*Journal of Pharmaceutical & Biomedical Analysis*
Vol. 7, No. 12, pp. 1915–1918, 1989
Printed in Great Britain

0731–7085/89 $3.00 + 0.00
Pergamon Press plc

*Short Communication*

# Propafenone monitoring in patients with refractory ventricular arrhythmias*

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**Keywords**: *Propafenone; antiarrhythmic drug; liquid chromatography.*

## Introduction

Propafenone (Knoll AG) is a new antiarrhythmic agent effective in suppressing chronic recurrent supraventricular and ventricular tachycardias and ectopic beats [1–8]. Electrophysiological studies have shown that it prolongs sinus node recovery time, and lengthens the effective refractory period of the atrium and AV node [9]. To evaluate the correlation between clinical efficacy of propafenone and serum levels, several methods have been described for the determination of propafenone in serum [10–13].

This paper describes a rapid high-performance liquid chromatographic procedure for measuring propafenone concentrations in biological fluids.

## Experimental

### *Chemical and reagents*

Propafenone (LU 29007: 2-(2-hydroxy-3-propylamino-propoxy)-3-phenyl-propiophenone hydrochloride), metabolites (LU 40545: 5′-hydroxy-2-2(2-hydroxy-3-3 propylamino-propoxy)-3-phenyl propiophenone-hydrochloride and LU 48686: 2-(2-hydroxy-3-aminopropoxy)-3 phenyl-propiophenone-fumarate), (Fig. 1), and the internal standard (LU 41263: 2-(2-hydroxy-3-propylamino-propoxy)-3-(3,4-dimethoxyphenyl)-propiophenone-hydrochloride), were obtained from Knoll (Ludwigshafen, FRG). Glass distilled solvents were obtained from Burdick & Jackson (Muskegon, MI, USA). Other chemicals were of reagent grade.

### *Instrumentation*

A Perkin–Elmer liquid chromatograph model 410 Bio was used to pump the mobile phase through a Perkin–Elmer (3 × 3 CR C18) column, particle size was 5 μm. The flow

*Presented at the "Third International Symposium on Drug Analysis", May 1989, Antwerp, Belgium.
This work was supported by a State Grant FIS SS, number 87/830.
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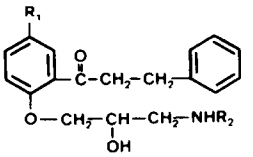

| | $R_1$ | $R_2$ |
|---|---|---|
| Propafenone | H | $CH_2CH_2CH_3$ |
| 5 hydroxy propafenone | OH | $CH_2CH_2CH_3$ |
| N-depropyl propafenone | H | H |

**Figure 1**
Chemical structures of propafenone, 5 hydroxy propafenone and despropyl propafenone.

rate was adjusted to 2 ml $min^{-1}$, and the mobile phase was acetonitrile–5 mM phosphate buffer (pH 2.4) (25:75% v/v) containing 0.01 M nonylamine. The detector was a Perkin–Elmer LC 95 with absorbance monitored at 209 nm.

*Calibration standards*

Calibration standards were prepared by adding weighed amounts of drug to distilled water. These standards were diluted to deliver between 500 and 2000 $\mu g\, l^{-1}$. Calibration curves were prepared as for the patient samples as described below. A 100 µl aliquot of each standard was pipetted into screw-capped tubes and 100 µl of internal standard (1000 $\mu g\, l^{-1}$) was added together with 0.5 ml of blank serum.

*Extraction procedure*

Aliquots of 0.1–1 ml of patients serum was added to centrifuge tubes together with 100 µl of internal standard. To each tube 200 µl of Tris buffer pH 10.6 was added and the tube contents were vortex-mixed for 10 min with 5 ml of diethyl ether. The organic phase was transferred to another tube and evaporated carefully to dryness with nitrogen. The residue was dissolved in 200 µl of 0.2 M phosphoric acid.

## Results and Discussion

Typical chromatograms of blank serum and serum from a patient taking propafenone are shown in Fig. 2. In general no peaks that interfered with either propafenone or the internal standard were encountered in the analysis of serum from different patients.

The quantitative determinations of propafenone in serum were performed by adding known amounts of drug in the range 500–2000 $\mu g\, l^{-1}$. The calibration curves were linear within the range used (Fig. 3). To demonstrate the accuracy and precision of this method replicate determinations were carried out, and the relative standard deviations (RSD) obtained were 9.80 (55.5 $\mu g\, l^{-1}$) and 11.10 (104.16 $\mu g\, l^{-1}$) ($n = 6$) respectively. The concentration of propafenone obtained in the serum of patients with refractory ventricular arrhythmias treated with different doses of this drug is shown in Table 1.

The method reported here to monitor propafenone uses a very short column which permits determination of this drug and its metabolites with very short retention times compared with conventional columns used in other methods [10–12].

