ORIGINAL PROF-1468

ANGINA PECTORIS;
ROLE OF TRIMETAZIDINE

DR. ISHTIAQ AHMED MALIK, MBBS, FCPS
Classified Medical Specialist & Cardiologist
AFIC / NIHD, The Mall Road,
Rawalpindi

DR. ALI NAWAZ KHAN, MBBS, FCPS
Classified Medical Specialist & PG Trainee Cardiology
AFIC / NIHD, The Mall Road,
Rawalpindi

DR. KHALID MAHMOOD, MBBS, FCPS-I
PG Trainee Medicine
Garrison Medical Centre
Pannu Aqil

Article Citation:
Malik IA, Khan AN, Mahmood K. Angina pectoris; Role of trimetazidine. Professional Med J Jun 2009; 16(2): 202-208.

ABSTRACT… Objective: To assess the clinical efficacy, cost effectiveness and side effect profile of trimetazidine in the management of stable angina pectoris. **Patients and Methods:** An open label, uncontrolled study was conducted in 200 patients with stable angina in armed forces institute of cardiology, Rawalpindi Pakistan. Patients were treated for 4weeks with modified release trimetazidine tablet (35mg) twice daily in addition to their conventional therapy. **Results:** As compared to base line trimetazidine significantly reduced the number of anginal episodes per week from 10 to 3 ($p<0.005$), improved exercise duration time on standard exercise tolerance test (ETT) (410 vs. 370 sec; $p<0.01$), time to onset of typical angina (380 vs, 290sec; $p<0.05$), time to 1mm or more ST segment depression (340 vs. 290 sec; $p<0.01$)).There was no drop out of patients due to side effects or non compliance. **Conclusion:** These results indicate that trimetazidine is effective and well tolerated when used in combination with existing antianginal therapy in patients with angina pectoris

Key words: ACS. STEMI. NSTEMI. ECG. ETT. CAD.

INTRODUCTION

Acute coronary syndrome (ACS) is the term collectively used for spectrum of ischemic heart disease ranging from effort angina, unstable angina, non ST elevation myocardial infarction (NSTEMI) to ST elevation myocardial infarction (STEMI).

Cardiovascular diseases, in particular ischemic heart disease (IHD) or coronary artery disease (CAD), are one of the leading causes of death worldwide, they are now particularly common in developing countries[1].

Previous research has suggested that patients with stable coronary artery disease (CAD) fare well when treated with medical management (use of medications alone)[2]. Many patients with this particular disease profile, however, are often treated more aggressively with invasive procedures including the placement of coronary stents or bypass grafting procedures. It was not known if delaying invasive treatment and managing patients with stable coronary disease medically was a viable and safe alternative to immediate invasive treatment[3]. The initial aims of treatment of stable angina are to decrease the frequency and severity of attacks and increase the

Article received on: 29/01/2009
Accepted for Publication: 19/02/2009
Received after proof reading: 07/05/2009
Correspondence Address:
Dr. Ishtiaq Ahmed Malik, MBBS, FCPS
Classified Medical Specialist & Cardiologist
AFIC / NIHD, The Mall Road,
Rawalpindi
dr_ishtiaq@live.com

functional capacity of patients, with minimal adverse events. Ultimately, however, the aim should also be to improve prognosis, i.e. prevent MI and death[4].

Trimetazidine (1-[2,3,4-trimethoxy benzyl] piperazine hydrochloride) is a metabolic agent with anti-ischaemic properties that operates independently of any haemodynamic changes. As demonstrated in studies in isolated myocytes and working rat hearts, trimetazidine acts by optimising cardiac metabolism during and after ischaemia Indeed, it now seems clear that trimetazidine acts by changing the patterns of myocardial energy substrate use during ischaemia, leading to increased ATP production with less oxygen consumption. By decreasing fatty acid beta-oxidation, trimetazidine secondarily stimulates glucose oxidation, restoring the coupling between glycolysis and carbohydrate oxidation. In turn, the development of intracellular acidosis is minimized, which maintains cellular homeostasis and the contractile properties of the heart. By stimulating membrane phospholipids turnover during ischaemia/ reperfusion, trimetazidine redirects fatty acids toward phospholipids[5]. This further decreases the availability of fatty acids for beta-oxidation. These anti-ischaemic properties of trimetazidine have been confirmed in clinical studies, both when used as monotherapy in comparison with standard antianginal therapy and in combination with other antianginal agents such as calcium antagonists or beta-blockers.

