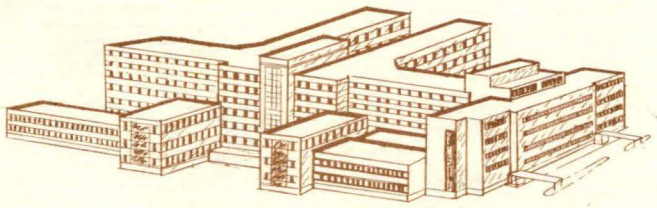

THE MOSES H. CONE MEMORIAL HOSPITAL

GREENSBORO, NORTH CAROLINA

# PHARMACY COMMITTEE NOTES

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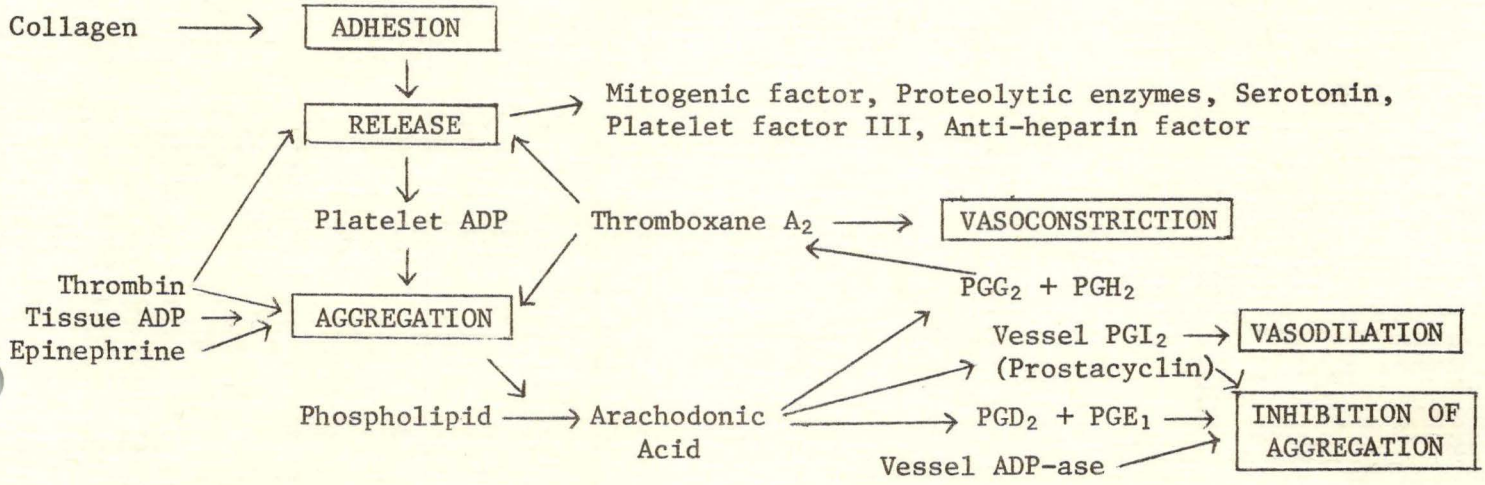
## THE ROLE OF ANTIPLATELET THERAPY AFTER MYOCARDIAL INFARCTION

The impairment of coronary blood flow has been regarded as a major cause of angina pectoris, myocardial infarction, ventricular arrhythmias and sudden cardiac death. Although the involvement of platelet activity in the precipitation of coronary blood flow impairment is incompletely understood, platelets do play an established role in the initiation of arterial thrombosis. Recent evidence also suggests that transient platelet aggregates in the coronary microcirculation and platelet derived vasoconstrictor substances play a role in producing cardiac ischemia. Interest has therefore continued in the drugs aspirin, sulfinpyrazone and dipyridamole on the basis that their antiplatelet activity may help prevent myocardial reinfarction and sudden cardiac death.[1,2,3,4,5,6,7,8,9]

The following figure depicts what is presently known about platelet aggregation activity. In addition, platelet activity may also involve the coagulation process through the release of Platelet factor III and Anti-heparin factor.[3,6,10,11,12,13,14]

### PLATELET ACTIVITY



Drugs that are considered to have antiplatelet activity must share several characteristics which include: the inhibition of a measurable platelet property such as adhesion, secretion, aggregation or retention; the inhibition of platelet induced thrombus formation; and the prolongation of platelet survival under clinical or experimental conditions of decreased platelet survival time.[11]

