Gender difference in antidiuretic response to desmopressin

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Submitted 27 December 2010; accepted in final form 25 February 2011

Juul KV, Klein BM, Sandström R, Erichsen L, Nørgaard JP. Gender difference in antidiuretic response to desmopressin. *Am J Physiol Renal Physiol* 300: F1116–F1122, 2011. First published March 2, 2011; doi:10.1152/ajprenal.00741.2010.—In increased age and female gender are well-known risk factors for the development of desmopressin-induced hyponatremia. However, little focus has been on exploring gender differences in the antidiuretic response to desmopressin. Based on an exploratory analysis from three clinical trials, we report a significant gender difference in the effects of desmopressin on nocturnal urine volume that could not be explained by pharmacokinetic differences. Mean desmopressin concentration profiles were tested for covariates, and age and gender were not statistically significant and only weight was significant for log(Cmax) (P = 0.0183) and borderline significant for log(AUC) (P = 0.0571). The decrease in nocturnal urine volume in nocturia patients treated with desmopressin over 28 days was significantly larger for women at the lower desmopressin melt doses of 10 and 25 μg than for men. The ED50 for men was modeled to be 43.2 μg and 16.1 μg for women, with the ED50 men/women estimated to be 2.7 (1.3–8.1 95% CI), corresponding to significantly higher sensitivity to desmopressin in women. An increasing incidence of hyponatremia with increasing dose was found, and at the highest dose level of 100 μg decreases in serum sodium were approximately twofold greater in women over 50 yr of age than in men. A new dose recommendation stratified by gender is suggested in the treatment of nocturia: for men, 50- to 100-μg melt is an efficacious and safe dose, while for women a dose of 25 μg melt is recommended as efficacious with no observed incidences of hyponatremia. Areas for further research are proposed to uncover pathophysiological mechanism(s) behind these gender differences.

AN IMPORTANT CAUSE OF SEVERE NOCTURIA in the elderly population is reduced nocturnal arginine vasopressin (AVP) release (14), a condition associated with gender. In particular, elderly women have lower plasma AVP levels than men (4), and the pronounced estrogen deficiency following menopause is identified, among other contributing factors, as leading to nocturnal polyuria (22).

Desmopressin, the synthetic AVP analog, is approved in the EU and several other countries worldwide in the treatment of nocturia, mimicking the antidiuretic action of AVP. Due to its prolonged duration of action, desmopressin indirectly leads to hyponatremia in rare cases by blocking the mechanism of compensatory diuresis (18). In the treatment of nocturia with desmopressin, patients at age extremes and women have been identified as being at the highest risk of developing this type of dilutional hyponatremia (10, 18).

Recently, it was shown by Liu et al. (11) that female rats express significantly more V2 receptor (V2R) mRNA and protein in kidneys than men and that this results physiologically in a greater sensitivity to V2R agonist administration (11), but so far no human data have been published confirming a gender difference in the antidiuretic action of desmopressin that could explain the higher hyponatremia risk in elderly women. However, we believe that the literature on V2R expression and AVP secretion offers a scientific basis for the existence of such gender differences, especially based on the genetic X-inactivation mechanism of action and the influence of sex hormones on osmoregulation, as summarized below.

X inactivation and mutations of AVPR2: gender differences. Novel human genetic and preclinical findings provide insight into a genetic mechanism of action potentially responsible for gender differences in renal V2R expression and thereby indirectly also on the phenotypic antidiuretic response to desmopressin. It is well known that during embryonic development the second X chromosome is silenced in female mammals by “X inactivation” (15). Some genes “escape” this X inactivation with the result that they are expressed on both the active and inactive X chromosome in the same cell, causing phenotypic variability in X-linked conditions. As a result of this mechanism, in a number of X-linked renal diseases, males either have the disease and females have no disease or at least milder manifestations, or only females have the disease because the mutation is lethal in males (13).

