Acute peri-operative beta-blockade in South Africa

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Introduction
This paper considers the effect of physiochemical and/or pharmacokinetic properties on the cardioprotective efficacy of acute peri-operative beta-blockade, indications for peri-operative beta-blockers and economic viability in South Africa.

1. Is there a preferable peri-operative beta-blocker based on physiochemical and pharmacokinetic properties?

a. *Physiochemical/ ancillary properties*
Beta-blockers are protective against sudden arrhythmic death following myocardial infarction (MI).[1-2] Although, all beta-blockers are anti-arrhythmic[3-5], the beta-blockers with the greatest efficacy in decreasing sudden arrhythmic death following MI and/or congestive heart failure are lipophilic.[6-7] It was proposed that lipophilic beta-blockers may, in addition, attenuate vagal withdrawal during myocardial ischaemia, decreasing ventricular fibrillation.[8]

Recent reports suggest that the cardioprotective efficacy of atenolol, a hydrophilic, cardioselective beta-blocker[9-10] may be less than that of lipophilic congeners.[6] We conducted a limited systematic review comparing the incidence of in hospital ventricular fibrillation following acute MI in beta-blocker naive patients, who either received atenolol (a theoretically undesirable beta-blocker) or metoprolol (a theoretically desirable beta-blocker).[11] However, neither drug significantly decreased in-hospital ventricular fibrillation following MI.[31]

Conclusion
Although the medical literature suggests that the combination of a hydrophilic, cardioselective beta-blocker (atenolol) may minimise cardioprotection in medical patients[12,13,41], in the context of ventricular fibrillation following acute MI we could not show a difference between atenolol and metoprolol.[11]

b. *Pharmacokinetics: the duration of action*
A recent report suggested that in acute peri-operative beta-blockade, shorter acting beta-blockers (metoprolol) were associated with an increased mortality in comparison to the longer acting beta-blockers (atenolol). This was ascribed to the detrimental effects of acute beta-blocker withdrawal.[12]

This paper is unfortunately misleading.[13] Firstly, when the potential cardioprotective benefits of peri-operative beta-blockade are discussed, they refer specifically to acute peri-operative beta-blocker administration.[14] However, the paper describes patients undergoing surgery on chronic (as opposed to acute) beta-blockade. This distinction is vital, as although acute peri-operative beta-blockade may provide peri-operative cardioprotection[15], there is currently no evidence of cardioprotective efficacy of chronic beta-blockade in the peri-operative period.[16] Secondly, there was no control group of patients not on beta-blocker therapy in the peri-operative period. The concern therefore, is that although atenolol was shown to be safer than metoprolol[12], this does not imply that chronic atenolol therapy is cardioprotective in the peri-operative period.[16]

Conclusion
There is currently no evidence to suggest that withdrawal of acute peri-operative beta-blockade increases cardiovascular risk.

Conclusions regarding the choice of peri-operative beta-blocker
As both atenolol[17] and bisoprolol[18] may be cardioprotective in the surgical patient, it is possible that the prevention of myocardial ischaemia is significantly more important peri-operatively than other factors such as physiochemical or pharmacokinetic properties.

2. In which surgical patients are beta-blockers indicated and are they economically viable in South Africa?

a. *Acute peri-operative beta-blockade and the high-risk surgical patient (patients at risk of major peri-operative cardiovascular complications)*
In the published prospective studies examining acute peri-operative beta-blockade where major cardiovascular complications were reported[18-26], beta-blockers significantly decreased peri-operative MI, late cardiovascular deaths and all postoperative deaths up to two years. However, the beta-blocked patients had significantly increased drug associated adverse events (Table 1). Based on these reported outcomes, a pharmaco-economic analysis was conducted using the Discovery Health 2004 claims costs for patients in the age band 61 to 75 years[27], comparing the total expected cost of treating surgical patients with 200 mg of metoprolol for 30 days versus placebo for 30 days

Table 1. Reported cardiovascular complications and adverse events in prospective studies of acute peri-operative beta-blocker therapy in high-risk surgical patients.[17-26 31] Values are number (percentage).

