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Chronotolerance of a Nickel (II) Complex with the 5-Methyl 2-Furaldehyde Thiosemicarbazone Ligand in Male Swiss Mice

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Abstract

In vitro nickel (II) complex presents antimitotic effects. In this work, we have studied the in vivo seasonal effects of nickel (II), ligand and the complex $[NiCl_2(M5FTSC)_2]$ in male Swiss mice. During spring, an intra peritoneal (i.p.) injection of $NiCl_2$ in aqueous NaCl up to $1.0.10^{-2}$ mmol.kg^{-1} body weight (b.w.) killed 10% of the rodents after 6 days. Lethal dose 100% (LD100) was up $1.91.10^{-2}$ mmol.kg^{-1} b.w.; ligand was less toxic than Ni (II), while the complex was 25% lethal at $1.37.10^{-2}$ mmol.kg^{-1} b.w. In autumn, mice were less sensitive to $NiCl_2$. The ligand and the complex, on the contrary, were more toxic. This leads us to the conclusion that, *in vivo*, chronotolerance of nickel (II), ligand and complex in aqueous solution, are quite different in spring and autumn seasons.

Keywords: Male Swiss mice, nickel (II), complex, thiosemicarbazone, chronotolerance.

Introduction

Generally, *in vivo* effects studies do not take into account the rhythmic changes in internal biologic susceptibility to drugs or chemical molecules, as well as the ethology of experimental animals. Mice are rodents that are active in spring and summer and rest in autumn and winter. Many research workers such as Reinberg et al. (1991), Cambar et al. (1994), Touitou and Haus (1994) related experiments on rodents and human beings on the subject of the moment of administration of drugs and their toxic effects. Cambar et al. (1994) showed that the same dose of mercuric chloride in intra peritoneal injection (ip) induced a different mortality rate when given in November and in February. In rats, a vitamin D_3 metabolite was more active during the night than the day on renal enzymatic markers, which presented annual variations (Do

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et al., 1994, 1995). Effects of cobalt (II), 1,25-dihydroxyvitamin D_3 and their complex were quite different in spring and autumn (Do et al., 1996).

One of the main fields of research of our laboratory is the study of chemical and/or physiological effects of transition metals, various organic ligands and their mutual complexes. It has been reported that copper (II) is an anti-inflammatory metal and has some effects in carcinogenesis with different chronotolerances in spring and autumn (Hall et al., 1996).

We have already published the results concerning the chronotoxicity of a copper (II) complex (Do et al., 2001). In the present study, we continue our investigation on the new antimitotic metal complexes for which we have synthesised a series of complexes with nickel (II) and various furanic ligands. Preliminary *in vitro* studies revealed that these compounds presented anti-mitotic effects towards cultured colon adenocarcinoma cells (Jouad et al., 2002). It is therefore interesting to study their toxic effects in mice, in spring and autumn before further *in vivo* experiments, as knowledge of the administration time, can coincide with best effectiveness. We have chosen to perform our experiments during spring and autumn, because these seasons correspond to important hormonal variations whereas winter and summer correspond to hormonal stability. These data are useful in order to optimise both timing and dosage of any anti-mitotic molecule.

Materials and Methods

Preparation of the compounds

Nickel (II) chloride $NiCl_2$, 6 H_2O (Fluka, p.a.) was used without further treatment. The ligand 5-methyl 2-furaldehyde thiosemicarbazone (M5FTSC), presented in Figure 1 and the complex $[NiCl_2(M5FTSC)_2]$ were prepared and purified as previously described (Jouad et al., 2001). They were all dissolved in aqueous $9\,g.L^{-1}$ sodium chloride.

Animals

Male Swiss mice from Debré (Saint Doulchard, France) weighing from 18 to 25 g were used. They were chosen because of their regular weight gain and the absence of oestral cycle with changes in sexual hormonal status which could lead to errors in *in vivo* experiments (Laroche & Rousselet, 1990). Rodents have free access to both water and standard diet containing 0.8% Ca, 0.7% P and $3\,IU.g^{-1}$ vitamin D. They

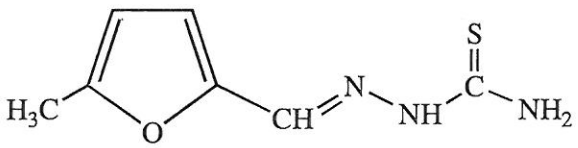

Figure 1. Chemical structure of the ligand.

were placed at room temperature (20 ± 2°C) and exposed to light/dark cycle (12 h/12 h) alternatively. The daily cycle was inverted and the animals were kept in light during the night and in darkness during the day for 5 weeks, allowing us to observe their active phase from 8:00 a.m. to 8:00 p.m.

