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EFFECT OF AGE ON PLASMA PROPRANOLOL LEVELS

After giving a single 40 mg oral dose of propranolol, Castleden & George (1979) found significantly higher plasma drug levels in elderly subjects than in young, healthy volunteers. These results are similar to those described by Castleden, Kaye, & Parsons (1975), although the mean plasma propranolol levels in the young group in the more recent paper are almost double those found in 1975 and at variance with other published data (Parsons, Kaye, Raymond, Trounce & Turner, 1976; Schneider, Babb, Bishop, Mitchard, Hoare & Hawkins, 1976). The elderly subjects in both cases were drawn at least in part from long-stay geriatric wards, and presumably could not be described as healthy and active. In these studies, therefore the pharmacokinetic differences from youthful controls might be attributable to age associated disease rather than to age itself.

Logically, investigation of the influence of age *per se* on pharmacokinetic parameters can only be carried out in elderly volunteers with *no* evidence of disease or drug use which might influence the results obtained. We have therefore determined the plasma propranolol concentrations obtained after single oral doses of 40 mg and of 80 mg propranolol in elderly (63–81 years) volunteers in excellent health who were living and in some cases working independently in the community. These results have been compared with results obtained under identical conditions in healthy active young (19–25 years) volunteers. Different volunteers were involved in the investigation of each of the 40 mg and 80 mg doses so that each volunteer received only one dose of propranolol. All volunteers in both young and elderly groups were non-smokers in whom no abnormality was detected on clinical examination or on biochemical or haematological profiles and who had an ESR of < 20 mm/h.

Mean plasma propranolol concentrations after the smaller dose (40 mg) were almost identical in the two groups at all sampling times (Figure 1). The mean areas under the plasma concentration-time curves (AUC) were almost similar, being 82.5 ± 14.1 (s.e. mean) ng ml^{-1} h in the young group and 81.3 ± 8.4 (s.e. mean) ng ml^{-1} h in the elderly group. After 80 mg, there was no difference between the peak levels of the mean plasma concentration-time curves of the young and elderly groups, although the peaks occurred at different times (Figure 2). The mean AUCs were 665 ± 149 (s.e. mean) ng ml^{-1}h in the young group and 466 ± 52 (s.e. mean) ng ml^{-1} h in the elderly group but this difference was not significant at the 5% level. The results of this study therefore indicate that the pharmacokinetics of oral propranolol in healthy active elderly volunteers are similar to those in healthy young volunteers.

These results are supported by a recent detailed study by Vestal, Wood, Branch, Shand & Wilkinson (1979) on the effect of age and cigarette smoking on propranolol disposition. They stated that 'the decline in intrinsic total clearance (of propranolol) with age was critically dependent on the smoking habits of the subjects' and concluded that the drug-metabolizing capacity of non-smokers did not alter with age.

It has been the practice of most workers to describe volunteers used for drug studies as being free from

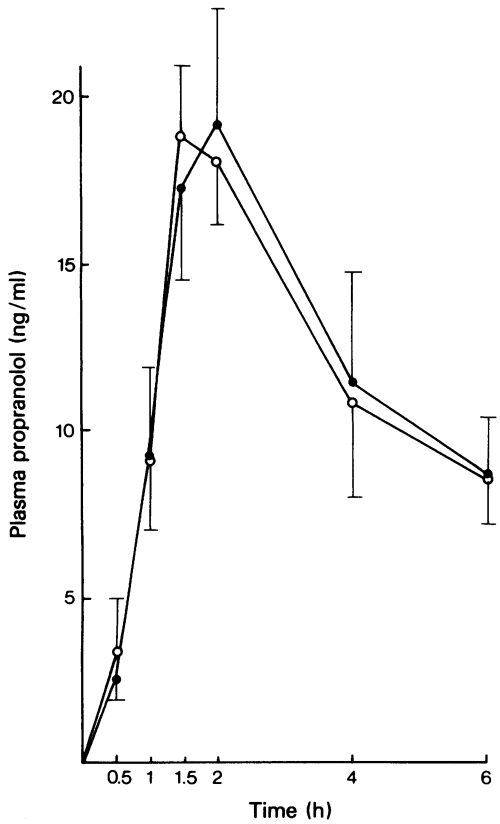

Figure 1 Mean plasma propranolol concentrations (±s.e. mean) after a 40 mg oral dose in twelve subjects aged < 25 years (●) and in five subjects aged ⩾ 63 years (○).

cardiac, renal, hepatic and gastrointestinal disease. The discrepancy between our results and those of Castleden & George (1979) and Castleden *et al.* (1975) suggests that these may not be adequate criteria for selection of volunteers for investigation of age related changes in drug handling. This view is supported by the demonstration of an effect on plasma levels of propranolol and oxprenolol, of any inflammatory disease, however minor, when associated with a raised ESR, (Schneider, Bishop & Hawkins, 1979; Kendall, Quarterman, Bishop & Schneider, 1979).

We therefore conclude that only elderly subjects who are independent, active and objectively disease free are appropriate for investigation of the effect of age on pharmacokinetic parameters. Otherwise, changes in drug handling in the elderly may be ascribed to age, when they are in fact caused by some other factor. This study, using such elderly subjects, suggests that age does not significantly alter the pharmacokinetics of propranolol in man.