	ß-blocker therapy (n = 642)	*No ß-blocker therapy (n = 607)*	*p value*	*Odds ratio (95% CI)*
Cardiovascular complications:				
Non-fatal cardiac arrest	2 (0.3%)	5 (0.8%)	0.28	0.38 (0.05-1.82)
Non-fatal MI	24 (3.7%)	42 (6.9%)	0.02	0.52 (0.31-0.88)
Death within 30 days of surgery (A)	12 (1.9%)	20 (3.3%)	0.15	0.56 (0.26-1.15)
Death up to 2 years after hospital discharge† (B)	15/148 (10.1%)	30/145 (20.7%)	0.01	0.43 (0.21-0.88)
All deaths up to 2 years (C=A+B)	27 (4.2%)	50 (8.2%)	0.003	0.49 (0.30-0.80)
Potential adverse drug events:				
Congestive heart failure	28 (4.4%)	17 (2.8%)	0.173	1.58 (0.86-3.07)
Hypotension needing treatment	200 (31.2%)	144 (23.7%)	0.004	1.46 (1.13-1.88)
Bradycardia needing treatment	63 (9.8%)	24 (4.0%)	<0.0001	2.84 (1.72-4.68)
Bronchospasm	20 (3.2%)	19 (3.1%)	1.00	1.00 (0.52-1.94)
Non-fatal CVA	5 (0.8%)	1 (0.2%)	0.22	4.76 (0.66-110.98)
Total	316 (49.2%)	205 (33.8%)	<0.0001	1.90 (1.51-2.40)

† From the studies of Mangano et al17 and Poldermans et al[31]

Table 2. Cost analysis of peri-operative beta-blocker therapy per patient (based on Buller et al32). Costs are presented as South African rands (ZAR).

	ß-blocker therapy	*No ß-blocker therapy*
Cost of peri-operative cardiovascular complications (A)	3732.62	7168.04
Cost of adverse drug events (B)	7784.90	5596.67
Cost of beta-blocker or placebo therapy (C)	378	0
Total cost (D= A + B+C)	11 895.52	12 764.71
Incremental cost of beta-blocker therapy (E = D with beta-blockers – D without beta-blockers)	-869.19	–
Incremental cost per major peri-operative cardiovascular complication¶ avoided (E x NNT† (20))	-17 383.80	–

†NNT: number-needed-to-treat, ¶ Non-fatal cardiac arrest: non-fatal myocardial infarction, all-cause mortality within 30 days of surgery

peri-operatively as per the POISE protocol.[28] The cost of avoiding cardiovascular complications with beta-blocker therapy, per patient was shown to be cost-effective (Table 2).

Conclusions

a. Patients in whom acute beta-blockade is indicated. Acute peri-operative beta-blockade is cost-effective in South African patients of similar surgical and cardiovascular risk;[29] that is with an expected major cardiovascular complication rate of 11% (Revised Cardiac Risk Index (RCRI) of ≥3 risk factors[30]) following major noncardiac surgery.

b. Minimising side-effects associated with peri-operative beta-blocker therapy in high-risk surgical patients. The high incidence of major peri-operative cardiovascular events in the untreated patients suggests that these patients should routinely have further cardiac investigation prior to surgery. This would identify patients who require optimisation of ventricular function as opposed to beta-blockade increasing cost-effectiveness.

b. Acute peri-operative beta-blockade and the intermediate-risk surgical patient (patients at risk of peri-operative myocardial ischaemia without reported major peri-operative cardiovascular complications)

It is possible that decreasing peri-operative myocardial ischaemia with acute beta-blockade may improve long-term outcome.[33-34] However, no reports exist of the efficacy of acute peri-operative beta-blockers on long-term cardiovascular outcome in intermediate-risk patients. We attempted to quantify the effect of peri-operative beta-blockers on long-

Table 3. Reported cardiovascular complications and drug-related adverse events in prospective studies of peri-operative beta-blocker therapy in studies which only report myocardial ischaemia.36-40 Values are number (proportion).

