FIRST-PASS LUNG UPTAKE OF PROPRANOLOL ENHANCED IN ANAESTHETIZED DOGS


SUMMARY

Uptake of $^{14}$C-propranolol after a single passage through the pulmonary circulation was studied in three groups of Labrador dogs using a double indicator dilution method. Uptake in conscious, ambulant animals was 53%. This increased to 81% in dogs anaesthetized with thiopentone, nitrous oxide and halothane and to 64% in dogs anaesthetized with thiopentone, nitrous oxide and fentanyl. Interaction between lipid-soluble anaesthetic agents and pulmonary endothelial cell membranes may be an important factor in increasing lung uptake of lipophilic propranolol, although alteration in pulmonary perfusion associated with a reduction in cardiac output during general anaesthesia may play a part. The pharmacological effects of propranolol administered i.v. during general anaesthesia may be unpredictable.

Many pharmacologically active substances are influenced by passage through the pulmonary circulation (Brown, 1974; Bakhle and Vane, 1977). Anaesthetic agents modify some of these pharmacokinetic functions of the lung. For example, both rabbit lungs in vitro (Naito and Gillis, 1973) and dog lungs in vivo (Bakhle and Block, 1976) removed less noradrenaline in the presence of halothane. In contrast, concentration of propranolol in isolated, perfused rat lung was increased by lignocaine (Dollery and Junod, 1976) and lungs removed from rats given propranolol and atenolol i.v. during halothane in nitrous oxide anaesthesia had increased drug concentrations compared with conscious controls (Street et al., 1979).

The underlying mechanism is unclear, but may have possible therapeutic relevance. We investigated first-pass lung uptake of propranolol in conscious, ambulant dogs and in dogs anaesthetized with two standard techniques.

METHODS

Uptake of $^{14}$C-propranolol after a single passage through the pulmonary circulation was measured in three groups of Labrador dogs with cardiac catheters implanted in the right atrium (RA), pulmonary artery (PA) and descending aorta. Group A (control) consisted of three conscious, ambulant dogs catheterized 3–4 days previously. Group B consisted of three dogs catheterized and studied under general anaesthesia. After induction with thiopentone 15 mg kg$^{-1}$ the trachea was intubated and the lungs ventilated artificially (minute volume 3.5–4.0 litre min$^{-1}$) with 0.5–1% halothane, nitrous oxide and oxygen. Group C consisted of three dogs investigated as in group B except that halothane was omitted, and fentanyl 0.001 mg kg$^{-1}$ i.v. was given before and at intervals during the experiment (total dose 0.003–0.004 mg kg$^{-1}$).

Three to five measurements of propranolol uptake were made in each dog at intervals of 20 min. One dog in group A was studied on two separate occasions.

Propranolol uptake was measured with a double indicator dilution method. A mixture of 0.2 mg of $^{14}$C-propranolol (I.C.I., specific activity 22.83 μCi mg$^{-1}$; carbon-14 at the α position of the naphthalene to which the side chain is attached) and 1.875 mg of indocyanine green (ICG) (Hynson, Westcott and Dunning Inc.), total volume 1.75 ml, was rapidly injected as a bolus to RA while blood was withdrawn from the aortic catheter through a Gilford densitometer (Model 103 IR) at 0.8 ml s$^{-1}$. The dye curve was recorded and cardiac output calculated by standard techniques (Bloomfield, 1974). The dye curve was used to time the collection of an aortic blood sample; blood was collected from the start of the curve to a point just before recirculation. Preliminary
experiments showed that the $^{14}$C-propranolol and ICG outflow curves occurred virtually synchronously, so an aortic sample collected in this way would include most of the outflow of both substances. This blood sample was centrifuged immediately at 3000 rev min$^{-1}$. The plasma fraction was then assayed for ICG in a Unicam spectrophotometer at 805 nm, and for $^{14}$C-radioactivity in a Packard liquid scintillation counter after mixing with Biofluor scintillation fluid (N.E.N.). An external standard was used to monitor counting efficiency. The concentrations of ICG and $^{14}$C-propranolol in blood were estimated from previously constructed calibration curves.

