PAPERS AND SHORT REPORTS

Patterns of urine flow and electrolyte excretion in healthy elderly people

J L KIRKLAND, MICHAEL LYE, D W LEVY, A K BANERJEE

Abstract

Twenty four young (mean age 29·2 years, range 25-35) and 21 elderly (mean age 66·5, range 60-80) healthy subjects collected their urine in timed aliquots over 24 hours. The elderly subjects had been selected for their fitness by clinical and laboratory examinations and all lived independently at home. Sodium and potassium excretions were reduced in the elderly subjects compared with the young subjects, potassium excretion considerably so. This was despite similar 24 hour urine volumes and total solute excretion by both groups.

The ratios of rates of excretion of water, electrolytes, and solutes during the night to the rates of excretion during the day were found to be higher in the elderly than the young subjects.

Reduced day to night ratios of urinary excretion may be partly responsible for complaints of nocturia and sleep disturbance in elderly people.

Introduction

For many years it has been known that urine flow is lower at night than during the day in healthy subjects.[1] There is also an accompanying nocturnal reduction in electrolyte excretion.[2] It has been speculated that reduction in urine flow at night in mammals may have evolved to permit undisturbed sleep.[3]

Several studies of excretory rhythms in old patients have been reported.[4-9] The first study was of patients in psychiatric hospitals[4 5]; the second of elderly patients in hospitals long term[6]; the third of nine patients in hospital, only two of whom were alert enough to collect urine[7 8]; and the fourth of patients with urological disease attending a clinic.[9] These studies indicated a reduction in day to night ratios of urinary excretion in older patients but did not exclude patients who had diseases or were taking drugs known to affect renal rhythms. Additionally, these studies did not allow for patients' sleeping habits, which may affect the outcome of studies of urinary rhythms.[10] Thus the pattern of water and electrolyte excretion in healthy elderly people living at home was not known, so we carried out a study to establish this.

Department of Geriatric Medicine, University Hospital of South Manchester, Manchester M20 8LR

J L KIRKLAND, MD, FRCP(C), research associate
MICHAEL LYE, MD, MRCP, senior lecturer in geriatric medicine

Department of Geriatric Medicine, Bolton General Hospital, Bolton BL4 0JR

D W LEVY, MB, MRCP, consultant physician
A K BANERJEE, MB, FRCP, consultant physician

Correspondence to: Dr M Lye, professor of geriatric medicine, University of Liverpool, Liverpool L69 3BX.

Subjects and methods

We recruited 21 elderly subjects from a voluntary clinic for retired people in Bolton. The intention of the clinic is to give preventive advice, and it does not solicit those who want attention for medical complaints. The subjects' mean age was 66·5 years (range 60 to 80), and 12 were women. Only subjects without evidence of cardiac, renal, endocrine, neurological, psychiatric, or hepatic disease, according to their history and clinical and laboratory examinations, were recruited. None had proteinuria or abnormalities on microscopic examination of the urine, and none admitted to symptomatic nocturia on questioning; none was taking diuretic or antihypertensive agents, digitalis, antidepressants, or steroids, and none took alcohol or any drugs during the study. All subjects were living independently at home.

Twenty four young subjects were recruited as controls from hospital staff and people living locally. Their mean age was 29·2 years (range 25 to 35), and eight were women. None had histories of renal, cardiac, or other serious illnesses, none took drugs, and all abstained from alcohol during the study. Both young and elderly subjects gave their informed consent before they participated in the study.

Each subject was given five numbered plastic containers and oral verbal and written instructions in their use. Subjects collected all urine passed over 24 hours, from 0800. They completed collections at, or near to, 1200, 1600, 2000, 2400, and 0800 the next day. They were instructed to record on a questionnaire the exact times of urine collection and the times of going to bed, going to sleep, waking, and rising in the morning.

To assess compliance with the protocol repeat sets of collections were obtained from 16 of the elderly and 19 of the young subjects at random. The volumes of the original and repeat collections were compared. Additionally, two young subjects each collected urine for 10 consecutive days, and the coefficients of variation in their 24 hour urine volumes were calculated[11] and compared with the coefficients of variation in the 24 hour urine volumes of the young and elderly subjects.

The volume of each sample was measured to within 5 ml, sodium and potassium concentrations were determined in triplicate by flame photometry, creatinine concentration was measured by the Jaffe method, and osmolarities were determined in duplicate by the freezing point depression method. A microprocessor program was developed to determine the area under histograms of excretion rates as a function of time and thus to measure the ratios of water, sodium, potassium, creatinine, and osmolar excretions while subjects were awake to those while they were asleep.[12] This is similar to the approach of Elithorn *et al*,[5] except that the effects of the subjects' sleeping habits were allowed for in our calculations. The distributions of the excretion ratios were compared by the Mann-Whitney U test.[13] Twenty four hour excretions were compared by unpaired two tailed Student's *t* tests.[11] Results are given as means (1 SEM).

