ELSEVIER

VARIATION IN OUTPUT POWER OF LASER PROSTATECTOMY FIBERS: A NEED FOR POWER MEASUREMENTS

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ABSTRACT

Objectives. The aim of this study was the assessment of the quality of side-firing fibers that are being used for laser prostatectomy, either by a laser light transmission measurement or by visual inspection.

Methods. A power meter (Aquarius) was developed to measure the actual power transmitted through a side-firing fiber and delivered to the prostatic tissue. The power measurements were performed under clinical conditions, that is, under water and at relatively high input power. Furthermore, a protocol was developed for visual inspection of the fibers. Eight types of side-firing fibers were measured before use. Before and after a procedure, three fiber types were measured: ProLase II (28 samples), UltraLine (23 samples), and UroLase (44 samples). All these fibers were used in standard treatment protocols.

Results. At 60 W the transmission of new fibers (not used) ranged between 49% and 83% when compared to a bare fiber. After use, a large variation was found in transmitted power between different samples of one device. A correlation with total transmitted power was not present. At higher power input, vapor bubbles are generated at the tip of the fibers. Depending on the fiber design, these bubbles have a major impact on the transmission. Only for the UroLase fiber was there a significant correlation between visual inspection and the transmission of used samples at 10, 20, and 40 W.

Conclusions. The transmission strongly varies between fibers and between different samples of one fiber during clinical use. Moreover, the transmission does not correlate with visual inspection. A power measurement during a clinical treatment will contribute to a more controlled procedure and to a better comparison of clinical laser prostatectomy studies. UROLOGY® **47**:672–678, 1996.

The possible use of the neodymium:yttrium-aluminum-garnet laser as a minimal invasive treatment of benign prostatic hyperplasia was already reported in 1988.[1,2] The inability, however, to direct the laser light to the prostatic tissue resulted in an ineffective laser treatment. In 1990 the first canine experiments were performed using a side-firing fiber that could be inserted through a cystoscope[3] or that was incorporated in a transurethral ultrasound device.[4] In both cases the laser light was directed almost perpendicular to the prostatic tissue. These initial experiments were soon followed by other canine and later by human studies[5,6] to find the optimal laser prostate treatment that is to compete with the gold standard, transurethral resection of the prostate. Until now, however, there is no consensus regarding treatment strategy for laser prostatectomy. To achieve such consensus, two questions need to be answered: How can we most effectively apply laser energy to the prostate? Does the delivered energy depend on the type of device and does the energy delivery change with time?

The success of a laser prostatectomy can be defined as the relief of symptoms, caused by obstructive prostatic tissue, by the application of laser energy with minimal complications. Removal of abundant tissue is possibly the key mechanism. In the case of laser irradiation, tissue removal can be obtained in two different ways: indirectly by heating of the tissue to a maximum of 100°C, thus

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causing the coagulated tissue to slough after the procedure, or instantaneously by vaporizing the tissue while temperatures rise over 300°C. Either way depends on the power density at the tissue surface in combination with the irradiation time.[7] The power density is the result of power output of the laser source and the transmission of the fiber, and the irradiated surface area (spot size), defined by the characteristics of the side-firing fiber that is used and its distance to the tissue.[8] This implies that, although using the same laser source and the same power settings, each type of fiber may deliver a different amount of energy to the tissue. Consequently, the results of different laser prostatectomy studies may not be comparable.

Presently, more than 15 different side-firing fibers are commercially available. All are designed to deflect the laser light laterally, thus directing it to the prostatic tissue. In a previous study,[9] we showed that the method used to deflect the laser light highly influences the power density on the prostatic tissue. Two types of side-firing fibers can be distinguished, depending on the deflection method that is used: metal reflector and total internal reflector.

During a laser procedure, changes in fiber characteristics may occur, due to deterioration of parts of the fiber that transmit or reflect the laser light. Both transmission and beam characteristics may change, thus influencing the tissue effects and the clinical outcome in the long term. Therefore, clinical and experimental studies are difficult to compare with respect to (ideal) power settings, since the total amount of energy irradiating the tissue can only be estimated within limits.

Apart from laser-related parameters, the tissue composition and the blood perfusion also play an important role in laser–tissue interaction. Blood vessels will cool the tissue surface efficiently and prevent heat deposition in deeper tissue layers.[10,11] Characterization of prostatic tissue prior to treatment may result in a better understanding of the clinical results.

In this study a method will be presented to measure the transmission of a side-firing fiber under controlled conditions similar to clinical settings. Consequently, the power that actually reaches the tissues, and thus is responsible for the tissue effects, can be determined. The measurements were done before and after clinical procedures, to monitor the behavior of side-firing fibers during use.

