Letters to the Editor

Infusion Schedules for Prescribed Blood Concentration Time Courses

To the Editor: Patlak and Pettigrew (J. Appl. Physiol. 40: 458–463, 1976) use impulse analysis to derive injection schedules for maintaining blood levels of an injected substance, following a prescribed mathematical form. We are interested in their comprehensive theoretical analysis because, for the past seven years, we have been using a simplified form of the impulse method (Daniel, Donaldson, and Pratt, J. Physiol., London 231: 8–9p, 1974; Med. Biol. Eng. 13: 214–221, 1975) to maintain in the blood a constant output function of radioactively labeled substances (Banos, Daniel, Moorhouse, and Pratt, J. Physiol., London 210: 149p, 1970; 246: 539–548, 1975).

A physiologist who wishes to measure unidirectional transport must measure the initial rate of influx, within a minute or less of the tracer substance being introduced into the circulation. By our method constant tracer blood levels can be achieved within about 10 s and maintained for upward of 5–10 min, even though we use a transport function which contains only two exponential terms.

Surprisingly this simplification works adequately but, as Patlak and Pettigrew point out, input schedules may be similar even though they are derived from a number of different transport functions, each of which fits the data. It therefore seems likely that, over the limited periods of time in which we are interested, our simplified procedure yields essentially the same schedules as do the more complicated analyses. Once a function has been fitted to the data from a “bolus” input, by any suitable means, the further calculations required in our procedure are trivial. The implementation of the exponentially declining input is made easy by using an electronically controlled, continuously variable, syringe drive (Pratt, J. Physiol., London 237: 5–6p, 1974), which is preset to follow the calculated input function, thus obviating the need for cumbersome calculation of averages and the use of manually stepped injections. To avoid such calculations Patlak and Pettigrew derive simpler input schedules for obtaining a constant level output, or a ramp output, by giving an initial “bolus” input, followed by a simple constant or linearly increasing input.

However, by this method a considerable period of time must elapse before the desired outputs are achieved, making this procedure unsuitable for transport measurements.

Our work has not been confined to radioactive tracer experiments, for we have also maintained constant output functions for glucose (Bachelard, Daniel, Love, and Pratt, Proc. Roy. Soc., London, Ser. B 183: 71–72, 1973) and for a wide range of amino acids (Banos, Daniel, Moorhouse, and Pratt, Proc. Roy. Soc., London, Ser. B 183: 59–70, 1973). In some experiments, blood levels were maintained which are well above the range over which “the system is linear with regard to the substance under analysis” (Patlak and Pettigrew). We have found that it is possible to maintain the desired output function even under nonlinear conditions, provided that suitable modifications are made to the input schedule (Banos, Daniel, Moorhouse, and Pratt, Psychol. Med. 4: 262–269, 1974). We would welcome discussion of the theoretical implications of these findings.

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REPLY

To the Editor: We thank Professors Daniel, Donaldson, and Pratt for bringing their articles to our attention. A few comments on their letter are in order.

As mentioned in our article, it is necessary to have an adequate fit of the data for the bolus experiment. We include in the transport function more than two exponential terms only when they are necessary to provide such an adequate fit. It is reasonable to assume that for limited periods of time of 5 or 10 min, two exponential terms will adequately represent the system. Hence the success of the simplification used by Daniel et al.

With our method, after the bolus experiment parameters have been estimated, the required calculations are trivial, and completely automatic in any laboratory with access to a computer or programmable calculator. One benefit in such a schedule is that it is easily used when a continuously variable input mechanism is not readily available. Although a continuously varying infusion input is preferable, the expense of the necessary device versus the frequency of usage may make the acquisition of such a device impractical. In this type of situation our approach might be more advantageous.

As is true for the procedure of Daniel et al., our method is also not restricted to radioactive tracer experiments, but is completely general for any substance where the system remains linear with regard to the substance.

Because a bolus input experiment was performed in every situation, those laboratories using our technique have always obtained a constant output level without having had to resort to empirical adjustments to the estimated parameters.

Finally, the question of applicability of Daniel et al.'s approach to nonlinear systems (involving amino acids): although it is true that the uptake of amino acids into the brain is nonlinear, this nonlinearity does not necessarily apply to the majority of amino acid loss from the blood into other organs. In this case, the linearity assumption may be accurate enough for the technique to be applicable.

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