Interaction between nortriptyline and lignocaine for uptake by lung in isolated lungs and *in vivo*

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The lungs have been shown to concentrate many basic amines (see Bakhle & Vane, 1974), including the local anaesthetic lignocaine (Benowitz, Forsyth, Melmon & Rowland, 1974). The uptake of lignocaine seems to be in part a saturable concentration-dependent diffusion process, not dependent on energy, and highly dependent on the physico-chemical properties of the substance (Post, Andersson, Ryrfeldt & Nilsson, 1978). As the tricyclic antidepressant drugs are also taken up by the lung (Junod, 1972; Orton, Anderson, Pickett, Eling & Fouts, 1973), we have investigated the possibility of interactions between lignocaine and the tricyclic antidepressant nortriptyline.

The displacement of [^{14}C]-labelled lignocaine by non-labelled lignocaine and nortriptyline has been studied in isolated perfused rat lungs and the displacement of nortriptyline by a bolus injection of lignocaine *in vivo* in anaesthetized pigs treated with nortriptyline.

Rat isolated lungs were perfused, at 10 ml/min with Krebs-Ringer bicarbonate buffer (pH 7.35) containing 4% bovine serum albumin and 0.1% glucose, and ventilated by negative pressure. After equilibration, [^{14}C]-lignocaine (37 μM final concentration) was added to the perfusate and lung effluent collected. At 3 min, when the extraction of lignocaine from the perfusate had reached a steady state (Post *et al.*, 1978), a bolus injection (0.1 ml, injected in less than 3 s) of unlabelled lignocaine (3.7 μmole) or nortriptyline (5.1 μmole) was given. Both drugs transiently increased the radioactivity in the effluent. For unlabelled lignocaine, the displaced [^{14}C]-lignocaine, calculated from the area under the peak of radioactivity, was 13 ± 5% (mean ± s.e. mean; $n = 4$) of that accumulated by 3 min (2.8×10^{-7} moles) whereas nortriptyline displaced 22 ± 2% ($n = 4$).

For the *in vivo* experiments, Swedish Landrace pigs (18–21 kg) were anaesthetized with sodium pentobarbitone and tracheotomized. Catheters were placed in the right atrium and the common carotid artery for injections of drugs and arterial blood sampling respectively. Arterial blood pressure and ECG were monitored continuously throughout the experiment.

The first-pass uptake of [^{14}C]-lignocaine (bolus injection 2.0 mg/kg) by the lung was 39 ± 5% ($n = 7$). In six pigs, nortriptyline-HCl was infused (330 mg/h to a total of 250 mg) and the first-pass uptake of [^{14}C]-lignocaine in these animals was not affected (30 ± 8%). However, the nortriptyline concentration in arterial blood (assayed by HPLC; Mellström & Braithwaite, 1978) which was about 5 μM by this time was raised transiently following the lignocaine bolus. The displacement of nortriptyline (cardiac output × area under the curve) was 0.66 ± 0.03 μmole ($n = 5$) which approximates to 0.2 mg nortriptyline-HCl.

Our results show that lignocaine and nortriptyline will interact in terms of uptake by lung in isolated preparations and more importantly *in vivo*. As a number of clinically important drugs are taken up by the lung, our results could have clinical relevance.

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