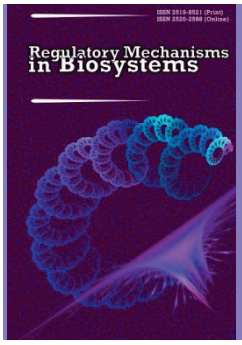

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Electrophysiological characteristics of experimental diabetes under the conditions of using niacin-oxy-ethylidene-diphosphonate germinate (MIGU-4)

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Diabetic retinopathy occupies the second leading cause of visual impairments and blindness all over the world. Oxidative stress contributes to diabetes-induced retinopathy and visual pathway deterioration as well. Determining compounds with heightened antioxidant potential involves increasing the effectiveness of diabetes complications treatment. Recently, it has been established that germanium-containing organic compounds possess antioxidative and neuroprotective activity. Hence, the estimation of retinopathy manifestations on a streptozotocin (STZ)-induced rodent model, which is one of the most commonly employed models in preclinical drug research for diabetic retinopathy under conditions of niacin-oxy-ethylidene-diphosphonate germanate (MIGU-4) treatment, is justified. The dynamics of visual evoked potential (VEP) and the comparison with the effects of α-tocopherol obtained in streptozotocin (STZ)-induced diabetes in Wistar rats were the objectives of the work. Treatment with MIGU-4 (25.0 mg/kg, i.p.) and α-tocopherol (100.0 mg/kg, i.p.) started one week after STZ administration (65.0 mg/kg, i.p.).and was performed daily with the measurement of VEP characteristics for six and twelve weeks. Intact and STZ-diabetes rats treated with 0.9% NaCl solution were observed as separate groups. The latency of P1, N1, and P2 in STZ-treated rats significantly exceeded corresponding indices in the control animals, and the amplitude of P1-N1 and N1-P2 was reduced in six and twelve weeks from the moment of STZ administration. Treatment with MIGU-4 six weeks after STZ resulted in a significant shortening of the P1 and N1 latency compared with the diabetes rats and heightened amplitude of waves. The latency of VEP waves in α-tocopherol treated rats did not differ from the control. MIGU-4 treatment twelve weeks after STZ significantly shortened the latency of P1 compared with the diabetes rats. The amplitude of VEP waves was not affected by MIGU-4, and α-tocopherol treatment failed to prevent diabetes-induced VEP deterioration in the twelve weeks after STZ. The conclusion was made that MIGU-4 (25.0 mg/kg) causes protection against enlargement of VEP wave latency and reduced amplitude in rats with STZ diabetes. The protective effect was more pronounced at the early stage of STZ-diabetes development (six weeks) and exceeded that caused with α-tocopherol (100.0 mg/kg) treatment. Further investigations of MIGU-4 in the complex treatment of diabetes retinopathy are in prospect.

Keywords: experimental diabetes; streptozotocin; organic compound of germanium; visual evoked potential; α-tocopherol.

Introduction

Diabetes is a disease with systemic severe complications, such as retinopathy, one of the most deteriorative conditions resistant to treatment (Tomita et al., 2021; Gonzalez-Cortes et al., 2022). Diabetes duration affects the development of retinopathy, and a history of disease over 20 years inevitably precipitates retinopathy with an extremely high risk of blindness (Lu et al., 2018; Liu et al., 2022).

The pathogenesis of retinopathy involves some common mechanisms of the nervous system and retina. Thus, excessive accumulation of glutamate causes neurodegeneration, microglial activation, neoangiogenesis, and oxidative stress (Vindeirinho et al., 2016; Rubsam et al., 2018). It was established that in the retina tissue of STZ-treated rats, the superoxide dismutase and catalase activities decreased by 40.7% and 32.0%, respectively, in comparison with the corresponding values in Wistar rats without diabetes (Kresyn & Godlevskii, 2014). Such effect was observed six weeks from the moment of STZ administration and was a marker of diabetes retinopathy precipitation, which presumably is followed by a decrease of VEP. Interestingly, cerebellar stimulations prevented a decrease in retinal antioxidative potential (Kresyn & Godlevskii, 2014).

