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Use of the Epidural Blood Patch in the Treatment of Chronic Headaches

To the Editor:—We have recently treated six patients with chronic (longer than 2 yr duration) headaches using the lumbar epidural blood[1] patch with 10 ml of autologous blood. All of the patients had been thoroughly investigated and treated beforehand through a variety of modalities and drugs without success. All six patients presented with common clinical features similar to patients with postdural puncture headaches.[2] Five of the six patients experienced complete and sustained pain relief immediately or very shortly after the blood patch. None of the patients derived any benefit from placebo injections. Currently, further randomized and blinded control studies are being undertaken to evaluate these preliminary and incomplete evaluations.

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Computer-assisted Infusions of Drugs

To the Editor:—Computer-assisted, or computer-driven, continuous infusion (CACI) of intravenous drugs is a new method with many promising features for future use in anesthesiology. In a recent article, Alvis *et al.*[1] compared manual administration of fentanyl with CACI in their ability to maintain stable hemodynamic conditions as a measure of adequate anesthesia during surgery.

To achieve and maintain a constant fentanyl plasma level, a complex input scheme has to be used in order to compensate for drug elimination and distribution in peripheral compartments. This input scheme is described in the above article by two equations. We should like to point out that one of these equations (equation 2) is incorrect and may result in unstable fentanyl concentrations.

The first equation:

$$u_0(t) = V_c \cdot C \cdot M_p \times (k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}) \quad (1)$$

describes the variation of infusion rate [$u_0(t)$] with time in order to maintain a stable fentanyl concentration (C) after an *initial* loading dose. M_p is a measure of body mass, V_c the volume of the central compartment, and k_{10}, k_{12}, k_{21}, k_{13}, and k_{31} are the constants defining the linear three-compartment open model.

The second equation:

$$u_N(t) = V_c \cdot NC \cdot M_p \times (k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}) \quad (2)$$

describes an input scheme that is supposed to maintain a new constant plasma level (NC) after administration of an additional loading dose (*i.e.*, $(NC - C) \cdot V_c \cdot M_p$). This equation is wrong, because at this time compartments two and three already contain some drug (from the initial loading dose and infusion rate). The amount of drug in these peripheral compartments will influence the rate of distribution from the central compartment. The greater this amount, the "slower" the distribution and the lower the infusion rate required to maintain a constant level in the central compartment. This is best demonstrated by a computer simulation of the plasma concentration time profile using equations 1 and 2 of Alvis *et al.*[1]

We simulated the following situation: using a drug with linear three-compartment pharmacokinetics, we wanted first to maintain a constant plasma level C from time t = 0 to time t = 60 min, and then raise the drug concentration to a new constant level, NC. Because, from the original article, it is not clear whether "t" in equation 2 represents time since the initiation of anesthesia (case A) or since the additional loading dose (case B), we simulated both cases. As can be seen in figures 1*A* and 1*B*, an infusion rate according to equation 2 does not maintain a stable NC. In case A it leads to an initial fall of plasma level below NC, whereas in case B the application of equation 2 results in an initial overshoot.

According to the superposition principle, equation 2 from Alvis *et al.*[1] has to be written for the infusion rate after the first additional loading dose as follows:

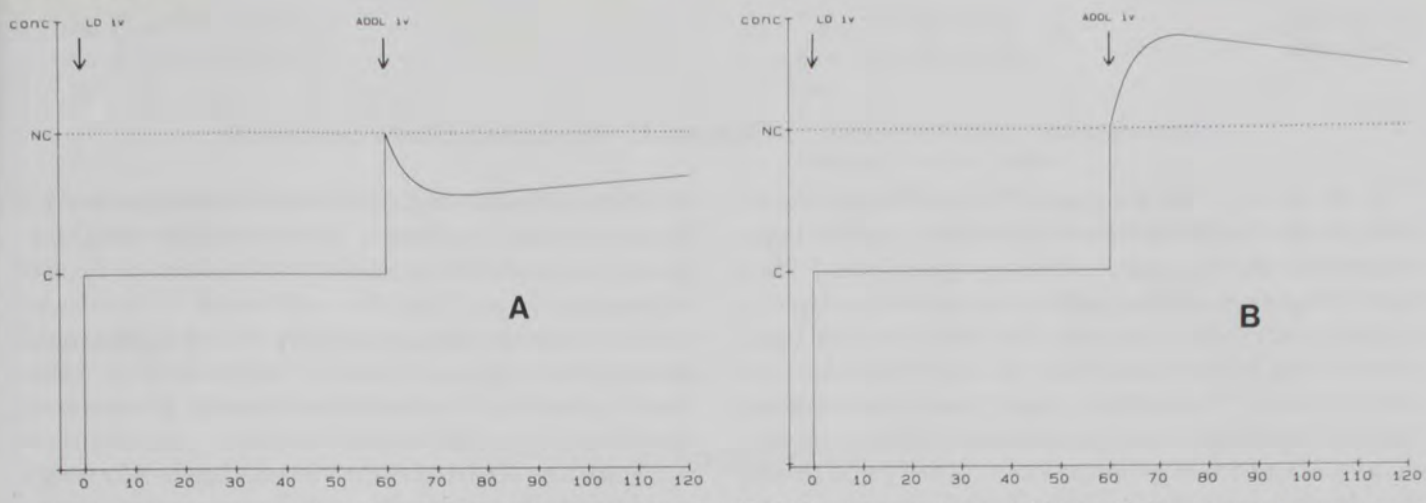

FIG. 1. A computer simulation of the predicted plasma concentration (CONC) using equation 2 of Alvis *et al.*[1] The proposed equations are adequate for the first desired concentration (C), but when a higher predicted concentration is desired (NC), an under prediction (*A*) or over prediction (*B*) from the desired level occurs, depending on the definition of "t" in equation 2.

$$u_1(t) = V_c \cdot C \cdot M_p \cdot (k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}) + V_c \cdot (NC - C) \cdot M_p \times (k_{10} + k_{12} \cdot e^{-k_{21} \cdot (t-t_1)} + k_{13} \cdot e^{-k_{31} \cdot (t-t_1)}) \quad (3)$$

where the origin of t is the time at which the *initial* loading dose was administered, and t_1 is the time at which the *first additional* loading dose is given. Similarly, although somewhat more complex, the solution can be derived for the infusion rate after the nth additional bolus, using again the superposition principle.

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In Reply:—We appreciate the insightful and thorough analysis offered by Drs. Maitre, Vozeh, and Stanski; we are continually modifying and upgrading our CACI software, and we will actively consider the relevance to our current system design of the suggestions provided. We find CACI to be a useful tool for both clinical research and patient management, and we are pleased to hear of others who share our interest in pharmacokinetically driven drug infusion.

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