JPP Journal of Pharmacy and Pharmacology

JPP 2002, 54: 1279–1285

Received February 13, 2002
Accepted May 16, 2002
ISSN 0022-3573

The influence of lithium on the antidiuretic effect of desmopressin

Torbjörn Callréus, Ing-Britt Holmquist, Stefan Lundin, Peter Höglund

Abstract

The objective of this study was to investigate the graded influence from lithium on the antidiuretic effects of desmopressin. Eight healthy male subjects participated in this open, randomised cross-over study with two periods comprising 6 days each. For each subject, one of the study days (6th day) was preceded by a period of lithium treatment. On the study days the subjects were orally water loaded to achieve a state of overhydration with a high urine flow rate. When a steady-state diuresis was achieved after approximately 2 h, 0.396 μg of desmopressin was administered intravenously as a bolus injection. An indirect-response model, where desmopressin was assumed to inhibit the elimination of response, was fitted to the urine osmolarity data. The effects of the independent variables, $U_{flow\ (baseline)}$ (baseline urine flow rate), R_0 (baseline osmolarity) and serum lithium concentration, on IC50 (concentration producing 50% of the maximum inhibition) could be expressed by multiple linear regression. In conclusion, we found that an indirect-response model can be a useful tool in investigating and describing the pharmacodynamic interaction between drugs, in this particular case, between lithium and desmopressin.

Introduction

Desmopressin (dDAVP), a synthetic analogue of the antidiuretic hormone vasopressin, is primarily used in the treatment of neurogenic diabetes insipidus (Robinson 1976) and in children with nocturnal enuresis (Gimpel et al 1998). To investigate the antidiuretic effect of desmopressin in healthy humans, a study design has been used where the subjects were orally (Callreus & Hoglund 1998) or intravenously (Rittig et al 1998) overhydrated during study sessions. This procedure is assumed to involve a suppression of endogenous vasopressin secretion. Lithium, a metallic cation used in the prophylaxis and treatment of manic-depressive disorders (Dollery 1999), antagonises the antidiuretic effect of endogenous vasopressin. Accordingly, drug-induced polyuria is one of its adverse effects. Acutely, lithium appears to reduce V_2 receptor-mediated stimulation of adenylate cyclase. The mechanism of this effect may involve attenuation of G_s-mediated activation of adenylate cyclase (Cogan & Abramow 1986; Goldberg et al 1988) or enhancement of G_i-mediated inhibition of adenylate cyclase (Yamaki et al 1991). Thus, an interaction between lithium and the vasopressin analogue desmopressin is likely to occur.

Integration of pharmacokinetic and pharmacodynamic modelling is a method that can improve our understanding of how drugs act in-vivo. A model (e.g. in the form of an indirect-response model) can be used to quantify the time course of pharmacodynamic responses in relation to the plasma drug concentrations. Also, it can help in estimating intermediate pharmacodynamic steps and parameters not easily accessible (Sharma & Jusko 1998). Preferably, the model selection should consider relevant physiology and the mechanism of action of the drug. In a previous study in overhydrated subjects, we examined whether an indirect-response model could be related to renal physiology and the pharmacological action of desmopressin (Callreus et al 1999b). Of importance for our choice of model was that, in contrast to the effect-compartment model, the indirect-response model predicts that the time of maximum response

Department of Clinical Pharmacology, Lund University Hospital, Lund, Sweden

Torbjörn Callréus, Ing-Britt Holmquist, Stefan Lundin and Peter Höglund

Correspondence: P. Höglund, Department of Clinical Pharmacology, Lund University Hospital, S-221 85 Lund, Sweden. E-mail: Peter.Hoglund@klinfarm.lu.se

Acknowledgments: We wish to thank Mrs Stina Ragnarsson and Mrs Birgitta Håkansson, Department of Clinical Pharmacology, Lund University Hospital, Sweden, for clinical assistance.

increases with increasing doses. This characteristic can be useful for model selection in pharmacokinetic–pharmacodynamic modelling (Wakelkamp et al 1998). As desmopressin (Hammer & Vilhardt 1985) and the vasopressin analogue F992 (Callreus et al 1999a) have exhibited dose-dependent times of maximum response with regard to urine osmolarity, the indirect-response model appeared to be appropriate for modelling the effect of desmopressin on urine osmolarity. Also, the indirect-response model seemed appealing to us from the perspective of the biological mechanisms involved. Hence, as we found that the structure and processes of the model could be related to renal anatomy and physiology, we concluded that the model, where desmopressin was assumed to inhibit the elimination of response (urine osmolarity), offered a mechanistic approach of modelling the antidiuretic effect.