Visual-evoked potentials (VEPs) are one of the most informative criteria of the functional state of visual pathways, and characteristic VEPs are pertinent for DR (Saadoun et al., 2020; Izadi et al., 2023). Increases in P100 latency and the reduction of N75–P100 amplitudes were demonstrated in patients with type I and type II diabetes mellitus (Pescosolido et al., 2015; Khatoon et al., 2016; Kumari et al., 2020). Pattern-reversal VEP responses are deranged in diabetic patients before retinopathy develops, allowing a better prognosis for visual dysfunction (Coppola et al., 2021). Prolonged VEP latency is observed in streptozotocin (STZ)-induced diabetes, but amplitude differences are contradictory (Mendonça et al., 2020). VEP may reflect disturbances at different locations in the visual pathway, but the contribution of retinopathy is prevalent (Ozkaya et al., 2007; Madsen et al., 2021).

Recently, the anti-inflammatory activity of germanium-containing organic compounds has been established (Wada et al., 2018). Also, germanium compounds exert an antioxidant effect, preventing cell degenerative changes (Wada et al., 2018). Low toxicity and high biological activity have been established for germanium substances bound to oxy-ethylidene-diphosphonate acid. Similar properties of germanium-containing agents ensure clinical effectiveness of regulation of mineral metabolism, antitumor treatment, detoxification, and anti-inflammatory action, including in the event of pathological processes, the basis of which is neuroimmune inflammation (Godovan & Kresyun, 2007; Al-Nadawi & Kresyun, 2023). It was determined that niacin-oxy-ethylidene-diphosphonate germanate quickly enters the systemic bloodstream, exchanges with the blood, is easily accessible to body tissues, exerts an antioxidant, hepato-

protective effect, and also reduces the excitability of brain structures (Kresyun & Al-Nadawi, 2023).

The objective of the study was to define the dynamics of visual evoked potentials in rats with experimental streptozotocin-induced diabetes under the conditions of the use of niacin-oxy-ethylidene-diphosphonate germanate and compare it with the effects of α-tocopherol.

Material and methods

All animal experiments adhered to the National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals and the Helsinki Declaration and ARRIVE demands. The study was approved by the Bioethics Committee of Odesa National Medical University (Meeting Minutes No. 3 dated March 14, 2018). 32 Wistar male rats, aged 6 to 9 months, were used in this experiment. They were maintained in an environmentally controlled room (23 ± 2 °C, 60% humidity) on a 12:12-h light-dark cycle, and fed and watered ad libitum.

Anesthesia was performed using ketamine (100 mg/kg, i.p., Farmak, Ukraine). The rat head was shaved of fur and cleaned with iodine prior to incision (Geiger et al., 2008). Rats were placed in a stereotaxic device "SEZh-5" (Bohomoletz Institute of Physiology, Kyiv, Ukraine, 2000) and anesthetized with a 0.5% Novokain solution (Darnitsa, Kyiv, Ukraine) infiltration at all pressure points and the site of skin incision. A 2-cm incision was made along the middle sagittal axis, and all soft tissues were removed from the skull surface for implantation of recording and stimulation electrodes. A 1.5–2.0-mm hole for recording and a 4.0 mm hole for stimulation electrodes were drilled through the skull using a standard dentistry portable drill (Colt 1, Charkov, Ukraine, 2015).

Nichrome monopolar intracortical electrodes for VEP registration were implanted in the visual cortexes (AP = –7.0; L = 3.0; H = 0.5) of both hemispheres, according to the rat brain atlas (Paxinos & Watson, 1998). The reference electrode was placed at the sagittal line in the nasal bones. Electrodes were fixed on the cranial surface using quick-solidifying dental cement. A 0.9% NaCl solution (5.0 mL at 35 °C) was injected i.p. at the end of surgery to prevent dehydration. A potassium salt of penicillin (100.000 IU/kg, i.m. injection) was administered every 12 h for 48 h postoperatively to prevent infection. Animals were single-housed after surgery and recovered for 10 to 14 days after surgery before observations.

Diabetes was induced using i.p. streptozotocin (STZ) (Sigma Aldrich, USA) (65.0 mg/kg, i.p.), which was dissolved in a sodium-citrate buffer solution (pH 4.5). Rats that exhibited glucose levels higher than 300 mg/dL in venous blood one week after STZ administration were included in the study. Glucose levels were determined in a fasted state at 9.00 AM. Rats received insulin injections (0.5–1.0 IU s.c., two to five injections per week) during all observation periods (Al-Nadawi & Kresyun, 2023).