MATERIALS AND METHODS

The subject study was an open, unicentre trial divided into two phases: a 1-week observation period (W-1 to W0) to confirm clinical stability on existing antianginal therapy (i.e. monotherapy with a long-acting nitrate, beta-blocker or calcium antagonist), followed by a 4-week treatment period (W0 to W4) during which patients received trimetazidine modified release tab-35mg twice daily in addition to existing antianginal therapy. Patients aged 28 to 60 years with a history of stable, effort-induced angina (for >/=3 months) and documented CAD [either >70% narrowing in at least one coronary artery on coronary angiography or previous myocardial infarction (MI)] were enrolled. Patients were also required to have positive treadmill exercise tests during visits W-1 and W0 . Clinical stability at inclusion was defined as a change of no greater than 20% in time to 1mm ST-segment depression between these time-points. Exclusion criteria included: MI or unstable angina in the previous 3 months; Prinzmetal angina; cardiac surgery; percutaneous transluminal coronary angioplasty, stroke or transient ischaemic attack in the previous 6 months; inadequately controlled arterial hypertension (blood pressure >160/95mm Hg); moderate or severe heart failure (New York Heart Association grade III or IV); clinically significant cardiac abnormalities; severe disease of other organs with a poor prognosis; inability to perform exercise tests; concomitant therapy with drugs or baseline ECG abnormalities (e.g. Wolff-Parkinson-White syndrome, bundle branch block) that might interfere with the interpretation of electrocardiographic ST-segment changes; and pregnancy.

Written informed consent was obtained from each patient before participation in the study.

Clinical examinations and maximal treadmill exercise tests (Bruce protocol) were performed at the initial assessment (W-1), at study baseline (W0), and after 4 weeks of treatment with trimetazidine (W4). Throughout the study, other therapies routinely used for CAD [e.g. aspirin, antiplatelet drugs, anticoagulants and hypolipidaemic agents] were permitted; along with the use of short-acting nitrates for the relief of anginal pain (patients completed a daily diary recording the number of anginal attacks and nitrate consumption). During exercise tests, grade of anginal pain was scored using the Canadian Cardiovascular Society scale. Positive exercise tests were characterized by either a horizontal or downward sloping depression of >/=1mm in the ST-segment (>80 msec after the J-point) and anginal pain, or >/=1.5mm ST depression without anginal pain, which occurred between the third and tenth minute of the test.

Laboratory safety assessments were made at W0 and W4. All adverse events, evaluated from investigators' questioning and by patients' volunteering information, were recorded. Patient compliance was assessed at the final visit.

RESULTS

Patient characteristics at baseline are shown in table I. Clinical stability on existing antianginal monotherapy was confirmed by the finding that no statistically significant differences were apparent for exercise stress test parameters during the 1-week observation period.

PRIMARY EFFICACY CRITERIA

All patients (n = 200) were evaluable for the primary efficacy criteria. After 4 weeks' treatment with trimetazidine 20mg three times daily, these patients showed significant symptomatic improvements and improvement in all exercise stress test parameters.

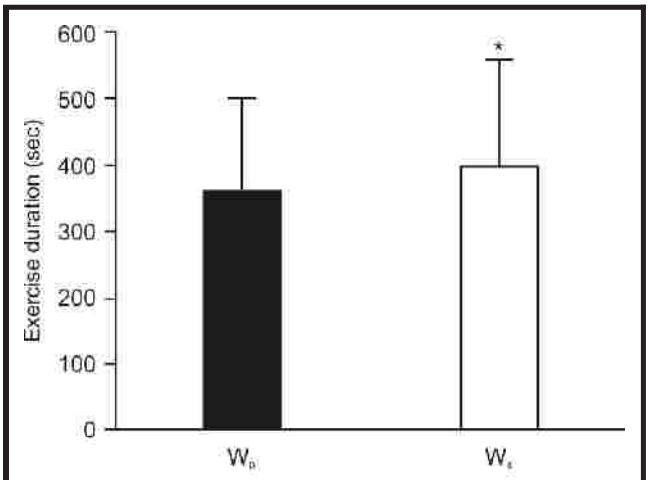

Fig-1. Increase in mean (± SD) total exercise duration in 200 patients with stable angina pectoris over 4 weeks' trimetazidine 35mg twice daily. Exercise duration was assessed during treadmill exercise testing. SD = standard deviation; W0 = baseline; W4 = end of treatment. *p <0.01 vs W0.