MATERIAL AND METHODS

Prior to clinical use, transmission measurements were performed on various samples of eight types of side-firing fibers. Three were metal reflectors: RotaLase (Xintec), SideFire (Myriadlase), and UroLase (Bard). Five were total internal reflectors: Angled Delivery Device (ADD; Laserscope), Laseguide (Laser Peripherals), ProLase II (Cytocare), SideFiber (Ceramoptec), and UltraLine (Heræus Lasersonics). Before and after clinical application, the transmission of three types of fibers was measured: ProLase II (28 samples), UltraLine (23), and UroLase (44).

Transmission Measurements

The transmission measurement in the experimental setting should be performed under conditions approaching those of the actual (clinical) laser treatment. Because the medium surrounding the device influences the way the laser light travels to the tissue, the measurement should take place under water. A measurement should include only that beam that contributes to the clinical effect. The transmission may be dependent on the power input, so a measurement needs to be performed with a power input similar to the clinical power setting. Figure 1A is a schematic illustration of a side-firing fiber inserted in the prostatic urethra during treatment. In Figure 1B the power meter setup is shown schematically, and in Figure 1C a photograph of the final version of the power meter, named "Aquarius," is shown.[12]

The detector head (power wizard, Synrad) is positioned behind a glass window at the outside of a water-filled container. A side-firing fiber is positioned through the fiber support in front of the window (detector). Through the use of this support, all fibers are positioned at the same distance (5 mm) to the detector. By repositioning the detector head (into another slot), the meter can be used to measure end-firing fibers as well (for reference). Parameters like distance of fiber to detector remain unchanged. It is possible to incorporate a water flush parallel with the fiber (through the support). The flow could be adjusted to a maximum of 3.0 mL/s. For each fiber sample, the measurements were repeated five times.

Visual Inspection

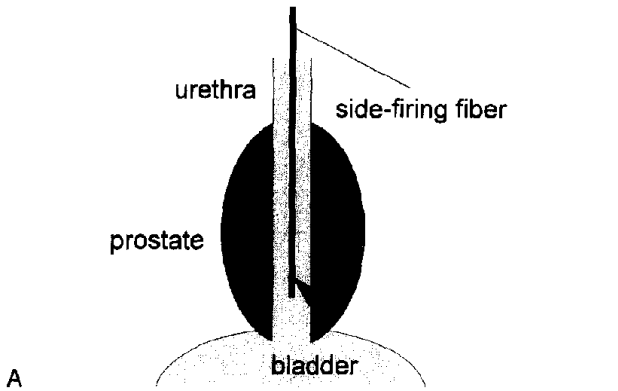
The simplest way of assessing the status of a side-firing fiber during clinical use is by direct visual inspection, as it can be done with minimal interruption of the procedure. It is discussed whether any visual objective characteristics of a used fiber correlate to its loss in transmission of laser light. Therefore, the same fibers for which the transmission was measured during clinical use were inspected visually. To obtain an objective measure, a classification scheme was designed. All fibers were scored in a range from 1 to 5, where 5 is a totally damaged fiber and 1 an undamaged fiber.[13] As an example, the different grades of deterioration for the UroLase fiber are presented in Figure 2. The fibers were evaluated by two independent observers (EtS, JdlR). The sum of the obtained scores resulted in a scale from 2 to 10.

RESULTS

New Fibers

The measurements were performed at input powers of 10, 20, 40, and 60 W, using the Aquarius power meter described before. Three new fiber samples were measured for each type. The transmission was calculated relative to the transmission of an end-firing fiber with the same diameter as each side-firing fiber. The results of these transmission measurements are presented in Figure 3.

The SideFire device has the lowest transmission at 60 W, especially when compared to its transmission at lower input power. This may be caused by the presence of vapor bubbles (caused by heating of the device) near the reflecting mirror that



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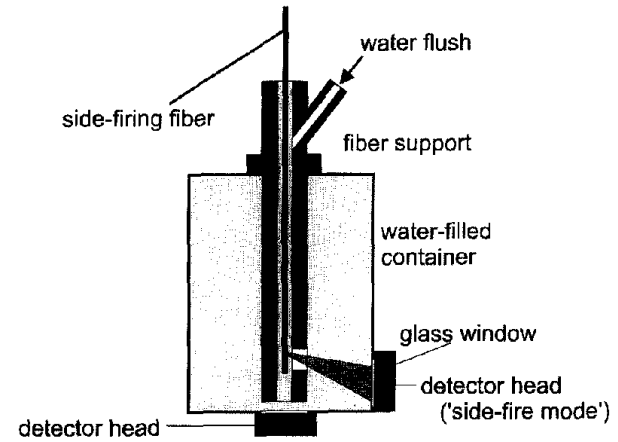