The objective of this study was to investigate the graded influence from lithium on the antidiuretic effects of desmopressin by applying the previously established indirect-response model.

Materials and Methods

Subjects

Eight healthy male subjects, aged 21–46 (mean 27.8) years and weighing 75–91 (mean 80.9) kg, participated in this study. All subjects were considered healthy according to medical history, physical examination, laboratory investigations and an ECG. None of the subjects smoked nor did they use any medications suspected to interfere with the outcome of the study. The study was approved by the University Ethics Committee and the Swedish Medical Products Agency. Written informed consent was given from each subject before their entry into the study.

Study design

This study was conducted using an open, randomised, cross-over design with two periods comprising 6 days each. The subjects were randomised to one of four dose groups (A–D) so that there were 2 subjects in each group (Table 1).

Table 1 Treatment schedule for each subject.

Subject	Period 1	Period 2
1	0	A/1 tablet/0.3
2	A/1 tablet/0.3	0
3	0	B/2 tablets/0.6
4	B/2 tablet/0.6	0
5	0	C/4 tablets/0.8
6	C/4 tablets/0.8	0
7	0	D/6 tablets/1.0
8	D/6 tablets/1.0	0

A–D, dose group; 0, no lithium pretreatment; starting dose is given as no. tablets/24 h; target concentration for lithium is given in mmol L^{-1} (dose group/starting dose/target lithium concn).

For each group there were different target concentrations of lithium to be reached. In half of the subjects, pretreatment with lithium according to the allotted group preceded the study days in the first period, whereas no pretreatment was administered during the second period. Consequently, the opposite sequence applied to the subjects in the other half. Lithium was administered as slow release tablets; each tablet contained 42 mg (6 mmol) of lithium in the form of lithium citrate (Litarex; Astra, Södertälje, Sweden). During periods with lithium pretreatment, the subjects were initially given $\frac{1}{2}$–3 tablets twice daily depending on the dose group (A–D). After 2–3 days of treatment, a blood sample was taken in the morning for analysis of the lithium concentration. Guided by the measured concentrations, the doses were adjusted to ensure a certain pre-defined range of lithium concentrations in the subjects. The subjects allotted to pretreatment with lithium were assumed to have reached their steady-state concentration by the 6th day (study day). On the study days the subjects were orally overhydrated with tap water and desmopressin was administered intravenously as a bolus dose. Thus, each subject participated in two study days, one preceded by lithium treatment and one without. There was a wash-out period of at least 7 (no pretreatment) or 14 (after pretreatment with lithium) days between the study days.

On each study day, breakfast (without tea or coffee) was eaten at home. At approximately 07:00 h, the subjects arrived at the laboratory; indwelling catheters were inserted into antecubital veins in each arm, one for drug administration and one for blood sampling, and the hydration procedure started. When steady-state diuresis was achieved after approximately 2 h, 10 mL of a saline solution containing 0.396 μg of desmopressin was administered intravenously as a bolus injection. This solution was prepared using the commercially available desmopressin solution containing 4 μg mL^{-1} (Minirin; Ferring Pharmaceuticals, Malmö, Sweden). Blood samples for determination of plasma concentrations of desmopressin were drawn before drug administration, at 3, 7.5, 12, 22.5, 37.5 and 52.5 min and at 1.125, 1.375, 1.875, 2.625, 3.375, 4.375, 5.625 and 7.125 h after the injection. These time points were selected to facilitate the initial analysis of the relationship between drug concentration and effect. Blood samples for determination of serum concentrations of lithium were drawn before drug administration and 1 and 6 h after the desmopressin injection. Throughout the study day, urine was voided every 15 min and the volumes were measured. Urine osmolality was assessed from samples of urine pooled during periods ranging from 15 min to 1 h 45 min. The pooling of urine was performed to ensure adequate sample volumes when the urine flow rate was low. Only spontaneously reported adverse events were recorded during study days. A standardised lunch was served 4 h after drug administration. The duration of a study day was approximately 10 h. Xanthine-containing beverages and alcohol were avoided throughout and 24 h before the study day. After the study session, the volunteers returned home and they were instructed not to drink more than 500 mL until the next morning.