Thus, significant increases in exercise capacity at W4 were apparent in comparison with baseline (W0), both in terms of exercise duration and total work during maximal exercise testing. Trimetazidine also reduced exercise-induced ischaemia, as demonstrated by significant increases in the time to 1mm ST-segment depression and the time to onset of anginal pain. Maximal ST-segment depression at W4 was also attenuated compared with baseline (1.76 and 1.87mm, respectively).

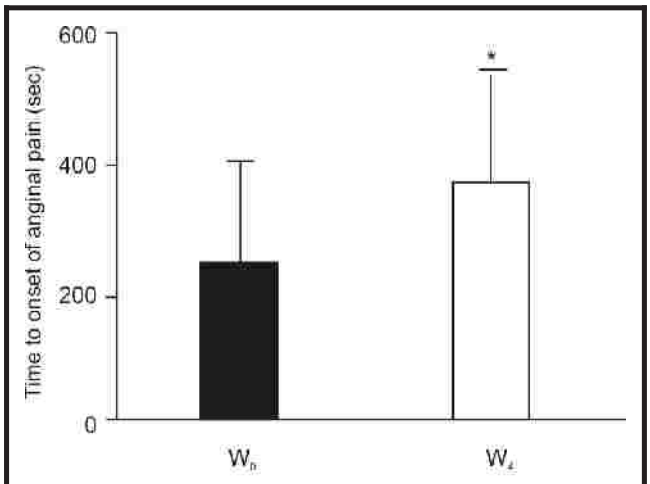

Fig-2. Increase in exercise test duration to 1mm ST-segment depression in 200 patients with stable angina pectoris over 4 weeks' treatment with trimetazidine 35mg twice daily. Time to 1mm ST-segment depression was assessed during treadmill exercise testing. SD = standard deviation; W0 = baseline; W4 = end of treatment; *p <0.01 vs W0.

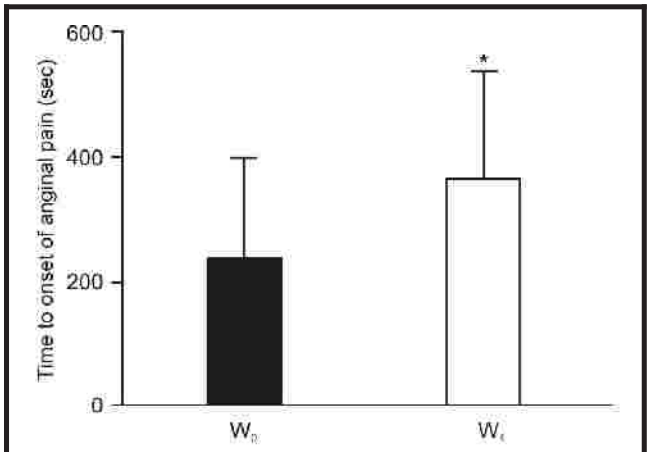

Fig-3. Increase in time to onset of anginal pain in 200 patients with stable angina pectoris over 4 weeks' treatment with trimetazidine 35mg twice daily. Time to onset of anginal pain was assessed during treadmill exercise testing. SD = standard deviation; W0 = baseline; W4 = end of treatment; *p <0.01 vs W0.

DISCUSSION

It has been shown that the quality of life of patients with angina pectoris is significantly correlated with the number of weekly anginal attacks. Patients with an average of two anginal attacks per week did not report any reduction in their enjoyment of life. In our study the number of

anginal attacks decreased continuously from 11.2 per week to 3.6 per week in 4 weeks; they had a moderate reduction in their enjoyment of life compared with a severe reduction in their enjoyment of life prior to trimetazidine MR treatment.[6] At the end of the study, 96% of the patients stated that they would like to continue treatment with trimetazidine MR. This formulation is not only cost effective but also adds to convenience of use by reducing dose frequency, thus providing an additional comfort to the patient. It can also reduce the mean peak-trough fluctuation of plasma concentration[7].