Results

Completeness of collections—The differences in the volumes between the first and second collections differed by similar amounts in the young and elderly subjects (0·44 (0·07) l in the young *v* 0·38 (0·06) l in the elderly; t (33) = 0·57; $p > 0·5$). The coefficients of variation in the 24 hour urine volumes of the two young subjects who collected urine for 10 days were 25% and 31%, which compared favourably with the 24% coefficient of variation in the elderly subjects' 24 hour volumes. The mean 24 hour volumes in the young and elderly groups were similar (table I).

Twenty four hour excretion of urinary constituents—Table I summarises the 24 hour excretions of each urinary constituent and the excretions corrected for the subjects' body surface area.[14] The 24 hour volumes and solute excretions of the two groups were similar; the elderly subjects' 24 hour potassium excretion was, however, less than 60% of that of the young subjects. Some of this difference could be accounted for by differences in lean body mass as assessed from calculation of body surface area. Twenty four hour excretions of sodium and creatinine were also lower in the elderly subjects.

Ratios of day to night excretion—Table II shows the ratios of day to night excretion. The average time (calculated trigonometrically) of going to sleep was 0001 in the young and 2347 in the elderly subjects. The duration of sleep was similar in both groups (young 7·25 (0·52) hours, elderly 7·22 (0·39) hours; t (43) = 0·24; $p > 0·5$). Elderly subjects excreted more urine (869 ml) while they were sleeping than while they were awake (783 ml). Young subjects excreted half the amount of urine while they slept (402 ml) as while they were awake (1209 ml). The difference in rates of urine flow and urine excretion ratios between the young and old subjects were all highly significant ($p < 0·001$). The elderly subjects also excreted sodium, potassium, and solutes at a proportionally higher rate at night compared with the young subjects. There was an opposite trend, however, towards a higher day to night ratio of creatinine excretion in the elderly.

TABLE I—*Twenty four hour excretion of urinary constituents by healthy young and elderly subjects (mean (SEM))*

	Flow (ml)	Sodium (mmol)	Potassium (mmol)	Creatinine (mmol)	Solutes (mmol)
	Twenty four hour excretion				
Young	1611 (88)	143 (10)	63 (3)	13·4 (0·7)	810 (40)
Elderly	1652 (87)	104 (7)	36 (4)	10·3 (0·7)	736 (59)
t (43)	0·33	3·27	5·85	2·49	1·04
p	>0·5	<0·01	<0·001	<0·02	>0·1
	*Twenty four hour excretion/m² body surface area**				
Young	905 (54)	80 (5)	35 (2)	7·4 (0·3)	451 (20)
Elderly	978 (52)	62 (4)	24 (2)	6·0 (0·3)	428 (28)
t (43)	0·97	2·81	4·50	3·37	0·68
p	>0·1	<0·01	<0·001	<0·01	>0·5

*Body surface areas calculated by method of Dubois and Dubois.[14]
Conversion: SI to traditional units—Sodium and potassium: 1 mmol = 1 mEq. Creatinine: 1 mmol ≈ 113 mg. Solutes: 1 mmol = 1 mosmol.

TABLE II—*Ratios of rates of excretion while awake to those during sleep*

	Flow	Sodium	Potassium	Creatinine	Solutes
Young:					
Median	2·07	1·78	2·37	1·06	1·42
Range:	0·50-5·26	0·56-9·23	0·73-6·38	0·66-2·60	0·55-4·45
Elderly:					
Median	1·08	1·24	1·60	1·17	1·27
Range	0·47-3·42	0·46-2·57	0·87-5·16	0·80-2·98	0·67-1·90
Mann-Whitney U test	99	130	164	170·5	153·5
p	<0·001	<0·01	<0·05	<0·1	<0·05

Discussion

Up to 70% of elderly people who live at home have nocturia,[15] and 40% micturate twice or more nightly.[16] From 21 to 43% of elderly people complain of nocturnal awakenings.[17 18] Some of these nocturnal awakenings have been ascribed to the need to pass urine.[17 19] It appears from our results that the nocturia and disturbed sleep associated with old age are occasioned, in part, by an increase in the proportion of urine old people excrete at night.

Our observation that healthy elderly people taking a normal diet excrete a higher proportion of their urinary water, sodium, potassium, and solute output at night than young people accords with previous reports of reduced day to night ratios of excretion in elderly patients in hospitals.[4-8] The reduced day to night ratios of excretion in our elderly subjects may have been caused by a delay in peak water and electrolyte excretion, greater variability in the timing of these peaks, or a reduction in the amplitudes of each of the subject's rhythms.

