Journal of Pharmaceutical & Biomedical Analysis
Vol. 8, No. 1, pp. 43–47, 1990
Printed in Great Britain

0731–7085/90 $3.00 + 0.00

A polarographic study of the photodegradation of nitrendipine

J.A. SQUELLA,* A. ZANOCCO,† S. PERNA and L.J. NUÑEZ-VERGARA‡

* *Electrochemistry Laboratory,* † *Photochemistry Laboratory,* ‡ *Pharmacology Laboratory, Facultad de Ciencias Quimicas y Farmaceuticas, Universidad de Chile, Casilla 233, Santiago, Chile*

Abstract: Nitrendipine produces a well-defined polarographic peak due to the four-electron reduction of the nitro group. This peak is used for tracking the photodecomposition of nitrendipine in both UV light and daylight conditions.

The results show that nitrendipine remains unaltered in the short time scale of a normal analytical procedure and no special care with visible light exposure is necessary. However nitrendipine is strongly altered with UV irradiation showing a first-order degradation kinetics. A degradation rate constant of 0.0665 min^{-1} with a $t_{1/2}$ of 10.423 min has been obtained.

The UV degradation product was isolated and identified as the nitro pyridine analogue of nitrendipine.

Keywords: *Differential pulse polarography; nitrendipine photodegradation.*

Introduction

Nitrendipine, a calcium antagonist, which is a 1,4-dihydropyridine derivative (Fig. 1a), was synthesized by Meyer *et al.* [1] at the Bayer research laboratories. Its antihypertensive activity in animals has been extensively studied [2–4] and also several clinical studies have been developed [5]. Like its predecessor, nifedipine, nitrendipine relaxes vascular smooth muscle, providing potent and reliable arterial antihypertensive effects. Nitrendipine inhibits calcium transport in the slow channels, reducing peripheral resistance and producing an arterial vasodilation with the consequent pressure diminution. For the above characteristics nitrendipine is extensively used in modern therapeutics.

Chemically, nitrendipine is closely related to nifedipine. Nitrendipine differs from nifedipine in that *m*-nitro instead of *o*-nitro substitution in the phenyl moiety and by carboethoxy instead of carbomethoxy substitution at 5-position of the dihydropyridine ring. Nitrendipine is metabolized in the human liver by dehydrogenation to the pyridine analogue and by cleavage of the ester groups by hydrolysis or oxidation and hydroxylation of the methyl groups. All known metabolites are pharmacologically about 1000 times less potent than nitrendipine [6]. Consequently, the dihydropyridine ring system is likely to be required for activity.

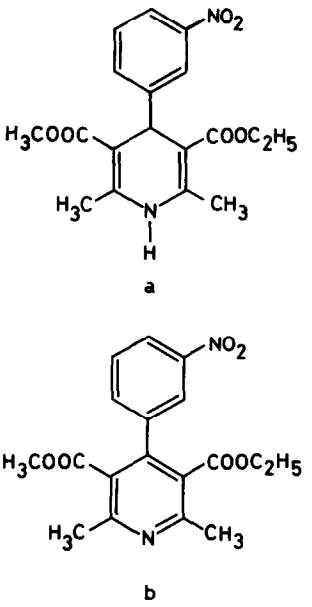

Figure 1
Molecular structure of (a) nitrendipine and (b) UV derivative.

Nifedipine is extremely light sensitive and several studies related to its photodecomposition have been reported [7–11]. However,

no systematic studies have been found in the literature related to nitrendipine photodecomposition, even though this drug is known to undergo rapid photooxidation to the inactive pyridine compound [5]. Recently, a polarographic method has been developed [12] in order to determine nitrendipine in pharmaceutical forms. This method is based on the electroactivity of the nitro group and is a very powerful tool for tracking the following possible changes in the molecule: disappearance of the nitro group, disappearance of the hydropyridine ring, appearance of the nitroso group, appearance of the pyridine ring and disappearance of the nitroso group. Consequently, with the above method should be an adequate instrument for carrying out nitrendipine photodecomposition studies. In this paper this polarographic method is used in a study of nitrendipine photodecomposition when exposed to different light conditions.