Although the knowledge of antiplatelet drug activity has increased, the effectiveness of antiplatelet drugs in the prevention of recurrent myocardial infarction and sudden cardiac death has not been clearly shown. Current research in this area is beset by several problems that have an undetermined impact on study outcomes. To begin with, the precise role of platelets in the development of coronary artery disease complications is still incompletely understood. Effective antiplatelet therapy results may be obscured in the final study outcomes by other physiological factors, such as coagulation, or risk factors, such as smoking, that also play roles in myocardial infarction and sudden cardiac death. Secondly, available study methods cannot differentiate changes in platelet functions as being pathogenic factors or consequences of pathological processes. Finally, there continues to be feasibility problems in conducting a large enough study that will yield significant results.[6,13,14] The use of aspirin, sulfinpyrazone and dipyridamole for the prevention of recurrent myocardial infarction and sudden cardiac death is summarized below.

## Aspirin

Aspirin is thought to acetylate cyclo-oxygenase irreversibly to prevent platelet aggregation and further release reactions initiated by collagen and epinephrine. Cyclo-oxygenase (also known as prostaglandin synthetase) is necessary for the conversion of arachodonic acid to the endoperoxides $PGD_2$, $PGE_1$, $PGG_2$ and $PGH_2$ within platelets and to $PGI_2$ (also known as prostacyclin) within the vessel endothelial tissue.

Aspirin probably does not affect thrombin or ADP induced primary aggregation since these substances induce primary aggregation by mechanisms not involving arachodonic acid metabolism.[6,12] Single doses of 150-600 mg of aspirin will inhibit almost all platelet cyclo-oxygenase activity and this effect will last for the lifespan of the affected platelets. However, daily dosing of aspirin is necessary due to rapid platelet turnover since only ten percent normal platelets are sufficient to normalize bleeding time in aspirin treated patients.[10,13,15] Aspirin may also inhibit vessel wall cyclo-oxygenase thereby decreasing $PGI_2$ production and presumably blocking the inhibition of platelet aggregation. This effect is probably only significant at doses exceeding 1.5 gm of aspirin per day since aortic endothelial cyclo-oxygenase has been shown to be 60-250 times less susceptible to aspirin acetylation than platelet cyclo-oxygenase.[10,16]

Retrospective analyses in the early 1970's showed a negative correlation between regular aspirin ingestion and myocardial infarction.[6,17] Five major subsequent prospective studies, including the Aspirin Myocardial Infarction Study Research Group and Persantine Aspirin Reinfarction Study Research Group, have shown statistically inconclusive trends reducing mortality in post myocardial infarction patients treated with 300 to 1000 mg of aspirin daily.[18,19,20,21,22] Two of the studies noted that, although statistically insignificant, better results were obtained in patients treated with aspirin within the first few weeks to six months after a myocardial infarction.

## Sulfinpyrazone

The mechanism of action of sulfinpyrazone (Anturane®) on platelet activity remains unclear, but it is thought to act similarly to aspirin by inhibiting platelet cyclo-oxygenase. However, this inhibition of cyclo-oxygenase is reversible and concentration dependent, requiring dosing of 200 mg of sulfinpyrazone three to four times daily. Sulfinpyrazone has also been shown in vitro to inhibit vessel wall cyclo-oxygenase and the production of $PGI_2$ theo-

retically blocking the inhibition of platelet aggregation, but it is one hundred times less potent, in this regard than aspirin.[23]

With respect to clinical trials, Blakely and Gent reported in 1974 a reduction of cardiovascular related mortality in institutionalized elderly male patients associated with sulfinpyrazone therapy in a double blind prospective study.[6] Subsequently, the only major prospective study of the use of sulfinpyrazone in patients after having myocardial infarctions has been the Anturane Reinfarction Trial. This group reported a statistically significant reduction of sudden cardiac death, occurring mainly during the second to seventh month post myocardial infarction and a statistically insignificant reduction in total cardiac mortality after an average of sixteen months post myocardial infarction in sulfinpyrazone treated patients.[24,25] However, this study has been criticized on its statistical analysis due to the exclusion of some patient deaths from the analysis of the results.[18] Also, this study has been criticized because no attempt was made to determine whether the efficacy of sulfinpyrazone therapy depended on any measurable platelet function effects.[13]