The elderly subjects appeared to comply with the experimental protocol as precisely as the young subjects, and differences between the groups in the completeness of their collections are unlikely to have influenced the outcome. The two groups had similar 24 hour urine volumes and total solute excretions; these factors are, therefore, unlikely to have produced a difference in the amplitudes of urinary rhythms in either of the groups. The elderly subjects excreted considerably less potassium and sodium than the young subjects, possibly indicating dietary differences that may have influenced the amplitudes of the rhythms of excretion of these constituents. Judge *et al* also found a reduced total 24 hour potassium excretion in older subjects.[20]

The reduction of glomerular filtration rate with aging,[21 22] changes in renal tubular function,[23] altered cardiac function, or undetected disease may have been responsible for the observed age related changes in day to night ratios of excretion. Possibly alterations with age in the function of the hypothalamic suprachiasmatic nucleuses, which are reported to control circadian rhythms,[24-26] or changes in the hormonal and neurological systems that mediate the effects of these nucleuses on fluid balance may have accounted for our findings. Changes in the period of circadian rhythms with age have been observed in rodents,[27] and age related alterations in the coordination between various rhythms within subjects have been described in man.[28] Further studies to investigate these possibilities are under way.

We acknowledge the help of Mrs G Poole, who collected many of the specimens from the subjects' homes and helped in other ways. Dr E Gerber helped in examining the elderly subjects. JLK is a recipient of an Ontario Gerontological Association fellowship.

References

1 Roberts W. Observations on some of the daily changes of the urine. *Edinburgh Medical Journal* 1859;**5**:817-906.
2 Norn M. Ueber Schwankungen der Kalium-, Natrium- und Chloridausscheidung durch die Niere im Laufe des Tages. *Skandinavisches Archiv fur Physiologie* 1929;**55**:184-210.
3 Minors DS, Waterhouse JM. *Circadian rhythms and the human*. Bristol: Wright, 1981:182.
4 Lobban MC, Tredre BE, Elithorn A, Bridges A. Diurnal rhythms of electrolyte excretion in depressive illness. *Nature* 1963;**199**:667-9.
5 Elithorn A, Bridges PK, Lobban MC, Tredre BE. Observations on some diurnal rhythms in depressive illness. *Br Med J* 1966;ii:1620-3.
6 Lobban MC, Tredre BE. Diurnal rhythms of renal excretion and of body temperature in aged subjects. *J Physiol* 1967;**189**:32-3P.
7 Scheving LE, Roig C, Halberg F, Pauli JE, Hand EA. Circadian variations in residents of a "senior citizens'" home. In: Scheving LE, Halberg F, Pauli JE, eds. *Chronobiology*. Tokyo: Igaku Shoin, 1974;353-7.
8 Scheving LE, Pauli JE, Tsai TH. Significance of the chronobiological

approach in carrying out aging studies. In: Samis HV, Capobianco S, eds. *Aging and biological rhythms*. New York: Plenum, 1978:57-96.
[9] George NJR, Barnard RJ, Blacklock NJ. Frequency volume charts revealing physiological abnormalities. In: Sundin T, Mattiasson A, eds. *Proceedings of the eleventh annual meeting of the international continence society*. Lund: Skogs Trelleborg, 1981:67-8.
[10] Aschoff J, Wever R. Human circadian rhythms: a multi-oscillatory system. *Fed Proc* 1976;**35**:2326-32.
[11] Spiegel MR. *Theory and problems of statistics*. New York: McGraw-Hill, 1961;73.
[12] Kirkland JL. *The effect of ageing on urinary circadian rhythms*. Manchester: University of Manchester, 1982. MSc thesis.
[13] Siegel M. *Nonparametric statistics for the behavioural sciences*. New York: McGraw-Hill, 1956:116-27.
[14] Dubois D, Dubois EF. A formula to estimate the approximate surface area if height and length are known. *Arch Intern Med* 1916;**17**:863-71.
[15] Brocklehurst JC, Dillane JB, Griffiths L, *et al*. The prevalence and symptomatology of urinary infection in an aged population. *Geront Clin* 1968;**10**:242-53.
[16] Sourander LB. Urinary tract infection in the aged. An epidemiological study. *Annales Medicinae Internae Fenniae* 1966;**55**, suppl 45:1-55.
[17] Hobson W, Pemberton J. *The health of the elderly at home*. London: Butterworths, 1955:79-80.
[18] McGhie A, Russell SM. The subjective assessment of normal sleep patterns. *J Ment Sci* 1962;**108**:642-54.
[19] Webb WB, Swinberne H. An observational study of sleep of the aged. *Percept Mot Skills* 1971;**32**:895-8.
[20] Judge TG, Caird FI, Leask RGS, MacLeod CC. Dietary intake and urinary excretion of potassium in the elderly. *Age Ageing* 1974;**3**:167-73.
[21] Lewis WH, Alving AS. Changes with age in the renal function of adult men. *Am J Physiol* 1938;**123**:500-15.
[22] Rowe JW, Andres R, Tobin JD, Norri AH, Shock NW. Age-adjusted standards for creatinine clearance. *Ann Intern Med* 1976;**84**:567-9.
[23] Dontas AS, Marketos SG, Papanayiatou P. Mechanisms of renal tubular defects in old age. *Postgrad Med J* 1972;**48**:295-303.
[24] Richter CP. *Biological clocks in medicine and biology*. Springfield: Thomas, 1965:21.
[25] Moore RY, Eichler VB. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Res* 1972;**42**:201-6.
[26] Stephan FK, Zuker I. Rat drinking rhythms: central visual pathways and endocrine factors mediating responsiveness to environmental illumination. *Physiol Behav* 1972;**8**:315-26.
[27] Pittendrigh CS, Daan S. Circadian oscillations in rodents: a systematic increase of their frequency with age. *Science* 1974;**186**:548-50.
[28] Wever RA. *The circadian system of man*. New York: Springer-Verlag, 1979:80-1.

