THROMBOSIS RESEARCH, Supplement IV; 93-104, 1983
0049-3848/83 $3.00 + .00 Printed in the USA.


# CLINICAL PHARMACOKINETICS OF DIPYRIDAMOLE

Thorir D. Bjornsson and Cheryl Mahony

Divisions of Clinical Pharmacology and Cardiology
Departments of Pharmacology and Medicine
Duke University Medical Center, Durham, North Carolina

ABSTRACT

The pharmacokinetics of dipyridamole were studied in six normal subjects and 20 patients. The normal subjects received 20 mg IV each and five also took a 50 mg oral dose. Concentrations after the intravenous dose showed a tri-exponential decline with a terminal half-life of 11.6 ± 2.2 hr (mean ± S.D.). Total plasma clearance was 138 ± 30 ml/min and the apparent volume of distribution was 141 ± 51 l. Peak concentrations after oral dipyridamole occurred 2 - 2.5 hr after the dose. Systemic availability of the oral dose was 52 ± 23%. Plasma protein binding was 99.13 ± 0.24%. Twenty patients, admitted for coronary artery bypass grafting, received total daily doses of 150 mg, either as 50 mg tid or 75 mg bid. Based on drug cumulation during chronic dosing, the terminal half-life averaged about half a day. There was wide interpatient variability, averaging about 10-fold, in observed plasma concentrations for both dosage regimens. The bid regimen was not associated with lower trough concentrations of the drug than the tid regimen. These results indicate that dipyridamole concentrations vary widely in patients receiving the drug, and suggest that it could be administered twice a day, and that dipyridamole levels should be monitored for the antithrombotic effect in clinical studies.

## INTRODUCTION

Dipyridamole, a pyrimido-pyrimidine derivative (Fig. 1), was originally introduced as a vasodilator and was evaluated for the treatment of angina pectoris, but has lately been the subject of numerous studies that have focused on its antiplatelet properties. Alone or in combination with warfarin or aspirin, dipyridamole has been shown to prolong platelet survival

Key Words: Dipyridamole, Pharmacokinetics, Antiplatelet Drugs

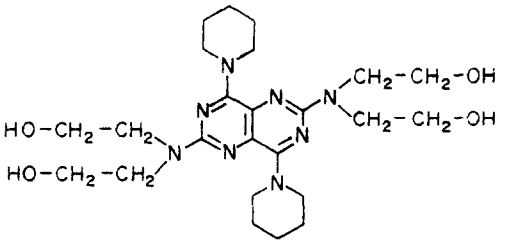

FIG. 1

Chemical structure of dipyridamole (2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido(5,4-d)pyrimidine).

in patients with shortened platelet survival and prosthetic heart valves, arterio-venous fistulae, and coronary atherosclerosis (1,2,3), to reduce the incidence of thromboembolism in patients with prosthetic heart valves (4), and to prevent occlusion of coronary artery bypass grafts (5). It has not, however, been found effective in the prevention of venous thrombosis (6) or in secondary prevention in patients with myocardial infarction (7), although a favorable trend was observed, or in patients with established cerebral vascular disease (8). It is presently being evaluated in patients with transient ischemic attacks.

Total daily doses of dipyridamole used in clinical studies for an antithrombotic effect have ranged from 100 to 800 mg/day. Since neither therapeutic plasma concentrations nor optimal antiplatelet effect have been established for the drug, no attempts have been made to individualize dipyridamole therapy. However, pharmacokinetic factors have been shown to contribute significantly to inter-patient variability in therapeutic responsiveness to numerous drugs. The objectives of the present studies were to define the pharmacokinetics of dipyridamole in normal subjects and to determine the inter-patient variability in plasma concentrations of the drug during chronic dosing using two different dosage regiments in coronary artery bypass patients. Studies on proposed mechanisms of action of the antithrombotic effect of the drug will be reviewed and discussed in light of the findings of the present studies.

