The validity of the sigmoid E_{max} model and efficiency concept in diuretic studies

Dr Noormohamed (1990) presents general and specific critical remarks on the efficiency concept as applied in a number of studies (e.g. Alván *et al.*, 1990; Hammarlund *et al.*, 1985; Kaojarern *et al.*, 1982). We find his arguments partly incorrect and sometimes stating the obvious. A fundamental key to understanding the issue under debate is however to separate the questions of steepness of the Hill curve from the concept of where to find the highest yield of net effect per stimulus (efficiency). Although composed by the same parameters, the sigmoid E_{max} model and the derived expression for efficiency (Eff, equation 1) differ importantly.

$$\text{Eff} = \frac{E - E_0}{C} = \frac{E_{max} \cdot C^{s-1}}{C_{50\%}^s + C^s} \qquad \text{Equation 1}$$

It follows that $C_{50\%}$, the point where the Hill curve is steepest and the concentration associated with highest efficiency will generally not coincide (shown in Figure 3 in Alván *et al.*, 1990). Dr Noormohamed and other readers could further consider equation 1 to find out how the efficiency curve is related to concentration for different values of S and then check the more or less 'surprising' result of this exercise with Figure 4 of Kaojarern *et al.* (1982).

The maximally efficient concentration (C_{effmax}) is mathematically found at $[C_{50\%}^s\ (s-1)]^{1/s}$ as derived by Kaojarern *et al.* (1982) (please note that this expression was erroneously printed without brackets by Alván *et al.*, 1990). C_{effmax} has no solution for $s \leq 1$ (assuming positive concentration and efficiency). When $s \leq 1$ efficiency will be ever increasing when C approaches zero as a consequence of equation 1.

The question whether to model hysteresis/proteresis or exclude some initial effect values when applying the Hill equation has nothing to do with the concept of efficiency. Negative values of efficiency and effect compared to E_0 are both seen at minimal effects and represent biological variation and experimental error.

It is important to separate dose response curve and efficiency concepts from the treatment of data for drugs showing tolerance development. As has been shown, frusemide pharmacodynamic data are dependent on the study design. In studies where full fluid/electrolyte replacement has been made (Alván *et al.*, 1990; Kaojarern *et al.*, 1982 and other papers cited in Hammarlund–Udenaes & Benet, 1989), frusemide can be considered to show no tolerance development and to follow the Hill equation. This certainly reflects the intrinsic renal sensitivity to frusemide. However, when the fluid/electrolyte replacement is lower than the urinary volume losses, acute tolerance develops (Hammarlund *et al.*, 1985; Sjöström *et al.*, 1988). In this situation and in response to Dr Noormohamed's question 'as to which limb of the hysteresis loop represents the "true" responses' the obvious answer is: both. The proteresis in this case describes a physiological course of events. Methods to treat data from such experiments necessarily have to preserve and utilise the information at hand.

Efficiency is solely the consequence of the sigmoid E_{max} model as shown by equation 1 and therefore applicable without regard to the mode of administration.

Dr Noormohamed also maintains the ratio E_0/E_{max} to be a superior explanation of the difference in the ratio $C_{effmax}/C_{50\%}$ compared with the expression $C_{effmax} = [C_{50\%}{}^s(s-1)]^{1/s}$ derived by Kaojarern *et al.* (1982). It is only possible to express the ordinate E_0/E_{max} as a function of the parameters E_{max}, $C_{50\%}$ and s of the model and the variables concentration as well as effect. It is up to Dr Noormohamed to explain what is achieved by his plot.

At last Alván *et al.* (1990) are incriminated of overlooking important information on the time course of pharmacological effect in relation to dosage schedule as presented in a classical paper by Wagner (1968). We think that it is reassuring that Wagner's analysis utilising response integrated over time and considerations on administration schedule and half-life, gives a similar result to when the efficiency concept is applied. The efficiency concept provides an alternative way to combine the time course of the drug concentration with the integrated pharmacological effect. We maintain that the efficiency concept as exemplified by us in the pharmacokinetic-pharmacodynamic modelling of loop diuretics, is valid and should receive more general consideration when designing dosage forms and dosage schedules.

G. ALVÁN
Department of Clinical Pharmacology, Huddinge University Hospital, S-141 86 Huddinge, Sweden

M. HAMMARLUND-UDENAES
Department of Biopharmaceutics and Pharmacokinetics, University of Uppsala, Box 580, S-751 23 Uppsala, Sweden

B. ODLIND
Department of Pharmacology, Faculty of Medicine, University of Uppsala, Box 593, S-751 23 Uppsala, Sweden

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References

Alván, G., Helleday, L., Lindholm, A., Sanz, E. & Villén, T. (1990). Diuretic effect and diuretic efficiency after intravenous dosage of frusemide. *Br. J. clin. Pharmac.*, **29**, 215–219.