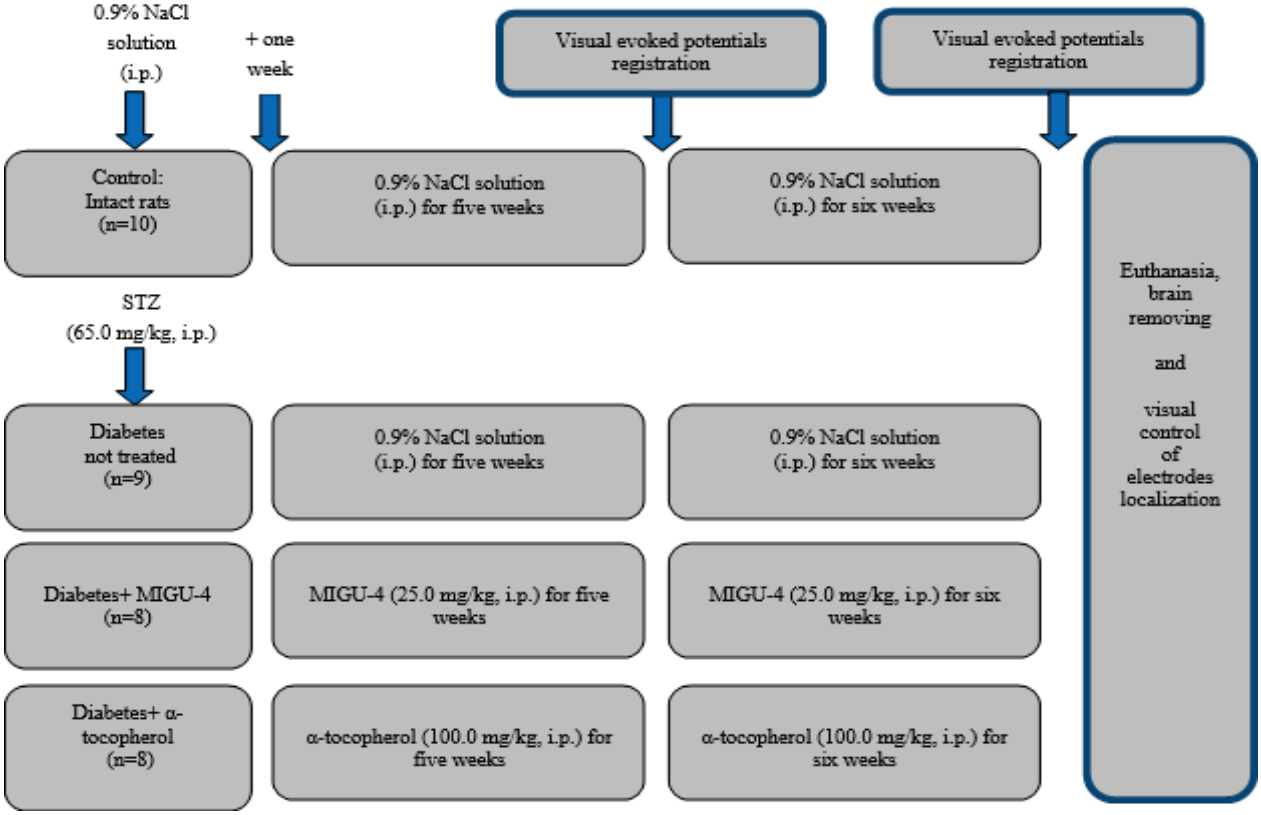

Fig. 1. Design of investigation

Control group included intact rats (n= 9) with implanted electrodes.

Animals with STZ administration were randomly assigned to the following groups:

– rats (n = 8), with implanted electrodes and i.p.administration of 0.9% NaCl solution;

– group (n = 7) received i.p., (±)-α-tocopherol, DL-rac-α- tocopherol (Sigma Aldrich, USA);

– rats (n = 8) were treated daily with MIGU-4 (25.0 mg/kg, i.p.).