In humans, a number of genes located at the X chromosome have been found to be involved in water homeostasis. These genes have been fully sequenced, and of special interest in this context is AVPR2, a gene located on the long arm of the X chromosome in chromosome region Xq28. Human mutations of AVPR2 have been shown to cause both polyuric and polydipsic disorders, such as nephrogenic diabetes insipidus (DI; mutated gene AVPR1A–), and antidiuretic disorders, such as nephrogenic syndrome of inappropriate antidiuresis (NSIAD; mutated gene AVPR2+) (13). In nephrogenic DI, the AVPR2 mutation means that V2R cannot reach the plasma membrane because they are trapped within the renal cell, leading to failure to concentrate urine in response to endogenous AVP. In NSIAD, a gain-of-function AVPR2 missense mutation (a point mutation in which just a single nucleotide is changed) was originally reported in male infants only, but later it became apparent that this X-linked antidiuretic condition is causative of episodes of hyponatremia in both boys and male and female adult carriers (17). Clinically, in both conditions, nephrogenic DI and NSIAD, the female renal phenotype, is usually less severe and yields milder symptoms compared with the male phenotype (13).

In X-inactivation tests in heterozygous human fibroblasts, the AVPR2 gene scored 9 of 9, suggesting that this gene has a particular high probability of escaping X inactivation (7). This could explain the gender differences seen in the clinical manifestations of many X-linked conditions, and overall these new genetic findings demonstrate gender differences in renal V2R expression that may result from both human mutations of
Gender differences in osmoregulation of vasopressin. Osmoregulation of AVP is maintained within a narrow range of blood tonicity detected by central osmoreceptors (5), but the mechanism by which these osmoreceptors translate tonicity into vasopressin release is not yet fully understood. It has been suggested that osmoreceptor neurons undergo volume changes as water moves into or out of them, resulting in a cationic current and depolarization (24).

Gender differences in the diurnal water homeostasis and the natural process of osmoregulation of endogenous AVP has been correlated to sex hormones in a number of studies (9, 19–21). Stachenfeld and coworkers (19) found that AVP plasma concentration is approximately twice as high during hypertonic saline infusion (HSI) in men compared with women. No gender differences in water clearance were observed, suggesting lower renal sensitivity in men. In the same study, a downward shift in plasma osmotic threshold for AVP was seen in women in the midluteal phase relative to the follicular phase. It was concluded that androgens are the most likely factor to influence AVP sensitivity whereas estrogens lower the plasma osmotic threshold for AVP. The latter was supported by results where exogenous estrogen was administered to postmenopausal and young women with suppressed endogenous estrogen, respectively, before HSI (20, 21).

Hvistendahl et al. (9) reported gender and age differences in elderly men and women with nocturnal polyuria compared with young and elderly controls. In this study, men were found to have higher nighttime AVP but similar urine osmolality compared with women, confirming the higher renal sensitivity in women compared with men. The antidiuretic action of desmopressin was prolonged in the elderly compared with younger subjects, resulting in postponed compensatory diuresis in elderly individuals. The latter is a likely factor for the increased risk of hyponatremia seen in the elderly compared with younger subjects.

The influence of exogenous sex hormones, more specifically oral contraceptives (OC), on diurnal urine regulation was investigated by Graugaard-Jensen et al. (8). Circadian rhythm in P-AVP was found in both natural cycling women in the midfollicular phase and in long-term OC users, but no difference was found between the two groups. Graugaard-Jensen et al. concluded that diurnal rhythm of AVP and diurnal urine production is unaffected by the use of OC but that high exogenous estrogen resets the osmoreceptors to a lower set point, in accordance with the studies cited above.

Purpose of this study. Based on the literature cited, a number of gender-related differences exist in natural AVP secretion and sensitivity, driven by either sex hormones or X inactivation, or most likely by a combination of both mechanisms. Whether similar gender-specific mechanisms influence the antidiuretic response of the AVP analog desmopressin have so far not been explored in humans, probably because the doses of desmopressin in clinical studies have been so high that all or the majority of patients regardless of gender have been on maximum effect in terms of water retention during treatment.