## METHODS

Subjects and sample collection. Six healthy subjects (3 males and 3 females), average age 27 ± 5 years and average weight 60 ± 13 kg, received two single doses of dipyridamole each, an intravenous dose of 20 mg and an oral dose of 50 mg (9). The intravenous dose was injected over 1 min, while the oral dose was administered as two tablets of 25 mg, after an overnight fast. The subjects remained without food for 3 hours after the oral dose. Otherwise, dietary and alcohol intake restrictions were not imposed on the subjects. Multiple blood samples were collected after each dose over a period of 3 days. The blood was collected in silanized glass tubes and anticoagulated with heparin (10 units/ml whole blood). Aliquots of whole blood and plasma separated by centrifugation were stored in silanized glass vials at -20°C until analyzed. The subjects, all non-smokers, received no medications for at least two weeks before or during the study, and at least two weeks elapsed between the two doses.

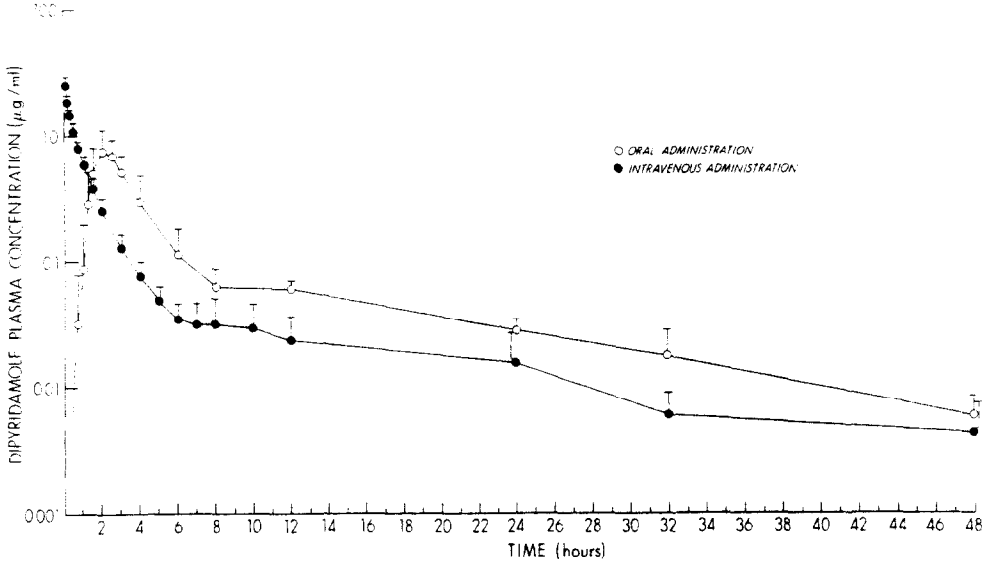


FIG. 2

Average plasma dipyridamole concentrations after 20 mg intravenously and 50 mg orally in normal subjects. The vertical bars represent standard deviations of the means.

Twenty patients (18 males and 2 females), average age 54 ± 9 years, who were admitted for coronary artery bypass grafting, received oral dipyridamole postoperatively by two different dosage regimens, either as 50 mg q8hr or 75 mg q12hr, with both regimens yielding a total daily dose of 150 mg (10). Ten patients received the drug by each dosage regimen. Blood samples were collected at 2 hr (peak concentration) and at the end (trough concentration) of the first dosing interval, either 8 or 12 hr after the first dose. After three to six days on dipyridamole, peak and trough blood samples were repeated; additionally, a trough sample from the previous dosing interval was obtained. The samples were handled and stored as before.

Drug measurement. Concentrations of dipyridamole in whole blood and plasma were determined by a sensitive and specific high performance liquid chromatographic method using paired-ion chromatography and fluorescence detection (11). The plasma protein binding of dipyridamole was measured by equilibrium dialysis, using $^{14}C$-dipyridamole and Sorensen's phosphate buffer, pH 7.4, containing 0.5% (w/v) sodium chloride.