Treatment started one week after STZ, and administrations were performed daily on the animals 30–40 minutes before eating till the end of the observation period (12 weeks). VEP recording was performed in all groups 6 and 12 weeks after the STZ administration. VEP recording was performed according to a previously described method (Iwamura et al., 2003). Animals were anesthetized with ketamine (100 mg/kg, i.p., Pharmak, Ukraine) and adapted to the dark for 10 min. The short time adaptation to the subsequent light flashes justified this approach. Body temperature was monitored using rectal thermometry (TPEM-1, FSU) and maintained at 37 °C. Tropicamide eyedrops (0.5%) (Pharmac, Ukraine) were given to induce mydriasis.

A custom-made electrode needle was inserted into the tail as the ground. The electrode impedance was maintained below five kΩ (MS5209, MasTech, Ukraine). Recordings were performed using Neuropack Four Model MEM-4104K (Nihon Kohden Corporation, Japan, 2010). EEG signals were recorded 200 ms after visual stimuli presentation, and the sample rate was 2 kHz.

Photostimulation was performed using a custom-made flexible panel of 20 white, high-brightness, light-emitting diodes (LEDs) (each of 5 W power) mounted on the concave surface with a focal distance of 15.0 cm.

We tried to place the stimulated eyeball in focus of the emitting device, with coinciding optical lines of the eyeball and the photostimulator.

Stimulation intensity was measured using the lux-meter "Yu-116" (FSU, 1990), and data were converted into candles-steradian per m^2 (cd-s/m^2) (Kohzaki et al., 2008). Therefore, stimulation intensity was 3.0 log of scotopic units. Photic stimulation was delivered 100 times at a frequency of 0.1 Hz. All procedures were performed under red illumination (λ_{max} = 650 nm). The opposite eye was covered with black tape during EEG recordings. All experimental animals were euthanized using nembutal (100 mg/kg, i.p., Ceva, France). The location of the electrodes was verified visually after the electrode was gently removed. Electrocoagulation was performed in the area of the electrode placement using the electrode as an anode to apply direct current with an amplitude of 5.0 mA over 30 seconds. The zone of coagulated tissue served as a visual marker of the placement of the electrode tip.

Parameters of the latency of certain waves (P1, N1, P2) and amplitude (P1-N1, N1-P2) were taken into account (Fig. 2).

Statistical procedures were performed using the SPSS 17.0. Values were compared using one-way ANOVA with Bonferroni post hoc test. Results were presented as x ± SE (main ± standard error). The Shapiro-Wilk test for normality was used. P values < 0.05 were considered significant.

Results

Monitoring the body weight of rats with simulated STZ-diabetes showed that six weeks after the disease was reproduced, the body weight of the non-treated diabetes rats was significantly lower compared to the control (Table. 1). The content of glucose in the blood exceeded that in the control group by 3.0–3.4 times. Twelve weeks after the start of experimental treatment, the body weight of rats with STZ diabetes remained significantly lower than in the control group.

In rats treated with MIGU-4 (25.0 mg/kg) twelve weeks after STZ administration, the blood glucose content was significantly lower than in rats with untreated diabetes (P = 0.004). Against the background of administration of α-tocopherol (100.0 mg/kg, i.p.), the glucose level was also significantly lower than in rats with diabetes (P = 0.021, Table 1).

A significant decrease in body weight compared to control animals was registered in all experimental groups during all observation periods. The latencies of P1, N1, and P2 in diabetes animals significantly exceeded the latencies of the control group (Table 2). Rats with the MIGU-4 treatment (25.0 mg/kg, i.p.) exhibited significantly shorter P1 and N2 latencies than diabetic rats. The wave latency in rats exposed to α-tocopherol (100.0 mg/kg, i.p.) did not differ from the diabetes rats.

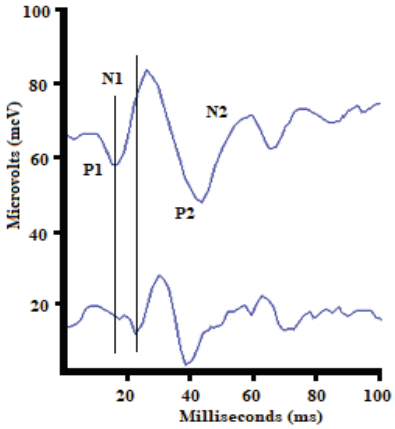

Fig. 2. Characteristics of VEP waves in a rat with STZ-induced experimental diabetes (6 weeks from applying STZ at a dose of 65.0 mg/kg, i.p.): vertical lines mark the moments of P1 wave latency measurement

The amplitude of the P1-N1 was two times lower in diabetic rats compared to the control group (P = 0.006), and the amplitude of the N1-P2 was 43.0% lower (P = 0.027). The amplitude of VEP waves in the group treated with MIGU-4 did not differ from that of control and diabetes rats. The α-tocopherol treatment did not affect the amplitude of waves that maintained a significant difference from the control (Table 2).