Thus the purpose of this study is to quantify the pharmacokinetic (PK) and dynamic (PD) effects of desmopressin by an exploratory age- and gender-stratified analysis from three desmopressin clinical trials. Data from these desmopressin trials in nocturia patients and in healthy volunteers were selected with the aim of providing kinetic and dynamic data on a broad range of desmopressin dose levels of the oral melt formulation and also to provide a sufficiently large sample size to enable statistically meaningful age and gender stratifications on both the antidiuretic effect and on clinically relevant hyponatremia events.

METHODS

The following sets of data were included in the present analysis.

1) PD data from a recent phase III double-blind, placebo-controlled study of desmopressin in the treatment of nocturia administered orally in subjects with an average of ≥2 voids/night and a serum sodium >135 mmol/L (ClinicalTrials.gov; Identifier: NCT00477490, NCT00615836) (23). Data were extracted from part I of this study that included 554 nocturia patients (ITT on active dose supplying PD data) receiving daily oral doses of 10, 25, 50, or 100 µg desmopressin melt before bedtime for 28 days. The clinical and safety results of this study have been reported elsewhere (23).

2) PK data (plasma desmopressin concentrations, 0–14 h postdosing) from two phase I studies in healthy male or female subjects, 18–55 yr of age. Twenty-five healthy subjects (15 men and 10 women) received 60, 120, and 240 µg desmopressin in a crossover design (FE992026 CS20 Clinical Study Report: Relative Bioavailability Of The Oral Lyophilisate Versus Minirin Tablets; unpublished data), and 28 healthy subjects (14 men, 14 women) received 240 µg desmopressin (FE992026 CS21 Clinical Study Report: Single-Dose Desmopressin Administered as an Oral Lyophilisate of 60, 120, or 240 µg; unpublished data).

All three studies were approved by the institutional review board or ethics committee for each site, the Declaration of Helsinki was followed, and informed consent was obtained from all patients and healthy volunteers. All data used are based on the Minirin melt formulation of desmopressin. The PK and PD data were analyzed separately. Weight, gender, and age were included in all data sets.

Software. S-PLUS 8.0 was used for graphics, linear mixed effects modeling of PK data, and generalized linear modeling of hyponatremia event data. Nomogram VI was used for dose-response modeling of nocturnal urine volume.

Pharmacokinetics. The quantitative determination of desmopressin in human plasma was performed using a validated radioimmunoassay, as described previously (1). The log-transformed area under the curve (AUC; 0–14 h) and maximum concentration (Cmax) were used as response variables in linear mixed-effect models with log(dose), log(weight), log(age), and gender as covariates and subjects as random effects.

Nocturnal urine volume. A maximal response (Emax) dose-response model with weight-adjusted dose (dose/weight) and with a linear placebo effect was used to describe the effect on nocturnal urine volume

\[
V = \left[\alpha + \beta \cdot V_{\text{base}}\right] \cdot \left[1 - \frac{E_{\text{max}} \cdot d_n}{E_{50} + d_n}\right]
\]

where V is the nocturnal urine volume at day 28, and Vbase is the corresponding predose value. The term \(\alpha + \beta \cdot V_{\text{base}}\) is the baseline volume corrected for placebo effect, and the term in the second bracket is the relative dose effect. Tests of categorized covariates gender, weight (grouped according to <, ≥80 kg), and age (grouped according to <, ≥60 yr) on ED50 were done, and the weight-corrected dose sensitivity for women relative to men was estimated as ED50 (men)/ED50 (women). Thus a sensitivity parameter >1 would indicate a higher sensitivity among women than men and vice versa. The model was fitted to active and placebo groups simultaneously.
Serum sodium levels and hyponatremia. Clinically relevant hypo-
natremia events were defined as sodium levels <130 mmol/l. The
number of subjects experiencing at least one hyponatremia event was
plotted against dose by age group and gender, and a test of "no
gender-difference" in the age group >50 yr (dose level 50 g) was
done assuming a binomial distribution and an approximate
2 distribution of the likelihood ratio test statistic.

