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Intravenous diclofenac as prophylactic treatment for verteporfin-associated low back pain

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PURPOSE. *The authors report on the therapeutic effect of intravenous diclofenac on verteporfin associated low back pain (LBP), which is the most frequent adverse effect of photodynamic therapy (PDT) for macular degeneration.*

METHODS. *The authors studied 818 patients who received PDT with verteporfin for choroidal neovascularization. Systemic blood pressures were recorded in all study participants half an hour before PDT treatment. All patients who experienced LBP during verteporfin infusion were asked to grade their pain as mild (1), moderate (2), severe (3), or unbearable (4).*

RESULTS. *Thirty-three patients had LBP during their first verteporfin infusion. Of these, 11 subjects (1.34% of all) reported increased pain scores (level 2 to 4) and received intravenous diclofenac ahead of their next PDT. Patients with LBP during verteporfin infusion had significantly higher systolic blood pressures than uncomplicated cases (180 mmHg vs 155 mmHg, p=0.01). Treatment with intravenous diclofenac short before PDT significantly reduced the patients' mean pain score by 1.8 levels (p=0.0001).*

CONCLUSIONS. *In this study, intravenous application of diclofenac short before verteporfin infusion effectively prevented verteporfin associated LBP in patients with systemic hypertension. (Eur J Ophthalmol 2008; 18: 805-8)*

KEY WORDS. *Verteporfin, Adverse effects, Low back pain, Diclofenac*

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INTRODUCTION

Photodynamic therapy (PDT) with verteporfin is a well-established therapy for choroidal neovascularization (CNV), and the spectrum of indications had broadened in recent years (1). Even though the introduction of vascular endothelial growth factor inhibitors (anti-VEGF) into clinical practice has reduced the indications for a monotherapy with PDT, there is evidence that in patients with classic, subfoveal CNV monotherapy with PDT provides a greater improvement in quality of life as compared to monotherapy with pegaptanib (2). The combination of PDT with bevacizumab suggests promising visual outcomes and may combine reduced costs and improved quality of life as opposed to the use of intravitreal angiogenesis inhibitors alone (3). In contrast to other anti-VEGF substances, ranibizumab offers a maximum of quality of life improvement in subfoveal CNV (4), and a combination with PDT may merge the advantages of both treatment options while reducing the number of interventions (5).

Among various systemic side effects, low back pain (LBP) appears to be the most important adverse event of PDT (6). Sometimes the level of LBP might be so harsh that further treatment by PDT may be abandoned by the patient. Therefore, prophylactic treatment with indomethacin or ketorolac intravenously has been proposed for patients

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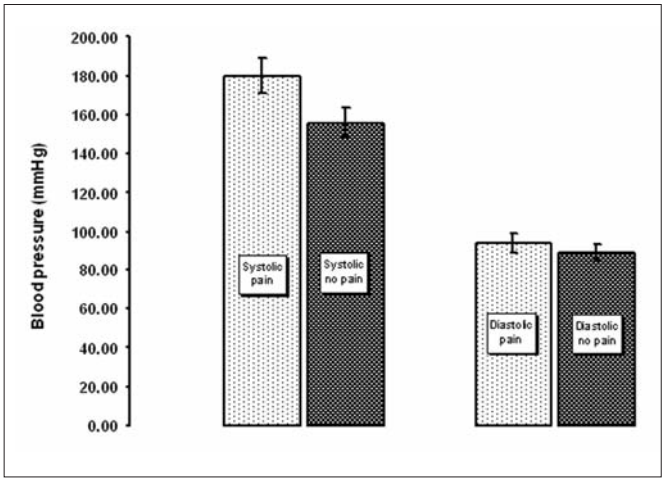

Fig. 1 - *Mean systemic blood pressures in patients undergoing photodynamic therapy with verteporfin. Systolic blood pressures were significantly higher when verteporfin-related low back pain was reported (light grey columns) (p=0.01, independent samples t-test). Diastolic values also tended to be higher in pain patients; however, the difference vs uncomplicated cases was not significant.*

with a history of LBP during previous verteporfin application (7). In our present study we report on the prophylactic therapeutic effect of intravenous diclofenac in patients with verteporfin associated LBP.

METHODS

We retrospectively studied 818 patients (mean age 85±19 years) who underwent PDT treatment according to established guidelines (8) at the Department of Ophthalmology, The Dutch Eye Care Foundation (SOZN), Velp, The Netherlands, between July 2003 and March 2006. The study was done in accordance with the tenets of the Declaration of Helsinki (1983 revision). As treatment analysis was based on anonymous, retrospective data, no official decision of the institutional review board was required.

The CNVs originated in age-related macular degeneration (AMD, n=644), pathologic myopia (n=135), angioid streaks (n=8), presumed ocular histoplasmosis syndrome (n=6), multifocal uveitis (n=10), or idiopathic genesis (n=15). In all patients, systemic blood pressures were recorded half an hour before a scheduled treatment with PDT, and systemic side effects of Visudyne infusions were documented if occurring.

