

## GC Determination of Pilocarpine and Isopilocarpine

Although Urbányi *et al.*<sup>1</sup> recently reported an interesting method for the determination of pilocarpine and its *trans*-isomer, isopilocarpine, in pharmaceutical preparations using liquid chromatography, I would like to draw attention to a report by Aboul-Enein<sup>2</sup> which described the separation of pilocarpine and isopilocarpine by GC.

A Beckman 45G instrument was used, and the separation was effective using a 1.8-m (6-ft) long column packed with 5% OV-17 on Gas Chrom P (80–100 mesh). The injector, column, and detector temperatures were 235, 225, and 235°, respectively. The gas flow rates were: hydrogen, 40 ml/min; air, 250 ml/min; and helium as a carrier gas, 100 ml/min. This method is applicable for the analysis of commercial pilocarpine ophthalmic preparations and for the detection and determination of isopilocarpine in these solutions.

This method is suitable and sensitive, and it offers an alternative method to the liquid chromatographic technique.

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<sup>1</sup> T. Urbányi, A. Piedmont, E. Willis, and G. Manning, *J. Pharm. Sci.*, **65**, 257(1976).

<sup>2</sup> H. Y. Aboul-Enein, *Acta Pharm. Suec.*, **11**, 387(1974).

## Bolus Intravenous Injections: Round 2

Dr. Wagner<sup>1</sup> recently criticized my paper<sup>2</sup>, stating that the limiting assumption:

$$\frac{1 - e^{-b_i\theta}}{b_i\theta} = 1 \quad (\text{Eq. 1})$$

is "incorrect" and cautioned readers "not to make such corrections" as suggested. I believe this criticism resulted due to the different terminology Dr. Wagner uses in his calculations. The plasma concentration following infusion is given by<sup>1</sup>:

$$C_p = \sum_{i=1}^n C_i \frac{(e^{+b_i\theta} - 1)}{b_i\theta} e^{-b_i t} \quad (\text{Eq. 2})$$

where  $t$  is time from the start of infusion, and  $\theta$  is the infusion time. I used the terminology  $t'$ , which is:

$$t' = t - \theta \quad (\text{Eq. 3})$$

Substitution of Eq. 3 into Eq. 2 gives:

$$C_p = \sum_{i=1}^n C_i \frac{(1 - e^{-b_i\theta})}{b_i\theta} e^{-b_i t'} \quad (\text{Eq. 4})$$

This equation is identical to one described in the published report<sup>2</sup>. This terminology was used to allow direct comparisons between equations used for infusion and bolus administration since the term  $Y_i$  used by Dr. Wagner is:

$$Y_i = (\text{observed intercept, postinfusion}) e^{+b_i\theta} \quad (\text{Eq. 5})$$

If postinfusion data are used to calculate the pharmacokinetic parameters assuming an instantaneous input, an invalid assumption is made (Eq. 1), which should be corrected as described in the published report.

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<sup>1</sup> J. G. Wagner, *J. Pharm. Sci.*, **65**(8), viii(1976).

<sup>2</sup> S. Niazi, *ibid.*, **65**, 750(1976).

## Bolus Intravenous Injections: Round 3

The paper of Niazi<sup>1</sup> prompted me to make a comment in the Open Forum<sup>2</sup>. Now Niazi<sup>3</sup> has written a comment in the Open Forum, which implies that the only problem was his use of  $t'$  rather than my  $t$ . But this is not so.

If postinfusion data are fitted to a polyexponential equation, one uses the equations of Loo and Riegelman<sup>4</sup>; then no "corrections," as proposed by Niazi<sup>1</sup>, are needed. Such corrections are only needed when one applies equations derived from the bolus intravenous equation. Niazi is actually talking to scientists who give infusions and then disregard that they gave an infusion and treat the data as if they had administered a bolus intravenous injection. It is unfortunate that there is such misunderstanding of pharmacokinetics, but I wished to eliminate further misunderstanding. I do not believe that Dr. Niazi made it clear what he was discussing.

My comment<sup>2</sup> about the "incorrectness" of the equation shown as Eq. 1 in both my Open Forum comment<sup>2</sup> and his<sup>3</sup> refers to his approach. The equation is inconsistent for  $\theta = 0$  (case for bolus intravenous injection), since the left-hand side is equal to zero and the right-hand side is equal to unity. It is preferable to discuss the change of a coefficient obtained by fitting "during infusion" or "postinfusion" data to a coefficient that would have been obtained if the same dose had been administered as a bolus intravenous injection to the same subject; this is what I did in my Open Forum comment<sup>2</sup> in Eqs. 5 and 6.

I hope that this letter clarifies my comment<sup>2</sup>.

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<sup>1</sup> S. Niazi, *J. Pharm. Sci.*, **65**, 750(1976).

<sup>2</sup> J. G. Wagner, *ibid.*, **65**(8), viii(1976).

<sup>3</sup> S. Niazi, *ibid.*, **65**(12), iv(1976).

<sup>4</sup> J. C. K. Loo and S. Riegelman, *ibid.*, **59**, 53(1970).