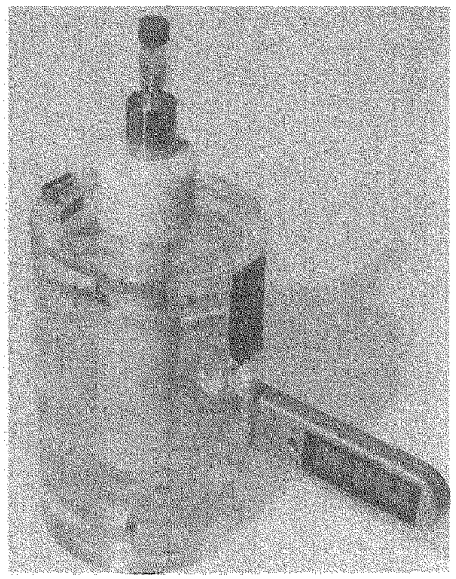

C

FIGURE 1. *A side-firing fiber in the prostatic (pr) urethra during laser light irradiation (A) and the same side-firing fiber positioned in the experimental power meter setup (B); the final version of the setup, the Aquarius power meter (C).*

spreads the beam over a larger area than the detector area. The measurements at 60 W of the other "true" reflecting type device, the UroLase, did show a large variation, probably for the same reason. Nevertheless, it is very likely that vapor

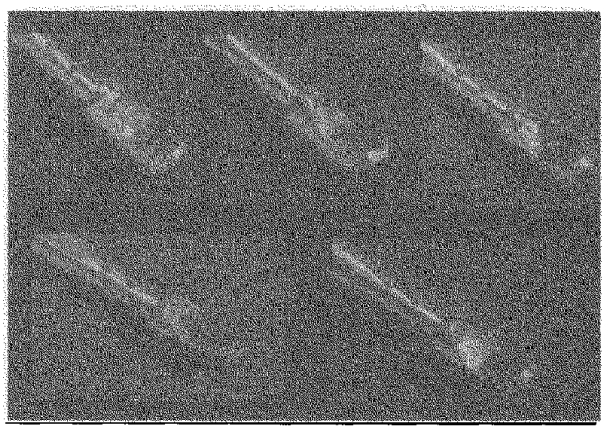

FIGURE 2. *Visual aspects of the laser fiber. Example of the scoring system for the UroLase fiber. Starting from the top right corner with score 1 (undamaged), then right to left and top to bottom to the bottom left corner with score 5 (totally damaged).*

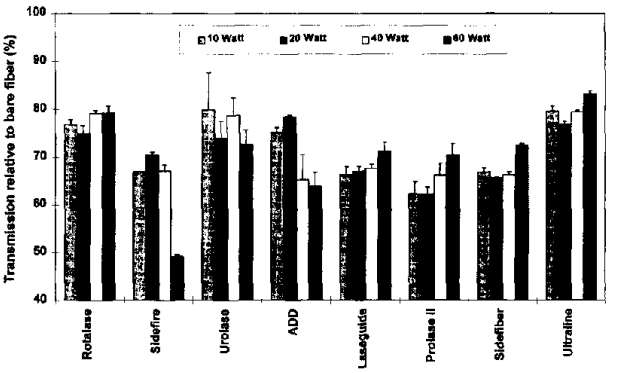

FIGURE 3. *Results of the transmission measurements of eight new side-firing fibers measured with the Aquarius power meter at 10, 20, 40, and 60 W input power (bars indicate standard deviation). ADD = Angled Delivery Device.*

bubbles are also generated with the other devices (internal reflectors) but, due to their shape, these bubbles do not stay in the laser light path.

Measurements During and After Clinical Use

Three different fibers, the UroLase, UltraLine, and ProLase II, were measured during and after clinical use and their transmission was compared to that before use (that is, of a new fiber). Each type of fiber was applied at its own clinical protocol. The ProLase II was used at 40 W either fixed or moved over the tissue (the "painting" method).[14] An average energy of 35,000 J was transmitted through the 28 samples. The UltraLine was used at 60 W while painting over the tissue.[15] At average a total of 51,000 J was transmitted through the 23 samples. The UroLase was used at 40 W at several fixed clock positions, depending on prostate volume.[15] The average amount of energy transmitted through the 44 UroLase fibers