Pharmacokinetic analysis. Plots of dipyridamole concentrations vs time data for each subject revealed a tri-exponential decline after the intravenous dose and a postabsorptive bi-exponential decay following the oral dose. Individual subject data were subsequently analyzed by the nonlinear least-squares regression program NONLIN (12) in conjunction with subroutines for the three-compartment open mammillary model to yield the three sets of coefficients and exponents. The intercompartmental rate constants and the

TABLE 1

Pharmacokinetic Parameters of Dipyridamole in Normal Subjects

| t1/2 α min | t1/2 β min | t1/2 γ hr | Cl ml/min |
|---|---|---|---|
| 12 ± 10 (2 - 28) | 62 ± 29 (39 - 103) | 11.6 ± 2.2 (8.8 - 14.4) | 138 ± 30 (105 - 182) |
| V 1 | Vd 1 | Vd 1 | F % |
| 6.2 ± 2.9 (1.9 - 10.2) | 37.3 ± 8.0 (28.3 - 49.8) | 141 ± 51 (90 - 220) | 52 ± 23 (27 - 88) |

Values are mean ± S.D. Values in parentheses represent ranges in parameter values.

apparent volumes of distribution of the central compartment ($V_c$) and at steady state ($Vd_{ss}$) were calculated using standard formulae (13,14). Total clearance (Cl) was calculated as D/AUC, where D is dose and AUC is the total area under the concentration vs time curve, and the apparent volume of distribution by area ($Vd_{area}$) was calculated as $Cl/\gamma$, where $\gamma$ is the exponent corresponding to the terminal phase half-life. The fraction of the dose that was absorbed after oral administration (F) was calculated as the ratio of AUC after oral dose to the AUC after intravenous dose, correcting for dose differences. In the patient study, the final elimination half-life of dipyridamole was caluclated from a two-point determination of the drug cumulation factor (15).

The data are expressed as mean ± S.D., unless otherwise indicated.

## RESULTS

A plot of the time courses of average plasma concentrations of dipyridamole after both the intravenous and oral doses are shown in Fig. 2. Table 1 lists mean values and ranges for pharmacokinetic parameters derived from plasma concentration data after the intravenous dose. There were no significant differences between pharmacokinetic parameters derived from whole blood concentration data and those derived from plasma data. However, values for clearance and volume terms were slightly higher when based on blood data, because of significant time-dependent changes in the blood/plasma concentration ratio of dipyridamole, which rose from an average of 0.70 ± 0.11 over the first hour to an average of 1.18 ± 0.20 from 6 to 48 hr after the intravenous dose. In the three female subjects, concentrations in both plasma and blood rose at 6 to 10 hr after intravenous dosing. The average fraction of administered dose represented by this apparent recirculation in the females was 0.16 ± 0.03. The average plasma protein binding of dipyridamole was 99.13 ± 0.24%, with the free fraction ranging from 0.55 to 1.19%.

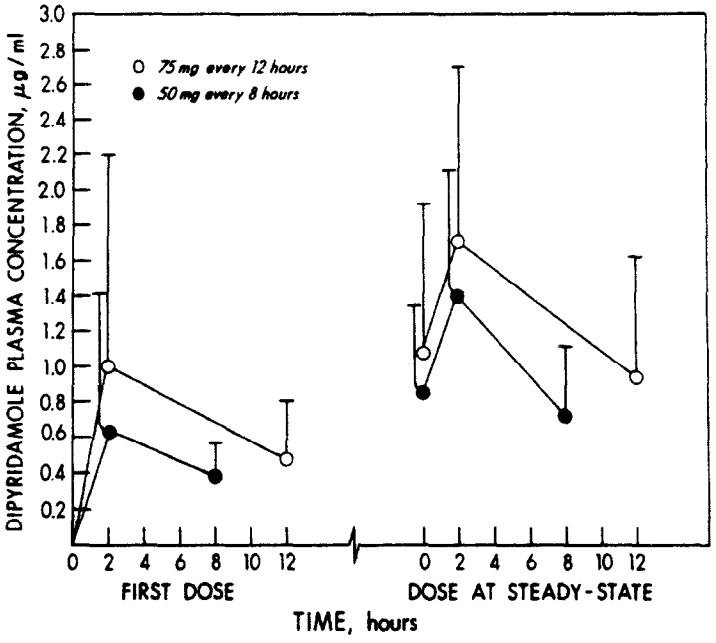


FIG. 3

Average plasma dipyridamole concentrations after two different dosage regimens in patients. Levels were obtained after the first dose and a dose at steady state. The vertical bars indicate standard deviations of the means.

After oral administration there was a significant lag time in absorption of the drug, resulting in peak concentrations at 2 to 2.5 hr after dosing. Average plasma half-lives were 1000 ± 57 min and 11.4 ± 2.9 hr for the two postabsorptive exponential declines. The bio-availability for the five subjects studied is shown in Table 1.

