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Comparative pharmacokinetics of propranolol and 4-hydroxypropranolol using conventional and long-acting propranolol

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Long-acting propranolol (L.A. propranolol) is a new preparation formulated so that the drug is leached into the gastrointestinal fluids at a constant rate, providing delayed and controlled release into the circulation. Previous studies showed that L.A. propranolol produces lower peak plasma concentrations of drug and longer times to peak than after administration of the conventional preparation (McAinsh et al 1978; Leahey et al 1980). Neither of these studies reported the pharmacokinetics of a metabolite, 4-hydroxypropranolol, which possesses β-blocking activity comparable to the parent drug (Fitzgerald & O'Donnell 1971). We have investigated the pharmacokinetics of propranolol and 4-hydroxypropranolol from commencement of therapy to steady-state, comparing conventional and L.A. propranolol formulations.

Ten healthy male subjects, aged 17 to 25 years (mean 20), each having given informed, written consent, participated. Treatment 1 consisted of a conventional propranolol (Inderal) 160 mg tablet administered 12 hourly for 4 days. In Treatment 2, L.A. propranolol (Inderal L.A.) was administered as 2 by 160 mg capsules once daily, for 4 days. The subjects received each of the treatments randomly on different occasions, separated by at least 10 days. The tablets in Treatment 1 were given at 0900 h and 2100 h, the capsules in Treatment 2 were given at 0900 h. No other medication was permitted. Normal diet was allowed and the subjects remained ambulatory during the study.

Blood (4 ml) was withdrawn daily, just before the morning dose. During day 4, additional samples were taken at 1, 2, 3, 4, 5, 6, 8, 12 and 24 h after the morning dose. Sera were stored at −25 °C until assayed for propranolol and 4-hydroxypropranolol by our modification of the method of Nation et al (1978). The profiles in Fig. 1 show mean serum propranolol and 4-hydroxypropranolol concentrations measured after daily administration of conventional and L.A. propranolol over four days. Using a higher propranolol dose, we confirmed the results of previous studies that serum propranolol profiles were lower and flatter when L.A. propranolol was given compared with conventional propranolol. In most subjects, steady-state propranolol concentrations were achieved two days after administration of either preparation. In contrast, 4-hydroxypropranolol concentrations were low and did not accumulate. At steady-state, the mean (±s.e.m.) peak concentration of propranolol (381·9 ± 77·3 ng ml^{-1}) from conventional propranolol differed significantly (paired t-test, $P < 0.005$) from that obtained with the L.A. preparation (128·0 ± 21·6 ng ml^{-1}). The time taken to reach peak propranolol concentration after L.A. propranolol administration (5·9 ± 0·6 h) was significantly different ($P < 0.001$) from that observed with conventional propranolol (2·6 ± 0·5 h). Average peak 4-hydroxypropranolol concentrations of 26·3 ± 6·1 ng ml^{-1} and 13·5 ± 1·7 ng ml^{-1} were obtained using the conventional and L.A. preparations, respectively. These were statistically insignificant ($P > 0.05$) although a peak of 73·9 ng ml^{-1} was measured in one subject taking conventional propranolol. The time to reach peak metabolite concentration was greater ($P = 0.005$) for L.A. (4·4 ± 0·4 h) than for conventional propranolol (2·3 ± 0·5 h).

For propranolol at steady-state, peak to trough ratios of 4·0 ± 0·9 and 2·2 ± 0·3 were obtained with conventional and L.A. propranolol, respectively. Similar results were obtained for the metabolite. With both propranolol and 4-hydroxypropranolol, tests of significance for correlated variances (Snedecor & Cochran 1967) showed that the variance of the peak to trough ratios after L.A. propranolol administration was significantly less ($P < 0.01$) than that obtained using conventional propranolol. In our subjects, the pharmacokinetic characteristics of the L.A. preparation were advantageous in maintaining reasonably constant serum propranolol concentrations over 24 h, compared with the conventional product. These characteristics may be important clinically in the treatment of angina, cardiac arrhythmias and thyrotoxicosis where the efficacy of the drug is related to β-adrenoceptor blockade.

We studied the systemic availability of propranolol and 4-hydroxypropranolol by comparing the areas under the serum concentration-time curve (AUC) following admin-

Table 1. Comparison of the mean (±s.e.m.) AUC (ng ml^{-1} h) of propranolol and 4-hydroxypropranolol at steady-state during administration of conventional propranolol (160 mg 12 hly, corrected to 320 mg dose per day) and L.A. propranolol (320 mg once daily) to normal subjects. Results of statistical analysis of the data are given as the Student's t-value (probability) as determined by the paired t-test.

	Conventional propranolol	L.A. propranolol	Student's t (P)
Propranolol	4786·0 ± 859·0	2203·2 ± 403·2	4·2 (0·005)*
4-Hydroxypropranolol	219·4 ± 35·6	190·5 ± 20·6	1·0 (0·35)

* Correspondence.

* Statistically significant.

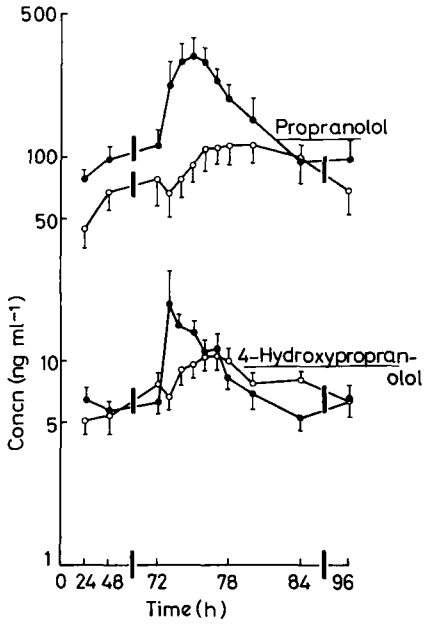

FIG. 1. Serum propranolol and 4-hydroxypropranolol concentrations measured over 4 days following the administration of L.A. propranolol (320 mg once daily) and conventional propranolol (160 mg 12 hly) to ten normal subjects. The expanded time scale between the breakers contains data obtained during day 4. Results are expressed as the mean (s.e.m.) serum concentration of propranolol and 4-hydroxypropranolol. (○) L.A. propranolol; (●) conventional propranolol.

istration of conventional and L.A. propranolol at steady-state. For comparison between preparations, the AUCs of 4-hydroxypropranolol and propranolol from the conventional product were corrected to a dose of 320 mg day^{-1}. The results in Table 1 show that the AUCs for 4-hydroxypropranolol were not different ($P = 0{\cdot}35$) when either preparation was given, although the AUCs for propranolol following the L.A. preparation were half that obtained from the conventional preparation.

This suggests that the slower rate of absorption of drug from L.A. propranolol affects the drug's metabolism compared with that of the conventional preparation. Further, since glucuronidation is an important elimination pathway for propranolol and 4-hydroxypropranolol (Walle et al 1979, 1980) it is likely that, relative to propranolol, increased serum concentrations of 4-hydroxypropranolol glucuronide may occur during L.A. propranolol therapy. This could have important clinical implications for patients with renal failure who are treated with this preparation since 4-hydroxypropranolol glucuronide may serve as a storage pool for 4-hydroxypropranolol in the body (Walle et al 1980). Saturable propranolol metabolism may partly explain differences in the systemic availability of propranolol between the two preparations, although drug dissolution effects would also need to be considered. It is unlikely that altered gastrointestinal motility significantly affects the bioavailability of L.A. propranolol (Charles et al 1981).

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