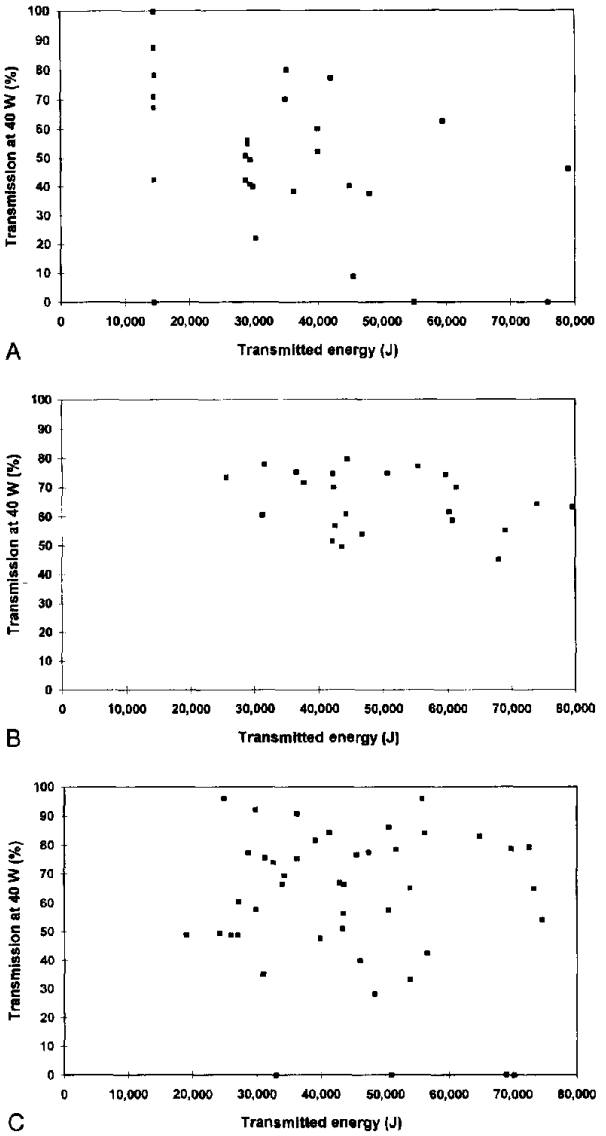

FIGURE 4. *Scatter plot of the percentage transmission relative to a new fiber at 40 W of all 28 used ProLase II (A), 23 used UltraLine (B), and 44 used UroLase fibers (C) as a function of energy transmitted.*

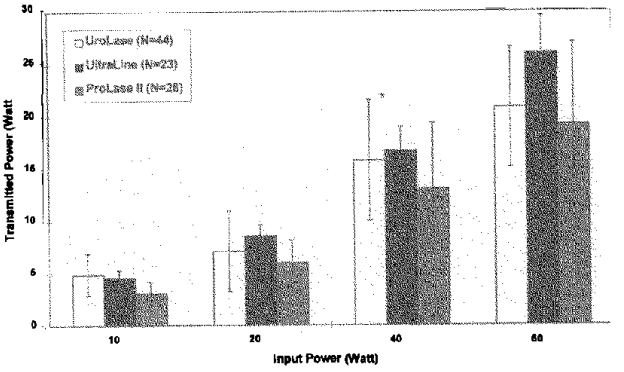

FIGURE 5. *Mean power transmission of used ProLase II, UltraLine, and UroLase fibers at 10, 20, 40, and 60 W input power (bars indicate standard deviation).*

was 44,000 J. The measurements were performed at 10, 20, 40, and 60 W. As an example, the transmission at 40 W of all used ProLase II, UltraLine, and UroLase fibers is presented as a function of energy transmitted in a scatter plot in Figure 4. The mean values and standard deviations of the transmission of the three different fiber types are presented in Figure 5. The differences in efficiency of laser light transmission are only significant between the UltraLine and the ProLase II at 10, 20, 30, and 40 W, between the UroLase and the ProLase II at 10 W, and the UroLase and UltraLine at 60 W (t test, two-tailed, $P < 0.01$).

A water flush was incorporated in the measuring device with a flow rate of 3 mL/s parallel with a used side-firing fiber. The water is used normally for enhanced cooling of the fiber tip. The transmission was calculated for five used samples of the ProLase II, UltraLine, and UroLase, again at 10, 20, 40, and 60 W. Only at high-power input (40 and 60 W) did the transmission increase slightly compared to the no-flush situation, as less vapor bubbles are generated at the tip. Therefore, for further experiments, the transmission measured without flush was considered similar to the situation with flush.

Visual Inspection

The ProLase II, UltraLine, and UroLase fibers were all inspected visually. The scored values (in a scale from 2 to 10) were correlated with the transmission measurements reported before. The fibers were grouped in two categories based on this visual aspect score: medium (score from 2 to 5) and high (score from 6 to 10) decay. In Figure 6 the transmission at different input powers is presented for these two categories for each of the three fibers.