The mean plasma concentrations of dipyridamole in patients receiving the drug by the two different dosage regimens are shown in Fig. 3. After the 50 mg q8hr dosage regimen, both mean and median peak and trough concentrations at steady state were 1.4 and 0.8 ug/ml, respectively. The mean peak concentration was 1.40 ± 0.72 ug/ml, while the mean concentrations at the beginning and at the end of the dosing interval were 0.85 ± 0.50 and 0.72 ± 0.39 ug/ml, respectively. The mean and median cumulation factor were 2.73 and 2.36, indicating a terminal half-life of 12.2 and 10.1 hr, respectively. After the 75 mg q12hr dosage regimen, both mean and median peak concentrations at steady state were about 1.7 ug/ml, while mean and median trough concentrations were 1.0 and 0.8 ug/ml, respectively. The mean peak concentration was 1.71 ± 0.98 ug/ml, while the mean concentrations at the beginning and at the end of the dosing interval were 1.08 ± 0.84 and 0.93 ± 0.69 ug/ml, respectively. The mean and median cumulation factor were 2.48 and 2.14, indicating a terminal half-life of 16.1 and 13.2 hr, respectively. There was wide inter-patient variation in dipyridamole plasma concentrations at steady state for both dosage regimens. Peak concentrations showed 6.6 and 7.2-fold variation for the 50 mg q8hr and 75 mg q12hr dosage regimens, respectively, while trough concentrations at the end of the dosing interval showed 13.9 and 21.7-fold variation, respectively.

## DISCUSSION

These studies have shown that dipyridamole concentrations in plasma and blood follow a tri-exponential decline after intravenous dosing, with a final elimination half-life varying between 8.8 and 14.4 hr, averaging about half a day. Previous studies on the pharmacokinetics of dipyridamole had reported a terminal half-life ranging from 0.5 to 2.5 hr (16,17). These shorter half-life values correspond to the second of three exponential declines observed in the present studies. A final elimination half-life of about half a day was confirmed by multiple dose studies in patients based on drug cumulation during chronic dosing. The studies in patients also demonstrated that the 75 mg bid dosage regimen did not result in lower trough plasma concentrations than the 50 mg tid dosage regimen, suggesting that dipyridamole could be administered twice a day instead of three times a day as is now recommended.

The patient studies revealed considerable inter-patient variability in plasma dipyridamole concentrations during chronic dosing, averaging about 7-fold in peak concentrations and about 15-fold in trough concentrations. Somewhat similar variability has been observed in other studies (18,19). The most likely explanation for this variation in observed plasma concentrations is variable absorption of the drug, which averaged 52% in our pharmacokinetic study, ranging from 27 to 88%, most likely due to variable dissolution and poor solubility. Other studies have reported average bio-availability of 53%, ranging from 37 to 66% (17). Other pharmacokinetic variables that will contribute to intersubject variability in dipyridamole concentrations during chronic dosing are primarily the second and third half-lives, total clearance, and volume terms, all of which showed about 2-fold variation in our pharmacokinetic study. This suggests that in order to achieve optimal antithrombotic therapy with dipyridamole in the individual patient, doses of the drug have to be adjusted to reach a given concentration range or a given measure of its pharmacologic effect. However, since both of these remain to be established, the results of the present study clearly indicate that dipyridamole levels should be monitored in all studies, clinical or experimental, designed to evaluate the antithrombotic effect of the drug.

The elimination of dipyridamole is primarily through biliary excretion of glucuronide conjugates of the drug (16), but a small fraction of the drug is eliminated through urinary excretion. Circulating levels of the conjugates only constitute about 10-20% of the total drug (16). Enterohepatic circulation of dipyridamole has been demonstrated in animals (16), but no direct evidence of this has been observed in man. The rise in dipyridamole concentrations observed between 6 and 10 hr after the drug in the female subjects may represent enterohepatic circulation of the drug. After intravenous and oral administration of 50 mg of radiolabeled dipyridamole to ten normal subjects an average of 86 and 92% of the radioactive dose, respectively, was recovered in the feces, while 9 and 6% of the dose, respectively, was recovered in the urine.* Thus, since drug conjugation tends to be spared in liver disease (20) and only a small fraction of the drug is eliminated through the kidneys, dosage adjustments are not expected to be required in patients with liver or kidney diseases.

