Does Theophylline Have a Role as an Adjunct Agent for Immunosupression in Heart Transplantation Patients?

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ÖZET

KALP NAKLİ HASTALARINDA İMMÜNSÜPRESYON İÇİN TEOFİLİN'İN YARDIMCI İLAÇ OLARAK ROLÜ VAR MI?

Yeni gelişmekte olan immünsüpresif tedavi rejimlerine rağmen kalp nakli ameliyatlarında özellikle ilk üç ayda görülen rejeksiyon epizodları önemli morbidite ve mortalite nedeni olmaya devam etmektedir.

Teofilin post-transplant görülebilen bradikardinin tedavisinde yeri olan bir ilaçtır. Bu ilacın aynı zamanda bir takım immün düzenleyici etkilerinin olduğu bilinmektedir. Bu çalışmada post-transplant bradikardi nedeniyle teofilin kullanılan 27 hasta ile aynı immünsüpresif rejimle tedavi edilmiş ve rejeksiyon risk faktörleri benzer olan 29 hastanın endomiyokardiyal biopsi sonuçları, hücresel ve humoral rejeksiyon epizodları sıklığı, hemodinamik bozukluğa yol açan rejeksiyon epizodları ve ilk rejeksiyona kadar geçen süre retrospektif olarak araştırıldı. Teofilin kullanımının hücresel ve humoral rejeksiyon epizodlarının sıklığını azaltmadığı, hemodinamik bozukluğa yol açan rejeksiyon epizodlarına da etkisi olmadığı görüldü. Ancak teofilin kullanımı ile 3 aylık ortalama biyopsi skorlarında anlamlı azalma (kontrol grubu 0.98 ± 0.51, teofilin grubu 0.73 ± 0.42) (p=0.04) ve ilk rejeksiyonun görülme süresinde uzama tespit edildi (kontrol grubu 24 ± 21 gün, teofilin grubu 51 ± 26 gün) (p=0.05).

Sonuç olarak teofilinin immün süpresif tedavi rejimlerine eklenmesinin rejeksiyon epizodları yönünden olumlu etkisinin olabileceğini düşündük. Prospektif, randomize daha fazla hastayla yapılacak çalışmaların, ilacın immünsupresif tedavi rejimlerine adjuvan olarak eklenme potansiyelini daha iyi ortaya koyacağını düşünüyoruz.

Anahtar kelimeler: *Teofilin, kardiyak transplantasyon, bradikardi*

Theophylline, an old drug mainly used for asthma, chronic obstructive pulmonary disease and treating apnea of preterm infants has been demonstrated to have some immunmodulatory effects in several studies [1-3]. It has also proved to be effective in treating post cardiac transplant bradycardia [4-6].

Despite improvements in immunosuppressive drugs, incidence of rejection in heart transplantation patients is still high, especially in the first 3 months, causing increased morbidity and mortality [7]. This study is performed to investigate the effects of theophylline on cardiac allograft rejection in the first 3 months in patients treated with this drug to correct post transplant bradycardia.

PATIENTS and METHODS

To elucidate possible effects of theophylline on patterns of cardiac allograft rejection we examined 56 consecutive patients between February 1994 and December 1997. There were 2 group of patients. Group 1 was the theophylline group, group 2 was the control group.

Inclusion criteria: To be included all the patients were to have at least 3 months of survival. All needed to be on the same standard regimen of immunosuppressive therapy which consisted of cyclosporin A, azathiopurine and prednisolone. Patients on theophylline, who formed the study group must have used the drug for at least 4 weeks in the first 3 months of transplantation.

Exclusion criteria: Patients who died in the first 3 months and patients who were on a different immunosuppressive regimen other than the standard regimen and patients who had used theophylline less than 4 weeks were excluded.

Twenty-seven of the patients received theophylline within 72 hours of transplantation for post transplant bradycardia defined as a pulse rate of less than 70 / min. and formed the study group. Rest of the patients [29] formed the control group.

Detailed donor and recipient related risk factors for rejection were collected. These were donors` and recipients` age, gender and race, panel reactive antibodies (PRA) of the recipients closest to the transplantation, cytomegalovirus (CMV) serology of the donor and the recipient, average number of HLA mismatches, and retrospective crossmatch results.

