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# Pharmacodynamics of Propofol and Free Drug Concentrations

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*To the Editor:*—The study by Vuyk *et al.*[1] on the concentration-effect relationship of propofol was interesting because it attempted to achieve blood-brain equilibrium of propofol concentrations. However, the authors did not comment on the wide range of concentrations required to produce the same effect in a presumably homogeneous group of patients. The highest whole blood propofol concentration for loss of eyelash reflex was 3.92 μg/ml, more than double the lowest concentration of 1.88 μg/ml.

The effects of highly protein bound drugs may correlate better with the free fraction of drug.[2] Propofol has a more shallow dose-response curve compared with thiopental,[3] but it has not been generally acknowledged that this may be a result of propofol being highly protein bound. The protein binding of propofol may vary from 97% to 99%,[4,5] there being a 300% increase in free fraction from 1% to 3%. The free drug exerts the effect, and so there may be marked variation in the total propofol concentrations for a given effect while the free concentrations are similar. If data on the free concentration-effect relationship of propofol proves to be less variable, it would then be useful to try and predict the degree of protein binding in a particular patient.

Propofol binds to albumin and erythrocytes. The induction dose of propofol was correlated significantly with albumin concentrations,[6] although the correlation coefficient was only 0.28. There are no studies correlating protein binding of propofol with physiologic data such as albumin and hemoglobin concentration. I do not disagree with the important results from Vuyk *et al.*, but suggest that it would be valuable to measure free propofol concentrations in future studies.

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*In Reply:*—We studied the concentration-effect relationships for loss of eyelash reflex and loss of consciousness of propofol in healthy female patients and indeed found a twofold interindividual variability[1] in our patients with respect to the response to similar blood propofol concentrations. However, this variability, in our opinion, is small compared to the four- to five-fold interindividual variability previously described for other intravenous anesthetic agents.[2,3]

The range of the concentrations required to produce a similar effect in this group of patients can be partially explained by the following factors. First, as stated in the paper, some patients in our study lost eyelash reflex and consciousness before blood-brain equilibration had occurred. In these patients, the blood propofol concentration still exceeded the theoretical effect compartment concentration, thereby contributing to the above mentioned interindividual variability. A second factor is the variation in the analysis of the blood propofol concentration by high-performance liquid chromatography (a coefficient of variation ≤ 7%). Third, we agree with Gin that, for highly protein-bound drugs, interindividual differences in protein binding might be a factor influencing the magnitude of the pharmacodynamic interindividual variability as well. For alfentanil, for example, Lemmens *et al.* showed that 45% of the variability in the CP50 of alfentanil for the intraabdominal part of surgery could be explained by the variability in the protein binding of alfentanil.[4]

In conclusion, we agree with Gin that differences in protein bind-

ing, along with the other factors described above, might contribute to the interindividual variability in the response to similar blood propofol concentrations.

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# Were They Subdural Injections?

*To the Editor:*—The recent report by Chadwick *et al.*[1] of suspected subdural local anesthetic and morphine administration raises two issues.

First, the suspicion of subdural injection during three intended epidural anesthetics was raised by the development of extensive sensory block, but were these extraordinarily extensive? All three patients were significantly obese (body mass index of 38–61 kg/m$^2$, at the extreme of the range for a comparable group of pregnant patients[2]), which is known to increase the extent of blockade,[2] as does pregnancy.[3] In two cases, the catheters were identified as entering at the L3–4 and L1–2 interspaces. The other insertion level was not confirmed, and although L2–3 was intended, the actual level is often higher than determined by palpation in obese subjects.[4] Upper lumbar epidural injection is another cause of high blockade.[5] There is great variability in extent of blockade from epidural anesthesia, which is only loosely dose related.[6,7] As observed by Bromage,[8] that some epidural blocks should extend to above T2 using these doses is expected. The sensory levels achieved in the three reported cases (using 13–16 ml 2% lidocaine with epinephrine, a potent solution) are not exceptional for epidural administration.

Second, the central topic of the report was the effect of subdurally placed drugs, but was the subdural passage of the injected solution really "radiologically confirmed?" Although no radiologist was credited in the report, we assume that the traditional criteria of thin layering of contrast and lock of passage through the intervertebral foramina were used. We are unaware of any investigation confirming the ability to distinguish epidural from subdural contrast injection on a plain radiograph, for instance using computed tomography for more definitive imaging. The cases reported by Chadwick *et al.* used small volume contrast injections (4–7 ml) in obese patients who have diminished epidural compliance, making thin layering also likely in the case of epidural injection. Water-soluble contrast, as was used, has a low viscosity and spreads thinly. Other epidural injections that have showed thick layering have typically required injectate volumes of 15–20 ml.[9] The epidural injectate volume necessary to outline nerve root sleeves is 8–14 ml.[10] Finally, passage out the foramina ("extravasation") was observed in one of the reported cases of Chadwick *et al.*

In our neuroradiology division, we are unable to reliably discern epidural from subdural contrast injection during plain radiograph· myelography and prefer to state only that the injection was "extra-arachnoid." This also may be prudent in the anesthesia literature.

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