Experiments with nickel (II)

In addition to the control series, seven series of 10 mice were used and each rodent received a single i.p. injection (200 µL.20 g^{-1} body weight, b.w.) between 10:00 and 12:00 a.m. On the 2nd of June, animals were treated as follows:

- Control series: animals received the vehicle, aqueous 9 g.L^{-1} NaCl.
- Series 1: $2.74.10^{-3}$ mmol.kg^{-1}
- Series 2: $5.48.10^{-3}$ mmol.kg^{-1}
- Series 3: $8.02.10^{-3}$ mmol.kg^{-1}
- Series 4: $12.02.10^{-3}$ mmol.kg^{-1}
- Series 5: $13.71.10^{-3}$ mmol.kg^{-1}
- Series 6: $14.77.10^{-3}$ mmol.kg^{-1}
- Series 7: $19.00.10^{-3}$ mmol.kg^{-1}

All animals were placed again at room temperature and 12 h light/12 h dark (12L/12D) during 7 days. The same protocol was used in autumn (2nd of December).

Experiments with the ligand

Six series of 10 mice, in addition to the control series, were used and each animal received a single i.p. injection (200 µL.20 g^{-1} b.w.) between 10:00 and 12:00 a.m. On the 2nd of June, rodents were treated as follows:

- Control series: animals received the vehicle, aqueous 9 g.L^{-1} NaCl.
- Series 1: $5.41.10^{-3}$ mmol.kg^{-1}
- Series 2: $10.11.10^{-3}$ mmol.kg^{-1}
- Series 3: $15.03.10^{-3}$ mmol.kg^{-1}
- Series 4: $25.14.10^{-3}$ mmol.kg^{-1}
- Series 5: $29.23.10^{-3}$ mmol.kg^{-1}
- Series 6: $30.05.10^{-3}$ mmol.kg^{-1}

The same protocol was used in the autumn (2nd of December).

Experiments with the complex

Seven series of 10 mice and the control series were used and each animal received a single i.p. injection (200 µL.20 g^{-1} b.w.) between 10:00 and 12:00 a.m. On the 2nd of June, rodents were treated as follows:

- Control series: animals received the vehicle, aqueous 9 g.L^{-1} NaCl.
- Series 1: 5.55.10^{-3} mmol.kg^{-1}
- Series 2: 11.00.10^{-3} mmol.kg^{-1}
- Series 3: 13.72.10^{-3} mmol.kg^{-1}
- Series 4: 16.44.10^{-3} mmol.kg^{-1}
- Series 5: 22.00.10^{-3} mmol.kg^{-1}
- Series 6: 25.22.10^{-3} mmol.kg^{-1}
- Series 7: 33.08.10^{-3} mmol.kg^{-1}

The same protocol was used in autumn (2nd of December).

Results

In spring, NaCl and nickel (II) chloride at 2.74.10^{-3} mmol.kg^{-1} b.w. did not harm mice under study as shown in Table 1. But, 8.02.10^{-3} mmol.kg^{-1} b.w. was LD_{50}. A dose up to 14.77.10^{-3} mmol.kg^{-1} was the LD_{100}, 24 hours only after injection.

Table 1. Toxic effects of $NiCl_2$ in aqueous NaCl 9 g.L^{-1} in spring.

Doses (mmol.kg^{-1})	Living animals 7 days after injection	
Control	10	
0.65	10	LD_0
1.30	9	LD_{10}
1.90	8	LD_{20}
2.60	5	LD_{50}
2.85	2	LD_{80}
3.25	0	LD_{100}
3.50	0	

Table 2. Toxic effects of the ligand in aqueous NaCl 9 g.L^{-1} in spring.

Doses (mmol.kg^{-1})	Living animals 7 days after injection	
Control	10	
0.90	10	LD_0
1.85	8	LD_{20}
2.75	5	LD_{50}
4.60	3	LD_{70}
5.35	1	LD_{90}
5.50	0	LD_{100}
6.25	0	

LD_0 for the ligand was $5.41.10^{-3}$ mmol.kg^{-1} b.w.; LD_{50} was about $15.03.10^{-3}$ mmol.kg^{-1} b.w. and LD_{100} was up to $30.05.10^{-3}$ mmol.kg^{-1} b.w.

For the complex, $LD_{20} = 13.72.10^{-3}$ mmol.kg^{-1} b.w.; $LD_{50} = 16.44.10^{-3}$ mmol.kg^{-1} b.w. and $LD_{100} = 33.08.10^{-3}$ mmol.kg^{-1} b.w.