We focused on rejection parameters in the first 3 months. We examined results of follow-up endomyocardial biop-

Recieved: 28 August, revision accepted 31 October 2000
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Sunulan çalışma Ochsner Medical Instutions, New Orleans, LA, USA'de yapılmıştır.
Bu çalışma "American Society of Transplantation" 1999 Mayıs toplantısında Chicago'da sözlü bildiri olarak sunulmuştur.

sies (EMB), immunfluorescent staining microscopy analysis for vascular rejection, echocardiographic studies and right heart catheterization results.

Cellular rejection was diagnosed with EMB results graded with standard ISHLT (International Society of Heart and Lung Transplantation) grading system [7] and clinical assessment. Grade 2 and higher endomyocardial biopsy result with clinical signs of rejection was noted as an episode of cellular rejection to be treated. Vascular rejection was diagnosed with clinical assessment and echocardiographic findings and/or immunfluorescent microscopy findings without a cellular rejection pattern on EMB [8]. Hemodynamic compromise was noted to be present if patients had signs and symptoms of heart failure and/or they had a previously normal cardiac index or ejection fraction less than 2.2 lt/min/m^2 or 45% respectively. We also examined time to first rejection in terms of days for both groups.

To examine groups in detail in terms of comparability, we collected cumulative dosages of immunosuppressive therapy and exposure to induction therapy with monoclonal antibody directed against CD3 (helper) lymphocyte (OKT3) in the first 3 months.

A biopsy score was calculated for both groups for the biopsies done in the first 3 months. Total score of biopsies in the study period was divided by the number of the biopsies to have the biopsy score for each patient. Scoring for an EMB result is demonstrated in Table 1.

Table 1. Scoring system for biopsy results

ISHLT grade	Score
0	0
1A	1
1B	2
2	3
3A	4
3B	5
4	6

ISHLT: International Society of Heart and Lung Transplantation

According to that system, for example a patient with biopsy results of once zero, twice 1A and once 3A will have a biopsy score of {(1x0)+(2x1)+(1x4)} / 4 which equals to 1.5.

Statistical analysis: Statistical analysis was done using the program "Statistical Program for Social Sciences" with the computer. Biopsy scores, time to first rejection in terms of days, demographic factors, rejection related risk factors, and cumulative immunosuppressive regimen were all compared using Student's t test and chi-square tests where appropriate.

RESULTS

Demographics of patients and their donors are are presented in Table 2. Both groups were similar in terms of age, gender and race.

We analyzed distribution of rejection related risk factors, cumulative immunosuppressive drugs in the first 3 months, CMV serology of donors and recipients, and CMV infection episodes in the first 3 months. Theophylline exposure was 440 ± 104 mg/day for a period of 142 ± 39 days. There were no statistically significant differences between the theophylline and control group in terms of these parameters (Table 3).

We also analyzed number of treated rejection episodes, vascular rejection episodes, rejection episodes with hemodynamic compromise, mean biopsy scores, and time to first rejection episodes in both groups. There was no statistically significant difference between groups in terms of rejection episodes, but there was a statistically significant difference related with average biopsy scores and time to first rejection (Table 4).

DISSCUSSION

This study demonstrates that theophylline may have a positive impact on subclinical (mean biopsy scores and time to first rejection) indices of cellular cardiac allograft rejection. There were no differences between the groups regarding episodes of treated rejec-

Table 2. Demographics of patients and donors

	Theophylline gr.	Control gr.	P value
Mean age of recipients (years)	51.1 ± 11.2	53.7 ± 9.4	NS
Female / Total in recipients	3 / 27 (%11.1)	5 / 29 (%17.2)	NS
Afro-american /Total in recipients	4 / 27 (%14.8)	7 / 29 (%24.1)	NS
Mean age of donors (years)	30 ± 12.4	26.4 ± 10.8	NS
Female / Total in donors	9 / 27 ± (%33.3)	10 / 29 (%34.4)	NS
Afro-american / Total in donors	10 / 27 (%37)	8 / 29 (%27.5)	NS