Hydration procedure

To achieve a steady-state diuresis, the subjects were requested to drink a volume of tap water corresponding to 15 mL (kg body weight)$^{-1}$. This hydration procedure started approximately 2 h before the injection of desmopressin. Every 15 min during the study session, urine was voided and the volume was measured. To ensure continuous overhydration, the subjects replaced their fluid loss with a volume of tap water equivalent to urine voided plus 10 mL. The additional 10 mL of water ingested every 15 min was administered to compensate for extrarenal water loss. The subjects maintained their level of hydration for 8 h following the injection of desmopressin.

Laboratory methods

Blood samples (7 mL) were collected in vacuum tubes containing tripotassium edetate (K_3-EDTA; Vacutainer, Becton-Dickinson, Meylan, France) for analysis of desmopressin. The samples were centrifuged as soon as possible, but always within 45 min. Plasma was stored at $-20°C$ until assay. Before analysis all samples were extracted with acetone and petroleum ether. The dry extracts were stored in a refrigerator until analysis. Plasma desmopressin levels were measured with a radioimmunoassay technique, using a specific antiserum raised in rabbits as described by Lundin et al (1985). The lower limit of quantification of the assay was determined to 1 pg desmopressin (mL plasma)$^{-1}$ and the recovery was 60%. The intra- and interassay coefficients of variation at 10 pg mL^{-1} were 6.0% and 7.1%, respectively. The values presented for urine osmolarity were approximated by using the same values as for urine osmolality (mOsm L^{-1} instead of mOsm kg^{-1}). Urine osmolality was determined by freezing-point depression using an osmometer (Svenska Labex, Helsingborg, Sweden). Serum lithium concentrations were analysed using a colorimetric method (Ektachem 700 Analyzer; Johnson & Johnson, Rochester, NY).

Data analysis

In an earlier study, we concluded that the indirect-response model used to estimate pharmacodynamic parameters for desmopressin offered a mechanistic approach to modelling the antidiuretic effect of the drug in overhydrated subjects (Callreus et al 1999b). In a first step in this study, plasma desmopressin concentrations after the intravenous injection were analysed using a two-compartment model in WinNonlin (version 1.1; Statistical Consultants Inc., Cary, NC). For each subject and each study day, weighted least squares estimations were performed using the reciprocals of the observed concentrations as weighting factors. The pharmacokinetic parameters were derived using the fitted model. Clearance and volumes of distribution were normalised using the body weight of each subject. The estimates of the pharmacokinetic parameters were fixed and the pharmacokinetic model served as input to the indirect-response model that subsequently was fitted to urine osmolarity data. Also in this second step, individual analyses were performed for each subject and each study day. The reciprocals of the observed urine osmolarities were used as weighting factors.

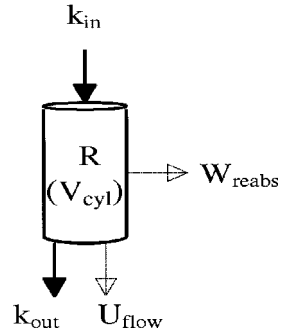

Figure 1 A hypothetical cylinder outlines the structure of the indirect-response model used for modelling the effects of desmopressin. V_{cyl}, volume of the hypothetical cylinder; R, osmolarity in the cylinder; k_{in}, the zero-order constant describing the inflow of solutes per volume of cylinder and time; k_{out}, the first-order constant describing the loss of solutes from the cylinder; W_{reabs}, rate of reabsorption of water; U_{flow}, urine flow rate.

The basis of the indirect-response model is the assumption that a measured change in response (R) to a drug is produced by indirect mechanisms. Physiological processes involved in the production (k_{in}) or elimination (k_{out}) of the response can be either inhibited or stimulated by a drug (Dayneka et al 1993). In this study, the measured response variable is the urine osmolarity (mOsm L^{-1}). The rate of change of response with no desmopressin present can be described by equation 1:

