Br. J. clin. Pharmac. (1987), **24**, 820–822

Flecainide distribution in human tissues

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The distribution of antiarrhythmic drugs in human tissues may yield a better understanding of their therapeutic action and side effects. We report tissue distribution of flecainide in a patient who died suddenly while being treated chronically with the drug. Lungs showed the highest concentration of flecainide (143 $\mu g\ g^{-1}$ wet tissue); liver, kidney and heart, in decreasing order, have good affinity for the drug. Flecainide was present also in the central nervous system in lower concentrations. The lowest concentration was found in the adipose tissue.

Keywords flecainide antiarrhythmic

Introduction

Flecainide is a new antiarrhythmic agent that is very effective in the treatment of ventricular arrhythmias. Its plasma pharmacokinetics have been extensively described (Holmes & Heel, 1985), but its tissue distribution has been studied only in animals (Piovan *et al.*, 1986; Conard *et al.*, 1975). Knowledge of the tissue distribution of flecainide in humans could provide a better understanding of both its therapeutic and adverse effects. We measured flecainide in tissues sampled at autopsy from a patient who died suddenly out of hospital during chronic treatment with flecainide.

Case report

A 60 year-old man, 78 kg body weight, with a history of anterior myocardial infarction and hypertension, came to our observation because of complex ventricular arrhythmias. Two-dimensional echocardiogram disclosed an enlarged left ventricle with extensive asynergic areas. Holter monitoring for 24 h showed frequent PVCs ($> 40\ h^{-1}$), 36 ventricular couplets and six episodes of nonsustained ventricular tachycardia. The patient entered a randomized antiarrhythmic drug trial and was given propafenone, 450 and 900 mg day^{-1}. Since he did not respond to this drug, according to the study protocol, propafenone was withdrawn and flecainide was started, and was successful at the total daily dose of 150 mg twice daily. Four months later, shortly after the acute onset of dyspnoea, the patient died in the emergency room, 5 h after the last flecainide dose of 150 mg. Drug plasma concentrations measured 1 and 4 months before were respectively 387 and 493 ng ml^{-1}, in the range of variability found in other patients given the same dose of flecainide within the same trial (132-882 ng ml^{-1}, mean 345 ng ml^{-1}).

Autopsy, performed 30 h after death, disclosed pulmonary oedema, severe coronary atherosclerosis and signs of a healed myocardial infarction. Tissue samples of 1–2 g were excised, blotted on gauze and frozen until analyzed. Tissues were homogenized in methyl alcohol, centrifuged and the clear supernatant was dried at 60 °C under nitrogen; 1 ml of distilled water was added to the dry residue, which was processed as described (Chang *et al.*, 1984). Recovery, calculated from rat blank tissues spiked with known amounts of flecainide, was 78%; between day and within day coefficients of variation were respectively 1.1% and 2.7%, at concentrations of 100–1000 ng ml^{-1}. The minimal concentration of flecainide quantifiable in tissues was 30 ng g^{-1} wet weight.

Tissue concentrations ranged from 1.6 in fat, to 143 $\mu g\ g^{-1}$ of wet weight in the lung (Figure 1). Unfortunately, blood could not be drawn from the patient before he suddenly died so that the

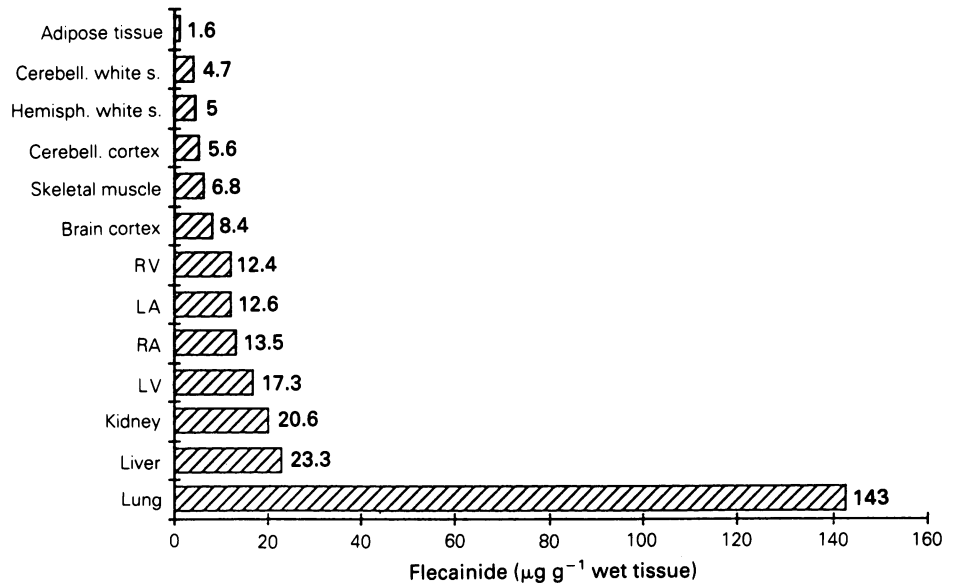

Figure 1 Flecainide distribution in autopsy specimens from a patient treated chronically with the drug. Cerebell. white s. = cerebellar white substance; Hemisph. white s. = hemisphere white substance; Cerebell. cortex = cerebellar cortex; RV = right ventricle; LA = left atrium; RA = right atrium; LV = left ventricle.

only reference concentrations of flecainide are those measured in the course of treatment, which was stable until the time of death. If we take the mean of the two values, 440 ng ml^{-1}, indicative tissue/plasma ratios can be calculated, ranging from 3.6 for fat, to 325 for lung.

Discussion

The extremely high concentration of flecainide in the lung suggests a high affinity of the drug for that tissue, which has also been described for other drugs such as propafenone (Latini *et al.*, 1987) and amiodarone (Latini *et al.*, 1984), for example. The second highest concentration, in the liver, might in fact be an underestimate, since some metabolic degradation could have occurred between death and autopsy. Similar concentrations were found in atrial and ventricular myocardium, the left ventricle showing the highest. The relatively high hydrophilicity of flecainide might account for its low concentrations in adipose tissue and thereby for its levels being lower in cerebral white matter than grey matter. The presence of flecainide in cerebral tissues is consistent with CNS side effects reported frequently in patients treated with the drug. Fat cannot be considered a reservoir of the drug, as has been shown for admiodarone. As a whole, there is good agreement between the flecainide distribution pattern described in the rat by previous authors (Piovan *et al.*, 1986) and our data.

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(Received 14 April 1987, accepted 8 August 1987)