In autumn, the nickel solution was more effective than in spring. LD_{100} was up to $13.71.10^{-3}$ mmol.kg^{-1} b.w. The results proved that $NiCl_2$ was toxic in mice, more toxic in autumn than during spring (Tables 1 and 4).

The ligand, in autumn, was not tolerated, as in spring (Tables 2 and 5), while the complex in autumn killed mice more rapidly, with LD_{100} up to $25.25.10^{-3}$ mmol.kg^{-1} b.w. as compared to $33.08.10^{-3}$ mmol.kg^{-1} b.w. in spring. Our experiments indicated, once more that $NiCl_2$ modifies its toxicity when it is complexed with the present ligand (Tables 3 and 6).

Discussion

This work shows that in male Swiss mice, tolerances of aqueous $NiCl_2$ were quantitatively different in spring as compared to rodents in autumn maintained under

Table 3. Toxic effects of the complex in aqueous NaCl 9 g.L^{-1} in spring.

Doses (mmol.kg^{-1})	Living animals 7 days after injection	
Control		
2.75		
5.45	10	LD_0
6.80	8	LD_{20}
8.15	5	LD_{50}
10.90	2	LD_{80}
12.50	2	
16.00	0	LD_{100}

Table 4. Toxic effects of $NiCl_2$ in aqueous NaCl 9 g.L^{-1} in autumn.

Doses (mmol.kg^{-1})	Living animals 7 days after injection	
Control	10	
0.65	10	LD_0
1.30	9	
1.90	9	
2.60	8	LD_{20}
2.85	4	LD_{60}
3.25	3	LD_{70}
3.50	0	LD_{100}

Table 5. Toxic effects of the ligand in aqueous NaCl 9 g.L^{-1} in autumn.

Doses (mmol.kg^{-1})	Living animals 7 days after injection	
Control	10	
0.90	10	LD_0
1.85	6	LD_{40}
2.75	5	LD_{50}
4.60	3	
5.35	1	LD_{90}
5.50	0	LD_{100}
6.25	0	

Table 6. Toxic effects of the complex in aqueous NaCl 9 g.L^{-1} in autumn.

Doses (mmol.kg^{-1})	Living animals 7 days after injection	
Control	10	
2.75	10	LD_0
5.45	10	LD_0
6.80	7	LD_{30}
8.15	5	LD_{50}
10.90	2	LD_{80}
12.50	0	LD_{100}
16.00	0	

constant conditions. In Debré laboratories, rodents are kept under artificial light and dark (12L/12D) at 20 ± 2°C, so we maintained our animals under the same conditions, as indicated in our experimental section.

Experiments on laboratory animals during many seasons, under constant parameters such as light and temperature, showed that their seasonal rhythms are not altered. This has been reported by Cambar et al. (1994) and Reinberg et al. (1991). The discovery of clock genes such as Per, Cry, Clock or B mal enhanced the hypothesis that most biological rhythms are genetically programmed (Fukada & Ohano, 2002). According to Pevet (2000) and Novak and Zawilska (1999) seasonal rhythms could be regulated by a hormone (melatonin) secreted by the pineal gland in mammals.

Few papers showed seasonal chrono-effectiveness of drugs. This may be due to the size and the cost of such experiments (Cambar et al., 1994). Our toxic effects study, dealing with periodic changes of activity of nickel chloride and the complex could be correlated with previous works. According to Levi (1987), the tolerance of

adriamycine in rodents was maximal in autumn and less in spring as our nickel complex. Brugerolle et al. (1988) demonstrated that the acute toxicity of phenobarbital in mice varies during the year: The compound is more toxic in January and it is well supported in July.

We can explain the chronesthesia of nickel chloride and the studied complex on the basis of biovariability. All living beings present biovariability under control of a biochemical clock which could be melatonin (Pevet, 2000; Novak & Zawilska, 1999), so they could react differently to the same drugs when injected during various seasons in the same year. This has been explicitly shown in the cases of other molecules, while observing the variations of their kidney and brain tolerances (Levy, 1987; Cambar et al., 1987; Dorian et al., 1987; Do et al., 1987; Do et al., 2000).

For further experiments, we will have to take into account the importance of seasonal changes. We might hypothesise that circadian acrophases and bathyphases of the structural and functional parameters of rodents responsible for the susceptibility resistance cycle change along the year. This can be a result of an endogenous circumannual rhythm along a 12-month period, based upon melatonin influence (Pevet, 2000; Fukada & Okano, 2002).

