Time-Dependent Effect of Oral Procainamide in Patients with Exertional Arrhythmias

Keyphrases □ Procainamide, oral—time-dependent effect, patients with exertional arrhythmias □ Arrhythmias, exertional—time-dependent effect of oral procainamide □ Antiarrhythmic agents—time-dependent effect of oral procainamide in patients with exertional arrhythmias

To the Editor:

The direct translation of procainamide pharmacokinetic data such as absorption and elimination half-lives into practical dosage regimen recommendations involves the assumption that procainamide is reversibly acting, *i.e.*, its antiarrhythmic effect is directly related to its presence in plasma (1). Studies (2–4) have established effective plasma concentration ranges of 4–8 and 4–10 μg/ml in hospitalized patients with acute myocardial infarction or coronary artery disease.

In a more recent study, Gey *et al.* (5) studied the relationship between procainamide plasma level and prevalence of *exertional* arrhythmias in ambulatory patients and established that the same plasma level range, 4–8 μg/ml, was effective also in suppressing most arrhythmias. The drug was administered in single oral doses and its antiarrhythmic effect was assessed before and 1 hr after drug administration, during maximal treadmill exercise testing, and during the immediate recovery period.

Nine patients performed a third exercise test at 2.5 hr, after receiving a 15-mg/kg dose, to assess the time dependency of the antiarrhythmic effect. In four patients there was a tendency for arrhythmias to reappear as plasma levels decreased between 1 and 2.5 hr, but this effect was not statistically significant (5). The phenomenon of time dependency was pursued further, and the additional information obtained to date is presented here.

Six patients who exhibited only partial suppression of arrhythmias at the 1-hr exercise test, following a 15-mg/kg dose, were tested again using a 22.5-mg/kg dose with exercise tests before and at 1.0 and 2.5 hr after drug administration. The methods of ECG recording and analysis as well as of procainamide plasma determination were the same as those previously described (5). The individual patient data are shown in Table I.

When mean plasma concentration rose from 0 to 8.86 μg/ml at 1 hr, the mean prevalence of arrhythmia dropped from 164 to 15 ($p < 0.05$). The corresponding decrease in the severity index was from 12.8 to 5.8 ($p < 0.01$). All patients exhibited more than 78% reduction in prevalence of arrhythmia, but only one (C. F.) showed total suppression.

Of greater significance, when mean plasma levels dropped to 6.93 μg/ml at 2.5 hr, the corresponding arrhythmia count increased to a mean value of 48, a statistically significant increase ($p < 0.016$). In other words, between 1 and 2.5 hr, a 20% decrease in plasma level was accompanied by more than a 200% increase in arrhythmia count. Similarly, the severity index increased by 32%. An examination of individual patient data shows that there was only one exception to this pattern (H. E., severity data).

These results lend support to the hypothesis that, in the patients studied, procainamide is reversibly acting against *exertional* arrhythmias during the single-dose *oral* administration. (The possible role played by metabolites cannot be assessed in view of the total lack of quantitative kinetic information.)

These findings have several therapeutic consequences:

1. When only temporary protection from exertional arrhythmias is required, *e.g.*, joggers, a single oral dose (15 or 22.5 mg/kg) might be sufficient.
2. If protection is required on a 24-hr basis (patients exhibiting similar arrhythmias at rest), the short biological half-life of procainamide, 2.5–4.5 hr (2, 3), would require short dosing intervals (3–4 hr).
3. The approach of a standard maximal treadmill exercise test (6) in conjunction with plasma level

Table I—Plasma Concentrations, Prevalence of Arrhythmia[a], and Severity following a 22.5-mg/kg Oral Dose of Procainamide

	Control		1 hr			2.5 hr		
Patient	Prevalence of Arrhythmia	Severity Index	Prevalence of Arrhythmia	Severity Index	Plasma Concentration, μg/ml	Prevalence of Arrhythmia	Severity Index	Plasma Concentration, μg/ml
A. G.	137	15	29	11	8.89	55	11	6.24
C. F.	55	13	0	0	8.67	5	2	7.37
H. E.	113	12	16	10	8.85	41	8	6.05
O. N.	79	9	6	5	7.91	26	9	7.21
R. L.	467	15	24	4	11.73	91	9	8.25
H. J.	133	13	16	5	7.13	70	7	6.48
Mean ± *SD*	164 ± 152	12.8 ± 2.2	15 ± 11	5.8 ± 4.1	8.86 ± 1.56	48 ± 31	7.7 ± 3.1	6.93 ± 0.83

[a] Number of premature ventricular beats during exercise and the immediate recovery period.

measurements provides an objective and rapid method of optimizing dosage regimens of procainamide for individual patients.