Hammarlund, M. M., Odlind, B. & Paalzow, L. K. (1985). Acute tolerance to furosemide diuresis in humans. Pharmacokinetic-pharmacodynamic modelling. *J. Pharmac. exp. Ther.*, **233**, 447–453.

Hammarlund–Udenaes, M. & Benet, L. Z. (1989). Furosemide pharmacokinetics and pharmacodynamics in health and disease — an update. *J. Pharmacokin. Biopharm.*, **17**, 1–46.

Kaojarern, S., Day, B. & Brater, D. C. (1982). The time course of delivery of furosemide into urine: an independent determinant of overall response. *Kidney Int.*, **22**, 69–74.

Noormohamed, F. H. (1990). Use of E_{max} model in diuretic studies. *Br. J. clin. Pharmac.*, **30**, 907–908.

Sjöström, P. A., Odlind, B. G., Beermann, B. A. & Hammarlund-Udenaes, M. (1988). On the mechanism of acute tolerance to furosemide diuresis. *Scand. J. Urol. Nephrol.*, **22**, 133–140.

Wagner, J. G. (1968). Kinetics of pharmacologic response. I. Proposed relationships between response and drug concentration in the intact animal and man. *J. theoret. Biol.*, **20**, 173–201.

Pharmacological activity of the dinitrate metabolites of nitroglycerin following their oral administration to healthy volunteers

The clinical efficacy of oral sustained release nitroglycerin (GTN) in the prophylactic management of stable angina is recognised (Davidov & Mroczek, 1977; Winsor & Berger, 1975), although there is little correlation between systemic GTN concentration and effect. Kohli *et al.* (1985) reported that in patients with stable angina, an oral dose of 6.5 mg sustained release GTN results in improved treadmill exercise times, despite no measurable GTN in plasma. The dinitrate metabolites of GTN i.e., 1,2 glyceryl dinitrate (1,2-GDN) and 1,3 glyceryl dinitrate (1,3-GDN) may play a significant role in the anti-anginal efficacy of GTN. This communication describes a preliminary study to determine if the GDNs possess pharmacological activity when administered to man.

The 1,2- and 1,3-GDN manufacturing, formulation and clinical study procedures were carried out under Investigational New Drug application 32,278. The clinical study was approved by the University of California, San Francisco Committee on Human Research and performed with volunteer 'informed consent'. The 1,2- and 1,3-GDNs were purified and characterised in our laboratory (Gumbleton *et al.*, 1989). Six healthy male volunteers between the ages 21 and 35 years, were recruited into the study. Following an overnight fast, three subjects received an oral dose of 4.2 mg 1,2-GDN, while a further three subjects received an oral dose of 2.4 mg 1,3-GDN. These first doses of GDNs administered to man were chosen to yield the approximate plasma dinitrate concentrations measured following oral 6.5 mg GTN solution doses (Nakashima *et al.*, 1990). The GDNs were administered as solutions in 50 ml of purified water. Serial blood samples were collected into chilled heparinized polyethylene syringes for 6 h after the dose. Processing of the blood samples, and the analysis of 1,2- and 1,3-GDN in plasma were described previously (Nakashima *et al.*, 1990). Cardiovascular monitoring (Dinamap®; Critikon Inc, Tampa, FL) was performed for 20 min immediately prior to dosing, to record stable basal values, and throughout the 6 h study period. The subjects remained in a supine/semi-recumbent position throughout the study, receiving 100 ml of water to drink every hour, and a low fat lunch at 4 h post-dose.

Figure 1 shows the mean log plasma concentration-time curves together with mean systolic and diastolic blood pressure-time profiles for 1,2-GDN and 1,3-GDN. Both GDNs resulted in time-dependent decreases in systolic and diastolic blood pressures. Maximal decreases in systolic blood pressure ranged from 6–16 mm Hg for 1,2-GDN, and 14–17 mm Hg for 1,3-GDN; maximal decreases in diastolic pressure ranged from 11–27 mm Hg for 1,2-GDN, and 20–26 mm Hg for 1,3-GDN. The observed peak plasma 1,2-GDN concentrations ranged from 15.7 to 47.1 ng ml^{-1}, with the time to peak concentration ranging from 20 to 30 min. Peak concentrations following 1,3-GDN, ranged from 10.4 to 13.9 ng ml^{-1}, with a time to peak of 25 min. These preliminary results show an apparent correlation between the plasma 1,2- and 1,3-GDN concentration-time profiles and the blood pressure-time profiles, with effects upon diastolic blood pressure reflecting marked decreases in peripheral vascular resistance. No interconversion between the 1,2- and 1,3-GDN isomers was observed.

Although a decrease in blood pressure, measured in healthy volunteers, does not necessarily predict anti-anginal efficacy in patients, these preliminary results suggest that the GDNs may contribute significantly to the therapeutic effects of GTN. Furthermore, although the data reported here are limited, it is intriguing to note

Correspondence: Professor L. Z. Benet, Department of Pharmacy, University of California, San Francisco, San Francisco, CA 94143-0446, USA