Diuretic effect and diuretic efficiency after intravenous dosage of frusemide

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1 Frusemide was given intravenously at a dose of 5 mg kg^{-1} to five healthy volunteers and the diuresis was assessed by frequent spontaneous voiding over 5 h. Urinary volume and contents of sodium, chloride, potassium and frusemide were measured.

2 Diuretic response was evaluated using the sigmoid $E_{\max}$ model and non linear regression of diuresis vs frusemide excretion rate. The time courses of diuresis (pharmacological effect) and diuretic efficiency were constructed from the fitted parameters of the sigmoid $E_{\max}$ model.

3 The frusemide excretion rate associated with maximum efficiency was found, as predicted theoretically, to be less than the excretion rate associated with 50% of maximum effect in four of the five subjects in whom the slope factor was less than 2.

4 The effect over time is dependent both on the instantaneous drug effect but also on its pharmacokinetic properties and mode of administration. An intravenous bolus is the least efficient mode of administration while a controlled input producing a frusemide excretion at maximum efficiency should yield up to a 2.3 times higher diuretic response.

Keywords frusemide diuretic effect diuretic efficiency dosage forms pharmacokinetics

Introduction

Instantaneous and reversible pharmacological effects are often described by the Hill equation (equation 1, Hill, 1910). However, in clinical settings, the total pharmacological response over time reflecting the therapeutic effect of a given dose is also of interest. This measurement is simply the integral (AUC) of the relationship between response and time. Another useful approach is to derive from equation 1 an alternative variable which denotes drug effect per stimulus $((E-E_o)/C)$. This variable is called efficiency (Eff) (Kaojarern *et al.*, 1982). It can be obtained by dividing both sides of the Hill equation (equation 1) by stimulus (C) to give equation 2. It follows that the model for efficiency as a function of stimulus or concentration

(equation 2) is dependent on the same parameters as the model for effect (equation 1).

$$E = \frac{E_{\max} \cdot C^s}{C_{50\%}^s + C^s} + E_o \quad \text{Equation 1}$$

$$\text{Eff} = \frac{E-E_o}{C} = \frac{E_{\max} \cdot C^{s-1}}{C_{50\%}^s + C^s} \quad \text{Equation 2}$$

(E is effect, $E_{\max}$ is the maximum drug effect, E_o is basal effect without stimulus, C is the drug concentration stimulus, $C_{50\%}$ is the concentration at which 50% of the maximum drug effect is obtained, s is a slope factor, Eff is efficiency).

Kaojarern *et al.* (1982) identified 'the time course of delivery of frusemide into urine' to be 'an independent determinant of overall response'. The administration and pharmacokinetics of the drug will thus greatly influence the pharmacological response over time. This study was done to illustrate the course of diuretic effect and diuretic efficiency in urine for volume, Na^+ , Cl^- and K^+ .

Methods

Five healthy Caucasian subjects, of whom two were males participated in the study after giving informed consent and after approval had been obtained from an Ethics Committee. Their ages ranged between 26 and 34 years and their body weights from 55 to 80 kg. They fasted overnight and drank one glass of water (150 ml) after waking up in the morning and another (150 ml) just prior to dosing. Frusemide was injected i.v. at a dose of 0.5 mg kg^{-1} . Saline was infused throughout the experiment to replace the volume excreted. The subjects voided urine at 5 min intervals for 45 min, at 15 min intervals for 45 min and then half hourly up to 5 h after frusemide administration. The urine volumes were measured and aliquots were frozen at -20°C until assay.

Frusemide was measured by h.p.l.c. (Lindström, 1974) using piretanide as the internal standard. The electrolytes were assayed by ion selective electrodes and chloride titration.

Diuretic effects as a function of frusemide excretion rate were fitted by algebraic transformation of equation 1 (Brater *et al.*, 1983) using the non linear regression program NLIN (SAS Institute). The estimated parameters were used to construct the relationships between diuretic effect and diuretic efficiency vs frusemide excretion rate, respectively. Diuretic efficiency was also expressed directly by dividing the urinary output minus basal diuresis (E_o) by the amount of frusemide recovered in the respective time intervals.

The C value for which maximum efficiency is obtained is $C_{\text{effmax}} = C_{50\%}^s \cdot (s-1)^{1/s}$ (Kaojarern *et al.*, 1982). The maximally efficient diuretic effect (E_{effmax}) was calculated by substituting C_{effmax} and the appropriate parameter values into equation 1.