(*Accepted 14 September 1983*)

Intranasal treatment with luteinising hormone releasing hormone agonist in women with endometriosis

R W SHAW, H M FRASER, H BOYLE

Abstract

An agonist analogue of luteinising hormone releasing hormone (buserelin) was successfully used to treat women with endometriosis. A dose of 200 μg administered intranasally thrice daily was found to be effective in five patients, in whom the endometriotic lesions resolved after six months' treatment. Failure occurred in a sixth patient, who received only 400 μg once daily. Anovulation was induced in all subjects together with suppression of menstruation after the first month of treatment. Symptoms of abdominal pain, dysmenorrhoea, and dyspareunia were relieved during treatment, and one previously infertile patient conceived within two months of stopping treatment.

No side effects were reported with this dosage, and the results suggest a new form of treatment for patients with endometriosis.

Introduction

Endometriosis presents many problems with regard to aetiology, diagnosis, treatment, and management. Medical management of endometriosis has undergone important evolution during the past four decades, from the initial approaches of high dose diethylstilboestrol treatment[1] and progestin only and pseudopregnancy regimens[2] to the more recent use of the antigonadotrophic agent danazol.[3 4] These treatments are often effective, but considerable numbers of patients experience side effects severe enough to cause treatment to be stopped.

During the past few years long term studies of the effects of chronic treatment with agonist analogues of luteinising hormone releasing hormone in women and primates have shown that the pituitary cells secreting gonadotrophin become insensitive to stimulation by endogenous luteinising hormone releasing hormone with resultant suppression of ovarian secretion of steroid and anovulation.[5-8] We report the results of a six month trial of the effect of such treatment on six patients with endometriosis and describe their hormonal and symptomatic response to treatment.

Patients and methods

The six patients studied were recruited from the infertility and gynaecology clinics of one of us. Endometriosis was diagnosed at laparoscopy or laparotomy in all patients while they were undergoing investigation for infertility or abdominal or pelvic pain. The format of the study was explained to each patient, and after giving their informed consent they were entered into the trial, which had been approved by the hospital ethical committee.

The first complete menstrual cycle after diagnosis served as a control cycle, during which no treatment was given but early morning urine samples were collected three times a week. On the second day of their next menstrual period the patients started treatment with the luteinising hormone releasing hormone agonist buserelin (D-ser (but)[6] desgly[10]—luteinising hormone releasing hormone ethylamide) (Hoechst Pharmaceuticals). This was administered intranasally with a spray giving a measured dose of 100 μg. One patients (case 1) received 400 μg buserelin once daily; the five other patients received 200 μg buserelin intranasally three times daily.

Treatment was continued for 26-28 weeks except in the patient taking the analogue once daily, in whom it was stopped after 13 weeks (see below). At the end of this period laparoscopy was performed to assess the response to treatment and an endometrial biopsy specimen was taken. Buserelin was then stopped, and the patients were monitored until their first menstrual period.

Throughout the study the patients collected early morning urine

Centre for Reproductive Biology, Edinburgh EH3 9EW
R W SHAW, MD, FRCS, senior lecturer, department of obstetrics and gynaecology
H M FRASER, PHD, research scientist, Medical Research Council reproductive biology unit
H BOYLE, HNC, chief technician, National Health Service reproductive endocrine laboratory

Correspondence to: Professor R W Shaw, Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, London NW3 2QG.