Although the three major types of treatment for chronic angina pectoris - medical, surgical and angioplasty –are available, differences in risks and possible benefits are apparent[8]. The initial aims of treatment of stable angina are to decrease the frequency and severity of attacks and increase the functional capacity of patients, with minimal adverse events. Ultimately, however, the aim should also be to improve prognosis, i.e. prevent MI and death.

With advancing age, alterations occur in the cardiovascular system (and in renal and hepatic function) that may be relevant when considering drug therapy in the elderly. Inadequate myocardial blood supply in the elderly is caused by age-related changes in cardiovascular structure and function: increased arterial stiffness; increases in blood pressure, muscle mass, systemic vascular resistance, and aortic impedance; and decreases in early diastolic left ventricular (LV) filling and early diastolic LV volume. Pharmacokinetic changes associated with aging may be related to decreased renal clearance, as well as alterations in hepatic drug metabolism and changes in drug absorption. Thus, drug dosages in older patients have to be chosen with great care and should be lowered for those drugs that have a reduced clearance in the elderly.

With advancing age, patients may have diagnosed or undiagnosed concomitant diseases, which may be responsible for adverse responses to cardiovascular drugs or necessitate co-administration of additional agents and trimetazidine is a very useful addition in this group of patients. Because of the frequency of multiple drug therapies, which are often prescribed by different practitioners, the elderly are particularly at risk of drug interactions and compliance may be a problem[9]. Adverse effects of antianginal drugs are also more common in the elderly. Nitrates, for example, are associated with a number of adverse effects including headache, flushing and syncope. Specifically, hypotension due to decreases in baroreceptor function with age is often seen in elderly patients receiving nitrate therapy, while impaired atrioventricular conduction can be caused by verapamil and diltiazem. Flushing, headaches, dizziness and peripheral edema are relatively common events associated with calcium antagonists, and may even occur at lower doses. Furthermore, caution is advised over the use of beta-blockers in the elderly, because symptomatic bradycardia, sinus node disease or atrioventricular block, heart failure or worsening intermittent claudication may occur at lower doses than in younger patients [9]. It is therefore important to closely monitor the haemodynamic effects of existing antianginal drugs in the elderly.

In an attempt to identify new and better tolerated anti-ischaemic therapies for angina pectoris, a number of clinical trials have been conducted to assess the efficacy and tolerability of trimetazidine, either as monotherapy or in combination with other antianginal agents. In a double-blind, parallel-group multicentre study, for example, trimetazidine was as effective as the beta-blocker propranolol in patients with stable angina[10]. Another double-blind study[16] showed that both trimetazidine and isosorbide_ dinitrate were associated with significant decreases in anginal severity, but this was more pronounced in patients treated with trimetazidine. Furthermore, only trimetazidine significantly increased exercise duration and time to 1mm ST-segment depression, which is considered the most objective measures of anti-ischaemic efficacy. Other studies in patients with stable angina who remained symptomatic on diltiazem reported clinically significant improvements after combination treatment with trimetazidine, without adverse haemodynamic effects or an increased incidence of adverse events[11,12]. The results of the present study confirm previous observations: trimetazidine was associated with a marked anti-

ischaemic effect without changes in systemic haemodynamics during maximal exercise testing. Trimetazidine increased the time to ST-segment depression and anginal pain during exercise (the limited number of patients precluded further evaluation according to baseline severity of angina), as well as exercise duration and total work. However, there were no significant changes in rate-pressure product at maximal exercise. Previous studies in dogs found no evidence of coronary haemodynamic effects for trimetazidine,[13] which suggests that an increase in coronary blood flow does not explain the anti-ischaemic effect of this agent. These findings are supported by the experimental evidence that the anti-ischaemic efficacy of trimetazidine is mediated by a reduction in fatty acid oxidation within ischaemic cardiac myocytes.