Results

The urinary recovery of the dose ranged from 74 to 95%. The frusemide excretion rate and the diuretic response are shown for one subject

(number 1) in Figure 1. The effect parameters obtained by fitting the model to the data and the derived efficiency parameters are shown in Table 1. The experimental data for diuretic effect and diuretic efficiency, respectively, in subjects 1 and 5 are shown in Figure 2 together with curves generated from the sets of fitted parameters. Values of frusemide excretion rate associated with maximum diuretic efficiency (C_{effmax}) and $C_{50\%}$ are also indicated in the figures.

Discussion

Previous studies (Alván *et al.*, 1988; Brater *et al.*, 1983; Hammarlund *et al.*, 1985) have shown that the diuretic effect of frusemide is well described by conventional concentration-effect modelling according to the Hill equation or the so called sigmoid E_{max} model (Holford & Sheiner, 1981). It has been shown (Burg, 1976; Odland & Beermann, 1980) that frusemide acts from the tubular side of the nephron. Therefore, frusemide excretion rate is the relevant stimulus parameter for effect-stimulus evaluation. Figure 1 shows the experimental observations of diuretic effect and frusemide excretion rate vs time. Initially there was some dissociation between effect and stimulus showing a counterclockwise hysteresis in 1-4 of the 5 min sampling intervals. These observations were excluded from the analysis. Diuretics like frusemide are known to inhibit sodium and chloride cotransport from the luminal side of the thick ascending limb of the loop of Henle. The increased electrolyte excretion will then increase tubular flow and urinary volume. This pharmacological effect is described by the estimated Hill parameters for the excretion of urine, sodium and chloride as shown in Table 1.

Figure 1 Relationships between frusemide excretion rate (○) and diuretic effect (●) with time in subject 1.

Table 1 Estimated parameters for the sigmoid $E_{\max}$ model, E_0 is basal diuresis without any diuretic stimulation, $E_{\max}$ is maximum obtainable diuresis caused by the drug, E_{effmax} is induced diuresis occurring at $C_{\max}$, s is slope factor, $C_{50\%}$ is frusemide excretion rate that gives half of the maximum induced diuresis and C_{effmax} is the frusemide excretion rate that has maximum diuretic efficiency

		1	2	3	Subject 4	5	Mean	s.d.
<i>Volume</i>								
E_0	(ml min ⁻¹)	0.22	1.67	0.67	1.05	2.99	1.32	1.07
$E_{\max}$	(ml min ⁻¹)	33.8	30.3	25.3	19.0	15.0	24.7	7.77
E_{effmax}	(ml min ⁻¹)	10.8	12.4	9.9	9.9	10.4	10.2	3.1
s		1.47	1.69	1.64	2.09	3.26	2.03	0.72
$C_{50\%}$	($\mu\text{g min}^{-1}$)	152	161	145	127	67	130	38
C_{effmax}	($\mu\text{g min}^{-1}$)	91	129	110	132	86	110	21
<i>Sodium</i>								
E_0	(mmol min ⁻¹)	0.07	0.22	0.05	0.01	0.37	0.14	0.15
$E_{\max}$	(mmol min ⁻¹)	3.99	3.08	2.65	2.29	1.28	2.66	1.00
E_{effmax}	(mmol min ⁻¹)	1.16	1.13	1.08	0.47	0.79	0.85	0.44
s		1.41	1.58	1.69	1.26	2.60	1.71	0.52
$C_{50\%}$	($\mu\text{g min}^{-1}$)	164	197	133	168	65	145	50
C_{effmax}	($\mu\text{g min}^{-1}$)	87	140	107	58	78	94	31
<i>Chloride</i>								
E_0	(mmol min ⁻¹)	0.0	0.23	0.06	0.06	0.38	0.15	0.16
$E_{\max}$	(mmol min ⁻¹)	4.88	3.43	3.24	1.74	1.55	2.97	1.37
E_{effmax}	(mmol min ⁻¹)	0.64	1.11	1.09	0.58	0.80	0.82	0.60
s		1.15	1.48	1.51	1.50	2.08	1.54	0.34
$C_{50\%}$	($\mu\text{g min}^{-1}$)	198	185	124	91	64	132	58
C_{effmax}	($\mu\text{g min}^{-1}$)	38	113	79	57	66	71	28
<i>Potassium</i>								
E_0	(mmol min ⁻¹)	0.05	0.12	0.05	nd	0.05	0.07	0.04
$E_{\max}$	(mmol min ⁻¹)	0.57	0.30	0.53	nd	0.10	0.38	0.22
E_{effmax}	(mmol min ⁻¹)	0.06	0.08	—	nd	0.07	0.06	0.04
s		1.11	1.37	0.85	nd	3.56	1.72	1.24
$C_{50\%}$	($\mu\text{g min}^{-1}$)	311	232	169	nd	58	193	107
C_{effmax}	($\mu\text{g min}^{-1}$)	43	112	—	nd	76	77	35

Figure 2 Observed diuresis of volume (O) and observed volume diuretic efficiency (●) vs frusemide excretion rate in subjects 1 (a) and 5 (b). The solid lines were generated from the fitted model parameters. The dashed lines indicate C_{effmax} and $C_{50\%}$, respectively. Their relative magnitude is dependent on the value of the slope factor which is < 2 in a and > 2 in b.