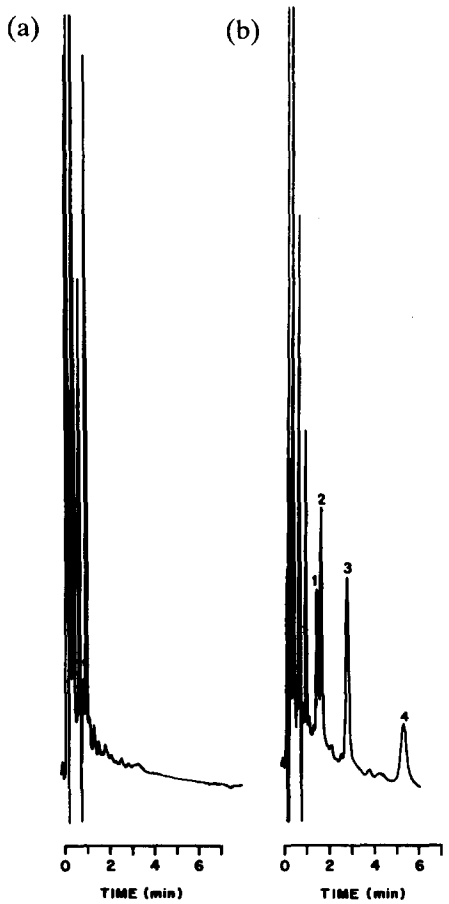


**Figure 2**
Chromatograms of extracted patient serum (a) not taking propafenene and (b) taking 150 mg of propafenone orally. Peaks: 1 = 5 hydroxy propafene, 2 = despropyl propafenone, 3 = internal standard and 4 = propafenone.

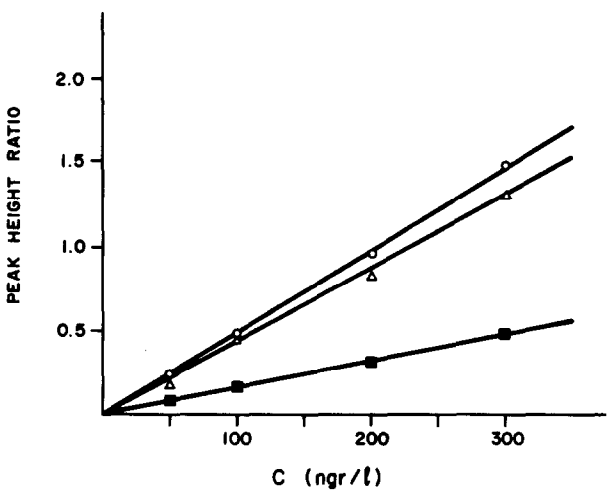


**Figure 3**
Peak height ratio of 5 hydroxy propafenone (△), despropyl propafenone (○) and propafenone (■). The regression equation for 5 hydroxy propafenone was $y = 0.002x + 0.012$, for despropyl propafenone it was $y = 0.005x + 0.012$ and for propafenone it was $y = 0.004x + 0.009$.

**Table 1**
Propafenone dosage and obtained blood concentrations

| Patient number | Age (years) | Dose | Propafenone concentration ($\mu g\ l^{-1}$) |
|---|---|---|---|
| 1 | 69 | 900 mg/24 H | 244.0 |
| 2 | 68 | 600 mg/24 H | 58.6 |
| 3 | 83 | 300 mg/24 H | 786.0 |
| 4 | 65 | 900 mg/24 H | 578.9 |
| 5 | 65 | 450 mg/24 H | 45.5 |
| 6 | 50 | 450 mg/24 H | 36.9 |
| 7 | 54 | 900 mg/24 H | 244.0 |
| 8 | 68 | 165 mg I.V. | 392.0 |
| 9 | 68 | 175 mg I.V. | 2154.0 |
| 10 | 69 | 160 mg I.V. | 864.0 |
| 11 | 49 | 180 mg I.V. | 844.0 |
| 12 | 64 | 280 mg I.V. | 642.0 |
| 13 | 69 | 160 mg I.V. | 567.0 |

Patients numbers 1–7 were chronically treated for ventricular or supraventricular arrhythmias with the oral daily mentioned dose, and the blood sample was taken after one month after initiation of the therapy and before the morning dose. Patients 8–13 received I.V. propafenone (2.5 mg $kg^{-1}$) at the electrophysiological study for ventricular tachyarrhythmias and the blood sample was obtained 10–15 min after dosing administration.

*Acknowledgements* — The authors are indebted to Knoll AG for the gift of pure samples propafenone, 5 hydroxy propafenone, despropyl propafenone and internal standard LU 41263 and to Miss A. Reviriego and C. Coello for expert technical assistance.

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[*Received for review 16 May 1989; revised manuscript received 31 July 1989*]