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ANTIMUSCARINIC AGENT IMPROVES NOCTURIA WITH REDUCTION IN NOCTURNAL URINE VOLUME

Hypothesis / aims of study

Nocturia has a major impact on quality of life and affects numerous aspects of health.
It is caused by nocturnal polyuria (nocturnal urine overproduction), a diminished nocturnal bladder capacity or a combination of the two conditions. It was reported that an antimuscarinic agent, solifenacin, is effective for storage symptoms and nocturia, but it is not effective for nocturnal polyuria [1]. However, nocturnal polyuria shows a high prevalence. We evaluated the effects of a novel antimuscarinic agent (imidafenacin), which has been marketed in Japan, on nocturnal polyuria in patients with overactive bladder (OAB).

Study design, materials and methods

Stratified analyses were conducted on data from patients in Phase III trial of imidafenacin [2], which was a randomized, double-blind, placebo- and active comparator controlled trial conducted at 158 centers in Japan. The Phase III trial included men and woman aged ≥20 years, who had urinary incontinence (≥5 episodes/week), frequent micturition (≥8 voids/day), and urgency (≥1 episode/day). Patients received imidafenacin oral tablets (0.2 mg) twice daily (Group I) or placebo tablets twice daily (Group P). A total 46 patients (mean age 66.54±9.38 years: 9 males, 37 females) with nocturia and/or nocturnal polyuria (>33% urine production during the night) were selected for the study. The 24-h urinary volume, daytime/nighttime voiding frequency and volume voided/urination were evaluated from consecutive 3 day voiding diaries once every 4 weeks during the 12-week study period. Longitudinal data analysis was performed and all values are expressed as LSMEAN ± SE.

Results

1) In the data set analyzed (Group I: n = 35; Group P: n = 11), no differences were seen at baseline between the groups in terms of the daily voided volume, concurrent diseases such as diabetes mellitus, hypertension, or hyperlipidemia, or age or body weight; however, a difference was seen in terms of the average number of micturitions per day (Group I: 11.22 ± 2.17; Group P: 14.45 ± 2.85). In addition, a longitual data analysis was performed by adding a factor at a 15% significance level to the adjustment factor at baseline (Table).
2) The number of nighttime micturitions was significantly lower in Group I than in Group P.
3) No difference was seen between the groups in terms of the 24-hour production (daytime urine volume plus nighttime urine volume). However, the proportion (%) of the 24-hour production accounted for by the nocturnal urine volume was significantly lower in Group I than in Group P.
4) The time to the first nighttime voiding (HUS; hours of undisturbed sleep) was significantly greater in Group I than in Group P, but no difference was seen between the groups in terms of the first nighttime void volume.
5) The daily average volume per void was significantly higher in Group I than in Group P.

		Baseline	4 weeks	8 weeks	12 weeks	P-value	
24-hour frequency	Imidafenacin	11.82 ± 0.11	10.49 ± 0.22	10.31 ± 0.26	10.24 ± 0.27	p=0.8313	N.S.
	Placebo	12.75 ± 0.26	11.22 ± 0.51	11.10 ± 0.65	11.29 ± 0.53		
Nighttime frequency	Imidafenacin	2.63 ± 0.04	2.05 ± 0.09	1.99 ± 0.12	2.00 ± 0.12	p=0.0292	*
	Placebo	2.89 ± 0.09	2.65 ± 0.28	2.56 ± 0.23	2.84 ± 0.21		
Daytime frequency	Imidafenacin	9.19 ± 0.10	8.44 ± 0.19	8.32 ± 0.20	8.24 ± 0.20	p=0.5643	N.S.
	Placebo	9.87 ± 0.23	8.58 ± 0.43	8.54 ± 0.58	8.46 ± 0.40		
24-hour production	Imidafenacin	1728.60 ± 30.04	1740.89 ± 49.58	1767.50 ± 75.00	1805.17 ± 76.65	p=0.0508	N.S.
	Placebo	1716.25 ± 64.15	1498.92 ± 69.80	1499.44 ± 95.23	1622.25 ± 105.14		
Percentage of Nocturnal urine volume/24-hour production	Imidafenacin	46.18 ± 0.96	38.34 ± 1.49	39.83 ± 1.76	37.04 ± 1.78	p=0.0053	*
	Placebo	44.77 ± 1.25	46.23 ± 2.94	46.47 ± 3.48	47.01 ± 2.34		
Time of the first voiding at night	Imidafenacin	152.77 ± 3.06	200.28 ± 10.57	210.32 ± 10.63	215.19 ± 12.71	p<0.0001	*
	Placebo	158.29 ± 7.17	152.86 ± 12.29	154.66 ± 10.36	145.11 ± 16.06		
First volume voided/void after sleep	Imidafenacin	241.89 ± 16.65	243.18 ± 15.68	243.57 ± 14.14	236.17 ± 16.68	p=0.7928	N.S.
	Placebo	203.27 ± 19.00	194.25 ± 30.20	202.25 ± 28.07	216.92 ± 35.28		
volume voided/void	Imidafenacin	152.05 ± 2.55	175.94 ± 5.83	182.01 ± 6.62	181.35 ± 8.47	p<0.0001	*
	Placebo	149.61 ± 6.23	148.66 ± 7.29	150.47 ± 8.63	153.70 ± 9.62		

Data were adjusted for daytime frequency and nighttime frequency, nighttime urine volume, 24-urinary, production, Time of the first voiding at night, volume void/void at daytime. Longitual data analysis : imidafenacin(n=35) vs. placebo(n=11), P<0.05: *,

Table. Longitual data analysis of chages in frequency and urine volume in patients with nocturnal polyuria.

Interpretation of results

These are the first results that demonstrate the possibility to improve the balance between the nighttime urine volume and daytime urine volume by an anticholinergic agent. Imidafenacin prolonged HUS by suppressing the nighttime urine volume and decreased the number of nighttime micturitions. It has been reported that sleep disorders themselves cause nocturia, and that improvement of sleep disorder not only suppresses nighttime urine production but also results in an improvement in nocturia [3]. As no significant increase was seen in terms of the volume per urination at the first nighttime voiding, it is likely that the improvement in sleep disorders as a result of HUS prolongation by imidafenacin suppressed the nighttime urine volume. Acetylcholine receptors in the pituitary gland mediate the release of vasopressin. The blood-brain barrier (BBB) does not exist in

circumventricular organs (pineal body, pituitary gland, area postrema, etc.). Accordingly, imidafenacin may mediate the release of vasopressin, which will be assessed in the future.

Concluding message

Imidafenacin, a novel antimuscarinic agent, decreases the number of urination and urine production at night, thereby improving not only nocturia but also nocturnal polyuria.

References

1. Int Urogynecol J (2007) 18: 737-741
2. Int J Urol (2009) 16, 499-506
3. J Psychosom Res(2004) 56: 517-525

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Clinicaltrials.gov NCT00212732**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Approved by Independent Ethics Committee and/or Institutional Review Board (IRB) at each participanting center**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**