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Loss of Propofol during *In Vitro* Experiments

To the Editor:—Lipophilic drugs, such as propofol, are easily lost when a solution is in contact with reservoirs, tubings, or valves made of materials that are not inert. However, the extent and the rapidity with which almost complete loss can occur (within a few hours) is not always appreciated. Conflicting reports in the scientific literature regarding effective concentration values for the inhibition by propofol of various *in vitro* experimental systems prompted us to look at this issue more closely.

In vitro pharmacologic effects of anesthetic agents on biologic systems are studied with use of a variety of techniques and drug application systems. A combination of the patch clamp technique with a rapid drug-application system allows the study of the kinetics of drug interactions with the molecular target.[1] Rapid drug-application systems based on hydrostatic pressure used in such studies necessitate long lengths of tubing (here, ~ 120 cm) and large (200–500 ml) solution reservoirs. The concentration of propofol in the solution reaching the membrane patch is found to be highly dependent on the materials used for the reservoir, the duration of storage within the reservoir (fig. 1), and the material of the tubing of the drug application system.

Propofol solutions (10–100 μM) added to a reservoir consisting of hard glass bottles (500 ml, 90% capacity, stored in a dark compartment) maintained a constant concentration (as measured by high-performance liquid chromatography)[2] for more than 24 h (fig. 1), irrespective of whether the solution was stirred (polytetrafluoroethylene-coated magnetic stirrer). In a reservoir consisting of a conventional plastic drip bag (ethylvinylacetate, 250 ml, light protection as above, 90% capacity, unstirred), the propofol concentration in the test solution decreased to approximately 20% of the initial concentration within 4 h (fig. 1 and table 1). After 24-h storage in plastic drip bags, the decrease was even more pronounced (less than 5% of the initial concentration, see fig. 1).

Propofol concentrations were also measured after the test solution passed through the tubing of the drug-application system (120 cm, 2 mm and 0.3 mm in diameter at the outflow, flow rate 1 ml/min). The test solution was collected in a glass test tube from the outlet of the system where membrane patches would normally be positioned. The test solution containing propofol was collected before and after the drug-application system was equipped with inert materials. A loss of 95% of the initial concentration (table 1) resulted within the duration of a typical patch clamp experiment (≤ 4 h) when a plastic drip bag

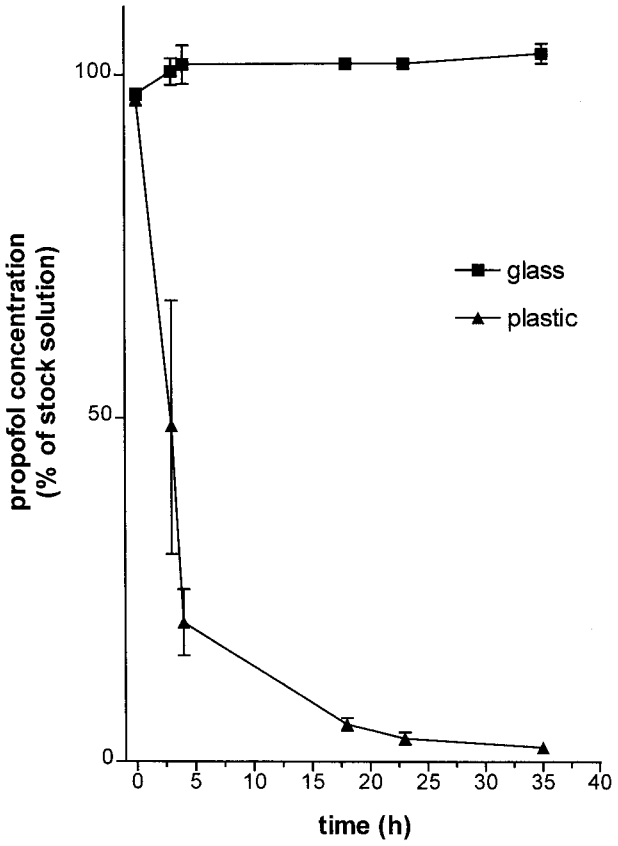

Fig. 1. Time course of concentration decrease within solution reservoirs. Test solutions containing propofol (100 μM) were stored in a glass bottle (■) or in a plastic drip bag (▲). Shown as mean ± SEM of 2–4 determinations.

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Table 1. Comparison of Propofol Concentrations in Solution Reservoirs and Final Concentrations after Passage of the Drug through the Tubing of Delivery System within Typical Experimental Durations

	Ethylvinylacetate Drip Bag	Hard Glass Bottle
Reservoir concentration (%)		
Immediately (1–5 min)	94 ± 2	98 ± 1
After 4 h	21 ± 5	101 ± 2
	Ethylvinylacetate drip bag + PVC tubing	Hard glass bottle + PTFE tubing
Final concentration (%)		
After 4 h	5 ± 3	80 ± 4

Data are given as percentages of the initial concentrations (10–100 μM), shown as means ± SEM of 2–6 experiments.

PVC = polyvinylchloride; PFTE = polytetrafluoroethylene.

was used as reservoir, combined with plastic (polyvinylchloride) tubing connecting the reservoir with the experimental chamber. The overall loss of propofol was reduced by altering the material of the reservoir (hard glass) and the tubing (polytetrafluoroethylene): 80% of the initial concentration of propofol was recovered after 4 h when the test solution passed through the entire drug application system (table 1).

Because the propofol concentration at the pharmacologic site of action depends not only on the propofol concentration in the stock solution, but also on the material properties of the drug-application system and the timing of the drug application (fig. 1), it must be measured directly in each experiment. Albeit demonstrated for drug-application systems commonly used in patch clamp studies, our findings will be valid for other experimental techniques as well. The use of inert materials, such as hard glass and polytetrafluoroethylene, limits but does not entirely eliminate the loss of this highly lipophilic compound.

The great extent of propofol loss found in this study strongly suggests the need for (1) constructing drug-application systems from inert materials, such as hard glass or polytetrafluoroethylene, (2) determining the propofol concentration in the test solution before and after passage through the entire drug-application system for each experiment, and (3) describing the details of the analytical procedures.

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