## Dipyridamole

The antiplatelet activity of dipyridamole (Persantine®) is poorly understood. Evidence suggests that dipyridamole may act by inhibiting platelet phosphodiesterase resulting in the accumulation of intra-platelet cyclic AMP. Increased cyclic AMP levels may then block platelet aggregation and release reactions associated with thromboxane $A_2$ inhibition of platelet membrane adenyl cyclase and subsequent decreased cyclic AMP levels.[6,12,13] Dipyridamole's antiplatelet effect is reversible and concentration dependent. To reverse reduced platelet survival times requires doses of 100 mg four times daily or 100 mg daily with 1 gm of aspirin.[10] The inhibition of collagen induced platelet adhesion and aggregation requires much larger doses of dipyridamole, exceeding these usual prescribed amounts, in order to attain an effective serum concentration of approximately 100 μM.[11] While it appears that dipyridamole may be extensively bound to circulating alpha-acid glycoproteins and therefore not available to affect platelet function, the combined use of aspirin may make more dipyridamole available by the acetylation of these glycoproteins.[26]

Major interest in the use of dipyridamole for post myocardial infarction therapy developed after a study in 1972 which showed dipyridamole to be effective in protecting dogs from myocardial infarction necrosis induced by epinephrine infusion.[12] However, a subsequent human study reported dipyridamole to be ineffective in prolonging survival after myocardial infarction at doses of 100 mg qid. More recently the Persantine-Aspirin Reinfarction Study Research Group reported that the use of 75 mg dipyridamole and 325 mg aspirin tid produced only a statistically insignificant reduction of mortality from post myocardial infarction, with the best results occurring in patients who began treatment within six months after a myocardial infarction.[18]

## Conclusion

The role of antiplatelet therapy following myocardial infarction remains uncertain. The results of the completed Aspirin Myocardial Infarction Study, Sulfinpyrazone Myocardial Reinfarction Study and Persantine®-Aspirin Reinfarction Study trials continue to suggest that there is some benefit from antiplatelet therapy after myocardial infarction. However, the results reported to date cannot support any specific recommendations for prevention of secondary myocardial infarction and/or sudden cardiac death.

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## References

1. Weiss, H J: Antiplatelet therapy: NEJM: 1978, 298: 1403-1406.
2. Mehta, J, et al: Platelet function studies in coronary artery disease. Effect of aspirin and tachycardia stress on aortic and coronary venous blood: AM J CARDIOL:

1980, 45: 945-951.
3. Kumpuris, A G, et al: Production of circulating platelet aggregates by exercise in coronary patients: CIRCULATION: 1980: 61:62-65.
4. Weiss, H J: Platelets and ischemic heart disease (editorial). NEJM: 1980: 302:225-226.
5. Green, L H, Seroppian, E, Handin, R I: Platelet activation during exercise induced myocardial ischemia: NEJM: 1980: 302:193-197.
6. Mustard, J F, Packham, M A: Platelets, thrombosis and drugs: DRUGS: 1975: 9:19-76.
7. Huijgens, P C, Imandt, L, Van den Berg, T: Letter on aspirin and platelets. LANCET: 1980, 1:94.
8. Weiss, H J: Antiplatelet drugs - a new pharmacological approach to the prevention of thrombosis: AM HEART J: 1976: 92:86-102.
9. Neill, W A, et al: Acute coronary insufficiency - coronary occlusion after intermittent ischemic attacks: NEJM: 1980: 302:1157-1162.
10. Gallus, A S: Antiplatelet drugs; clinical pharmacology and therapeutic use: DRUGS: 1979: 18:439-477.
11. Weiss, H J: Antiplatelet therapy: NEJM: 1978: 298:1344-1347.
12. Packham, M A, Mustard, J A: Clinical pharmacology of platelets: BLOOD: 1977: 50:555-573.
13. Schaefer, A J, Handin, R I: The role of platelets in thrombotic and vascular disease: PROG CARDIOVASCULAR DIS: 1979: 22:31-52.
14. Aspirin after myocardial infarction: LANCET: 1980: 1:1172-1173.
15. Burch, J W, et al: Proceedings of National Academy of Science: 1978: 75:5181.
16. Pareti, F I, et al: Letter on platelets and the vessel wall; how much aspirin? LANCET: 1980: 1:371-372.
17. Boston Collaborative Drug Surveillance Group. Regular aspirin intake and acute myocardial infarction: BR MED J: 1974: 1:440-443.
18. Antiplatelet drugs after myocardial infarction: The Medical Letter: 1980: 22: 25-26.
19. Elwood, P C: A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction: BRIT MED J: 1974: 1: 436-440.
20. Aspirin Myocardial Infarction Study Research Group: JAMA: 1980: 243:661.
21. Coronary Drug Project Research Group. Aspirin in coronary heart disease. J CHRONIC DIS: 1976: 29:625-642.
22. Elwood, P C, Sweetnam, P M: Aspirin and secondary inability after myocardial infarction: LANCET: 1979: 2:1313-1315.
23. Mehta, J, Mehta, P: Status of antiplatelet drugs in coronary heart disease. JAMA: 1979: 241:2649-2651.
24. Sulfinpyrazone in the prevention of cardiac death after myocardial infarction: NEJM: 1978: 298:289-295.
25. Sulfinpyrazone in the prevention of sudden death after myocardial infarction: NEJM: 1980: 302:250-256.
26. Sirridge, M, et al: Effects of antiplatelet drugs on platelet function tests: MISSOURI MED: 1979: 76:212-217.
27. Gent, A E, et al: Dipyridamole; a controlled trial of its effect in acute myocardial infarction: BRIT MED J: 1968: 4:361-368.