Figure 6 reveals a gross relationship between the visual aspect and the transmission for the ProLase II and the UroLase fibers. For each individual sample, the correlation between the visual aspect and the transmission increased with decreasing input power. A significant statistical level could be reached only for the UroLase fiber at 10, 20, and 40 W input power (t test, two-tailed, $P < 0.01$). Therefore, when using 40 or 60 W for a clinical treatment, visual inspection does not give sufficient information on the transmission or quality of the side-firing fibers discussed here.

COMMENT

Since the clinical introduction of laser prostatectomy, many side-firing fiber devices have been developed for this procedure. The results that are reported in the literature using these devices are promising regarding both objective and subjective

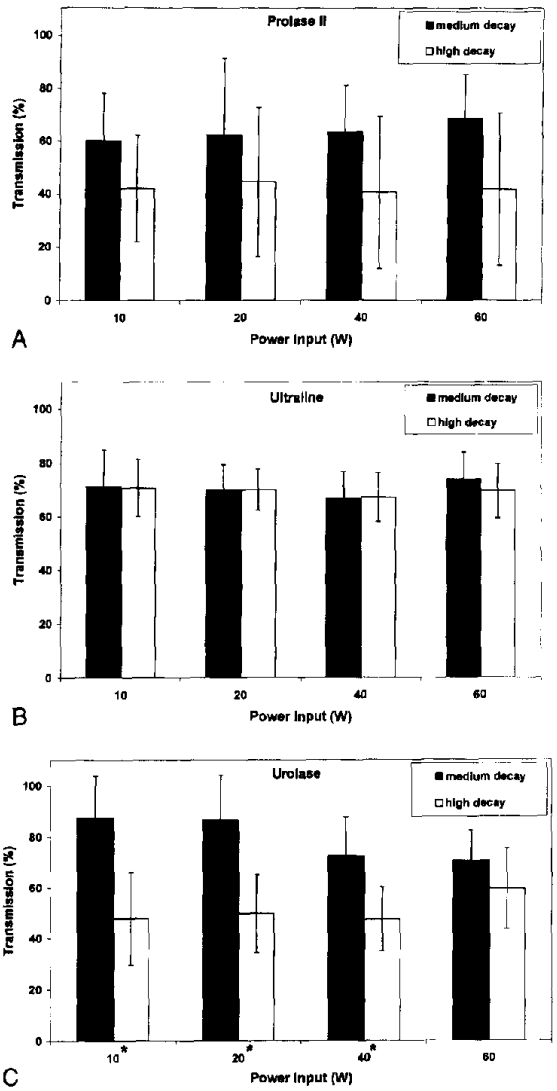

FIGURE 6. *The relationship between the visual aspect (either medium or high decay) and the transmission for the ProLase II (A), UltraLine (B), and UroLase (C) at 10, 20, 40, and 60 W input power (bars indicate standard deviation). *The difference in transmission is statistically significant, P <0.01.*

improvements, but there is a large variation. An explanation may be the difference in characteristics[9,16,17] and the durability of the fibers during use, because for clinical relevance not the power delivered by the laser source but the power delivered by the fiber to the tissue is important, the first being the parameter reported in the literature. The laser light transmission of the fibers is one of the major parameters that describe the characteristics of the fiber and that can be used to quantify the durability.

The transmission of eight different side-firing devices was studied here. Three devices (ProLase II, UltraLine, and UroLase) were studied during and after clinical use (durability). The study shows a large difference in laser light transmission, not only between the new devices, but also after use between different samples of one device. In general, the transmission decreased with increasing total transmitted energy. However, the correlation was poor. This suggests that transmission should be considered for a proper evaluation study of a device. The inclusion of a transmission measurement during a clinical procedure, as the change in transmission is unpredictable, would be the preferred situation.

Contamination of the reflecting (gold mirror) or transmitting (glass capillary) parts of the fiber tip will lead to absorption of laser light. As a result, the temperature at the contaminated place will rise easily over the boiling temperature of water, thus creating vapor bubbles. Of course, this happens both in clinical application and inside the power meter. The bubbles will (back) scatter the light, thus influencing the transmission. As bubbles are formed as a result of light absorption, it is impossible to determine the independent effect of absorption or scattering on the transmission of laser light. In the case of the UroLase fibers at 10, 20, and 40 W, there was a significant relationship between visual inspection and transmission. It should, however, be remembered that the situation may be different for a particular sample. For the other two fibers, ProLase II and UltraLine, no correlation could be found.