* R. Brickl (Dr. Karl Thomae GmbH), Unpublished results.

The only drugs reported to interact with dipyridamole pharmacokinetically are aspirin and salicylate; concurrent administration resulted in higher plasma concentrations of dipyridamole (19,21). The clinical significance and underlying mechanism remain unclear, although it has been suggested that the interaction may be due to inhibition of glucuronide conjugation of dipyridamole and may contribute to the increased antiplatelet effect seen with the combination treatment (21).

Dipyridamole is bound primarily to plasma proteins. Mean plasma protein binding was 99.13 $\pm$ 0.24%. The plasma binding proteins are albumin and, like for other basic drugs, alpha-1-acid glycoprotein (22,23). Dipyridamole binds to the latter protein with very high affinity (24). Studies have shown that the antiplatelet effect of dipyridamole, determined both as inhibition of platelet aggregation and adenosine uptake, is markedly inhibited in the presence of alpha-1-acid glycoprotein (25,26). Other studies have shown that the plasma binding of dipyridamole to alpha-1-acid glycoprotein determines its coronary vasodilatory effect and its inhibition of adenosine uptake by erythrocytes (27,28). This suggests that only the unbound drug is available to bind to target organs and to exert its pharmacologic effect. The monoglucuronide of dipyridamole apparently binds to a similar extent to alpha-1-acid glycoprotein as does the parent drug, but has only about 0.5% of the potency of the parent drug with respect to antiplatelet effects (29). Several disease states, e.g., inflammatory diseases, rheumatoid arthritis, and malignancies, are associated with elevated plasma levels of alpha-1-acid glycoproteins (23), which is an acute phase protein, but at present it is not known if this would result in sufficient reduction in free fraction of the drug to affect its pharmacologic and therapeutic effect.

Dipyridamole prolongs platelet survival in patients with shortened platelet survival and prosthetic heart valves, arteriovenous fistulae, and coronary atherosclerosis (1,2,3). In spite of numerous reports demonstrating that dipyridamole has antithrombotic properties, the precise mechanism of action underlying this effect has not been established. This has made it difficult to anticipate what might be therapeutically active plasma concentrations of the drug in patients. Its in vitro platelet antiaggregatory effect is rather weak and may require plasma concentrations as high as 50 ug/ml (25,30,31,32,33,34). While several biochemical mechanisms have been implicated, three mechanisms have received most attention, i.e., inhibition of phosphodiesterase activity and adenosine uptake in platelets and stimulation of prostacyclin synthesis in vascular wall cells. These different pharmacologic effects have widely different ranges of effective concentrations of dipyridamole. First, dipyridamole inhibits cyclic AMP phosphodiesterase activity in platelets in the concentration range of 1 to 10 ug/ml (33,34,35,36). It has been postulated that this will result in a rise in intra-platelet cyclic AMP levels, which could account for its antiplatelet effect (35,36). However, a rise in intra-platelet cyclic AMP levels has only been demonstrated conclusively when dipyridamole is used with agents that stimulate adenylate cyclase, primarily prostacyclin (33,37). This has led to the hypothesis that dipyridamole acts by potentiating the antithrombotic effects of endogenous circulating prostacycln (33,37). Second, dipyridamole inhibits the uptake of purine and pyrimidine nucleosides into various normal and malignant mammalian cells, including human platelets, endothelial cells, erythrocytes, and lymphocytes (26,31,38,39,40,41). Concentrations of dipyridamole associated with significant inhibition of nucleoside transport have been in the 50 ng/ml of 0.5 ug/ml range. In platelets, concentrations of 0.1 ug/ml were associated

with 50% inhibition of adenosine uptake by platelets in normal subjects after injection of the drug (42). It has been suggested that this inhibition of adenosine uptake by endothelial cells and blood cells may result in sufficiently elevated levels of circulating adenosine to have significant platelet antiaggregatory effect (43). Third, recent studies have shown that dipyridamole in concentrations between 1 and 100 ug/ml increases prostacyclin synthesis, by stimulation of cyclo-oxygenase activity, in various in vitro preparations, including pig aorta microsomes and rabbit vessel preparations (44). This possible mechanism of action of dipyridamole has been confirmed in studies in normal subjects using a bio-assay of prostacyclin (45) but not in studies using a chemical assay (46). In addition to explaining its antithrombotic effect, these last two actions of dipyridamole might also contribute to its vasodilatory effect. However, in view of the plasma dipyridamole concentrations observed in our pharmacokinetic studies and the ranges of effective concentrations of dipyridamole in the pharmacologic studies, it appears that the mechanism involving adenosine is the most likely to be operative clinically.