$$dR/dt = k_{in} - k_{out} \times R \quad (1)$$

where k_{in} represents the zero-order constant for production of the response, k_{out} defines the first-order rate constant for elimination of response and R is the response variable representing urine osmolarity. According to this basic indirect-response model, a drug-induced increase in response may be produced by either a stimulation of k_{in} or an inhibition of k_{out} by the drug. An outline of the structure of our indirect-response model is seen in Figure 1. In the centre is a hypothetical cylinder representing a volume (V_{cyl}) of urine having a certain osmolarity (R). Anatomically, this volume is assumed to be contained in the distal parts of the renal tubules where water reabsorption is governed by vasopressin and reabsorption or secretion of solutes is negligible. Thus, it is assumed that k_{in} and k_{out} fully account for production and loss of response. Furthermore, in our model we assume that into this cylinder is continuously transported a certain amount of solutes per volume of cylinder and unit of time. This process is represented by k_{in} and has the unit mOsm L^{-1} h^{-1}. The product of the first-order constant k_{out} (unit: h^{-1}) and R (unit: mOsm L^{-1}) gives the loss of solutes per volume of cylinder and time. Desmopressin inhibits the urine flow rate (U_{flow}) by increasing the rate of reabsorption of water (W_{reabs}) from the distal parts of the renal tubular system

(Figure 1). A lower urine flow rate, produced by an increased water reabsorption, causes the loss of solutes from the cylinder to decrease. Based on the mechanism of action, desmopressin is considered to inhibit k_{out} in the indirect-response model according to an inhibition function I(C):

$$I(C) = 1 - [(I_{max} \times C^{\gamma})/(IC50^{\gamma} + C^{\gamma})] \quad (2)$$

where C is the concentration of desmopressin in plasma, I_{max} represents the maximum effect attributed to desmopressin ($0 < I_{max} \leq 1$), IC50 represents the concentration producing 50% of the maximum inhibition and γ is a sigmoidicity factor. The limits for the inhibition function are: $1 \geq I(C) \geq 1 - I_{max}$. The two-compartment pharmacokinetic model was used to estimate the concentration (C) as a function of dose and time. The rate of change of osmolarity in the cylinder over time with desmopressin can then be described by equation 3:

$$dR/dt = k_{in} - k_{out} \times I(C) \times R \quad (3)$$

Maximum inhibition is obtained when $C \gg IC50$ causing I(C) to approach $1 - I_{max}$. When $C \ll IC_{50}$, I(C) is close to 1 and the net effect approaches the baseline effect (R_0). The inhibition function in our model is assumed to describe the ratio between the urine flow rate (U_{flow}) and the urine flow rate at baseline before the administration of desmopressin ($U_{flow\ (baseline)}$):

$$I(C) = U_{flow}/U_{flow\ (baseline)} \quad (4)$$

Furthermore, this reduction of the urine flow rate is assumed to be an intermediary process, closely related to the concentration of desmopressin, in the production of an increase of urine osmolarity. The urine flow rate is assumed to depend on the urine flow at baseline ($U_{flow\ (baseline)}$) and the rate of reabsorption of water (W_{reabs}):

$$U_{flow} = U_{flow\ (baseline)} - W_{reabs} \quad (5)$$

Rearranging equations 4 and 5 gives us an expression for the desmopressin-dependent rate of reabsorption of water:

$$W_{reabs} = U_{flow\ (baseline)} \times (1 - I(C)) \quad (6)$$

The observations of $U_{flow\ (baseline)}$ and estimates for: R_0, k_{in}, k_{out}, I_{max}, IC50 and γ, from study days with or without pretreatment with lithium, were subsequently subject to statistical analysis.

Statistics

Statistical evaluation of the pharmacokinetic and pharmacodynamic parameters at different serum concentrations of lithium was performed using multiple linear regression with subjects, serum lithium concentration, urine osmolarity at baseline (before the injection of desmopressin) and achieved urine flow rate at baseline as independent variables. In the analysis of potency, logarithmically transformed estimates of IC50 were used. The degree of correlation between urine osmolarity and achieved urine flow rate at baseline had first been tested using an analysis of variance model. As it turned out, there was no significant correlation and, consequently, both variables were used as independent variables in the final analysis. The value used for a serum lithium concentration was the mean of the 3 samples drawn during a study session. The distributions of the estimated variables were tested by the Shapiro-Wilk statistics, setting $P = 0.10$ as the limit for rejection of the null hypothesis of normal distribution. Normally distributed variables are presented as mean (s.d.). Non-normally distributed variables are presented as median (25–75 percentiles). The level of significance was set at $P = 0.05$. SAS software was used for all statistical calculations.