Apart from the visual inspection as described here, one can make use of other (cystoscopic) indicators to assess the aging of a side-firing fiber. The absence of tissue effects (blanching or carbonization), white flashes generated at the tip of the device due to overheating of the tip, or excessive formation of vapor bubbles at the tip surface (not coming from the tissue) indicate that the device may be deteriorating. A proper transmission measurement can be used to confirm these indicators.

Some parts of the power meter influence the amount of light that is detected. The glass window in front of the detector reflects and absorbs a small part of the laser light. The amount of water between fiber and detector or tissue absorbs some of the laser light as well. The total amount of laser light that does not reach the detector is estimated at about 5%. The results presented here are not influenced by these "errors," because the measurements are calculated relative to an end-firing fiber or relative to a new sample of a side-firing device. The mentioned percentile aberrations are constant in all circumstances. Only when calculating the energy that actually irradiates the tissue in the clinical situation should this 5% difference be considered.

The patients treated with the ProLase II, UltraLine, and UroLase fibers who were included

in this study were all evaluated regarding symptom score and voiding parameters.[14,15] The change in these parameters, however, did not correlate with the decay in transmission of these fibers as assessed in this study. Although the number of patients is small, the absence of correlation may be explained by the fact that transmission of the fiber does not decrease linearly during a procedure. In that case, more accuracy can be obtained by measuring at fixed intervals during a procedure.

Although the transmission is an important factor to take into account, at least for the transmission differences considered here, it does not disqualify one of these side-firing fibers for laser prostatectomy. It does, however, strongly indicate that the transmission should be considered when comparing different fibers. By measuring the delivered energy to the tissue more accurately with a setup such as the Aquarius power meter, one will be able to compare the results of different laser prostatectomy studies and understand the differences better.

CONCLUSIONS

The present study shows a difference in laser light transmission between side-firing devices for laser prostatectomy. This transmission may change during clinical application in an unpredictable way. Despite using the same device and applying the same power settings, the energy delivered to the tissue during a clinical procedure can vary significantly.

Power measurement during a clinical treatment will contribute to a more controlled procedure and to a better comparison of clinical laser prostatectomy studies.

REFERENCES

1. Littrup PJ, Lee F, Borlaza GS, Sacknoff EJ, Torp-Pedersen S, and Gray JM: Percutaneous ablation of canine prostate using transrectal ultrasound guidance absolute ethanol and Nd:YAG laser. Invest Radiol 23: 734–739, 1988.

2. Bloiso G, Warner R, and Cohen M: Treatment of urethral diseases with neodymium:YAG laser. Urology 32: 106–110, 1988.

3. Johnson DE, Levinson AK, Greskovich FJ, Cromeens DM, Ro JY, Costello AJ, and Wishnow KI: Transurethral laser prostatectomy using a right-angle delivery system, in Watson GM, Steiner RW, Pietrafitta JJ (Eds): *Lasers in Urology, Laparoscopy and General Surgery*. Bellingham, Wash, SPIE, 1991, vol. 1421, pp 36–41.

4. Roth RA, and Aretz HT: Transurethral ultrasound-guided laser-induced prostatectomy (TULIP procedure): a canine prostate feasibility study. J Urol 146: 1128–1135, 1991.

5. Johnson DE, Price RE, and Cromeens DM: Pathologic changes occurring in the prostate following transurethral laser prostatectomy. Lasers Surg Med 12: 254–263, 1992.

6. Kabalin JN: Laser prostatectomy performed with a right angle firing neodymium:YAG laser fiber at 40 watts power setting. J Urol 150: 95–99, 1993.

7. Verdaasdonk RM, Borst C, and van Gemert MJ: Explosive onset of continuous wave laser tissue ablation. Phys Med Biol 35: 1129–1144, 1990.

8. Van Swol CF, Verdaasdonk RM, Mooibroek J, Lock MT, and Boon TA: Prediction of the necrotic zone depending on the optical and thermal characteristics of laser prostatectomy modalities. J Urol 151: 332, 1994.

9. Van Swol CF, Verdaasdonk RM, van Vliet RJ, Molenaar DG, and Boon TA: Side-firing devices for laser prostatectomy. An overview. World J Urol 13: 88–93, 1995.

10. Van Swol CFP, Verdaasdonk RM, Mooibroek J, and Boon TA: Optimization of laser prostatectomy. Prog Clin Biol Res 386: 511–519, 1994.

11. Cowles RS 3rd, and Rawlings CA: The effect of intraprostatic blood flow on laser energy penetration in the canine prostate. Lasers Surg Med 7(suppl): 63, 1995.

12. Van Swol CFP, Verdaasdonk RM, Hermans F, van Vliet RM, and Boon TA: Monitoring of the quality of side-firing fibers using a special design power meter "Aquarius," in Watson GM, Steiner RW, and Johnson DE (Eds): *Laser Prostatectomy and Lasers in Urology*. Bellingham, Wash, SPIE, 1995, vol. 2395A, pp 14–19.