NS: Not significant

Table 3. Distribution of rejection related risk factors

	Theophylline gr.	Control gr.	P value
No. of patients with PRA> % 10	0	1	NS
Mean no. of HLA mismatches	5.07 ± 0.81	5.14 ± 0.8	NS
No. of patients with (+) retrospective crossmatch	2	3	NS
Mean Cy A in 3 months (mg)	38250 ± 8451 mg	38098 ± 11188	NS
Mean azotiopurine in 3 months (mg)	9296 ± 3977	8974 ± 2121	NS
Mean prednisolone in 3 months (mg)	3869 ± 1038	3572 ± 947	NS
No. of patients with OKT3 exposure in 3 months	12	16	NS
No. of (+) CMV serology in recipients	24	19	NS
No. of (+) CMV serology in donors	18	18	NS
No. of Tx. With CMV (+) donor to CMV (-) recipient.	3	5	NS
No of CMV infection episodes	4	3	NS

Tx: Transplantation *PRA: Panel reactive antibodies*
CMV: Cytomegalovirus *Cy A: Cyclosporine A*

Table 4. Outcomes of rejection episodes in 3 months

	Theophylline gr.	Control gr.	P value
No. of treated rejection episodes	7	7	NS
No. of vascular rejection episodes	6	4	NS
No. of episodes with hemodynamic compromise	2	2	NS
Mean biopsy score in 3 months	0.73 ± 0.42	0.98 ± 0.51	0.04
Time to first rejection (days)	51 ± 26	24 ± 21	0.05

tion, vascular rejection and rejection episodes with hemodynamic compromise.

Although theophylline has been used for many years, the exact mode of action is unclear [10]. The most approved hypothesis are phosphodiesterase enzyme inhibition, adenosine receptor antagonism, effect on cathecholamine secretion and influence on calcium ions [10,11]. Possibly more than one mechanism participate in producing the effects of theophylline. In the past decade several studies have demonstrated the immunmodulatory effects of theophylline [12,13,14].

The conversion of cAMP is catalyzed by the enzyme phophodiesterase and inhibition of the activity of this enzyme results in intracellular accumulation of cAMP and activation of immunologically paralytic pathway [15,16]. Theophylline has several other effects on T lymphocyte function. Reduced T cell proliferation after antigenic [1] and mitogenic [2] stimulation as well as diminished E-rosette formation [3] have been demonstrated. Phytohemagglutinin stimulated IL-2 production and IL-2 dependent proliferation of T lymphocytes are diminished by theophylline in vitro [2,17]. Long term theophylline therapy in patients with asthma increases the number of CD8 or suppressor T cells in peripheral blood and also impairs the graft versus host reaction of these lymphocytes [1,18].

Theophylline also acts as an anti-inflammatory drug through modulation of cytosine production. After exposure to theophylline, reduction of the anti-inflammatory cytokine IL-10 is increased, an outcome that results in an inhibitory effect of on the production of other proinflammatory cytokines like IL-2, interferon γ, IL-5, tumor necrosis factor alpha and IL-8 [19].

In a previous study Shapira et al [12] could successfully treat steroid resistant renal rejections with aminophylline (theophylline ethylenediamine), and they also demonstrated that aminophylline treated patients did not show local xenogenic graft-versus host reaction indicating increased T-suppressor activity.

In an animal model of heart transplantation with rats in which theophylline was used as a single immunmodulator, the authors were able to prolong survival

hypothesizing two possibilities: first a reduction in the recruitment of specific effector lymphocytes through a direct inhibition of their mitogenic response, owing to a theophylline induced cAMP levels in these cells; second a possible cAMP dependent activation of suppressor T lymphocytes [13].

To our knowledge, this is the first study investigating effects of theophylline exposure on rejection in heart transplantation in man. We found a positive impact on subclinical rejection episodes (mean biopsy score) and time to first rejection. Despite improvements in immunsupressive regimens, rejection is still a major cause of morbidity and mortality. That is why we believe that any drug that may have a positive impact on this process is worth closer scrutiny.