Further studies are now in progress to test nickel (II) chloride, free ligand and the complex in rats presenting induced colorectal cancer. The above results show that their effects should be followed during different seasons of the year in order to determine the best time for optimal tolerance as well as the best period for higher therapeutic activity.

References

Brugerolle B (1994): Chronopharmacology. In: Touitou Y, Haus E, eds., *Biological Rhythms in Clinical and Laboratory Medicine*. Berlin-Heidelberg: Springer, pp. 114–137.

Brugerolle B, Prat M, Douillez C, Dorfan P (1988): Are there circadian and circannual variations in acute toxicity of phenobarbital in mice? *Fundam Clin Pharmacol 35*: 301–304.

Cambar J, Dorian C, Cal JC (1987): Chronobiologie et chronophysiopathologie rénale. *Path Biol 35*: 977–984.

Cambar J, L'Azou B, Cal JC (1994): Chronotoxicoly. In: Touitou Y, Haus E, eds., *Biological Rhythms in Clinical and Laboratory Medicine*. Berlin-Heidelberg: Springer, pp. 138–150.

Do Thanh X, Boisnard P, Khan MA, Girault A (1994): Day time and night time effects of 24,25-$(OH)_2$ cholecalciferol on renal alkaline phosphatase and γ-glutamyl transpeptidase activities in intact rats. *Arch IntPhysiol Biochim Biophys 102*: 221–224.

Do Thanh X, Coquin AS, Saïd M, Khan MA, Bouet G (1996): Spring time and autumn time effects of 1,25-dihydroxy vitamin D_3, cobalt (II) and $[CoCl_2(1,25\text{-}(OH)_2D_3)]$ complex on renal and cerebral enzymatic markers. *Biol Rhythm Res 27*: 105–112.

Do Thanh X, Peter JC, Annaix V, Girault A, Darcy F, Breger R, Bouet G (1995): Annual variation of cerebral and renal alkaline phosphatase and γ-glutamyl transpeptidase activities in rats. *Biol Rhythm Res 26*: 486–492.

Do Thanh X, Djebbar-Sid S, Duchêne S, Benali-Baïtich O, Bouet G, Khan MA (2001): Chronotoxicity of a copper (II) complex with a linear tetradentate ligand in mice. *Biol Rhythm Res 32*: 423–429.

Dorian C, Catroux PH, Cambar J (1987): Mise en évidence des variations saisonnières des rythmes circadiens de la chrononéphrotoxicité de l'Amikacine chez le rat. *Path Biol 35*: 731–734.

Fukada Y, Okano T (2002): Circadian clock system in the pineal gland. *Mol Neurobiol 25*: 19–30.

Hall IH, Chen SY, Tajendrah KG, West DX (1996): The anti-infammatory activity of metal complexes of heterocyclic thiosemicarbazones, 2-substituted pyridines N-oxides and 2-pyridylthioureas. *Appl Organomet Chem 10*: 485–493.

Jouad EM, Larcher G, Allain M, Riou A, Bouet G, Khan MA, Do Thanh X (2001): Synthesis, structure and biological activity of Nickel (II) complexes of 5-methyl 2-furaldehyde thiosemicarbazone. *J Inorg Biochem 86*: 565–571.

Jouad EM, Do Thanh X, Bouet G, Bonneau S, Khan MA (2002): *In vitro* and *in vivo* effects of $[Ni(M5FTSC)_2Cl_2]$ complex in cancer: Preliminary tests. *Anticancer Research 22*: 1713–1716.

Laroche MJ, Rousselet F (1990): La souris. In: *Les animaux de laboratoire: éthique et bonnes pratiques.* Paris: Masson, pp. 143–164.

Levi F (1987): Chronobiologie et cancers. *Path Biol 35*: 960–968.

Novak JZ, Zawilska JB (1999): Melatonin and its role in the circadian function. *Postepy Hig Med Dosw 53*: 445–471.

Pevet P (2000): La mélatonine: hormone donneuse de temps. *Rhythms 32*: 11.

Reinberg AE, Labrecque G, Smolenski MH (1991): Chronotoxicité et chronotolérance. In: Labrecque G, Somlenski MH, eds., *Chronobiologie et chronothérapeutique.* Paris: Flammarion Médecine-Sciences, pp. 23–24.

Touitou Y, Haus E (1994): Biological rhythms and aging. In: Touitou Y, Haus E, eds., *Biological Rhythms in Clinical and Laboratory Medicine.* Berlin-Heidelberg: Springer, pp. 188–207.