13. te Slaa E, van Ettergen AF, van't Hof CA, Debruyne FMJ, and de la Rosette JJ: Durability of laser fibers. World J Urol 13: 83–87, 1995.

14. Boon TA, van Swol CF, van Venrooij GE, Beerlage HP, and Verdaasdonk RM: Laser prostatectomy for patients with benign prostatic hyperplasia: a prospective randomized study comparing two different techniques using the Prolase II fiber. World J Urol 13: 123–125, 1995.

15. de la Rosette JJ, te Slaa E, de Wildt MJ, and Debruyne FM: Experience with the Ultraline and Urolase laser fibers: is there any difference? World J Urol 13: 98–103, 1995.

16. Anson K, Buonaccorsi G, Eddowes M, MacRobert A, Mills T, and Watson G: A comparative optical analysis of laser side-firing devices: a guide to treatment. Br J Urol 75: 328–334, 1995.

17. Perlmutter AP, and Muschter R: The optimization of laser prostatectomy. Part I: free beam side fire coagulation. Urology 44: 847–855, 1994.

EDITORIAL COMMENT

The authors present an interesting investigation of common side-firing neodymium:yttrium-aluminum-garnet (Nd:YAG) laser delivery fibers used for treatment of benign prostatic hyperplasia. Their findings may explain some variations in clinical outcomes achieved in individual men undergoing laser prostatectomy. First, the authors demonstrate once again the well-documented fact—but a fact that is too often neglected in clinical application—that even at baseline the laser light transmission characteristics of different fiber designs differ significantly.[1,2] Thus, laser dosimetry and operative technique must be adjusted to maximize tissue effects and clinical outcomes.[3,4] Second, the authors studied deterioration of fiber transmission of laser light during laser prostatectomy. Deterioration was observed with all three distinct categories of side-firing fiber design: those with external metal mirrors (such as UroLase) and polished-end silica glass fibers with a glass capillary cover (such as UltraLine) or without (such as ProLase II). Not only were all designs susceptible to intraoperative damage, but the external metal mirror design was not significantly more susceptible to deterioration, contrary to popular discourse but in agreement with prior objective studies.[5] In fact, the metal mirror design conferred some advantage to the operator, since this was the only design wherein the extent of deterioration of transmission could be readily correlated with the visual appearance of the external metal mirror. With polished-end glass fibers, which rely on internal reflection of light, the authors could not accurately

FAMVIR: Safety/tolerability

- Generally well-tolerated therapy in clinical trials
- The most commonly reported adverse events for FAMVIR and placebo, respectively, are headache (zoster: 22.7% vs 17.8%; genital herpes: 23.6% vs 16.4%) and nausea (zoster: 12.5% vs 11.6%; genital herpes: 10% vs 8%)

The efficacy or safety of FAMVIR has not been established in children, immunocompromised hosts, patients with herpes zoster complications, patients with first episode genital herpes, or suppression of recurrent genital herpes, or in patients with renal or hepatic insufficiency. All clinical trial populations consisted of otherwise healthy adult populations.

FAMVIR® (famciclovir) Tablets

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature. The following is a brief summary.

INDICATIONS AND USAGE: *Famvir* is indicated for the management of acute herpes zoster (shingles) and for the treatment of recurrent episodes of genital herpes.

CONTRAINDICATIONS: *Famvir* is contraindicated in patients with known hypersensitivity to the product.

PRECAUTIONS: Efficacy has not been established for initial episode genital herpes infection, suppression of recurrent genital herpes, ophthalmic zoster, disseminated zoster or in immunocompromised patients. Adjust dosage when administering to patients with creatinine clearance <60 mL/min. The safety of administering *Famvir* to patients with renal dysfunction is unknown. Safety and efficacy in children under the age of 18 years have not been established.

No clinically significant alterations in penciclovir pharmacokinetics were observed following single-dose administration of 500 mg famciclovir after pre-treatment with multiple doses of cimetidine, allopurinol, or theophylline. Probenecid and other drugs significantly eliminated by active renal tubular secretion may result in increased penciclovir plasma concentrations. Conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could occur.