## PROTOCOL FOR USE OF YUTOPAR® AT MOSES CONE MEMORIAL HOSPITAL

### INTRODUCTION

The incidence of preterm birth in the United States is approximately 8%. Seventy-five percent of the perinatal deaths in this country are a direct result of preterm delivery. The immediate cost of care in the newborn intensive care unit may be greater than $1,000 a day at Moses Cone Hospital. Surviving, but damaged, infants may incur enormous expense

over their lifetime. In most cases, maternal uterus remains the best incubator for the fetus.

Until recently there has been no clearly effective means of therapy for premature labor. Although betamimetic agents have been used for approximately 20 years, the new generation of drugs with selective Beta 2 receptor activity appears to have distinct advantage over the older agents and are significantly more effective. Several Beta 2 selective agents have been used without FDA approval in this institution and across the country. The safety of ritodrine appears to be superior to these agents, and it is now approved by the FDA for use to suppress premature labor.

Because of the complexity of administering this agent safely in effective doses, protocol use of this drug is recommended. The risk of major cardiac complications and pulmonary edema may be decreased also by an awareness of risk factors.

## YUTOPAR® PROTOCOL

### INDICATIONS

Used to prevent or delay preterm labor.

### CONTRAINDICATIONS

1. Before the 20th week of pregnancy
2. Antepartum hemorrhage which demands immediate delivery
3. Eclampsia and severe preeclampsia
4. Intrauterine fetal death
5. Chorioamnionitis
6. Maternal cardiac disease
7. Pulmonary hypertension
8. Maternal hyperthyroidism
9. Uncontrolled maternal diabetes mellitus
10. Known hypersensitivity to the product

### PRECAUTIONS

Pulmonary edema and heart failure are the most frequent serious complications of ritodrine therapy. Although ritodrine appears to be safer than other beta-mimetic agents, several deaths have been reported. These risk factors have been identified:

1. Evaluate patient carefully to rule out undiagnosed cardiac disease prior to therapy with ritodrine.
2. Avoid fluid overload. No more than 2500 ml I.V. daily.
3. Monitor electrolytes daily when on I.V. ritodrine therapy and avoid hypokalemia.
4. Extreme care should be used in the diabetic patient because of biochemical changes induced by this drug.
5. Steroid use to mature the fetal lung may increase the risk of pulmonary edema.

### DOSAGE AND ADMINISTRATION

1. 150 mg of ritodrine hydrochloride (3 ampules of 50 mg/5 ml) in 500 ml of 5% w/v dextrose will constitute the standard Yutopar® solution.
2. Will yield a solution with a final concentration of 0.3 mg/ml.
3. Alternate solutions in which Yutopar® is compatible include:

a. 0.9% w/v sodium chloride
b. 10% w/v Dextran 40 in 0.9% w/v sodium chloride
c. 10% w/v invert sugar
d. Ringer's
e. Lactated Ringer's

4. Will be given an expiration date of 24 hours.
5. Parenteral Yutopar® should not be given if the solution is discolored or contains any precipitate or particulate matter.
6. Must use IVAC® pumps to control rate of infusion accurately.