The latencies of P1, N1, and P2 in diabetes rats treated exceeded significantly the corresponding indices in control rats (Table 3). The amplitude of P1-N1 was reduced by 55.4% (P = 0.008) and N1-P2 – by 46.0% (P < 0.026) when compared with control values. The latency of P1 in diabetic rats treated with MIGU-4 was reduced significantly compared to diabetes rats by (P = 0.025). The latency of N1 and P2 did not differ from the corresponding data in the control group, and the amplitude of P1-N1 and N1-P2 was still significantly reduced compared to the control. The investigated indices maintained the difference with the control group under treatment conditions with α-tocopherol (100.0 mg/kg, i.p., Table 3).

Table 1

Dynamics of body weight and blood glucose content of rats with STZ-induced diabetes under the conditions of experimental treatment (x ± SE)

No.	Groups of rats	Before STZ administration		Period after STZ administration			
				six weeks		twelve weeks	
		body weight, g	glucose, mmol/L	body weight, g	glucose, mmol/L	body weight, g	glucose, mmol/L
1	Control (n = 10)	257.2 ± 15.3	6.35 ± 0.29	293.4 ± 16.8	6.25 ± 0.34	335.3 ± 21.2	6.7 ± 0.5
2	Diabetes (n = 9)	264.7 ± 16.2	6.31 ± 0.26	227.4 ± 13.9*	20.71 ± 0.90*	207.2 ± 12.2*	22.4 ± 0.9*
3	Diabetes+ MIGU-4 (25.0 mg/kg) (n = 8)	253.4 ±15.0	6.01 ± 0.32	230.2 ± 14.1*	19.63 ± 0.56*	228.1 ± 13.6*	18.5 ± 0.7*#
4	α-tocopherol (100.0 mg/kg, i.p.) (n = 7)	252.4 ± 15.0	6.23 ± 0.30	214.5 ± 12.9*	20.35 ± 0.80*	227.7 ± 13.8*	19.3 ± 0.8*#

Notes: * – P < 0.05 vs. control group; # – P < 0.05 vs. sham-stimulated rats with diabetes (ANOVA followed with Bonferroni post hoc test).

Table 2

Characteristics of VEP 6 weeks after STZ administration (x ± SE)

Investigated parameters		Control (n = 9)	Diabetes rats (0.9% NaCl i.p.) (n = 8)	MIGU-4 (25.0 mg/kg, i.p.) (n = 8)	α-tocopherol (100.0 mg/kg, i.p.) (n = 7)
Latency, ms	P1	26.8 ± 1.2	34.5 ± 1.6 *	27.9 ± 1.3#	30.6 ± 1.4
	N1	43.1 ± 2.0	53.0 ± 2.5*	44.7 ± 2.1#	49.1 ± 2.2
	P2	63.3 ± 2.8	78.9 ± 3.8*	67.3 ± 3.5	73.0 ± 3.4
Amplitude, μV	P1-N1	23.6 ± 2.6	12.3 ± 2.4*	19.5 ± 2.7	11.3 ± 2.2*
	N1-P2	45.8 ± 6.2	26.1 ± 4.9*	33.7 ± 4.1	29.1 ± 3.4*

Note: see Nable 1.

