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THE EFFECT OF AGE ON PLASMA LEVELS OF PROPRANOLOL AND PRACTOLOL IN MAN

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1 Plasma levels of propranolol and practolol were measured in groups of elderly and young subjects, after the oral administration of propranolol (40 mg) and practolol (200 mg) on separate occasions.

2 At all sampling times the mean plasma propranolol level in the group of elderly subjects was substantially greater than the corresponding level in the group of young subjects, there being a significant difference between the two, and a fourfold difference in the mean peak levels.

3 After practolol, there was no significant difference between the mean plasma concentrations of the drug in the two groups for the first 2 hours. Subsequently, the mean plasma levels in the group of elderly subjects were somewhat higher than the corresponding levels in the young group, the differences between the two reaching significance.

4 It is suggested that there is a need to substantially reduce the dose of propranolol given to elderly patients. With practolol, however, no reduction is necessary providing renal function is normal for the patient's age.

Introduction

Adverse drug reactions are more common in the elderly than in the young (Hurwitz, 1969). Whilst patient error (Harman, 1971), multiple diseases inviting polypharmacy (Davison, 1971), increased tissue sensitivity (Hall, Ettinger & Banting, 1936), and a lowering of the threshold to activate receptors (Chen & Brown Robbins, 1943) may account for some of these adverse drug reactions, they are more likely to be due to an increase in the concentration of circulating drug. Such an increase could result from decreased efficiency of drug metabolizing enzymes. Reduced levels of cytochrome P-450 with advancing age has been directly demonstrated in rats (Kato & Takanaka, 1968a), and this decrease in *in vitro* enzyme activity is paralleled by impairment of drug metabolizing activity (Kato & Takanaka, 1968b). In man, the evidence for impaired drug metabolism associated with advancing age is only indirect. The plasma half-lives of antipyrine and phenylbutazone have been shown to be increased in geriatric patients (O'Malley, Crooks, Duke & Stevenson, 1971), and the rate of hydroxylation of amylobarbitone is reduced in the elderly (Irvine, Grove, Toseland & Trounce, 1974). Drugs may also accumulate as a result of impairment of renal function associated with advancing age (Shock, 1946). Higher plasma levels of digoxin in the elderly have been shown to correlate well with their reduced creatinine clearances (Jelliffe & Blankenhorn, 1967). Impaired renal excretion of penicillin in the elderly has also been shown to occur (Mølholm Hansen, Kampmann & Laursen, 1970).

Despite the implications of this work in man, large areas of drug pharmacokinetics in the elderly remain unexplored at the present time. With the possible exception of digoxin (Jelliffe, 1968) there is a paucity of objective advice about drug doses in the elderly. In order to elucidate further the influence of age on the metabolism and excretion of commonly used drugs, we have studied young and elderly subjects, measuring their plasma levels of propranolol and practolol after drug administration. These two β-adrenoceptor blocking

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agents have similar pKa values (9.45 and 9.50, respectively), but different routes of elimination – hepatic in the case of propranolol (Paterson, Conolly, Dollery, Hayes & Cooper, 1970; Shand & Rangno, 1972), and renal in the case of practolol (Bodem & Chidsey, 1973).

Methods

After approval of the subject by the Ethical Committee of Guy's Hospital Medical School and St. Mary's General Hospital, Portsmouth, nine young subjects (five men and four women), mean ± s.e. mean age 27 ± 2 years and nine elderly subjects (three men and six women), mean ± s.e. mean age 77 ± 2 years, took part in the propranolol study. In the practolol study there were thirteen young subjects (seven men and six women), mean ± s.e. mean age 27 ± 2 years and eight elderly subjects (three men and five women), mean ± s.e. mean age 80 ± 3 years. Nine of the young and five of the elderly subjects participated in both studies. The two groups in each study were matched for height and weight. The elderly subjects were either resident in a continuing-care ward or lived in the community. They had normal chest X-rays and electrocardiograms, and like the young subjects had no clinical evidence of disease affecting the gastrointestinal tract, cardiac or respiratory systems. In all subjects the haemoglobin, plasma proteins, serum bilirubin, creatinine, alkaline phosphatase, aspartate amino transferase and blood urea were within normal limits. The mean ± s.e. mean creatinine clearance in the subjects participating in the practolol study was 114 ± 7 ml/min for the young group and 62 ± 11 ml/min for the elderly group, this difference being highly significant ($P < 0.0005$).

After an overnight fast, propranolol (40 mg) or

Table 1 Mean plasma levels of propranolol after 40 mg was taken orally by a group of elderly subjects and a group of young subjects.

Sampling time (h)	*Plasma propranolol level (ng/ml, mean ± s.e. mean)* *Young (n = 9)*	*Elderly (n = 9)*	*Significance levels*
0.5	5.2 ± 2.6	31.6 ± 11.8	$P < 0.05$
1	22.8 ± 8.0	87.2 ± 24.4	$P < 0.05$
1.5	26.9 ± 6.2	108.7 ± 24.9	$P < 0.01$
2	27.3 ± 6.4	111.3 ± 22.1	$P < 0.005$
4	16.2 ± 4.1	80.6 ± 15.3	$P < 0.001$
6	7.2 ± 2.0	54.8 ± 10.6	$P < 0.001$
8	5.8 ± 1.9	33.4 ± 7.2	$P < 0.001$

Statistical analysis was carried out using Student's *t*-test.

