so‘ng, spetsifik anksiolitik faolligini o‘rganish zarurati paydo bo‘ldi. Shu maqsadda ushbu modelda his-hayajonga qarshi faolligini baholab chiqdik. Sog‘lom guruh va tajriba guruhining har bir dozasini 2 daqiqa vaqt davomida sinovdan o‘tkazildi. Olingan natijalar quyidagi 4-jadvalga keltirildi.

4-jadval

Epitriazolinni surunkali yuborilganda his-hayajonga qarshi faolligini baholash

Yuborilgan modda	Yorug‘ kamerada bo‘lish vaqti soniyalarda (Yo)	Qorong‘u kamerada bo‘lish vaqti soniyalarda (Q)	Yorig‘ va qorong‘u kamerada bo‘lish vaqti nisbati K=Yo/Q
So‘lom guruh (dist. suv)	42.8±5.42	77.2±6.31	0.55
Epitriazolin *0.25 mg/kg*	82.1±6.8*	37.9±6.8*	2.1*
Epitriazolin *2.5 mg/kg*	68.2±9.4*	51.8±9.4*	1.32*
Epitriazolin *25 mg/kg*	67.4±5.6*	52.6±5.6*	1.28*

Eslatma.*p≤0,05 nazorat guruhiga nisbatan

Tajriba natijalariga ko‘ra, sinovning 30-kunida Epitriazolin 025; 2.5 va 25 mg/kg dozalarda sog‘lom guruhga nisbatan mos ravishda 2.1; 1.32 va 1.28 marta his-hayajonga qarshi yuqori faollik namoyon qilganligini eksperimental tadqiqotlar ko‘rsatdi.

Olingan natijalarga ko‘ra, Epitriazolin sog‘lom guruhga nisbatan yuqori anksiolitik xususiyatga ega ekanligini ko‘rishimiz mumkin.

Xulosa. Yangi farmakologik faollikka ega bo‘lgan dori vositalarini tibbiyot amaliyotiga qo‘llash uchun nafaqat klinik oldi sinovlari, balki, surunkali davrda berish davomida uning xavfsizligini eksperimental tadqiqotlar bilan asoslsh eng muhim omillardan sanaladi. Shu sababdan so‘nggi yillarda O‘zbekiston olimlari tomonidan o‘simlik asosida va sintetik preparatlarni surunkali zaharliligini aniqlash bo‘yich keng ko‘lamdagi izlanishlar olib borilmoqda [30-32]. Tutqanoqqa qarshi yuqori faollik namoyon qilgan Epitriazolin birikmasi tibbiyot amaliyotida keng qo‘llanilib kelinayotgan karbamazepin va konvuleks preparatlaridan ustunligi bilan ajralib turadi. 0.25; 2.5 va 25 mg/kg dozalarda og‘iz orqali berilganda tajriba hayvonlarining umumiy va jun holatiga, tana massasining o‘zgarishiga 90 kun davomida salbiy ta’sir etmasligi isbotlandi. Tajribalar davomida harakatlanish aktivligini nazorat guruhiga nisbatan kamaytirganligi, harakat va qidiruv faolligini oshirganligi va yaqqol anksiolitik faollikni namoyon

qilganligini ko‘rishimiz mumkin. Ushbu olingan natijalardan shunday xulosaga kelish mumkinki, Epitriazolin birikmasi surunkali davrda berilganda nojo‘ya ta’sirlarni yuzaga keltirmasligi, epilepsiya bilan kasallangan bemorlarda sedativ xossani namoyon qilishi hamda anksiolitik xususiyatni yuzaga keltirishi o‘rganiluvchi birikmani amaliyotda qo‘llash imkoniyatini oshiradi.

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