Limitations of the study: There are several limitations of this study. First, it was a retrospective one having inherent kind of problems with that type of research. Second, it was a non-randomized study. Other than those, theophylline levels were not routinely screened but mainly usual conventional dosages were used. The time interval that theophylline was used may not be long enough (patients who used theophylline for at least four weeks were enrolled in the study).

Conclusion: Theophylline therapy for cardiac transplantation does not have any effect on treated rejection episodes, vascular rejection episodes, and episodes with hemodynamic compromise, but it may decrease subclinical (mean biopsy score) indices of cellular cardiac allograft rejection and increase the time to first rejection. Large, prospective, randomized studies to further evaluate importance of theophylline as an adjunct therapy is probably indicated.

REFERENCES

1. Scordamaglia A, Ciprandi G, Ruffoni S et al: Theophylline and the immune response : in vitro and in vivo effects. Clin Immunol Immunopathol 1988;48:238-46

2. Bruserud O: The effect of theophyllamine on T-lymphocyte activation in vitro. Clin Immunol Immunopathol 1984;32:111-8

3. Limatibul S, Shore A, Dosch HM, Gelfand EW: Theophylline modulation of E-rosette formation: an indicator of T cell maturation. Clin Exp Immunol 1978;33:503-13

4. Bertolet BD, Eagle DA, Conti JB et al: Bradycardia after heart transplantation: reversal with theophylline. J Am Coll Cardiol 1996;28:396-9

5. Redmond JM, Zehr KJ, Gillinov MA et al: Use of theophylline for treatment of prolonged sinus node dysfunction in human orthotopic heart transplantation. J Heart Lung Transplant 1993;12:133-8

6. Heinz G, Kratochwill C, Buxbaum P et al: Immediate normalization of profound sinus node dysfunction by aminophylline after cardiac transplantation. Am J Cardiol 1993;71:346-9

7. Billingham ME, Cary NR, Hammond ME et al: A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. J Heart Transplant 1990;9:587-96

8. Costanzo MR, Cross AM, Haas GS: Post-Transplant Care/Medical Complications. In: Norman DJ, Suki WN editors, Primer On Transplantation. Aston Pub Ltd 1997, p: 445-58

9. Kobashiagawa JA, Kirlin JK, Naftel DC et al: Pretransplantation risk factors for acute rejection after heart transplantation: a multiinstitutional study. J Heart Lung Transplant 1993;12:355-66

10. Vassallo R, Lipsky JJ: Thepohylline: Recent advances in the understanding of its mode of action and uses in clinical practice. Mayo Clin Proc 1998;73:346-54

11. Serafin WE: Drugs used in the treatment of ashtma. In: Gilman AG, Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, editors. Goodman and Gilman`s The Pharmacological Basis of therapeutics. 9 th ed. New York: McGraw-Hill; 1996 p 672-8

12. Shapira Z, Shotat B, Boner G et al: Theophylline: a possible immunoregulator of T cells. Transplantation Proceedings 1982;14:113-6

13. Rugarli C, Marni A, Ferrero MA et al: Prolonged survival of experimental heart transplantation induced by theophylline. Immunology Letters 1983;6:247-50

14. Guillou PJ, Ramsden C, Kerr M et al: A prospective controlled clinical trial of aminophylline as an adjunctive immunosuppressive agent. Transplantation proceedings 1984;16:1218-20

15. Watson J, Epstein R, Cohn M: Cyclic nucleotides as intracellular mediators of the expression of antigen-sensitive cells. Nature 1973;246:405-9

16. Goto T, Herberman RB, Maluish A et al: Cyclic AMP as a mediator of prostaglandin E-induced suppression of human natural killer cell activity. J Immunol 1983;130:1350-5

17. Mary D, Aussel C, Ferrua B, Fehlmann M: Regulation of interleukin 2 synthesis by c AMP in human T cells. J Immunol 1987;139:1179-84

18. Fink G, Mittelman M, Shotat B, Spitzer SA: Theophylline-induced alterations in cellular immunity in asthmatic patients. Clin Allergy 1987;17:313-6

19. Mascali JJ, Cvietusa P, Negri J, Borish L: Anti-inflammatory effects of theophylline : modulation of cytokine production. Ann Allergy Asthma Immunol 1996;77:34-8