As ICG is not removed by the lungs, pulmonary uptake of propranolol can be calculated by comparing the ratio of $^{14}$C-propranolol to ICG in the injectate with their ratio in the aortic blood sample (Geddes et al., 1979):

$$\text{Percent single-pass lung uptake of }^{14}\text{C-propranolol} = \left(1 - \frac{P_A}{D_A}\right) \left(\frac{P_i}{D_i}\right) \times 100$$

where

- $P_i =$ concentration of $^{14}$C-propranolol in the injectate
- $D_i =$ concentration of ICG in the injectate
- $P_A =$ concentration of $^{14}$C-propranolol in the aortic blood sample, corrected for "residual" radioactivity
- $D_A =$ concentration of ICG in the aortic blood sample, corrected for "residual" dye

Aortic and pulmonary artery pressures were measured during each experiment and blood-gas analysis was also carried out.

Data were analysed for statistical significance using the Mann–Whitney $U$ test unless otherwise stated.

**RESULTS**

The results are summarized in table I. First-pass uptake of $^{14}$C-propranolol was greater in dogs under general anaesthesia compared with conscious animals ($P<0.02$). Moreover, uptake during the two techniques of anaesthesia was also different ($P<0.002$). The reproducibility of propranolol uptake measurements in each dog was good. No significant change was found over the duration of each experiment despite repeated doses (Kruskal–Wallis one-way analysis of variance). Cardiac output was significantly less in anaesthetized animals ($P<0.01$) while pulmonary artery pressure and blood-gas values remained within normal limits during all experiments.

**DISCUSSION**

The concentration of propranolol in the aortic blood sample was determined by counting carbon-14 radioactivity. It is possible that some metabolism of the drug occurred even during a single passage through the lungs. This is unlikely, as blood was collected for less than 15 s after injection of the bolus. Dollery and Junod (1976) showed that metabolism of propranolol did not occur in rat lungs perfused with propranolol for up to 10 min.

The study showed that propranolol uptake after a single passage through the canine pulmonary circulation in vivo was greater under general anaesthesia. This may be caused by changes in pulmonary ventilation and perfusion during general anaesthesia and positive pressure ventilation.

<table>
<thead>
<tr>
<th>Group</th>
<th>% Uptake $^{14}$C-propranolol</th>
<th>Cardiac output (litre min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A—Conscious</td>
<td>$52.6 \pm 7.6 \ (n = 16)$</td>
<td>$4.99 \pm 0.93 \ (n = 15)$</td>
</tr>
<tr>
<td></td>
<td>$P&lt;0.002$</td>
<td>$P&lt;0.001$</td>
</tr>
<tr>
<td>B—GA: Thiopentone, nitrous oxide, oxygen, halothane</td>
<td>$80.5 \pm 3.7 \ (n = 13)$</td>
<td>$3.08 \pm 0.88 \ (n = 13)$</td>
</tr>
<tr>
<td></td>
<td>$P&lt;0.002$</td>
<td>n.s.</td>
</tr>
<tr>
<td>C—GA: Thiopentone, nitrous oxide, oxygen, fentanyl</td>
<td>$63.6 \pm 11.7 \ (n = 10)$</td>
<td>$3.86 \pm 1.13 \ (n = 10)$</td>
</tr>
</tbody>
</table>
LUNG UPTAKE OF PROPRANOLOL

(Nunn, 1980). The reduction in cardiac output in the anaesthetized groups may be associated with an increase in the transit time through the lungs, so that the injected propranolol would be exposed to pulmonary endothelium for a longer period. Since uptake of the drug is thought to occur in endothelial cells (Junod, 1975), the increased duration of exposure should result in increased uptake. However, change in cardiac output is unlikely to be the only explanation since no correlation was found between propranolol uptake and cardiac output in conscious dogs (Pang et al., 1980), although the range of cardiac output was less in anaesthetized animals used in this study. Also, concentration of propranolol by isolated rat lungs was enhanced by lignocaine even when conditions of perfusion were identical (Dollery and Junod, 1976). Finally, Street and others (1979) found increased tissue concentrations of propranolol in lung and brain when the drug was administered i.v. under halothane and nitrous oxide anaesthesia. It is attractive to postulate a common mechanism of uptake in both organs.