INTRAVENOUS INFUSION

Equivalent Rates (Based on the concentration 0.3 mg/ml.)

| mg/min | = | ml/min | = | drops/min (microdrops) |
|---|---|---|---|---|
| 0.05 ( 50 µg/min) | | 0.16 | | 10 |
| 0.10 (100 µg/min) | | 0.33 | | 20 |
| 0.15 (150 µg/min) | | 0.50 | | 30 |
| 0.20 (200 µg/min) | | 0.67 | | 40 |
| 0.25 (250 µg/min) | | 0.83 | | 50 |
| 0.30 (300 µg/min) | | 1.00 | | 60 |
| 0.35 (350 µg/min) | | 1.17 | | 70 |

-Initial dose, 50 to 100 µg/min; then, increase dose by 50 µg/min every 10 minutes until contractions stop or unacceptable side effects develop.

-Monitor maternal heart rate and blood pressure, uterine activity and fetal heart rate.

-Reduce dose if side effects are poorly tolerated:
If maternal heart rate is greater than 140 b.p.m.

-Watch for fluid overload - no greater than 2500 ml I.V./day.

-Maximum dose 350 µg/min.

-Discontinue ritodrine if labor persists at maximum dose.

-If labor is successfully arrested, continue the infusion for at least 12 hours before beginning oral therapy.

ORAL THERAPY

-Will send twelve 10 mg tablets at initiation of oral therapy.

-Initial dose, 10 mg administered 30 minutes before stopping infusion; then 10 mg every 2 hours or 20 mg every 4 hours, for 24 hours; then, if the uterus remains quiescent, 10 to 20 mg every 4 to 6 hours until further inhibition of labor is not indicated.

-Maximum dose 120 mg/day.

-If labor recurs during oral administration, infusion may be repeated if the patient is qualified.

DRUG INTERACTIONS

1. Concomitant corticosteroid use - to induce pulmonary maturation of the fetus - may increase the risk of pulmonary edema.
2. Avoid beta-adrenergic blocking drugs - inhibit the action of Yutopar®.
3. Allow sufficient time between administration of another sympathomimetic agent - may have potentiation of the effects.
4. Use care when administering anesthetic agents - may have potentiation of the hypotensive effects.

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EVALUATION OF HEPARIN-INDUCED THROMBOCYTOPENIA

Due to recent articles in the New England Journal of Medicine, the Pharmacy Committee has approved a two month study of platelet counts in heparin protocol patients. In the article by Bell, et al, 24% of patients receiving bovine-lung heparin (the type used at Moses Cone) and 7% receiving either intestinal mucosa group A or group O heparin, experienced thrombocytopenia.

Since bovine-lung heparin has the advantage of less lot to lot variations in potency, the Pharmacy Committee has decided to evaluate the incidence of heparin-induced thrombocytopenia at our institution. The time frame for the study will be January 1, 1981 through March 1, 1981. The heparin protocol patients will have platelet count determination performed initially on Day 4 and then weekly through the remainder of their heparin therapy.

At the end of this two month period, the data will be evaluated by the Pharmacy Committee to determine which type of heparin should be used at our institution.

CEPHALOSPORIN UTILIZATION REVIEW

The second drug utilization review for cephamandole and cefoxitin was performed. The study was based on a six month review and criteria established by a committee of Drs. Tim Lane, Bob Sevier, Bob Gay, and Russ Myers, R.Ph. Appropriate selection of cefamandole was significantly improved since the initial utilization review, while cefoxitin use remained relatively unchanged. Both cefamandole and cefoxitin were accepted into the formulary without restriction.

PATIENT CHARGE COMPARISON OF SELECTED NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

At the request of the Cost Containment Committee, periodic price comparisons of selected patient charge items will be presented in the Pharmacy Committee Notes. This month non-steroidal anti-inflammatory drugs are featured.

| N5AID | Daily Dose (Gm) | Cost/Day |
|---|---|---|
| Aspirin | 3.0-6.0 | $1.00-2.00 |
| Ascriptin® | 3.0-6.0 | 1.00-2.00 |
| E. C. Aspirin | | 1.00-2.00 |
| Motrin® | 1.2-2.4 | 1.20-2.40 |
| Nalfon® | 2.4-3.2 | 0.80-1.25 |
| Naprosen® | 0.5-0.75 | 0.60-0.90 |
| Indocin® | 0.05-0.2 | 0.90-3.60 |
| Tolectin® | 1.0-2.0 | 0.75-1.50 |
| Clinoril® | 0.3-0.4 | 1.60-1.90 |