Results

Pharmacokinetics

No statistically significant effect was distinguished by different serum concentrations of lithium on the pharmacokinetic parameters derived from the fitted model. The mean (s.d.) of the volume of the central compartment (V_c) was calculated to be 143 (21) mL kg^{-1}, the medians (25–75 percentiles) for clearance (CL), volume of distribution at steady state (V_{ss}) and terminal half-life ($t_{\frac{1}{2}\beta}$) were estimated to be 0.88 (0.72–1.55) mL min^{-1} kg^{-1}, 366 (282–521) mL kg^{-1} and 4.86 (3.81–5.28) h, respectively.

Pharmacodynamics

The effects of desmopressin on urine osmolarity are depicted in Figure 2. The two subjects with the lowest and highest lithium concentrations are presented. The hydration procedure before administration of desmopressin, both without and with lithium pretreatment, generally produced a urine flow at baseline ($U_{flow\ (baseline)}$) of at least 10 mL min^{-1} and a urine osmolarity at baseline (R_0) below 100 mOsm L^{-1}. Compared with no pretreatment, lithium produced a lower urine flow at baseline ($U_{flow\ (baseline)}$) after water loading and higher values for R_0. The effects of lithium pretreatment on urine flow at baseline as expressed by the general linear model was:

$$U_{flow\ (baseline)} = \text{Subject intercept} - (4.22 \times [\text{lithium concn}]) \quad (7)$$

with subject intercepts in the range 12.3–18.6 mL min^{-1}, whereas the effect on urine osmolarity at baseline was:

$$R_0 = \text{Subject intercept} + (25.3 \times [\text{lithium concn}]) \quad (8)$$

with subject intercepts in the range 34.3–73.7 mOsm L^{-1}. The observed $U_{flow\ (baseline)}$ and estimates for R_0, k_{in} and IC50, without and with lithium pretreatment, are presented in Table 2. The statistical analysis did not reveal any significant effects of $U_{flow\ (baseline)}$, R_0 or lithium concen-

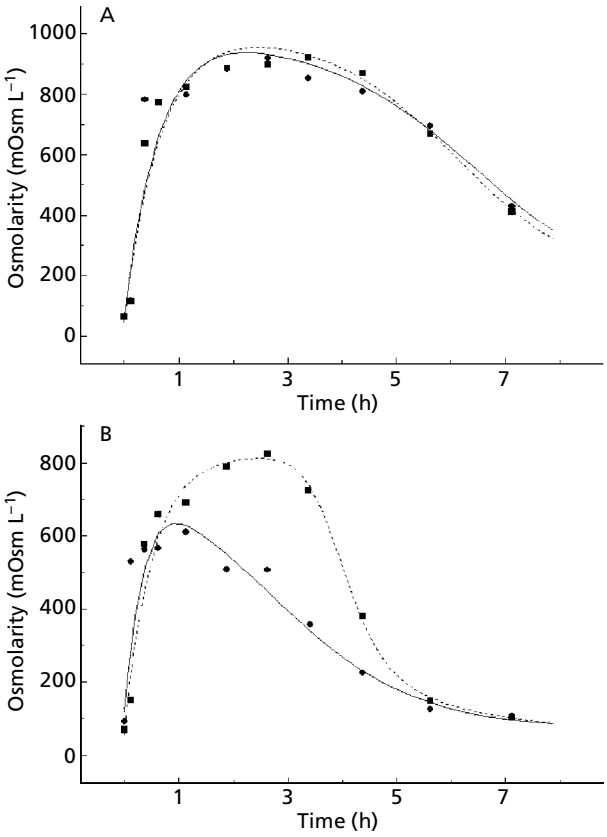

Figure 2 Graphical presentation of observed and predicted urine osmolarity vs time for the subjects who achieved the lowest (A) and the highest (B) serum lithium concentration. For both subjects, observations with (circles) and without (squares) pretreatment with lithium are given. The fitted curves represent predicted values with (solid line) and without (dashed line) pretreatment with lithium.

tration on the values of k_{out}, I_{max} and γ (sigmoidicity factor) and these parameters were estimated to be 13.0 (8.3–61.3) h^{-1}, 0.89 (0.08) and 11.3 (6.9), respectively. The effects of the independent variables, $U_{flow\,(baseline)}$, R_0 and serum lithium concentration, on IC50 (unit: pg mL^{-1}) as expressed by the general linear model was:

$$\log(IC50) = \text{Subject intercept} + (1.788 \times [\text{lithium concn}]) + (0.19 \times U_{flow\,(baseline)}) - (0.028 \times R_0) \quad (9)$$

with subject intercepts in the range −0.447 to −1.426. Figure 3 shows graphical presentations of the effect of the aforementioned independent variables, using the mean subject intercepts, on the value of IC50.