Famciclovir was administered orally unless otherwise stated. Two-year dietary carcinogenicity studies on famciclovir were conducted in rats and mice. The high dose tested in rats and mice was lowered after 7 to 8 months of drug administration to ensure long-term survival (female rats and male/female mice from 750 to 600 mg/kg/day; male rats from 300 to 240 mg/kg/day). A significant increase in the incidence of mammary adenocarcinoma was seen in female rats receiving 600 mg/kg/day (1.5 to 9.0 times the human systemic exposure at the recommended oral dose of 500 mg t.i.d. or 125 mg b.i.d. based on area under the plasma concentration curve comparisons [24 hr AUC] for penciclovir). Marginal increases in the incidence of subcutaneous tissue fibrosarcomas or squamous cell carcinomas of the skin were seen in female rats (dosed at 600 mg/kg/day) and male mice (dosed at 600 mg/kg/day; 0.4 to 2.4x the human systemic exposure, based on 24 hr AUC for penciclovir), respectively. No increases in tumor incidence were reported for male rats treated at doses up to 240 mg/kg/day (0.9 to 5.4x the human AUC), or in female mice at doses up to 600 mg/kg/day (0.4 to 2.4x the human AUC).

Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutations in bacteria (*S. typhimurium* or *E. coli*) and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5000 mcg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/mL), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 mcg/mL). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 mcg/mL). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/mL). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.9 to 11.4x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.2 to 1.2x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.4 to 2.4x the human AUC) and 150 mg/kg/day (1.7 to 10.2x the human AUC), respectively.

Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (3.6 to 21.6x the human AUC).

Pregnancy–Teratogenic Effects–Category B. Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 3.6 to 21.6x and 1.8 to 10.8x the human systemic exposure to penciclovir based on AUC comparisons for the rat and rabbit, respectively) and intravenous doses of 360 mg/kg/day in rats (2 to 12x the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.5 to 9.0x the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.4 to 2.6x the human dose [BSA]) or rabbits (60 mg/kg/day, 0.7 to 4.2x the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

ADVERSE REACTIONS

Herpes Zoster: In four clinical studies involving 816 *Famvir*-treated patients with herpes zoster (*Famvir*, 250 mg t.i.d. to 750 mg t.i.d.), the most frequent adverse events associated with *Famvir* were headache and nausea. The table below lists adverse events occurring on-therapy with an incidence of ≥2% per treatment group in *Famvir* clinical trials. The frequency and types of reported adverse events in trial 008 were representative of the safety experience in the active-controlled herpes zoster *Famvir* trials (007 and 054).

Recurrent Genital Herpes: In three placebo-controlled clinical trials involving 528 *Famvir*-treated patients with genital herpes (*Famvir*, 125 mg b.i.d. to 500 mg t.i.d.), the most frequent adverse events associated with *Famvir* were headache and nausea. The table lists adverse events occurring on-therapy in *Famvir* clinical trials with an incidence of ≥ 2% per treatment group.

Adverse Events Reported by ≥2% of Treatment Group in Patients in One Herpes Zoster and Three Placebo-controlled Recurrent Genital Herpes Famvir (famciclovir) Trials*

	Incidence			
	Herpes Zoster		Genital Herpes	
Event	*Famvir* (n=273) %	Placebo (n=146) %	*Famvir* (n=640) %	Placebo (n=225) %
Nervous System				
Headache	22.7	17.8	23.6	16.4
Dizziness	3.3	4.1	5.5	4.9
Insomnia	1.5	1.4	2.5	2.2
Somnolence	2.6	2.7	1.6	0.4
Paresthesia	2.6	0.0	1.3	0.0
Gastrointestinal				
Nausea	12.5	11.6	10.0	8.0
Diarrhea	7.7	4.8	4.5	7.6
Abdominal Pain	1.1	3.4	3.9	5.8
Dyspepsia	1.1	1.4	3.4	2.2
Flatulence	1.5	0.7	1.9	2.2
Constipation	4.4	4.8	1.4	0.9
Vomiting	4.8	3.4	1.3	0.9
Anorexia	2.6	4.1	1.1	0.9
Body as a Whole				
Fatigue	4.4	3.4	6.3	4.4
Pain	2.6	2.7	2.0	1.8
Injury	2.6	0.0	0.8	1.3
Fever	3.3	4.1	0.6	0.4
Rigors	1.5	2.7	0.5	0.4
Respiratory				
URI	0.7	0.7	3.3	2.7
Pharyngitis	2.6	4.8	2.7	2.2
Sinusitis	2.6	1.4	1.3	1.3
Musculoskeletal				
Back Pain	1.5	2.7	1.9	2.2
Arthralgia	1.5	2.1	1.3	0.0
Zoster/Genital Herpes-Related Signs/Symptoms/ Complications	2.9	3.4	1.7	2.2
Skin and Appendages				
Pruritus	3.7	2.7	0.9	0.0

*Patients may have entered into more than one clinical trial.

During clinical practice, confusion (including delirium, disorientation, confusional state) has been reported very rarely. Most of these spontaneous reports have occurred in the elderly.

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