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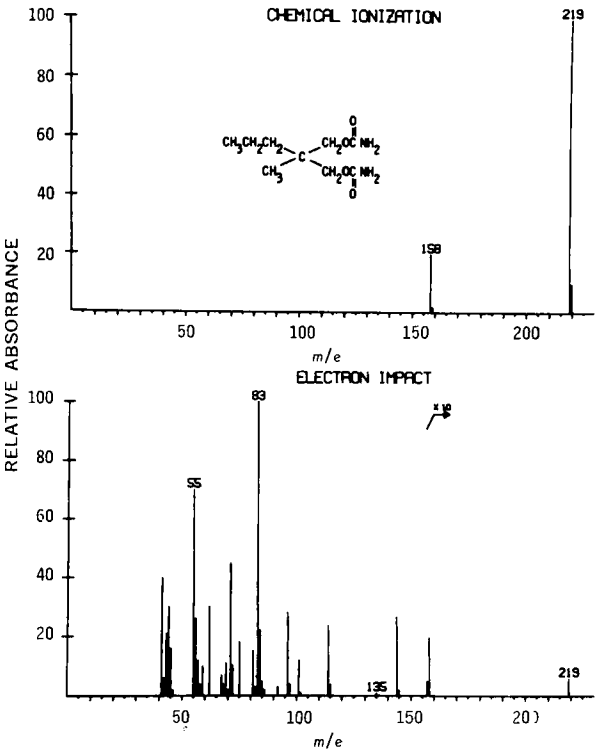

Figure 1—*Comparison of the normalized electron-impact and chemical ionization mass spectra of Compound Ia. All other dicarbamates listed in Table I gave similar spectra.*

Combined Application of High-Resolution Chemical Ionization and Electron-Impact Mass Spectrometry to Medicinal Dicarbamates

Keyphrases □ Mass spectrometry, electron impact and high-resolution chemical ionization—application to medicinal dicarbamates □ Dicarbamates, medicinal—combined application of high-resolution chemical ionization and electron-impact mass spectrometry

To the Editor:

A recent report on the application of field desorption mass spectrometry to a series of medicinal dicarbamates to determine the molecular weight (1) prompts us to communicate earlier results on the application of chemical ionization mass spectrometry to a series of structurally similar dicarbamates (2).

Several electron-impact mass spectral studies of monocarbamates have appeared (3–7). It has been pointed out that, in addition to having relatively predictable spectra, the volatility of carbamates, the small amounts of sample required for analysis, and the wealth of structural information contained in the spectra make mass spectrometry an excellent tool for structural elucidation (3). In addition, it was noted that relatively obvious molecular ions were obtained and that no recombination peaks were detected (3).

When a series of 10 dicarbamates having the general structure, I (Scheme I), were examined by high-resolution electron-impact mass spectrometry, spectra rich in readily interpretable fragment ions were obtained but molecular ions were conspicuously absent. Instead, peaks of less than 1% relative abundance were observed at *m/e* (M + 1) in all instances. Due to the difficulty in obtaining high-resolution data on the very weak M + 1 ions along with the desirability of directly determining the molecular formula[1], an investigation of the chemical ionization mass spectrometry was undertaken.

In an effort to minimize fragmentation, the combination of a low inlet temperature of 100°[2] and a mild chemical ionization reagent, isobutane, was used. In all chemical ionization (C.I.) spectra, the MH^+ ion was the most intense ion, with the only significant fragment ion arising from the direct loss of carbamic acid from the MH^+ ion[3]. Fast-scan high-resolution data were readily obtained.

A comparison of the spectra obtained in the chemical ionization and electron-impact modes for Ia [R_1 = CH_3, R_2 = $CH_2CH_2CH_3$ (meprobamate)] is given in Fig. 1 and is typical of all dicarbamates investigated.

[1] With only low-resolution data, the recombination M + 1 ion could be misinterpreted as the molecular ion.
[2] Dicarbamates are susceptible to thermal decomposition at higher inlet temperatures.
[3] The direct loss was established from metastable ions.