Safety

The treatments administered were well tolerated; no adverse events were reported by the subjects during the study.

Discussion

One application of the indirect-response models is that they may permit identification of the physiological component of drug action that is affected by disease, other drugs, gender, age and other variables (Levy 1994). This study represents an attempt to use an indirect-response model to investigate the influence of lithium on the antidiuretic effect of desmopressin. As the subjects were healthy, a commonly used overhydration procedure was used to facilitate measurements of the antidiuretic effects when the influence from endogenous vasopressin was abolished. An indirect-response model, where desmopressin was assumed to inhibit processes involved in the elimination of response, was used to estimate in-vivo pharmacodynamic parameters.

Essential assumptions of the model of current interest are that, in the distal parts of the renal tubules, reabsorption of water is governed by desmopressin and reabsorption or secretion of solutes are negligible. In a previous study, these assumptions seemed to be fulfilled at high levels

Table 2 Pharmacodynamic parameters estimated and R^2 from the curve fitting procedures, without or with pretreatment with lithium, after intravenous administration of desmopressin (0.396 μg) to eight healthy overhydrated males.

Subject	No lithium pretreatment					Lithium pretreatment						
	R^2	$U_{flow\,(baseline)}$ (mL min^{-1})	R_0 (MOsm L^{-1})	k_{in} (mOsm $L^{-1} \cdot h^{-1}$	IC50 (pg mL^{-1})	Final dose (no. tablets/24 h)	S (lithium mmol L^{-1})	R^2	$U_{flow\,(baseline)}$ (mL min^{-1})	R_0 (mOsM L^{-1})	k_{in} (mOsm $L^{-1} \cdot h^{-1}$)	IC50 (pg·mL^{-1})
1	0.99	15.2	46	1100	3.41	2	0.33	0.97	11.5	51	1198	2.82
2	0.96	15.3	40	1574	2.75	1	0.21	0.94	12.8	42	1491	1.07
4	0.95	14.8	50	1540	1.41	3	0.58	0.95	12.1	49	1405	2.56
5	0.97	12.1	46	1362	1.75	5 1/2	1.16	0.96	7.7	52	613	39.10
6	0.97	18.3	45	1616	7.02	6	0.81	0.96	14.1	63	1542	7.85
7	0.92	19.3	57	1326	7.99	7 1/2	1.11	0.96	13.3	83	1845	5.31
8	0.97	14.0	56	1632	4.12	6	1.13	0.92	13.6	120	2000	6.56
Mean		15.7	48	1384	4.03							
s.d.		2.3	6	261	2.35							

$U_{flow\,(baseline)}$, urine flow rate at baseline before administration of desmopressin; R_0, urine osmolarity at baseline before administration of desmopressin; k_{in}, the zero-order constant describing the inflow of solutes per volume of cylinder and time; IC50, the concentration producing 50% of the maximum inhibition. The final dose is the number of tablets prescribed to the subject in the end of the treatment period after the first analysis of the serum lithium concentration. Each tablet contained 42 mg (6 mmol) of lithium in the form of lithium citrate. The serum lithium concentration is the mean of the 3 samples drawn during a study session.