	ß-blocker therapy (n = 178)	*No ß-blocker therapy (n = 117)*	*p value*	*Odds ratio (95% CI)*
Cardiovascular complications:				
Myocardial ischaemia	8 (4.5%)	18 (15.4%)	0.003	0.24 (0.11-0.63)
Adverse events:				
Congestive heart failure	0 (0%)	1 (0.9%)	0.40	0.00 (0.00-12.49)
Hypotension needing treatment	24 (13.5%)	18 (15.4%)	0.73	0.86 (0.44-1.67)
Bradycardia needing treatment	16 (9.0%)	9 (7.7%)	0.83	1.19 (0.48-2.92)
Bronchospasm	1 (0.6%)	0 (0%)	1.00	∞ (0.03-∞)
Total	41 (23.0%)	28 (23.9%)	0.89	0.95 (0.53-1.69)

Table 4. Incidence of major cardiovascular complications associated with peri-operative silent myocardial ischaemia in the 12 months following surgery[41]

	Vascular surgery	*Orthopaedic/ General surgery*
Presence silent myocardial ischaemia	31%	10%
Absence silent myocardial ischaemia	15%	5%

Table 5. The predicted incidence of major cardiovascular complications in the year following intermediate-risk nonvascular noncardiac surgery[41]

	ß-blocked		*Not ß-blocked*	
	SMI	*No SMI*	*SMI*	*No SMI*
Reported incidence (Table 3)	4.5%	95.5%	15.4%	84.6%
Predicted incidence of CVS* complications	10% of 4.5%	5% of 95.5%	10% of 15.4%	5% of 84.6%
Calculated CVS complications	0.45%	4.78%	1.54%	4.23%
Overall incidence of CVS complications†	5.23%	5.77%		

*CVS cardiovascular; SMI silent myocardial ischaemia † ARR 0.54%, NNT 186

Table 6. The predicted incidence of major cardiovascular complications in the year following vascular surgery[41]

	ß-blocked		*Not ß-blocked*	
	SMI	*No SMI*	*SMI*	*No SMI*
Reported incidence (Table 3)	4.5%	95.5%	15.4%	84.6%
Predicted incidence of CVS* complications	31% of 4.5%	15% of 95.5%	31% of 15.4%	15% of 84.6%
Calculated CVS complications	1.4%	14.3%	4.8%	12.7%
Overall incidence of CVS complications†	15.7%	17.5%		

*CVS cardiovascular; SMI silent myocardial ischaemia † ARR 1.8%, NNT 56

term cardiovascular outcome in surgical patients in which only peri-operative myocardial ischaemia is reported.[35] We identified five such studies.[36-40] The patient demographics were such that the majority had 1 or 2 RCRI clinical risk factors.[30] The NNT to prevent myocardial ischaemia was 9.2.

In order to estimate the long-term cardiovascular outcome in similar patients experiencing peri-operative myocardial ischaemia to those reported in Table 3, we identified a SMI study by Higham et al, in which we considered the patient demographics to be comparable.[41] Based on these reported long-term cardiovascular events (Table 4), we estimated the theoretical impact of acute peri-operative beta-blockade on major cardiovascular complications in the year following surgery in patients with predominantly 1 or 2 RCRI[30] clinical risk factors undergoing intermediate-risk surgery (Table 5) and vascular surgery (Table 6).

Using the POISE protocol[27-28], it would cost R70308 to prevent a single major cardiovascular event in the year following intermediate-risk surgery (which is not cost-effective) and R21168 following vascular surgery (this may be cost-effective, although this would require a study of 6818 patients per group to confirm this analysis (significance level of 0.05 and a power of 80%)).

Conclusions

Preventing myocardial ischaemia with acute beta-blockade in patients with 1 to 2 RCRI[30], undergoing intermediate-risk surgery[42] is unattractive. In vascular surgical patients, this intervention may be protective.

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References available on request