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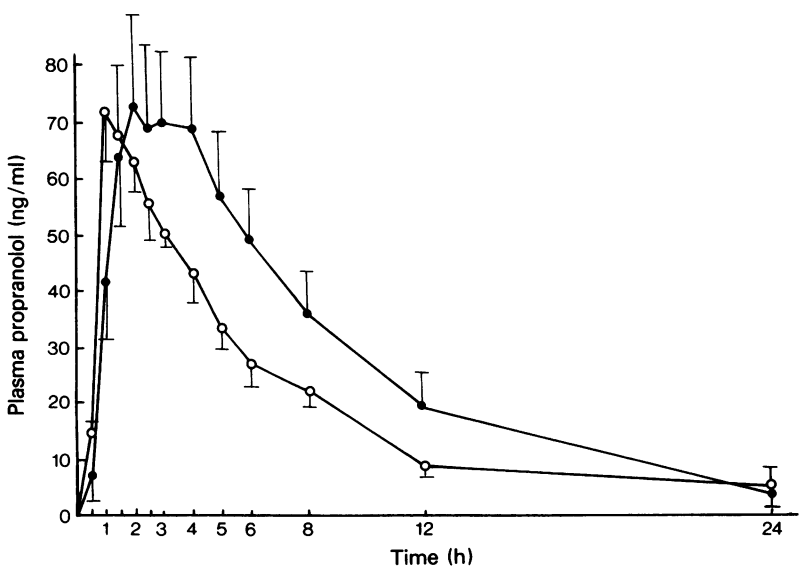

Figure 2 Mean plasma propranolol concentrations (±s.e. mean) after an 80 mg oral dose in six subjects aged < 25 years (●) and in five subjects aged ⩾ 63 years (○).

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THE EFFECTS OF RANITIDINE ON PITUITARY HORMONE SECRETION *IN VITRO*

Ranitidine is a new histamine receptor (H_2) antagonist. It is claimed to have higher potency and fewer side effects than cimetidine, an H_2 receptor antagonist currently in use for the treatment of peptic ulcers. The side effects reported for cimetidine therapy include hyperprolactinaemia and gynaecomastia (Hall 1976; Delle Fave, Tamburrano, De Magistris, Natoli, Santoro, Carratu & Torsoli, 1977). However, further study has shown that oral administration of conventional doses of cimetidine is unlikely to alter prolactin secretion although high parenteral doses do increase prolactin levels (Delitala, Stubbs, Wass, Jones, Williams & Besser, 1979). We have previously tested *in vitro* the hypothesis (Burland, Gleadle, Lee & Rowley-Jones, 1978) that cimetidine is a dopamine antagonist and shown it to be incorrect (Delitala, Stubbs, Yeo, Jones & Besser, 1979).

In the present study, we have investigated the ability of ranitidine to act as a dopamine agonist or antagonist by its action on prolactin secretion from isolated pituitary cells maintained in a column capable of being continuously perfused (Yeo, Thorner, Jones, Lowry & Besser, 1979). We have also investigated whether or not ranitidine has releasing-hormone activity with respect to the secretion of LH, TSH, GH and ACTH.

Pituitary cell columns for investigations of prolactin secretion were prepared as in previous reports (Yeo *et al.*, 1979; Delitala *et al.*, 1979b). For investigations of pituitary hormones other than prolactin, the columns were prepared in a similar manner except that dopamine was omitted. The column was perfused at 0.8 ml/min. One minute pulses of rat stalk median eminence extract, synthetic GnRH and TRH or ranitidine dissolved in Earle's basic salt solution (EBSS) containing BSA (0.25 g/100 ml) were passed through the column followed by 9 min of EBSS before the next pulse. Two minute fractions of column eluate were collected. Rat

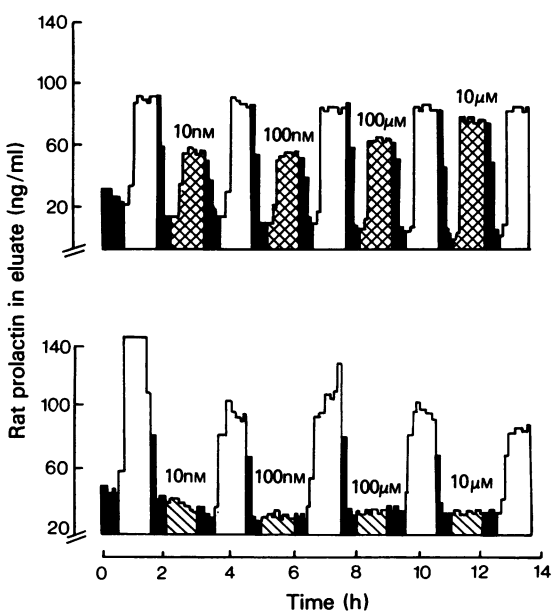

Figure 1 Rat prolactin concentrations in eluate from anterior pituitary cell columns exposed to pulses of medium containing dopamine (5 μM) (■), dopamine (5 μM) plus metoclopramide (10 nM to 10 μM) (▩) and dopamine (5 μM) plus ranitidine (10 nM to 10 μM) (▨). The concentrations of metoclopramide and ranitidine are as shown. Blank bars represent prolactin secretion when saline alone was added to the perfusing medium.