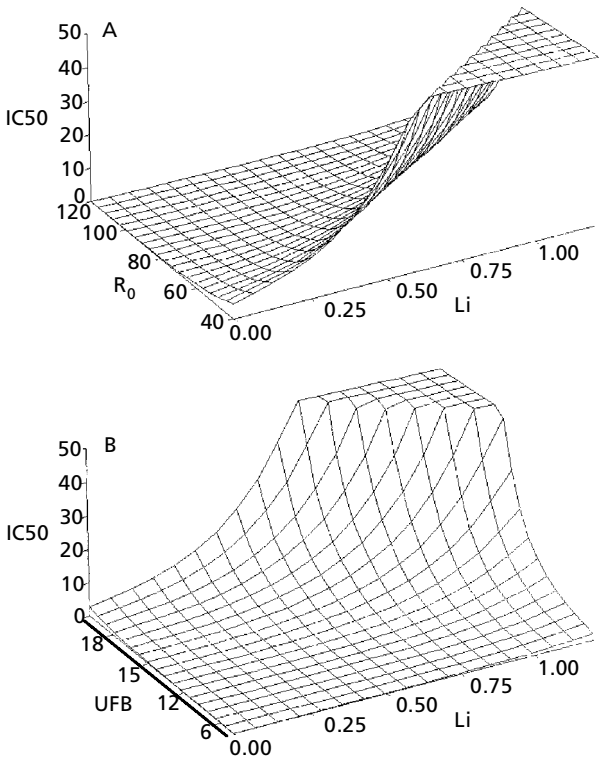

Figure 3 Graphical presentation, within the observed ranges, of the effect of the independent variables – urine flow at baseline (UFB), urine osmolarity at baseline (R_0) and lithium concentration (Li) – on the potency of desmopressin, as measured by the IC50 value. (A) The urine flow rate at baseline is 15 mL min^{-1}. (B) The urine osmolarity at baseline (R_0) is 80 mOsm L^{-1}. The units are mL min^{-1} for urine flow at baseline (UFB), mOsm L^{-1} for urine osmolarity at baseline (R_0), mmol L^{-1} for lithium concentration (Li) and pg mL^{-1} for the IC50 value.

(urine flow rate of at least 10 mL min^{-1}) of overhydration (Callreus et al 1999b). As the subjects in this study were adequately overhydrated, we believe that the model represents a valid mechanism-oriented approach of modelling the effect of desmopressin. Presumably, pretreatment with lithium does not change this situation. However, owing to the study procedure, extrapolation of the result to euhydrated subjects must be made with caution since endogenous vasopressin may also be present.

The pharmacokinetics of desmopressin were not affected by the different serum concentrations of lithium. The estimated parameters are in accordance with those calculated in a previous study where an identical dose (0.396 μg) was administered intravenously (Callreus et al 1999b). The serum lithium concentrations, obtained from the slow-release formulation, appeared stable during the study sessions. A further contributing factor may have been a reduced lithium clearance, caused by increased renal reabsorption induced by desmopressin (Walter et al 1996). Point estimates for k_{out}, I_{max} and γ were in accordance with those in a previous study (Callreus et al 1999b); the same applies to k_{in} and IC50 without pretreatment with lithium.

The urine flow rate at baseline was always lower after pretreatment with lithium (Table 2). Polyuria is a common adverse event during lithium treatment (Dollery 1999). Thus, the subjects probably had a high urine flow rate during the period with pretreatment resulting in a dehydrated state, just before the start of the hydration procedure, on the study day. Consequently, our water loading did not produce the same urine flow rate as when the subjects were in a euhydrated state. Dehydration causes the urine to be more concentrated, hence the higher urine osmolarity at baseline (R_0) on the study days. The mechanism is unclear regarding the higher values for k_{in} after pretreatment with lithium. Most probably, this pretreatment produced a higher rate of transport of solutes into the cylinder. Presumably, the lithium ions excreted in the urine make up a part of this increased rate. A smaller volume of the hypothetical cylinder is a less likely explanation for the higher value of k_{in}. Figure 3 graphically depicts how the independent variables, $U_{flow\,(baseline)}$, R_0 and lithium concentration, within the observed ranges, affect the IC50 value for desmopressin. The three-dimensional graphs, derived from the general linear model, demonstrate how the IC50 value increases as a result of higher lithium concentrations and $U_{flow\,(baseline)}$, whereas higher urine osmolarity at baseline (R_0) decreases the IC50 value. These relationships seem physiologically plausible and reasonable.

The antagonistic effect of lithium, on the antidiuretic effect of vasopressin/desmopressin, is assumed to be exercised in a non-competive manner by inhibition of adenylate cyclase. To our knowledge, an indirect-response model has previously not been used to investigate a similar interaction. The potency of desmopressin, as measured by the IC50 value, was lowered by lithium. Usually, non-competitive antagonism also involves a reduction of the observable maximum effect (efficacy). However, in this study, the urine flow rate was, on all study days, even on occasions with high lithium concentrations, reduced to below 1 mL min^{-1}. The lithium concentration in this study may have been too low to observe this change. An alternative method of producing more pronounced effects could have been to expose the subjects to changing concentrations of lithium. The rationale for this is that at steady-state concentrations, as in this study, homoeostatic mechanisms tend to counteract lithium effects (Mellerup et al 1987). However, changing lithium concentrations during the sessions would have been difficult to incorporate into the model. When the ordinary E_{max} model is applied to describe the data, a decrease in efficacy is normally reflected in a reduction of the E_{max} value. In contrast to this, the values for E_{max}/I_{max} have a different meaning, as factors of augmentation or attenuation, when an indirect-response model is used.