Experimental

Chemicals

Nitrendipine pure powder (99.8% activity, 100% chromatographically pure), was kindly provided by Laboratorio Saval (Santiago, Chile). Baypress pharmaceutical form (Lab. Bayer, Santiago, Chile), was obtained commercially. The solutions under study contained 10–30% ethanol and were buffered using (a) 0.02 M acetic acid–0.02 M phosphoric acid pH 6 and, (b) Sorensen, phosphate buffer pH 6. Ionic strength was kept constant at 0.18 M with KCl (Merck p.a.). All other chemicals were of analytical reagent grade (Merck p.a.).

Apparatus

An EPL-3 Tacussel recorder equipped with a TI-PULS module was employed in the polarographic measurements. A CPRA Tacussel thermostatted polarographic cell with a dropping mercury electrode (drop time 1.0 s), a Ag/AgCl reference electrode, and a platinum wire counter electrode were used. Unless otherwise stated, the following parameters were used in differential pulse polarography (DPP) mode: scan rate, 5 mV seg^{-1}; drop time, 1.0 seg; pulse amplitude, 60 mV. For degradation studies of the drug an UV lamp (313 nm, 125 W) and a white light lamp (200 W) were used. A Varian Anaspect EM — 360 (60 MH_z) NMR spectrometer and a Leitz Wetzlar, model III G, spectrometer for NMR and IR spectra involved in the elucidation of the photodecomposition products were used.

Isolation of the UV degradation product procedure

Nitrendipine (250 mg) dissolved in 100 ml ethanol was UV irradiated for approx. 14 h. When the peak at −550 mV of nitrendipine had disappeared, the solution was concentrated and subjected to column chromatography on silica gel using chloroform–petroleum ether (40–60°C) 75:25% (v/v) as an eluent. The chromatographically pure UV degradation product showed an R_f value of 0.283 with the same conditions of stationary and mobile phases. Nitrendipine showed an R_f value of 0.175 in the same conditions. The solution was evaporated to give an orange–yellow substance whose IR, NMR and polarographic data were obtained. The IR spectra were obtained in 1% potassium bromide pellets and the NMR spectra were carried out in deuterated chloroform with TMS as a standard.

Results and Discussion

Nitrendipine produces a well-defined polarographic peak over the entire pH range [13]. This peak turns out to be pH dependent, irreversible and shows a linear dependence on nitrendipine concentration. The peak is due to the four-electron reduction of the nitro group. Since the nitro group is the principal photoactive group in the nifedipine molecule, the same situation was assumed in this case. Consequently, a method for tracking the nitro group, such as polarography, is a very good alternative in photodecomposition studies. A peak with a potential of −550 mV versus Ag/AgCl electrode at pH 6 was used to track the nitro group disappearance in the nitrendipine molecule. Three different irradiation light modes were used: UV light, artificial daylight, and natural daylight. Three different conditions of sample exposure were also used: nitrendipine buffer solution pH 6 containing 30% ethanol, nitrendipine pure powder, and pharmaceutical form powder. When the irradiation procedure was carried out with visible light in both artificial or natural daylight no changes in all the different samples were observed for 30 h. These results show that nitrendipine remains unaltered in the short time scale of a normal analytical procedure and

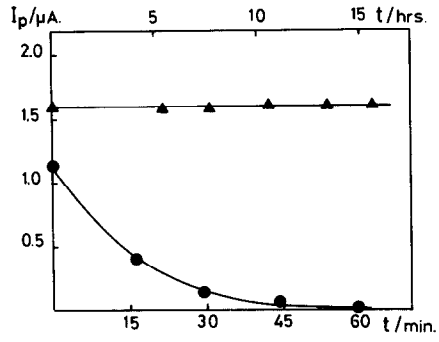

Figure 2
Upper abscissa: peak current dependence with room-daylight irradiation time. Lower abscissa: decrease of the peak current due to the peak at −550 mV in nitrendipine solution at pH 6.

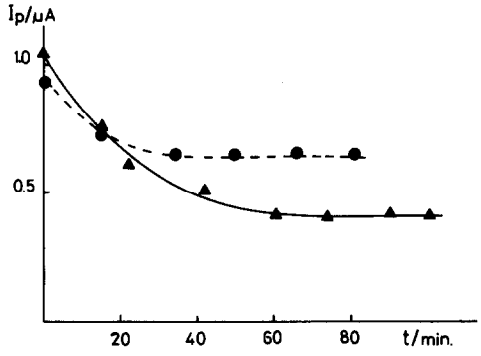

Figure 3
UV degradation curve for pure drug power sample and pharmaceutical form powder sample of nitrendipine.