Table 2 Mean plasma levels of practolol after 200 mg was taken orally by a group of elderly subjects and a group of young subjects.

Sampling time (h)	*Plasma practolol level (μg/ml, mean ± s.e. mean)* *Young (n = 13)*	*Elderly (n = 8)*	*Significance levels*
0.5	0.56 ± 0.13	0.28 ± 0.16	NS
1	1.04 ± 0.15	0.75 ± 0.27	NS
1.5	1.23 ± 0.21	1.19 ± 0.30	NS
2	1.32 ± 0.18	1.54 ± 0.27	NS
4	1.25 ± 0.10	2.13 ± 0.26	$P < 0.01$
6	1.01 ± 0.11	2.04 ± 0.27	$P < 0.01$
8	0.84 ± 0.08	1.73 ± 0.17	$P < 0.01$
10	0.66 ± 0.06	1.49 ± 0.19	$P < 0.01$

Statistical analysis was carried out using Student's *t*-test.
NS = not significant ($P > 0.05$).

practolol (200 mg) was taken orally on separate occasions. Venous blood samples were collected prior to dosing, and at 0.5, 1, 1.5, 2, 4, 6 and 8 h after dosing. During the practolol study an extra sample was taken at 10 hours. The plasma obtained from these samples was stored at -20° C until analysed. Propranolol was measured by a fluorimetric method (Shand, Nuckolls & Oates, 1970), which is specific for propranolol and does not measure the pharmacologically active metabolite 4-OH propranolol. Practolol was measured spectrophotometrically (Turner, Burman, Hicks, Cherrington, MacKinnon, Waller & Woolnough, 1971).

Results

The mean plasma propranolol levels in the two groups are given in Table 1. In the elderly group, the mean levels were significantly higher at all sampling times compared to the corresponding levels of the young group. The mean peak of 111 ng/ml was more than four times the comparable value in the young subjects (27 ng/ml). Both peaks occurred at 2 h, but the plasma propranolol level decayed more rapidly in the young group.

For the first 2 h the mean plasma practolol level was similar in both groups (Table 2). From Table 2 it might appear that the time taken to reach the peak was longer in the elderly than in the young, but this apparent difference was not significant due to individual variation. Although the duration of this study was only 10 h, the mean ± s.e. mean plasma elimination half-lives were calculated from the limited data available. These were 8.6 ± 0.8 h in the elderly group, and 7.1 ± 0.5 h in the young group. The longer mean elimination half-life in the elderly was accompanied by slightly higher plasma practolol levels from 4 to 10 h, and these differences in plasma levels between the two groups reached significance. The small differences between the two groups are consistent with their mean creatinine clearances.

Discussion

The results of this study demonstrate that after a relatively small oral dose, the elderly have markedly higher plasma propranolol levels than the young. Elderly patients commonly receive many times this dose of propranolol for the treatment of angina or hypertension, which may well magnify the difference. The higher levels might be due to variations between the groups in plasma (Evans, Nies & Shand, 1973) or tissue binding (Evans & Shand, 1973), or hepatic blood flow (Nies, Evans & Shand, 1973). Although changes in volume of distribution have not been excluded, differences in blood volume are unlikely as both groups were matched for height and weight. Decreased absorption in the young subjects is also unlikely as propranolol is normally 70-100% absorbed (Paterson *et al.*, 1970). Despite all subjects having apparently normal liver function, the tests used are insensitive as indices of drug metabolizing activity (O'Malley *et al.*, 1971), and reduced hepatic function is known to occur as age advances (Thompson & Williams, 1965). Since propranolol is almost entirely eliminated by the hepatic route (Paterson *et al.*, 1970; Shand & Rangno, 1972), higher plasma levels of this drug in the elderly are unlikely to be due to any diminution of renal function, but rather to reduced hepatic extraction and metabolism. As the levels were significantly different even at the earliest sampling time, it seems probable that these higher levels are due to elderly subjects having a substantially reduced first-pass effect.

There was no significant difference in the mean plasma levels of practolol in the elderly group compared to the young group for the first 2 hours. However, subsequent levels were raised in the elderly, although the mean peak was less than twice that of the young group. Since practolol is almost entirely eliminated by the kidneys (Bodem & Chidsey, 1973), the small differences between the groups are probably related to the normal reduction of creatinine clearance that occurs in the elderly (Shock, 1946). These small increases in practolol levels are not sufficient to warrant reduction in the usual maintenance dose of practolol when describing the drug for elderly patients whose renal function is within normal limits for their age.

Thus this preliminary study of the influence of age on drug elimination has demonstrated marked differences between elderly and young subjects. After only a small oral dose, substantial elevations of plasma propranolol levels occur in the elderly, even though they have no clinical evidence of cardiac, hepatic or renal disease. This difference was much less marked when comparing plasma practolol levels in the two groups. Therefore, provided there is no evidence of renal disease, elderly patients do not require a reduction in the dose of practolol from that usually prescribed. However, if undesirable effects are to be avoided, elderly patients require a considerable reduction in the dose of propranolol from that usually given, and also, perhaps, of other drugs which possess

both a pronounced first-pass effect and extensive hepatic metabolism.

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