Discussion

Hence, our data demonstrated that STZ-induced diabetes in rats and the deterioration of VEP were confined to an increase in latency and a reduction in amplitude of wave components. These findings are consistent with the altered VEP characteristics previously described in STZ-induced diabetes models (Ozkaya et al., 2007; Nagayach et al., 2014). Thus, the gained data favours the effective prevention of deterioration of VEP in STZ diabetes rats with MIGU-4 (25.0 mg/kg, i.p.) treatment. This effect is confined to the shortage of the latencies of VEP waves and heightening their amplitude at an early stage of diabetes development – six weeks from the moment of STZ administration. Meanwhile, the effectiveness of the treatment with MIGU-4 was alleviated twelve weeks after diabetes modeling. The shortening of the latency of P1 and P2 was pronounced, while effects upon the amplitude of VEP were absent. The intensification of retinal neurodegenerative changes over the developmental time course of experimental diabetes may explain this lessening of MIGU-4 effectiveness at later stages of diabetes development. Notably, glial activation, cellular apoptotic degeneration, and glutamate transport deterioration developed in the retina of rats with STZ-induced diabetes (Nagayach et al., 2014) may be responsible for the reduced effectiveness of MIGU-4.

The antioxidant effects of organic germanium compounds are associated with an increase in the content of α-tocopherol in the blood plasma of mice (Nakamura et al., 2014). The authors established that germanium

agents have changes in the activity of 1,220 genes by 1.5 times, among which the activation of genes regulating α-tocopherol metabolism by 1.62 times was observed (Nakamura et al., 2014). Thus, MIGU-4-induced neuroprotection may be based on the pronounced antioxidant effect of the drug (Godovan & Kresyun, 2007; Kresyun & Al-Nadawi, 2023). However, considering the low effectiveness of α-tocopherol in the correction of diabetes-induced deteriorations of VEP, with the absence of effect in 12 weeks of diabetes development, the mediatory role of Ge-induced heightening of α-tocopherol level does not contribute to the positive impact of treatment with MIGU-4.

Table 3
Characteristics of VEP 12 weeks after STZ administration (x ± SE)

Investigated parameters		Control (n = 9)	Diabetes rats (0.9% NaCl i.p.) (n = 8)	MIGU-4 (25.0 mg/kg, i.p.) (n = 8)	α-tocopherol (100.0 mg/kg, i.p.) (n = 7)
Latency, ms	P1	27.6 ± 1.1	33.7 ± 1.6*	29.0 ± 1.2#	32.2 ± 1.2*
	N1	39.6 ± 1.7	47.4 ± 2.3*	43.4 ± 1.8	46.4 ± 2.1*
	P2	61.9 ± 2.0	75.9 ± 4.1*	68.4 ± 2.2	73.6 ± 2.8*
Amplitude, μV	P1-N1	22.7 ± 3.5	10.1 ± 1.8*	13.9 ± 2.8*	11.6 ± 1.9*
	N1-P2	42.0 ± 6.6	22.7 ± 3.7*	26.3 ± 3.3*	24.8 ± 3.2*

Note: see Nable 1.

Earlier, it was shown that MIGU-4 treatment resulted in moderate hypoglycemia in STZ-treated rats (Al-Nadawi & Kresyun, 2023). Such an effect underlies neuroprotection due to treatment and prevention of retina degeneration (Tomita et al., 2021; Lelyte et al., 2022). Besides, reduced hyperglycemia is in line with the data showing that prolonged reliable control of hyperglycemia restores the typical characteristics of VEP (Miura, 2023) and abolishes the delay in restoring VEP after photostress (Coppola et al., 2021). Local stimulation of dopamine and adenosine release (Vindeirinho et al., 2016) and activation of Muller cells – the source of BDNF, to initiate the rebuilding of the retinal network (Lu et al., 2018) may also be valid for MIGU-4 neuroprotection.

Conclusions

STZ-induced diabetes caused the increase of the visual evoked potentials' latency and reduced their amplitude seen at six and twelve weeks after induction of diabetes. The course of treatment with niacin-oxy-ethylidene-diphosphonate germanate (MIGU-4) (25.0 mg/kg, i.p.) prevented VEP deterioration. The preventive effect resulted in both a shortening of the latency and a heightening of VEP amplitude observed in six weeks, while 12 weeks after diabetes induction, only a shortening of the P1 latency was observed. The effectiveness of treatment with MIGU-4 exceeded that of treatment with α-tocopherol (100.0 mg/kg, i.p.).

Complex experimental treatment of diabetes-induced complications with the inclusion of MIGU-4 is promising for achieving pronounced therapeutic effects and reducing side effects.

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The author declares that there is no competing interest.

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