The accumulation of propranolol in the lung may be caused by its high lipid solubility. This is supported by a positive correlation between the degree of lung uptake and the log partition coefficient of β-adrenoceptor antagonists between octanol and buffer (Street et al., 1978). This affinity for lipids may be an important factor in explaining our results. All the anaesthetic agents which have been associated with an increase in propranolol uptake—lignocaine, thiopentone, nitrous oxide and halothane—are themselves highly lipid-soluble. Therefore, it is possible they may interact with the endothelial cell membrane and facilitate uptake of the drug. If this hypothesis is true, it may explain why propranolol uptake in the brain also is enhanced by anaesthetic agents. Moreover, the difference observed between groups B and C in our experiments may be related to the absence of halothane, which is more lipid-soluble than nitrous oxide. Alternatively, it is possible that fentanyl may affect the uptake process.

Increased propranolol uptake by the lungs of animals under general anaesthesia will be associated with a smaller arterial concentration after i.v. administration of the drug. After withdrawal of anaesthetic, the pattern of release of previously accumulated drug into the systemic circulation is unknown. In man, oral administration of propranolol is associated with reduced lung uptake of an i.v. dose of the drug (Geddes et al., 1979). These considerations may be of therapeutic relevance in anaesthetic practice and the lungs should not be overlooked as a potential site for drug interaction.

ACKNOWLEDGEMENTS

We are grateful to I.C.I. for supplying 14C-propranolol. J. A. Pang is supported by a grant from the Kensington, Chelsea and Westminster A.H.A. This study has also been supported by a grant from the Research Fund of Westminster Hospital.

REFERENCES


FIXATION DE PROPRANOLOL ACCRUE APRES UN PREMIER PASSAGE DANS LES POUMONS DE CHIENS ANESTHESIES

On a étudié sur trois groupes de chiens Labrador la fixation du 14C-propranolol, après un seul passage dans la circulation pulmonaire en utilisant une méthode de dilution à double indicateur. Le fixateur sur les animaux conscients et capables de se déplacer a été de 53%. Elle est passée à 81% sur les chiens anesthésiés au thiopentone, protéoyde d'azote et halothane, et à
64% sur les chiens anesthésiés au thiopentone, protoxyde d’azote et fentanyl. L’interaction entre les agents anesthésiants solubles-lipides et les membranes des cellules endothéliales pulmonaires peut être un facteur important dans l’accroissement de la fixation du propranolol lipophile dans les poumons, bien que la modification de la perfusion pulmonaire associée à la réduction du débit cardiaque pendant l’anesthésie générale puisse jouer un rôle. Les effets pharmacologiques du propranolol administré par voie intraveineuse pendant l’anesthésie générale peuvent être imprévisibles.

ERHÖHUNG DER AUFNAHME VON PROPRANOLOL IN DER LUNGE UND NARKOTISIERTER HUNDE BEI EINMALIGEM DURCHGANG

ZUSAMMENFASSUNG

SUMARIO
Se estudió la absorción de 'C-propranolol después de haber pasado sólo una vez a través de la circulación pulmonar, en tres grupos de perros Labrador y haciendo uso de un método de dilución de indicador doble. La absorción en los perros conscientes y ambulantes fue del 53%. Esta incrementó al 81% en los perros anestesiados con tiopentona, óxido nítrico y halotano y a un 64% en perros anestesiados con tiopentona, óxido nítrico y fentanilo. La interacción entre los agentes anestésicos solubles en lipidos y las membranas de las células endoteliales del pulmón puede que sea un factor importante para incrementar la admisión pulmonar de propranolol lipofílico, aunque la variación en la perfusión pulmonar que viene asociada con una reducción de la producción cardíaca durante la anestesia general puede jugar un papel. Los efectos farmacológicos del propranolol intravenoso administrado durante la anestesia general pueden ser impredecibles.