The absence of systemic haemodynamic effects of trimetazidine probably explains its acceptable tolerability in the present study, the first investigation of this novel metabolic agent in treating angina in elderly patients. However, the study has several limitations that need to be considered when interpreting both the tolerability and efficacy findings. For example, the study did not have a placebo control group and the open-label design (although analogous to the true prescribing and practice patterns encountered in routine clinical practice) means that the results could have been subject to investigator bias. However, the consistency among all results, including the highly objective time to 1mmST-segment depression, argues against investigator bias and/or a significant placebo effect. In addition, the findings of the present study are consistent with those of a number of double-blind, placebo-controlled studies of trimetazidine[14,15]. Subsequent analysis of the TRIMPOL-1 findings has confirmed that such improvements are equivalent to those observed in younger patients.

Although the three major types of treatment for chronic angina pectoris - medical, surgical and angioplasty - are as applicable to the elderly as they are to younger patients, differences in risks and possible benefits are apparent[8]. The initial aims of treatment of stable angina are to decrease the frequency and severity of attacks and increase the functional capacity of patients, with minimal adverse events. Ultimately, however, the aim should also be to improve prognosis, i.e. prevent MI and death.

With advancing age, alterations occur in the cardiovascular system (and in renal and hepatic function) that may be relevant when considering drug therapy in the elderly. Inadequate myocardial blood supply in the elderly is caused by age-related changes in cardiovascular structure and function: increased arterial stiffness; increases in blood pressure, muscle mass, systemic vascular resistance, and aortic impedance; and decreases in early diastolic left ventricular (LV) filling and early diastolic LV volume. Pharmacokinetic changes associated with aging may be related to decreased renal clearance, as well as alterations in hepatic drug metabolism and changes in drug absorption. Thus, drug dosages in older patients have to be chosen with great care and should be lowered for those drugs that have a reduced clearance in the elderly.

With advancing age, patients may have diagnosed or undiagnosed concomitant diseases, which may be responsible for adverse responses to cardiovascular drugs or necessitate co-administration of additional agents. Because of the frequency of multiple drug therapies, which are often prescribed by different practitioners, the elderly are particularly at risk of drug interactions and compliance may be a problem[9]. Adverse effects of antianginal drugs are also more common in the elderly. Nitrates, for example, are associated with a number of adverse effects including headache, flushing and syncope. Specifically, hypotension due to decreases in baroreceptor function with age is often seen in elderly patients receiving nitrate therapy, while impaired atrioventricular conduction can be caused by verapamil and diltiazem. Flushing, headaches, dizziness and peripheral edema are relatively common events associated with calcium antagonists, and may even occur at lower doses. Furthermore, caution is advised over the use of beta-blockers in the elderly, because symptomatic bradycardia, sinus node disease or atrioventricular block, heart failure or worsening intermittent claudication may occur at lower doses than in younger patients[9]. It is therefore important to closely monitor the haemodynamic

effects of existing antianginal drugs in the elderly.

In an attempt to identify new and better tolerated anti-ischaemic therapies for angina pectoris, a number of clinical trials have been conducted to assess the efficacy and tolerability of trimetazidine, either as monotherapy or in combination with other antianginal agents. In a double-blind, parallel-group multicentre study, for example, trimetazidine was as effective as the beta-blocker propranolol in patients with stable angina[14]. Another double-blind study[15] showed that both trimetazidine and isosorbide dinitrate were associated with significant decreases in anginal severity, but this was more pronounced in patients treated with trimetazidine. Furthermore, only trimetazidine significantly increased exercise duration and time to 1mm ST-segment depression, which are considered the most objective measures of anti-ischaemic efficacy. Other studies in patients with stable angina who remained symptomatic on diltiazem reported clinically significant improvements after combination treatment with trimetazidine, without adverse haemodynamic effects or an increased incidence of adverse events[11,12]. The results of the present study confirm previous observations: trimetazidine was associated with a marked anti-ischaemic effect without changes in systemic haemodynamics during maximal exercise testing. Trimetazidine increased the time to ST-segment depression and anginal pain during exercise (the limited number of patients precluded further evaluation according to baseline severity of angina), as well as exercise duration and total work. However, there were no significant changes i.e. rate-pressure product at maximal exercise. Previous studies in dogs found no evidence of coronary haemodynamic effects for trimetazidine,[13] which suggests that an increase in coronary blood flow does not explain the anti-ischaemic effect of this agent. These findings are supported by the experimental evidence that the anti-ischaemic efficacy of trimetazidine is mediated by a reduction in fatty acid oxidation within ischaemic cardiac myocytes.