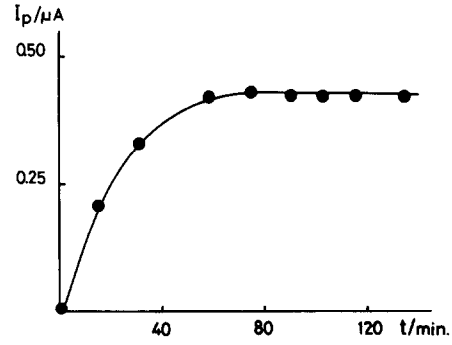

Figure 4
Degradation of nitrendipine with UV light. Increase of the peak current due to the peak at −1375 mV in UV derivative solution at pH 6.

no special care with visible light is necessary. Figure 2 shows the peak current and room-light exposure time dependence. On the other hand, when nitrendipine samples were irradiated with UV light the polarogram was altered, showing the following changes: (a) the peak at −550 mV due to the nitro group in nitrendipine vanished and a more anodic peak at −475 mV appeared; and (b) a new peak at −1375 mV appeared. Figure 2 shows the decrease in peak current due to the disappearance of the peak at −550 mV. From the decrease of the current peak with the irradiation time, and assuming a first-order kinetics (The graph ln i_p versus t is linear with a correlation coefficient of 0.9986), a UV degradation rate constant of 0.0665 min^{-1} with a $t_{1/2}$ of 10.423 min has been obtained. Similar changes were observed in the polarogram, with pure drug powder sample or pharmaceutical form powder sample. However, the disappearance of the peak at −550 mV is not complete. This fact can be explained as a consequence of the powder not being a monolayer during the exposure. Thus the external particles act as a shield preventing complete degradation. This effect is shown in Fig. 3. Furthermore, the degradation process can also be followed by tracking the appearance of both peaks, at −475 mV or at −1375, respectively. Figure 4 shows the degradation curve based on the increasing current of the more cathodic peak.

According to the above described isolation procedure, an UV degradation product has been obtained whose NMR and IR spectral data are summarized in Table 1. These data show principally the loss of the N—H and C=C IR absorption band in nitrendipine and the appearance of the C=N absorption band in the UV derivative. Furthermore, the NMR results show the loss of two protons in the dihydropiridine ring as a consequence of UV irradiation. The above results agree with a degradation of nitrendipine by dehydrogenation to the pyridine analogue (Figure 1b). The d.p. polarogram of the UV derivative shows two peaks (Fig. 5). The first peak at −475 is due to the four-electron reduction of the nitro group in the derivative and the second one is due to the two-electron reduction of the C=N in the pyridine ring. The current ratio between both peaks (2:1) is strongly consistent with this assignment. If the nitroso group were responsible for the peak at −475, a 1:1 ratio would be found. The difference between the potential peak of the nitro group in nitrendipine (−550 mV) and the nitro group in the UV derivative (−475 mV) is due to the aromaticity of the pyridine ring providing an electron density decrease over the nitro group in the UV derivative. Figure 6 shows a polarogram of

Table 1
Spectral data of nitrendipine and its derivative

Spectra	Nitrendipine	UV derivative
IR (cm^{-1})	3333 (N—H)	—
	1695 (C=O)	1727 (C=O)
	1667–1634 (C=C)	—
	1531 (NO_2)	1538 (NO_2)
	1539 (NO_2)	1531 (NO_2)
	1210 (—C—O—)	1235 (—C—O—)
	1124–1099 (—O—CH_3—O—CH_2—CH_3)	1107–1042 (—O—CH_3—O—CH_2—CH_3)
	—	1563 (C=N)
NMR (ppm)	6H 2,52 (C—CH_3)	6H 2,73 (C—CH_3)
	3H 3,75 (O—CH_3)	3H 3,67 (O—CH_3)
	3H 1,25 (C—CH_3)	3H 1,14 (C—CH_3)
	2H 4,21 (O—CH_2—)	2H 4,17 (O—CH_2—)
	1H 6,43 (N—H)	—
	1H 5,17 (C—H)	—
	4H 7,57–8,25 (arom H)	4H 7,68–8,36 (arom H)