RESULTS
Pharmacokinetics. Mean desmopressin concentration pro-
files are shown by dose and gender in Fig. 1. Unadjusted PK
data show similar PK profiles at 60 g for men and women,
while women have higher Cmax with increasing dose, espe-
cially at the 240-g dose level. However, successive tests of
covariates log(age), gender, and log(weight) were done in this
order (Table 1), and age and gender were not statistically
significant while weight was significant for log(Cmax) (P = 0.0183) and borderline significant for log(AUC) (P = 0.0571).
We conclude, that there are no significant gender-specific
differences in PK properties of desmopressin and that the
estimates of regression coefficients suggest dose proportionality
and inverse proportionality to weight.

Nocturnal urine volume. The nocturnal urine volume was
measured by asking patients to empty their bladder immedi-
ately before bedtime and to measure the volume of any noc-
turnal voids and the first morning void. Initial plots (Fig. 2) of
the mean decrease from baseline in nocturnal urine volume
(ml) show a clear gender difference at the lower doses, with a
larger antidiuretic effect for women significant at the 25-µg
dose (P = 0.00096), while at the higher 50- and 100-µg dose
levels a similar decrease from baseline in nocturnal urine
volume was seen between the genders.

Tests of covariate effects showed that the gender difference
in weight-corrected ED50 was statistically significant (P =
0.009). Parameter estimates of the final model are shown in
Table 2. These indicate that men have a higher ED50 corre-
sponding to a lower sensitivity than seen in women. The
relative sensitivity (ED50 for men/ED50 for women) is esti-
mated at 2.7 with a 95% CI of 1.3–8.1.

Serum sodium levels and hyponatremia events. The mean
decrease from baseline in serum sodium concentration vs. dose
is shown by gender and age groups in Fig. 3. This indicates no
dose-response relationship for subjects ≤50 yr of age but an
increasing response with increasing dose for subjects over 50
yr old, with women being the most sensitive, having approxi-
mately twofold greater decreases in sodium compared with
men at dose levels from 25 to 100 µg. For female subjects over
65 yr old, an even steeper decrease in serum sodium is seen following administration of all doses >25 μg.

The relative number of subjects experiencing at least one hyponatremia event, defined as a sodium level <130 mmol/l, is shown by gender and age groups in Fig. 4. No events were observed for women up to 50 yr of age and men up to 65 yr old. For the age group above 50, there was a gender difference at the 50-μg dose level, with women having a fivefold higher risk of hyponatremia than men (P = 0.015). No events were observed for women below 65 yr of age at doses up to 25 μg.

A summary of estimated dose effects \[\text{dose}/(ED_{50} + \text{dose})\] on nocturnal urine volume and changes in mean serum sodium levels are given in Table 3. For the \(E_{\text{max}}\) model, SE was calculated by simulation, assuming \(ED_{50}\) is log-normally distributed. Both genders saw a dose-dependent decrease in sodium, with women at the highest 100-μg desmopressin dose level experiencing almost twice the mean drop compared with men. Across all dose levels, a significant difference in dose-response on serum sodium between men and women was found (P = 0.0112).
DISCUSSION

In this post hoc analysis, we found that the relative male/female sensitivity to the antidiuretic effect of desmopressin in nocturia is 2.7, corresponding to significantly higher desmopressin sensitivity in women and thus, compared with men, a narrower therapeutic window for avoiding hyponatremia without compromising efficacy.

Our study was not designed to explain these gender differences, but the finding seems in accordance with the higher renal endogenous AVP sensitivity found in women compared with men. In particular, the finding reported by Stachenfeld and coworkers (19) of approximately twice as high plasma concentrations of AVP in men during HIS compared with women despite similar water clearance supports the relative male/female sensitivity to the antidiuretic action of desmopressin found in our study of 2.7. Also, animal data support our findings of this male/female ratio, since kidney V2R mRNA expression was recently found to be 2.7-fold higher in female compared with male MF-1 mice, \( P < 0.05 \) (12). Furthermore, Liu et al. (11) very recently confirmed in a water-loaded setting that female rats express significantly more V2R mRNA and protein in kidneys than males and that this resulted physiologically in a greater sensitivity to V2R agonist administration, concluding that the “potential pathophysiological implications...
of these results are that females may be more susceptible to
development of dilutional hyponatremia because of a greater
sensitivity to endogenously secreted AVP."