Ideally, antiplatelet drug therapy should be optimized in the individual patient on the basis of a desired antiplatelet effect. However, such a therapeutic goal, like specific coagulation test times for the anticoagulant drugs, has not been established for any of the antiplatelet drugs. The antiplatelet effect of dipyridamole in patients has been determined by inhibition of platelet aggregation and adhesion (18,30,34), and levels of platelet factor 4 and beta-thromboglobulin (18,47). However, until specific ranges of plasma concentrations of dipyridamole or specific measures of its antiplatelet effect can be related to its clinical efficacy, it is suggested that dipyridamole plasma levels be monitored in all studies evaluating its antithrombotic effect. Analysis of clinical outcome will then enable therapeutic efficacy to be evaluated for specific observed concentration ranges of the drug.

## ACKNOWLEDGEMENTS

Supported in part by NIH Grant No. NS-06233 and a grant from Boehringer Ingelheim Ltd. We thank Boehringer Ingelheim Ltd., Ridgefield, Connecticut, for providing us with intravenous and oral preparations of Persantine and Dr. Karl Thomae GmbH, Biberach an der Riss, W. Germany, for providing us with radiolabeled dipyrdimale. T.D.B. is a Nanaline H. Duke Scholar.

## REFERENCES

1. HARKER, L., and SLICHTER, S.J. Studies of platelet and fibrinogen kinetics in patients with prosthetic heart valves. N. Engl. J. Med. 283, 1302-1305, 1970.

2. HARKER, L.A., and SLICHTER, S.J. Platelet and fibrinogen consumption in man. N. Engl. J. Med. 287, 999-1005, 1972.

3. RITCHIE, J.L., and HARKER, L.A. Platelet and fibrinogen survival in coronary atherosclerosis. Am. J. Cardiol. 39, 595-598, 1977.

4. SULLIVAN, J.M., HARKEN, D.E., and GORLIN, R. Pharmacologic control of thromboembolic complications of cardiac-valve replacement. N. Engl. J. Med. 284, 1391-1394, 1971.

5. CHESEBORO, J.H., CLEMENTS, I.P., FUSTER, V., ELVEBACK, L.R., SMITH, H.C., BARDSLEY, W.T., FRYE, R.L., HOLMES, D.R., VLIETSTRA, R.E., PLUTH, J.R., WALLACE, R.B., PUGA, F.J., ORSZULAK, T.A., PIEHLER, J.M., SCHAFF, H.V., and DANIELSON, G.K. A platelet-inhibitor drug trial in coronary-artery bypass operations. Benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N. Engl. J. Med. 307, 73-78, 1982.

6. BROWSE, N.L., and HALL, J.H. Effect of dipyridamole on the incidence of clinically detectable deep-vein thrombosis. Lancet 2, 718-721, 1969.

7. THE PERSANTINE-ASPIRIN REINFARCTION STUDY RESEARCH GROUP. Persantine and aspirin in coronary heart disease. Circulation 62, 449-461, 1980.

8. ACHESON, J., DANTA, G., and HUTCHINSON, E.C. Controlled trial of dipyridamole in cerebral vascular disease. Br. Med. J. 1, 614-615, 1969.

9. MAHONY, C., WOLFRAM, K.M., COCCHETTO, D., and BJORNSSON, T.D. Dipyridamole kinetics. Clin. Pharmacol. Ther. 31, 330-338, 1982.

10. MAHONY, C., COX, J.L., and BJORNSSON, T.D. Plasma dipyridamole concentrations after two different dosage regimens in patients. J. Clin. Pharmacol. 1983, in press.

11. WOLFRAM, K.M., and BJORNSSON, T.D. High-performance liquid chromatographic analysis of dipyridamole in plasma and whole blood. J. Chromatogr. 183, 57-64, 1980.