In conclusion, in this study in overhydrated healthy subjects, we investigated the influence of lithium on the antidiuretic effect of desmopressin. An indirect-response model, where desmopressin was assumed to inhibit processes involved in the elimination of response, was used to estimate in-vivo pharmacodynamic parameters. We found that this model can be a useful tool in investigating and

describing the pharmacodynamic interaction between drugs.

References

Callreus, T., Hoglund, P. (1998) Pharmacokinetics and antidiuretic effect of intravenous administration of desmopressin in orally overhydrated male volunteers. *Pharmacol. Toxicol.* **83**: 259–262

Callreus, T., Lundahl, J., Broeders, A., Hoglund, P. (1999a) Pharmacokinetics and antidiuretic effect of a new vasopressin analogue (F992) in overhydrated male volunteers. *Eur. J. Clin. Pharmacol.* **55**: 293–298

Callreus, T., Odeberg, J., Lundin, S., Hoglund, P. (1999b) Indirect-response modeling of desmopressin at different levels of hydration. *J. Pharmacokinet. Biopharm.* **27**: 513–529

Cogan, E., Abramow, M. (1986) Inhibition by lithium of the hydro-osmotic action of vasopressin in the isolated perfused cortical collecting tubule of the rabbit. *J. Clin. Invest.* **77**: 1507–1514

Dayneka, N. L., Garg, V., Jusko, W. J. (1993) Comparison of four basic models of indirect pharmacodynamic responses. *J. Pharmacokinet. Biopharm.* **21**: 457–478

Dollery, C. (1999) Lithium. In: Boobis, A., Rawlins, M., Thomas, S., Wilkins, M. (eds) *Therapeutic drugs.* Edinburgh, Churchill Livingstone, pp L71–L75

Gimpel, G. A., Warzak, W. J., Kuhn, B. R., Walburn, J. N. (1998) Clinical perspectives in primary nocturnal enuresis. *Clin. Pediatr. (Phila)* **37**: 23–29

Goldberg, H., Clayman, P., Skorecki, K. (1988) Mechanism of Li inhibition of vasopressin-sensitive adenylate cyclase in cultured renal epithelial cells. *Am. J. Physiol.* **255**: F995–F1002

Hammer, M., Vilhardt, H. (1985) Peroral treatment of diabetes insipidus with a polypeptide hormone analog, desmopressin. *J. Pharmacol. Exp. Ther.* **234**: 754–760

Levy, G. (1994) Mechanism-based pharmacodynamic modeling. *Clin. Pharmacol. Ther.* **56**: 356–358

Lundin, S., Melin, P., Vilhardt, H. (1985) Plasma concentrations of 1-deamino-8-D-arginine vasopressin after intragastric administration in the rat. *Acta Endocrinol.* **108**: 179–183

Mellerup, E., Plenge, P., Rafaelsen, O. (1987). Renal and other controversial adverse effects of lithium. In: Meltzer, H (ed.) *Psychopharmacology: the third generation of progress.* New York, Raven Press, pp 1443–1448

Rittig, S., Jensen, A. R., Jensen, K. T., Pedersen, E. B. (1998) Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. *Clin. Endocrinol. (Oxf)* **48**: 235–241

Robinson, A. G. (1976) DDAVP in the treatment of central diabetes insipidus. *N. Engl. J. Med.* **294**: 507–511

Sharma, A., Jusko, W. J. (1998) Characteristics of indirect pharmacodynamic models and applications to clinical drug responses. *Br. J. Clin. Pharmacol.* **45**: 229–239

Wakelkamp, M., Alvan, G., Paintaud, G. (1998) The time of maximum effect for model selection in pharmacokinetic-pharmacodynamic analysis applied to frusemide. *Br. J. Clin. Pharmacol.* **45**: 63–70

Walter, S. J., Shirley, D. G., Unwin, R. J. (1996) Effect of vasopressin on renal lithium reabsorption: a micropuncture and microperfusion study. *Am. J. Physiol.* **271**: F223–F229

Yamaki, M., Kusano, E., Tetsuka, T., Takeda, S., Homma, S., Murayama, N., Asano, Y. (1991) Cellular mechanism of lithium-induced nephrogenic diabetes insipidus in rats. *Am. J. Physiol.* **261**: F505–F511