On the influence of age, the increased and dose-response-
related reduction of serum sodium found in patients >50 yr of
age could likely be linked to the prolonged antidiuretic action
of desmopressin previously reported in elderly individuals,
with postponed compensatory diuresis proposed as a likely
factor for the increased risk of hyponatremia (18).

Our findings seem supported by the animal data in MF-1
mice indicating that the kidney V2R is to some degree regu-
lated by ovarian hormones in females and that females may be
less able to escape antiuresis, whether it is induced by
endogenous AVP or by exogenous desmopressin because of
higher kidney V2R expression compared with males (11, 12).
However, the mechanism of action in humans needs further
research: Our suggestion is to explore the explanations for
gender-specific desmopressin sensitivity within a similar
framework of mechanisms regulating the gender differences
in natural AVP release and sensitivity, especially the influence of
estrogen, androgens, and X inactivation: We suggest a PET
scanning study in healthy male and female volunteers on renal
AVPR2 density to elucidate and quantify the gender differ-
cences in AVPR2 binding. Furthermore, the role of X inactiva-
tion should be explored in a genetic study of AVPR2 in
chromosomal region Xq28 to explore whether the X-linked
gender differences seen in renal phenotype and in the mani-
festations of both nephrogenic DI and SIADH apply to nocturia
as well, i.e., influence the gender-specific phenotype in terms
of the level of nightly antiuresis in response to endogenous
AVP.

Notwithstanding the underlying genetic mechanism of ac-
tion, the significantly higher sensitivity in women compared
with men has important implications for the therapeutic win-
dow and risk/benefit ratio of future antidiuretic treatment
of nocturia. We have found indications that serum sodium levels
and the subsequent risk of clinically relevant hyponatremia (Na
<130 mmol/l) due to desmopressin treatment is clearly gender
dependent, with the risk of an event being fivefold higher for
women compared with men at the 50-μg dose level (P =
0.015). By lowering the recommended dose in women to 25
μg, the risk of hyponatremia will be significantly reduced
according to this analysis, without compromising the antidi-
uretic effect. Additionally, elderly female patients over 65 yr of
age could also benefit from this new treatment regimen without
compromising safety in terms of increased hyponatremia risk.

For men, doses in the range from 50 to 100 μg were found
to be efficacious and safe. Modeling our finding of a 2.7 ratio
of male/female sensitivity to desmopressin’s antidiuretic effect
into the optimal female dose of 25 μg, an estimate of 67 μg as
the optimal male dose is suggested, which is safely within the
investigated ranges of 50–100 μg. However, large-scale phase
III trials testing both the lower dose level in female nocturia
patients and the 50- to 100-μg range in male nocturia patients
will be needed to confirm that the gender-specific therapeutic
window offers a decreased risk of hyponatremia without com-
promising efficacy on reduction of nocturnal voids.

Gender differences in drug exposure when single Minirin
melt doses between 60 and 240 μg were administered orally
were not statistically significant when adjusted for body
weight. Statistical PK comparisons between the genders were
not adjusted by estimates of blood volume, since the compart-
ment that desmopressin distributes to is much larger than the
blood volume: it has been estimated at 25–35 liters after
intravenous doses of desmopressin, and the size of this com-
partment correlates well with body weight (1). Since subjects
with renal impairment were not included in the analysis, the
observed differences in PD response between age groups and
between men and women are unlikely to be explained by PK
differences. However, a potential weakness of our exploratory
analysis was that PD and PK data were pooled from different
sources, since no PK data were collected in the phase III
double-blind, placebo-controlled study of desmopressin (23).
Furthermore, the dose levels used for PK analysis reflected the
currently marketed dose strengths and were thus generally
higher (60, 120, or 240 μg) than the doses ranging from 10 to
100 μg in the phase III study (23). For a future large-scale
phase III study to confirm the efficacy and safety of the 25-μg
dose in female nocturia patients, a population PK approach
should therefore be considered, allowing for direct PK/PD
modeling. Also, since this was a post hoc analysis of studies
conducted before the hypothesis of significant gender differ-
cences was generated, sex hormones levels and the numbers of
women with a hysterectomy and/or salpingo-oophorectomy
were not collected. For future phase III trials, such data should
be considered for a clarification of the role of sex hormones on
sensitivity to desmopressin’s antidiuretic effect.