12. METZLER, C.M., ELFRING, G.L., and MCEWEN, A.J. A user's manual for NONLIN and associated programs. Kalamazoo, Michigan, 1974, The Upjohn Company.

13. GIBALDI, M., and PERRIER, D. Pharmacokinetics. New York, 1975, Marcel Dekker, Inc., pp.89-95.

14. WAGNER, J.G. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J. Pharmacokin. Biopharm. 4, 443-467, 1976.

15. BJORNSSON, T.D., and SHAND, D.G. Estimation of kinetic parameters from a two-point determination of the drug cumulation factor. Clin. Pharmacol. Ther. 26, 540-547, 1979.

16. BEISENHERZ, G., KOSS, F.W., SCHULE, A., GEBAUER, I., BARISCH, R., and FRODE, R. The metabolism of 2,6-bis(diathanolamino)-4,8-dipiperidino-pyrimido(5,4-d)pyrimidine. Arzneimittelforsch. 10, 307-313, 1960.

17. NIELSEN-KUDSK, F., and PEDERSEN, A.K. Pharmacokinetics of dipyridamole. Acta. Pharmacol. Toxicol. 44, 391-399, 1979.

18. RAJAH, S.M., CROW, M.J., PENNY, A.F., AHMAD, R., and WATSON, D.A. The effect of dipyridamole on platelet function: correlation with blood levels in man. Br. J. Clin. Pharmacol. 4, 129-133, 1977.

19. TYCE, G.M., FUSTER, V., and OWEN, C.A. Dipyridamole levels in plasma of man and other species. Res. Commun. Chem. Pathol. Pharmacol. 26, 495-508, 1979.

20. KRAUS, J.W., DESMOND, P.V., MARSHALL, J.P., JOHNSON, R.F., SCHENKER, S., and WILKINSON, G.R. Effects of aging and liver disease on disposition of lorazepam. Clin. Pharmacol. Ther. 24, 411-419, 1978.

21. BUCHANAN, M.R., ROSENFELD, J., GENT, M., LAWRENCE, W., and HIRSH, J. Increased dipyridamole plasma concentrations associated with salicylate administration. Relationship to effects on platelet aggregation in vivo. Thromb. Res. 15, 803-820, 1979.

22. KOPIAR, Z., and WEISENBERGER, H. Specific binding of dipyridamole to human serum protein; its isolation, identification, and characterization as alpha-1-acidic glycoprotein. Arzneimittelforsch. 21, 859-862, 1971.

23. PIAFSKY, K.M. Disease-induced changes in the plasma binding of basic drugs. Clin. Pharmacokin. 5, 246-262, 1980.

24. EL-GAMEL, S., WOLLERT, U., and MULLER, W.E. Optical studies on the specific interaction of dipyridamole with alpha-1-acid glycoprotein (orosomucoid). J. Pharm. Pharmacol 34, 152-157, 1982.

25. NIEWIAROWSKI, S., LUKASIEWICZ, H., NRAPENDRA, N., and TAI SHA, A. Inhibition of human platelet aggregation by dipyridamole and two related compounds and its modification by acid glycoproteins of human plasma. J. Lab. Clin. Med. 86, 64-76, 1975.

26. SUBBARAO, K., RUCINSKI, B., RAUSCH, M.A., SCHMID, K., and NIEWIAROWSKI, S. Binding of dipyridamole to human platelets and to alpha-1-acid glycoprotein and its significance for the inhibition of adenosine uptake. J. Clin. Invest. 60, 936-944, 1977.

27. KUBLER, W. Die bindung des koronardilators dipyridamol an die plasmaerweisskorper des Menschen. Arch. Kreislaufforsch. 64, 115-128, 1971.

28. KOPITAR, Z., and KOMPA, H.E. Der Einfluss von Serumproteinen auf die Hemmung der Adenosin-Permeabilitat von Menschen- und Hunde-Erythrocytenmembranen durch 2,6-Bis(diathenolamino)-4,8-dipiperidino-pyrimido[5,4-d]pyrimidin. Arzneimittelforsch. 20, 253, 1970.

29. SUBBARAO, K., RUCINSKI, B., and NIEWIAROWSKI, S. