Urol Res (2003) 31: 25–31
DOI 10.1007/s00240-003-0296-3

ORIGINAL PAPER

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The effect of the somatostatin analogue lanreotide on the prevention of urethral strictures in a rabbit model

Received: 22 March 2002 / Accepted: 18 December 2002 / Published online: 8 February 2003

Abstract We evaluated the effect of the somatostatin analogue lanreotide on the development of surgically induced experimental strictures in the anterior urethra of the male rabbit. A total of 74 male rabbits were randomly allocated into four groups. Lanreotide was administered to the rabbits in groups 2 and 4 from day 0 to 14. To create a stricture, a resection was made in the urethra of the rabbits in groups 3 and 4 on day 2. On day 30, all rabbits were examined with urethrography, impedance planimetry and either histology or for collagen content. Urethrography and impedance planimetry demonstrated a urethral stricture in all operated animals. No difference was found between the two stricture groups, regardless of lanreotide administration, with respect to luminal cross-sectional area (CSA), circumferential tension-strain relation, histology or collagen content. The CSA of the urethra of the normal controls treated with lanreotide was smaller than the CSA of the normal controls not treated with lanreotide, however, no difference was found in histology or collagen content. Lanreotide had no measurable effect on the development of a surgically induced stricture in the male rabbit anterior urethra, however, lanreotide seems to exert an inhibitory effect on the normal growth of the urethra.

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Keywords Urethral stricture · Somatostatin · Lanreotide · Histology · Collagen · Animal

Introduction

Urethral strictures (US) are frequently encountered, especially in males [21]. More than 50% of US are iatrogenic, usually induced by instrumentation of the urethra or by an indwelling catheter. Treatment of US is unrewarding as they often recur. Direct vision internal urethrotomy is a simple and, initially, an effective treatment associated with few complications, but 50% of the strictures recur within the first year [1, 15, 16]. Better results are obtained with open urethroplasty, which is, however, a major operation associated with a high complication rate. Furthermore, the operation is time-consuming and requires surgical expertise [16]. It is an appealing thought to combine the simple internal urethrotomy with some kind of adjuvant drug therapy to decrease the recurrence rate. The regenerative process initiated by a trauma to the urethra involves a large number of growth factors and cell types. Inhibition or enhancement of either one of the growth factors or one of the cell types will probably influence the healing process. However, the end point of the process is a scar consisting mainly of dense collagen [4, 5, 27] which in all probability has been synthesized by smooth muscle cells. A drug capable of reducing the production of collagen after an internal urethrotomy may reduce the amount of scar tissue and thereby prevent or attenuate the recurrence of the stricture. Lanreotide (Angiopeptin, IPSEN International, London, England), a synthetic octapeptide analogue of somatostatin, is a candidate for this purpose. Lanreotide has been shown to reduce proliferation of smooth muscle cells, and thereby myointimal thickening, after balloon injury of the aorta in rabbits [7, 10, 17, 18] and the coronary arteries in pigs [26] as well as in humans [9].

An animal model of US was developed in our laboratory [3]. The purpose of the present study was to evaluate the possible effect of lanreotide on the prevention of the development of strictures in the model.

Material and methods

A total of 74 male, Danish white land-race rabbits were randomly allocated into four groups. Lanreotide was administered to the rabbits in groups 2 and 4 using a subcutaneous osmotic pump inserted on day 0 and removed on day 14. On day 2 a resection was made in the urethra of the rabbits in groups 3 and 4 to create a stricture. On day 30 all rabbits were examined with urethrography, impedance planimetry and either histology or by the determination of collagen content. Group 1 contained normal controls, group 2 normal rabbits treated with lanreotide, group 3 stricture rabbits and group 4 stricture rabbits treated with lanreotide. A flow chart of the study as well as the age and weight of the animals are given in Table 1.

The study complied with the Danish regulations for care and use of laboratory animals.

Procedures

All procedures were performed on anaesthetized rabbits. Anaesthesia was induced by premedication with i.m. fentanyl citrate 0.055 mg/kg and fluanisone 1.75 mg/kg (Hypnorm, Janssen-Cilag, Beerse, Belgium) and midazolam 1.25 mg/kg (Dormicum, Roche, Basel, Switzerland) and maintained with i.m. fentanyl citrate 0.032 mg/kg and fluanisone 1 mg/kg and i.v. midazolam 0.625 mg/kg every 20–30 min.

Administration of lanreotide

The rabbits in groups 2 and 4 received lanreotide 20 μg/kg/24 h delivered continuously from day 0 to day 14 by an Alzet osmotic pump, model 2ML2 (ALZA Corporation, Palo Alto, Calif.). The pump delivers a constant volume from 4 h after it is filled, and until 95% of the reservoir contents are delivered after 14 days. The rabbits were weighed and the pumps filled with lanreotide in a concentration ensuring delivery of the correct amount of drug for each rabbit. On premedicated animals, 2 ml of a local anaesthetic, lignocaine (Xylocain, Astra, Södertälje, Sweden) 10 mg/ml, was applied on the left thigh. Under sterile conditions, a subcutaneous pouch was made and the pump inserted. The pump was removed from the pouch on day 14.

Blood samples were taken from two rabbits not included in the study 1, 2, 3, 6, 9 and 14 days after insertion of the pump. The serum concentration of lanreotide, determined by radioimmunoassay [24, 33], was 2,763 ± 275 pg/ml. In all samples, the serum concentration was well over the usually accepted therapeutic level for treatment of patients with acromegaly. Moreover, blood samples were taken from 18 rabbits randomly selected from groups 2, 3 and 4 on days 2 or 14. Six samples from untreated rabbits in group 3 were all negative. The serum concentration of lanreotide in the samples from the rabbits treated with lanreotide in groups 2 and 4 was 3,210 ± 313 pg/ml.

Production of urethral strictures

To produce a US in the urethra of the rabbits in groups 3 and 4, a 2–3 mm wide resection was made at the transition from the spongious to the bulbous part of urethra from 2 to 10 o'clock using the electrical sling in a paediatric resectoscope Ch 13. The periurethral tissue was exposed in order to allow urine to leak from the lumen. I.v. ampicillin 300 mg (Anhypen, Yamanouchi Pharma, Leidersdorp, Holland) was administered before and after the resection and an additional 300 mg was administered twice daily i.m. for 2 days after the operation.

Urethrography

To visualize the lumen and the possible presence of a stricture in the urethra, a retrograde urethrography was performed. The tip of a 5 F catheter was passed through the external urethral orifice and under X-ray supervision contrast (Urografin, Schering, Berlin, Germany) was injected into urethra (Fig. 1). Two distension sites in the anterior urethra for the biomechanical investigation were defined from the urethrography: the distal site at the transition from the spongious to the bulbous part of urethra, the location of the resection in the resection group, and the proximal site 1 cm further up in the bulbous urethra.

Impedance planimetry

The principles of measurement of the luminal cross-sectional area (CSA) using impedance planimetry have been described in detail elsewhere [6, 11, 14]. The probe for the biomechanical measurement, validation data for the system as well as the procedure used have been described previously [3]. In short, a four electrode impedance measuring system located inside a balloon on a 7 F probe was constructed for the measurement of CSA according to the field-gradient principle. The electrodes were connected to an impedance planimeter (GateHouse, Nørresundby, Denmark). Through the lumen of the probe, the balloon was connected to a level container with a 0.09% saline solution. Under X-ray supervision, the probe was placed in the urethra with one detection electrode on each side of the distal dis-

Table 1 Flow chart indicating the number of rabbits in the four groups completing the study. The age in days and the weight in kg are given (mean ± SEM)

Group	*n*	Day 0	Day 2	Day 14	Day 30
1: Normal controls	16				Evaluation Age 236 ± 1.2 Weight 4.2 ± 0.1
2: Normal controls receiving lanreotid	16	Insertion ofpump Age 204 ± 0.2 Weight 3.9 ± 0.1		Removal of pump	Evaluation Age 234 ± 0.6 Weight 4.0 ± 0.1
3: Resected rabbits	14	Age 206 ± 0.1 Weight 4.1 ± 0.1	Resection		Evaluation Age 235 ± 0.9 Weight 4.1 ± 0.1
4: Resected rabbits receiving lanreotid	17	Insertion ofpump Age 206 ± 0.2 Weight 3.8 ± 0.1	Resection	Removal of pump	Evaluation Age 235 ± 0.5 Weight 3.9 ± 0.1

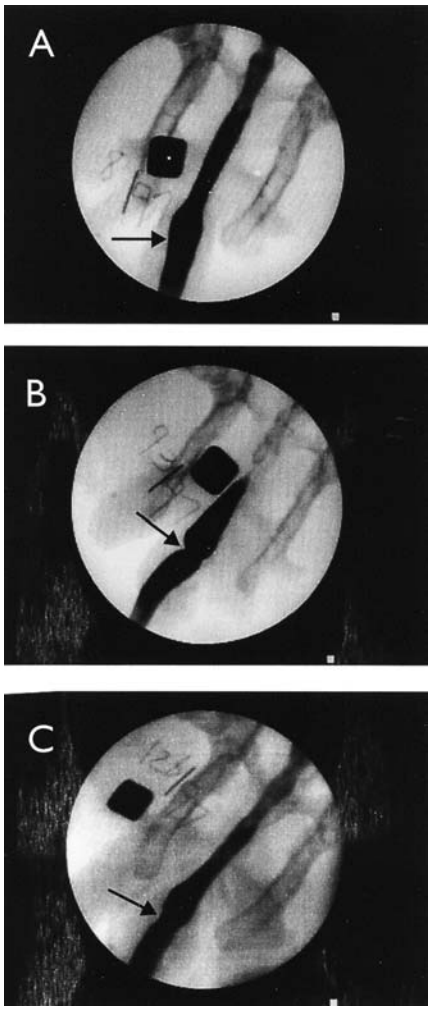

Fig. 1 **A** Urethrography of the normal male rabbit urethra. The passage from the spongious to the bulbous part of urethra is marked with an *arrow*. **B, C** Urethrography of induced strictures. The configuration of the strictures was either a short constriction of the lumen (**B**, *arrow*) or a wider area with unyielding walls (**C**, *arrow*). The *square* is 1 cm^2

tension site. The tissue was preconditioned by increasing and decreasing the pressure in the balloon in steps every 1.5 min (0, 1, 2.5, 4, 5 kPa) twice. In the third series of pressure increase, steady state CSA was awaited at each pressure step (0, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5 kPa). Related values of steady state CSA and pressure were registered. The balloon was emptied, the probe moved to the proximal distension site and the same preconditioning and measurement procedure carried out.

After the biomechanical investigation, the animals were killed by i.v. pentobarbital 200 mg (Mebumal, Nycomed DAK, Roskilde, Denmark) and the urethras removed.

Histology

The urethras from three rabbits in groups 1, 2 and 4 and four rabbits in group 3 were randomly selected and processed for histology. The procedure has been described previously [3]. Briefly, formaldehyde was injected into the urethra at a pressure of 1.8 kPa for 30 min. The urethra was removed, further fixed in formaldehyde for 24 h and then embedded in paraffin. Sections were cut, corresponding to the two distension sites, longitudinally from the posterior wall of the urethra and perpendicularly to the wall, and stained with Sirius red.

Analysis of collagen content

The urethras from 13 rabbits from groups 1 and 2, ten from group 3 and 14 from group 4, were processed for the analysis of collagen content. The tissue from the two distension sites in the urethra was separated, chopped, defatted in two parts chloroform and one part methanol for 24 h and freeze-dried. The hydroxyproline content was determined by the method of Stegeman and Stalder [29]. The total collagen concentration was estimated and expressed as μg/mg of dry, defatted tissue.

Data analysis

Impedance planimetry

The steady state CSA values at each distension step were analyzed in relation to the distension pressure. The values were used for the computation of circumferential wall tension and circumferential strain [12]. The calculations used and the assumptions for the use of the calculations have been described previously [3]. Briefly, the circumferential wall tension was calculated according to the law of Laplace for cylindrical, thin walled structures:

$$T = rP_{tm} \tag{1}$$

where r is the luminal radius calculated as the square-root of $(CSA\pi^{-1})$ assuming a circular shape of the urethra during distension. P_{tm} is the transmural pressure which is equal to the pressure inside the balloon due to the initial determination of the zero-pressure level. The law of Laplace for cylindrical structures was used since the urethra is, by nature, a tubular organ and the balloon length was considerably longer than the measured radii in the circumferential direction.

The circumferential strain was defined as:

$$\varepsilon = \frac{r - r_0}{r_0} \tag{2}$$

where r is the luminal radius. r_0 is the reference radius determined in the following way: the circumferential tension was plotted against the radius for all pressure steps then the smallest tension, T_0, common for all measurements was found and the corresponding radius, r_0, was found by linear interpolation of the first part of the curves.

Statistical methods

The results are expressed as mean ± SEM unless otherwise stated. The data distribution was tested by inspection of probability plots and Bartlett's test for variance homogeneity. To obtain homogeneity of variance, the natural logarithms of the CSA values were used. Only those parts of the pressure-CSA plots showing homogeneity of variance were tested using two-way analysis of variance. In case of differences between the groups, a Tukey test was used to determine which group differed. In order to compare the circumferential wall tension-strain distributions, the tension-strain plots were fitted to the equation $T = a\exp(b\varepsilon)$ (Table Curve 1.12, Jandel Scientific, Germany). The a and b constants were used for statistical comparisons. The constants is and the content of collagen were tested within groups using a paired *t*-test in the case of normally distribution of data, otherwise a Wilcoxon signed-rank test was used. Between groups, a one way analysis of variance or Kruskal-Wallis one way analysis of variance by ranks was used followed by Dunn's method of multiple comparison in case of differences between the groups. The results were considered significant if $P < 0.05$.

Results

It was planned to evaluate 18 rabbits in each group but because of technical problems with the X-ray and the impedance planimetry equipment only 16 rabbits in group 1, 16 in group 2, 14 in group 3 and 17 in group 4 were fully studied. In addition, 11 rabbits died before they were evaluated: one rabbit in group 4 died 5 days after the resection due to urinary retention and infection. Three rabbits had to be killed during the follow-up period as they failed to thrive: one in group 2 (day 25), one in group 3 (day 10) and one in group 4 (day 16). Two rabbits in group 2 died with diarrhoea on days 7 and 9, respectively, and five rabbits died during anaesthesia.

Urethrography

In all rabbits in groups 1 and 2, the urethrography displayed normal urethras (Fig. 1A). The passage from the spongious to the bulbous part of the urethra was easily identified. A stricture was seen in all rabbits in groups 3 and 4. The configuration of the stricture was most often a short constriction of the lumen (Fig. 1B) but in a few animals a wider area with unyielding walls was seen (Fig. 1C).

Impedance planimetry

In two rabbits, one in group 3 and one in group 4, the stricture was too tight for the passage of the probe for biomechanical measurement. Accordingly, these rabbits were omitted from the analysis. The relation between the increasing distension pressure and steady-state CSA was non-linear at both distension sites in all four groups (Fig. 2A). The CSA of group 1 for the pressure steps 1.5–5 kPa was significantly larger at both distension sites than the CSA of the three other groups ($P < 0.05$ both distally and proximally). At the distal distension site, the CSA of group 2 for all pressure levels was larger than the CSA of groups 3 and 4 ($P < 0.05$), whereas no difference in CSA was found between these two groups ($P > 0.05$). At the proximal distension site for all pressure levels no difference in CSA was found between groups 2, 3 and 4 ($P > 0.05$). In all four groups, the CSA of the proximal distension site for all pressure levels was significantly larger than the CSA of the distal site ($P < 0.05$, all four groups).

The circumferential wall tension-strain distribution showed an exponential relation (Fig. 2B). Applying the function $T = a\exp(b\varepsilon)$ gave determination coefficients of 0.99 (median, range 0.82–1.0). No difference in determination coefficients was found between the four groups ($P > 0.05$). No difference between the four groups in a- or b-values was found either distally or proximally ($P > 0.1$ for a-values both distally and proximally, $P > 0.2$ for b-values distally and $P > 0.3$ proximally). However, at both distension sites the tension-strain relation of group 1 was shifted to the right of the three other groups. Choosing a value of tension at the uppermost parts of the tension-strain plots (distally 15 kPamm and proximally 25 kPamm) the corresponding value of strain for group 1 was significantly larger at the distal distension site than the strain for groups 2, 3 and 4 ($P < 0.05$), whereas no difference was found between these three groups ($P > 0.05$). At the proximal distension site, the strain of group 1 was significantly larger than the strain of groups 3 and 4 ($P < 0.05$). No difference in strain was found between groups 1 and 2 or between groups 2, 3 and 4 ($P > 0.05$). In none of the four groups was a difference in a- or b-values found between the distal and the proximal distension site ($P > 0.1$, all four groups, both a- and b-values). However, in all four groups the proximal tension-strain relation was shifted to the right of the distal relation and the strain value corresponding to a tension of 15 kPamm was significantly larger proximally than distally ($P < 0.05$, all four groups).

Histology

The epithelium at the distal distension site of groups 1 and 2 was in most places abraded and, when present, difficult to identify, but did in some areas resemble transitional epithelium. A thin layer of dense collagen separated the epithelium and a layer of loosely woven collagen. In this network, especially near the lumen, collagen fibres forming longitudinally wavy lines were found. Some separation of the fibres was seen, suggesting oedema of the urethral wall. Small thin-walled vessels and longitudinally orientated smooth muscle cells were interspersed in the collagen network. Near the lumen, a few plasma cells and leucocytes were found. Extravasation in the wall was not pronounced but some erythrocytes were found between the fibres. The deeper part of the wall consisted of a dense collagen network with numerous large thin-walled cavernous blood vessels. A few smooth muscle cells were scattered in the network.

The epithelium at the distal distension site of groups 3 and 4 was also abraded in most places and difficult to identify. However, when present it resembled squamous epithelium in the strictures and transitional epithelium in the adjacent normal parts of the urethra. The strictures consisted of dense collagen forming mainly longitudinal, coarse, wavy lines. Tongues of dense collagen projected into the adjacent normal parts of the urethra. Only a few smooth muscle cells were seen embedded in the collagen, especially in the deepest parts of the wall, but an increasing number was found towards the normal parts of the urethra. A few small, thin-walled vessels were embedded in the collagen near the lumen. In the deepest parts of the wall, the collagen became even denser and a few thin-walled cavernous blood vessels were seen. Neither acute nor chronic inflammatory cells were found. Separation of the collagen fibres, but not extravasation, was present in the most luminal parts of the wall but was not as

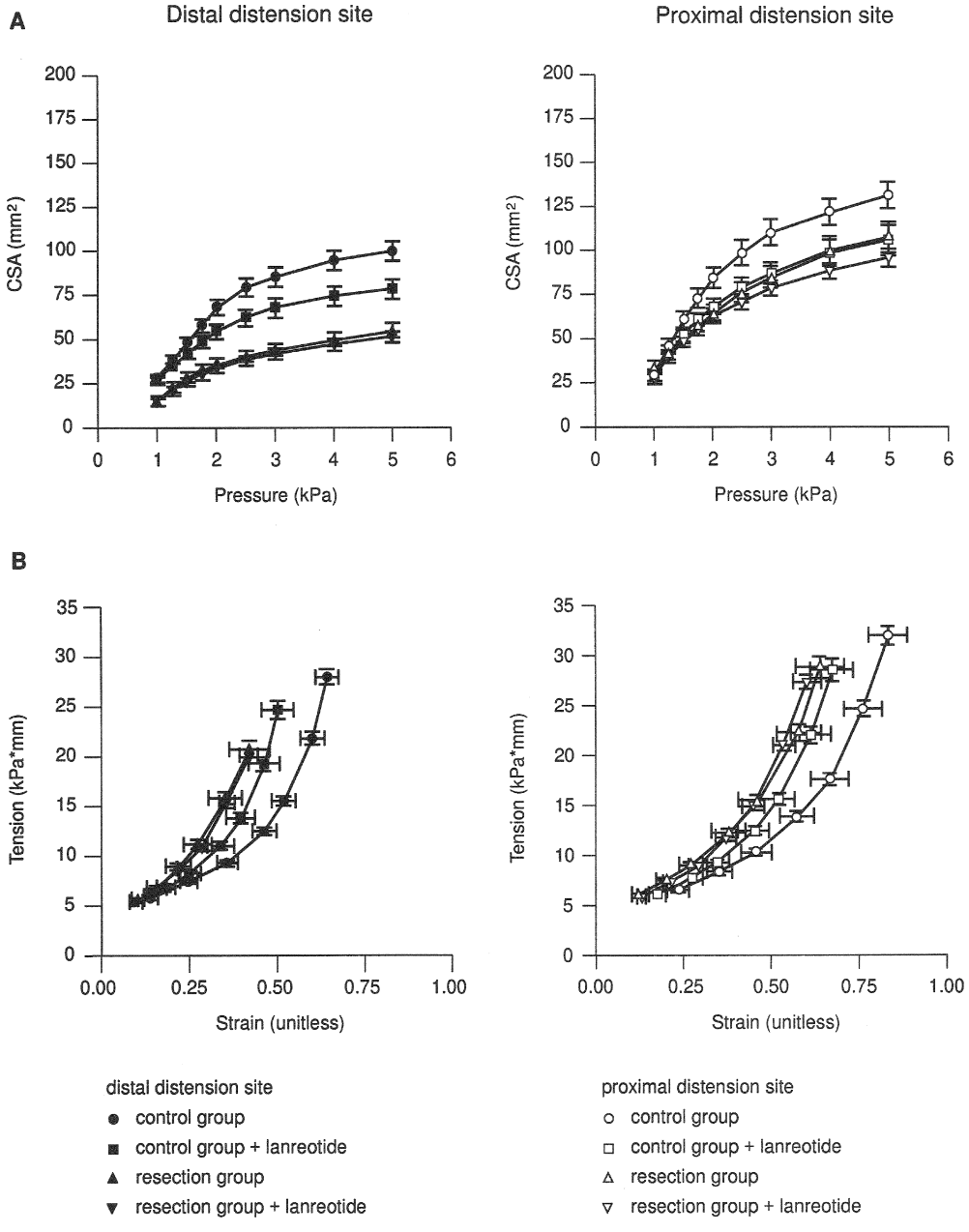

Fig. 2 **A** Pressure-CSA and **B** circumferential tension-strain relation for the distal and proximal distension sites. Mean ± SEM for 16 rabbits in groups 1, 2 and 4 and 13 rabbits in group 3

pronounced as in the urethras of groups 1 and 2. In the adjacent normal parts of the wall both separation of the collagen fibres and extravasation were seen.

The wall was thinner in the bulbous than in the spongio-bulbous region in all four groups. At the proximal distension site, the wall was lined with transitional epithelium on a thin layer of dense collagen. Beneath this, the collagen formed a network which became denser in the deeper part of the wall. Longitudinal wavy lines of collagen fibres were found in the network. The lines were coarser here than distally. Near the lumen, only a few smooth muscle cells were seen, whereas in the deeper parts of the wall an increasing number was found. Small and larger thin-walled vessels were distributed in the network. Near the lumen, a few plasma cells and leucocytes were found. Separation of the collagen fibres and extravasation in the wall were present but not as pronounced as distally. The wall was surrounded with striated muscles which formed an inner layer with mainly longitudinally orientated fibres and an outer layer with oblique fibres.

Collagen content

The collagen content is given in Table 2. No differences were found between the four groups at either the distal or the proximal distension sites ($P > 0.6$ distally and $P > 0.1$ proximally). In all four groups the collagen content of the distal distension site was significantly higher than at the proximal site (group 1 $P < 0.05$, group 2, 3 and 4 $P < 0.001$).

Discussion

In this study, we evaluated a possible effect of lanreotide on the development of a surgically induced stricture in the male rabbit anterior urethra. Lanreotide had no effect on neither the CSA, the circumferential tension-strain relation or on the histology of the strictures. However, in the normal rabbits the size of the urethra was smaller in those treated with lanreotide than those not treated with lanreotide.

Lanreotide is a synthetic octapeptide analogue of somatostatin with a plasma half life of about 2 h. It inhibits myointimal thickening and smooth muscle cell proliferation after balloon induced endothelial injury of the aorta and its large branches in the rabbit [7, 10, 18]. To be effective, lanreotide treatment must be started at the time of injury and continued for at least 1 day after the injury [10]. Its mechanism of action is unknown but might be due to an early inhibition of the accumulation of insulin-like growth factor 1 in the damaged tissue [17]. In pig coronary arteries, lanreotide inhibits intimal hyperplasia after overstretch-balloon injury [26]. Actually the inhibition was so complete that in some of the animals an unrepaired adventitial crater was found 14 days after the injury. In humans, subcutaneous nfusions of lanreotide reduce restenosis after percutaneous transluminal coronary artery balloon angioplasty [9]. The mechanism of restenosis is not known but smooth muscle cell proliferation is probably of importance [18]. Both lanreotide and octreotide, another somatostatin analogue, have anti-inflammatory effects in a rat model of acute, sterile inflammation: both volume and leukocyte concentration of the inflammatory exudate were reduced in the lanreotide and octreotide treated animals [20].

The anti-inflammatory and the antiproliferative effect of lanreotide led us to evaluate the effect of the drug on the development of US in an animal model. The pathogenesis of iatrogenic US is not fully clarified [8, 13, 19, 23, 25, 30, 31, 32]. Trauma is undoubtedly a significant factor. Lesion of the epithelial lining of the urethra, and possibly even the deeper parts of the wall, permits urine to leak into the urethral wall. This leads to an inflammatory reaction, scar formation and subsequently, if the reaction is severe enough, to a stricture. The development of a stricture can thus be regarded as a potentially beneficial, reparative process initiated by the trauma going astray. A US consists of dense, collagenous connective tissue [5, 27, 28]. As with arteries [18], smooth muscle cells are in all probability responsible for the formation of this connective tissue. Lanreotide was expected to attenuate the reparative process initiated by the resection and thereby prevent the production of a stricture or at least make the stricture less severe. However, neither the biomechanical parameters, CSA and the tension-strain relation, nor the histology or the amount of collagen in the tissue showed any differences between the two resection groups. The reason that lanreotide inhibits smooth muscle cell proliferation in the intima of the rabbit aorta but not in the urethra could be the presence of different somatostatin receptor subtypes on smooth muscle cells in the two organs. Lanreotide was shown to exert a different effect on two different somatostatin receptor subtypes in an in vitro model of cell proliferation [2]. Another explanation could be that the trauma induced in the urethra in this study was very pronounced and therefore initiates a proportionally extensive regenerative process involving a large number of mechanisms, resulting in scar formation and the development of a stricture. A possible inhibitory effect of lanreotide on smooth muscle cell proliferation might be overwhelmed in this process. A smaller trauma to the urethra resulting in a less extensive regenerative process might have allowed an effect of lanreotide to be disclosed. However, as smaller injuries to the urethra will not always result in a stricture [22], a beneficial effect of lanreotide, or any other drug, may be difficult to demonstrate.

Surprisingly, at the distal distension site, the CSA of group 2, the normal controls receiving lanreotide, was significantly smaller than the CSA of group 1, the normal controls not receiving lanreotide, but larger than the CSA of the two resection groups. Furthermore, the tension-strain relation of group 2 was shifted to the left of group 1. No difference in histology or collagen content could be demonstrated. We previously found a positive correlation between the CSA at the distal distension site at the maximal applied pressure and the age and weight of the animals [3]. That is, the size of the urethra increases as the rabbits grow older and heavier. It might be that, in the absence of a trauma, lanreotide exerts an inhibitory effect on the normal growth of the urethra.

The animal model of US used in this study provided the consistent development of a stricture: as demonstrated in the urethrography and substantiated by the biomechanical investigation all animals in the two resection groups developed a stricture. The circumferential wall tension-strain relation of the two resection groups was shifted to the left of the normal controls. This demonstrates that not only is the CSA of the strictures smaller than the CSA of the normal urethras, but that the tissue is also more rigid. The histological sections showed that the normal structure of the urethral wall was replaced by dense collagen and that the most abundant component of both the normal and the strictured urethra was collagen. It is reason-

Table 2 Collagen content of the distal and the proximal distension site. Micrograms collagen per mg of dry, defatted tissue. There were no significant differences between the four groups within either the distal or proximal sites. The collagen content of the proximal site was significantly smaller than the content of the distal site in all four groups

	Collagen content (μg/mg)	
	Distal distension site	Proximal distension site
Group 1	823 ± 94	486 ± 85
Group 2	872 ± 61	505 ± 35
Group 3	792 ± 64	337 ± 54
Group 4	770 ± 38	409 ± 34

able to believe that collagen determines the shape of the tension-strain relations. As no difference in the content of collagen was found between the four groups, the shift to the left of the tension-strain relations of the two resection groups must be a consequence of the change in the architecture of the urethral wall, the dense collagen in the strictures being less yielding than the loosely woven collagen in the normal wall.

In conclusion, lanreotide had no effect on the development of a surgically induced stricture in the male rabbit anterior urethra. The animal model of US used was very efficient, all resected animals developed a stricture suggesting that it may be suitable in future evaluations of the use of drugs for the prevention of development and recurrence of urethral strictures. By treating the animals with drugs inhibiting or enhancing single growth factors, we may in the future learn more about the mechanisms controlling the development of iatrogenic US.

Acknowledgements This study was supported by grants from IPSEN Scandinavia, Denmark, The Institute of Experimental Clinical Research, Aarhus University Research Foundation and The Danish Health Science Council, grant no. 9600822 (Growth and Regeneration Centre).

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