To our knowledge, gender difference affecting clinical effi-
cacy and safety in the magnitude that we found with desmop-
pressin in this analysis (relative male/female sensitivity of
desmopressin on antidiuretic effect of 2.7 and risk of hypona-
tremia up to fivefold higher for women compared with men) has
not been shown with other marketed drugs. Chlorproma-
zine, fluspirilene, and various antipsychotics have been shown
more effective in women than men at the same dose levels and
plasma concentration (16), but not in the same magnitude as
we found with desmopressin. Numerous examples of minor
gender-dependent differences in the pharmacokinetics and
pharmacodynamics exist, but in general the effect of gender
on clinical efficacy, dosing, and therapeutic window has just
begun to be explored (2). Of 163 new drug applications
including gender analysis reviewed by the Food and Drug
Administration between 1995 and 2000, 11 drugs showed a
>40% difference in pharmacokinetics between men and
women, but despite this no dosing recommendations were
made based on gender (3). A Danish review found that phar-
macoepidemiological studies have shown ~30% more adverse

Table 3. Estimated means (SE) dose effect on nocturnal
urine volume and change in serum sodium levels measured
as pre-IMP vs. post-IMP (first 28 days) as the average of all
postbaseline sodium values subtracted from the baseline

<table>
<thead>
<tr>
<th>Dose, μg</th>
<th>% of Maximum Effect (Men)</th>
<th>% of Maximum Effect (Women)</th>
<th>Change in Sodium, mmol/l</th>
<th>Change in Sodium, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>−0.48 (0.32)</td>
<td>0.31 (0.20)</td>
</tr>
<tr>
<td>10</td>
<td>19 (8)</td>
<td>38 (20)</td>
<td>−0.21 (0.35)</td>
<td>−0.57 (0.25)</td>
</tr>
<tr>
<td>25</td>
<td>37 (11)</td>
<td>61 (20)</td>
<td>−1.1 (0.31)</td>
<td>−0.51 (0.21)</td>
</tr>
<tr>
<td>50</td>
<td>54 (12)</td>
<td>76 (17)</td>
<td>−2.2 (0.40)</td>
<td>−0.89 (0.32)</td>
</tr>
<tr>
<td>100</td>
<td>70 (10)</td>
<td>86 (13)</td>
<td>−3.3 (0.50)</td>
<td>−1.7 (0.34)</td>
</tr>
</tbody>
</table>
drug reaction reports on women than on men, but the reason for this gender difference is unknown (6).

An increased evidence-based understanding of gender-specific drug response, not only in treatment of nocturia but in general, will allow the tailoring of pharmacological treatments in both men and women, improving the therapeutic windows for both genders.

In summary, this paper is the first to report a significant gender difference in the PD response of desmopressin on nocturnal urine volume. The findings also support earlier reports regarding the age and gender differences in the antidiuretic duration of action of desmopressin and the incidence of hyponatremia. The mechanism(s) for these gender and age differences is still unidentified, but there are strong indications that the desmopressin sensitivity and/or the expression of the V2R and phenotypes of human mutations of AVPR2 is different in men and women and that these differences are likely regulated by both hormonal and genetic differences. The findings have implications for future gender-differentiated treatment of nocturia but await a final confirmation in phase III studies.

DISCLOSURES
All authors are employees of Ferring Pharmaceutical.

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