The effect on potassium is considered to be transient and mainly secondary to increased tubular flow.

Over a relatively short sampling period, the urinary volume or the amount of electrolyte excreted per amount of frusemide, can be used as an estimate of the diuretic efficiency $(E - E_0)/C$. The detailed time course of diuretic effect and diuretic efficiency is shown in Figure 2a and b for two of the subjects. The experimental observations of diuresis and frusemide excretion rate have been used to express both effect and efficiency. A considerable scatter in estimated efficiency is expected at the lower end of frusemide excretion rate when diuresis is close to baseline and the excreted amounts of frusemide are very small. C_{effmax} is less than the corresponding $C_{50\%}$ value of the Hill equation for $1 < s < 2$ (Kaojarern *et al.*, 1982). When $s > 2$, C_{effmax} is greater than $C_{50\%}$ as illustrated in Table 1 and Figure 2. As seen from the expression $C_{\text{effmax}} = C_{50\%}^s \cdot (s-1)^{1/s}$, C_{effmax} and $C_{50\%}$ coincide when $s = 2$. C_{effmax} is not calculable when $s < 1$.

It might erroneously be thought that the steepest part of the curve associated with the Hill equation would be the point at which the highest yield of effect per stimulus is obtained. At this point the first derivative of the Hill equation with, units in the present case of $\text{ml } \mu\text{g}^{-1}$, will have a maximum. However, the expression for efficiency (similar units, $\text{ml } \mu\text{g}^{-1}$) is different from the Hill equation and peaks elsewhere when its first derivative is zero. This can be seen from Figure 3.

Intravenous bolus injection as used in this study is the least efficient mode of administration and will produce the smallest yield of urine. The

Figure 3 Relationships between diuretic effect (E), its first derivative (E'), diuretic efficiency (Eff) and its first derivative (Eff'), respectively, and frusemide excretion rate. The fitted parameters obtained for volume diuresis in subject 1 have been used to construct the graphs. The dashed lines indicate the steepest part of the effect graph (E) where E' has a maximum, the point of maximum efficiency where Eff' is zero and $C_{50\%}$, respectively.

urinary volume produced over 5 h and attributable to the drug effect, ranged from 978 to 1870 ml in the five subjects. Assuming a mode of administration that would ensure the recovered frusemide to be excreted at a constant rate equal to the individual C_{effmax} gives much higher urinary volumes. Comparing actual and calculated urinary volume indicates the latter to be 1.67 to 2.33 times the experimentally obtained volume. This calculation does not, however, consider possible drug tolerance which occurs with frusemide.

Thus, the overall drug effect is dependent on the acute concentration–effect relationship with its resulting concentration–efficiency relationship and the concentration–time profile of the drug. These two relationships are expected to be independent of each other. It follows that drug input and disposition are of great importance with regard to the integrated response over time and should receive more emphasis when designing dosage schedules in patients.

Conclusion

A drug will cause an acute effect by virtue of its intrinsic activity when interacting with a receptor. The most widely used model for the relationship between effect and stimulus is the sigmoid E_{max} model or the Hill equation. However, an alternate variable, efficiency, can be derived from this expression of effect by dividing both sides of the Hill equation by the magnitude of the stimulus. The new variable is thus a measure of effect per stimulus. After a dose has been given the cumulative effect over time will be dependent on a) the effect of the drug and hence derived efficiency and b) the pharmacokinetic properties of the drug as well as its rate of presentation to the body, which will together determine at what efficiencies the effect will be obtained during its time course. These relationships have been discussed and illustrated using data obtained from a study where i.v. frusemide was given to five healthy volunteers. The diuresis of water, chloride, sodium and potassium as well as frusemide excretion rate was followed for 5 h. An i.v. bolus dose is the least efficient mode of administration. A theoretical calculation assuming a frusemide excretion rate associated with maximum efficiency would yield 1.7 to 2.3 times the diuresis obtained after the i.v. bolus dose. We suggest that the efficiency concept should receive more consideration when designing dosage schedules.

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