The absence of systemic haemodynamic effects of trimetazidine probably explains its acceptable tolerability in the present study. However, the study has several limitations that need to be considered when interpreting both the tolerability and efficacy findings. For example, the study did not have a placebo control group and the open-label design (although analogous to the true prescribing and practice patterns encountered in routine clinical practice) means that the results could have been subject to investigator bias. However, the consistency among all results, including the highly objective time to 1mmST-segment depression, argues against investigator bias and/or a significant placebo effect. In addition, the findings of the present study are consistent with those of a number of double-blind, placebo-controlled studies of trimetazidine[14,15].

CONCLUSION

In conclusion, the results of this analysis suggest that the patients with angina pectoris not controlled by conventional antianginal drugs, the addition of the metabolic agent trimetazidine is well tolerated and improves the symptoms of angina and exercise tolerance. The most frequently reported adverse event that occurred after administration of trimetazidine MR was nausea, noted in four patients. More than 90% of both investigators and patients noted the high tolerance of trimetazidine MR therapy, and assessed it as ‘excellent' or ‘good'.

REFERENCES

1. Omran AR, Loper AD, The global burden of disease,Cambridge, MA, Harvard School of Public Health,1996.

2. Russel LB, Gold MR, Seigel JE et al; **The role of costeffectiveness analysis in health and medicine.** Panel on costeffectiveness and medicine, JAMA 276;1172,1996.

3. Weinstein MC,Seigel JE, Gold MR,et al; **Recommendations of the Panel on cost effectiveness in health and medicine,** JAMA 276;1253;1996.

4. Gibbons RJ,Abrams J, Chatterjee K, et al; ACC/AHA 2002 **Guidelines update for the management of patients with chronic stable angina** (available at www.acc.org/clinical/guidelines/stable/angina.pdf).

5. Rapp H, Zarain Herzberg A, Maisch B, **The role of partial fatty acid oxidationinhibitors for metabolic therapy of**

angina pectorisand heart failure. Herz 27;621-636,2002.

6. Willich SN. **European survey on circadian variation of angina pectoris (ESCVA): design and preliminary results.** J Cardio-vasc Pharmacol 1999; 34 Suppl. 2: S9-S13.

7. Genissel P, Chodjania Y, Delmolis JL, et al. **Assessment of the sustained release properties of a new oral formulation of trimetazidine in pigs and dogs and confirmation in healthy human volunteers.** Eur J Drug Metabol Pharmacokin 2004; 29 (1): 61-8.

8. Duprez DA. **Angina in the elderly.** Eur Heart J 1996; 17 Suppl. G: 8-13.

9. Wolfel EE. **Coronary artery disease. I**n: Schrier RW, editor. Geriatric medicine. Philadelphia: Saunders, 1990: 237-50

10. Detry JM, Sellier P, Pennaforte S, et al. **Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina.** Br J Clin Pharmacol 1994; 37: 279-88.

11. Manchandra SC, Krishnaswami S. **Combination treatment with trimetazidine and diltiazem in stable angina pectoris.** Heart 1997; 78: 353-7.

12. Levy S. **Combination therapy of trimetazidine with diltiazem in patients with coronary artery disease.** Am J Cardiol 1995; 76: 12B-16B.

13. Timour Q, Harpey C, Durr F, et al. **Is the antianginal action of trimetazidine independent of haemodynamic changes?** Cardiovasc Drug Ther 1991; 5: 1043-4.

14. Detry JM, Sellier P, Pennaforte S, et al. **Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina.** Br J Clin Pharmacol 1994; 37: 279-88.

15. Michaelides AP, Spiropoulos K, Dimopoulos K, et al. **Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina.** Clin Drug Invest 1997; 13: 8-14.