We tried diclofenac as prophylactic analgesia in patients with verteporfin associated LBP, since it has been proven to be effective and safe in the treatment of acute LBP (9). We routinely asked pain affected patients to qualify verteporfin related LBP as mild (1), moderate (2), severe (3), or unbearable (4). If pain was accounted to grade 2 or higher, the patient was given a single dose of 50 mg intravenous diclofenac at the next visit 10 minutes prior to verteporfin infusion, and LBP was requalified according the previously used pain score. The prophylaxis with diclofenac was repeated on each following visit prior to PDT treatment. Statistical data analysis was performed using SPSS 12.0.1 software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The total incidence of systemic adverse events was 6.23%, and LBP was the most frequent side effect (Tab. I). Eleven study patients (1.34% of all, mean age 80±11 years) reported LBP grade 2 to 4 (mean pain score 2.5±0.82) and therefore received intravenous diclofenac ahead of their next PDT treatment. Ten pain affected patients had AMD and one had high myopia. The patient with high myopia was considerably younger than the AMD patients (38 vs 84 years, mean age). As low blood pressure in this myopic patient could result from his young age, the patient was excluded from blood pressure analysis to prevent a systematic, outlier-related statistical error.

Within the AMD group the mean blood pressures were not correlated with age; however, the degree of pain sensations in AMD patients correlated considerably with the systemic blood pressure measured before PDT treatment, which was statistically significant for systolic blood pressures (p=0.01, independent samples *t*-test, Fig. 1). Higher systemic blood pressure was associated with stronger pain, and all AMD patients with LBP had higher mean systolic and diastolic blood pressures (180±30 mmHg and 94±14 mmHg) than uncomplicated cases (155±25 mmHg and 89±13 mmHg). The differences for diastolic values were not statistically significant.

After pretreatment with diclofenac the mean pain score decreased from 2.6±0.97 to 0.8±0.79, which is highly significant (p=0.0001, paired samples *t*-test). Only the patient with high myopia, who did not have increased blood pressure, reported no change in the degree of LBP after diclofenac medication.

TABLE I - NONOCULAR SIDE EFFECTS OBSERVED IN PATIENTS UNDERGOING PHOTODYNAMIC THERAPY WITH VERTEPORFIN

Adverse event	Affected subjects, n	Percent
Low back pain	33	4.03
Apprehensiveness	4	0.48
Nausea	3	0.36
Pain injection site	2	0.24
Cardiac extrasystoles	1	0.12
Syncope	1	0.12
Renal pain	1	0.12
Chest pain	1	0.12
Cutaneous burn	1	0.12
Periphlebitis	1	0.12
Allergic exanthema	1	0.12
Obstipation	1	0.12
Hair loss	1	0.12
Total	51	6.23

DISCUSSION

We report on prophylaxis of verteporfin-associated LBP by intravenous diclofenac in patients with increased systemic blood pressures. This prophylactic treatment was restricted to patients who reported moderate to unbearable LBP (grade 2 to 4 in this study) during or after a previous verteporfin infusion. In the 11 patients treated with diclofenac we did not observe systemic adverse effects of this single dose prophylaxis, and PDT to the CNV could be applied as normally.

Even though the origin of verteporfin-associated LBP is unclear, several risk factors have been addressed that may play a role in our study group (7). In patients with verteporfin-related LBP, post infusion neutropenia has been observed (10). This may be caused by the ability of liposomal drugs, like verteporfin, to cause an inflammatory reaction by activation of the complement cascade and eventual neutrophil vessel wall adhesion (11). It is noteworthy that in systemic hypertension endothelial cells may support this process by the expression of an increased rate of adhesion molecules (12). Consequently, neutrophil vessel adhesion may be a specific reaction on liposomal drugs in hypertensive patients. In our present study virtually all patients with LBP had significantly increased systolic blood pressure, and systemic diclofenac was an effective prophylactic analgesic in all hypertensive patients. This encouraging therapeutic outcome may be based on a chemotaxis inhibiting effect on the blood neutrophils (13), thus restraining the painful inflammatory reaction. Conversely, LBP in the normotensive patient could have origin in a different pathomechanism, which then may not respond to diclofenac.

Recently published results about CNV treatment with anti-VEGF have replaced PDT as monotherapy of first choice for CNV in patients with AMD (14). However, results of a combined therapy with verteporfin and anti-VEGF substances promise improved therapeutic success (15). This may result in a reduced need for repeated intravitreal anti-VEGF injections and could thus lower the risk for endophthalmitis and reduce overall treatment costs (5). Therefore, it is very likely that PDT will continue to play an important role as an adjunct in CNV treatment. Even though ophthalmologists may deal less frequently with PDT-associated LBP in the future, a sufficient prophylaxis of such cases is warranted for comprehensive patient care.

In conclusion, increased systolic blood pressures could enhance a verteporfin caused, complement-triggered, and neutrophil transmitted inflammation, which may lead to pain sensations. Intravenous diclofenac, administered briefly before the verteporfin infusion, offered effective pain prevention in our study.

The authors have no commercial, proprietary, or financial interest in any research or devices presented in this study. This study was done in compliance with the ethical standards laid down in the Declaration of Helsinki.

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