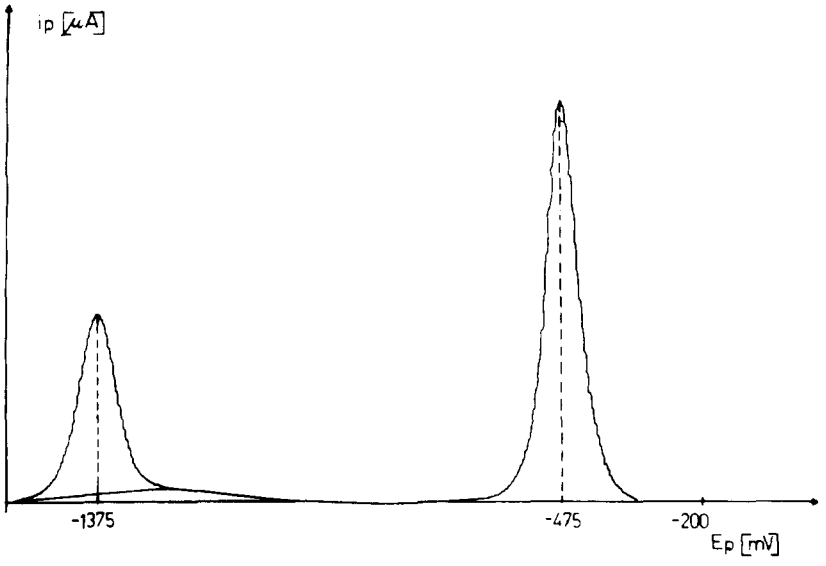

Figure 5
d.p. Polarogram of UV derivative buffer solution pH 6 containing 30% ethanol.

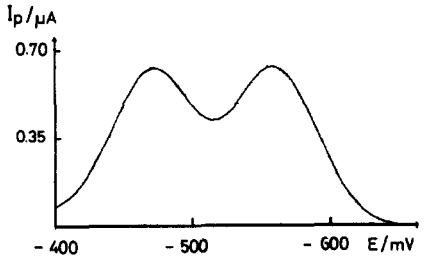

Figure 6
d.p. Polarogram of a nitrendipine solution after 10 min of UV irradiation.

a mixture of nitrendipine and its decomposition product showing the degree of peak shifting and the resolution between the two peaks at −550 mV and −475 mV.

The above study provides a very useful technique for degradation studies involving calcium antagonists belonging to the dihydropyridine derivative family.

Acknowledgements — This research was supported by grants Nos 192/88 from FONDECYT and Q2747-8823 from D.T.I., University of Chile. Furthermore, the authors express their gratitude to Fresia Pérez and Judith Gómez for their assistance in writing this paper.

References

[1] H. Meyer, F. Bossert, E. Wehinger and K. Stoepel, *Arzneim Forsch* **31**, 407–409 (1981).
[2] A. Knorr and K. Stoepel, *Arzneim-Forsch/Drug Res.* **31**, 2062–2064 (1981).
[3] K. Stoepel, A. Heise and S. Kazda, *Arzneim-Forsch/Drug Res.* **31**, 2056–2061 (1981).

[4] R. J. Towart, *Cardiovasc. Pharmac.* **4**, 895–902 (1982).
[5] A. Scriabine, S. Vanov and K. Deck (Eds), *Nitrendipine*. Urban & Schwarzenberg, Baltimore.
[6] *Drugs of Today*, Vol. 21, No. 12, 543–545 (1985).
[7] J. A. Berson and E. Brown, *JACS* **77**, 447–450 (1955).
[8] P. Jakobsen, O. Lederballe and E. Mikkelsen, *J. Chromat.* **162**, 81–87 (1979).
[9] R. Testa, E. Dolfini, C. Reschiotto, C. Secchi and P. A. Biondi, IL Farmaco **34**, 463–473 (1979).
[10] S. Ebel, H. Schutz and A. Hornitschek, *Arzneim-Forsch* **28**, 2188–2193 (1978).
[11] K. Bratin and P. Kissinger, *Current Separations* **4**, 4–8 (1982).
[12] S. Perna, L.J. Nuñez-Vergara and J. A. Squella, Thesis, Fac. Ciencias Químicas y Farmacéuticas. Univ. de Chile (1987).
[13] J.A. Squella, E. Barnafi, S. Perna and L.J. Nuñez-Vergara, *Analyt. Lett.* **21**, 2293–2305 (1988).

[*Received for review 18 November 1988; revised manuscript received 18 August 1989*]