Title: LUNG CONTRIBUTION TO PROPOFOL CLEARANCE: A STUDY IN ISOLATED RAT LUNGS

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Introduction. Propofol (diisopropylphenol) has a very high total body clearance,[1] suggesting the existence of extrahepatic metabolism. Lungs are known to be able to conjugate phenol over a wider dose range than liver.[2] This study was designed to investigate lung captation and conjugation of propofol in isolated ventilated rat lungs.

Methods. Wistar male rat lungs were isolated, perfused and ventilated according to a method derived from that described by Niemer.[3] Two infused doses were studied (2.5 and 5 $mg.kg^{-1}$ b.w.), each on 5 rats. The influence of infusion rate was then assessed with 1.5, 3 and 6 $ml.min^{-1}$, each on 3 rats with an administered dose of 5 $mg.kg^{-1}$ b.w.. The influence of albumin concentration was studied by adding 20 $g.l^{-1}$ bovine albumin to the propofol infusion (5 $mg.kg^{-1}$ b.w., 3 $ml.min^{-1}$ in 3 rats). In all cases, sampling times were 0, 0.5, 1, 1.5, 2, 5, 7, 10, 12 and 15 min during the infusion and 1, 2, 5, 10, 15 and 20 min after discontinuation of infusion during the rinsing procedure. At each experimental time, propofol concentration was measured when entering the lung (C_{in}) and when leaving it (C_{out}). The extraction coefficient $E = (C_{in} - C_{out})/C_{in}$ was calculated. Propofol concentrations were measured by a HPLC method. Lung was sampled at the end of the rinsing procedure (20 min). A closed loop study was performed to display lung propofol disappearance and conjugation. After having saturated the tubing by infusing in it a propofol solution at the same concentration as the experimental one during 15 min, the closed loop infusion including the lung lasted 60 min in 2 rats. The difference between the total quantity of propofol found at the end of the infusion and the initial quantity of propofol administered was considered to be due to metabolism. Conjugation was assessed by measuring metabolite concentrations using betaglucuronidase during closed loop infusion in 3 other rats.

Results. Our study shows that propofol was extracted by isolated rat lungs (Table 1). Extraction coefficient was low (E = 0,1), independent from dose and pulmonary blood flow, but dependent upon unbound fraction. Closed loop study shows that propofol actually disappeared (Table 2). The quantity of glucuronide reached 35% of the initial quantity of propofol after 40 min.

Discussion. In isolated rat lungs, propofol behaved like a substance with a low extraction coefficient, whose captation was therefore dependant upon protein concentration and upon interferences on the binding site. The captation seems independent from the blood flow. This finding differs from what is usually believed for the liver.[4] The closed loop study shows that propofol was conjugated by isolated rat lungs. The real importance of this extrahepatic route in the total body clearance of propofol remains to be determined, particularly in humans.

Table 1. Extraction coefficient

Infusion rate (ml/min)	Propofol dose (mg/kg b.w.)	Albumin conc. (g/l)	E
3	2.5	0	0.42±0.02
-	5.0	-	0.45±0.02
1.5	5	0	0.41±0.01
3	-	-	0.35±0.07
6	-	-	0.35±0.05
3	5	20	0.09±0.04

Table 2

Amount of propofol (ug)	Rat n° 1	Rat n° 2
- administered	530	498
- in the lung at 60 min	53	66
- in the tubing at 60 min	4	4
- eliminated by sampling	40	35
- accounted for	97	105
- disappeared	433	393

References

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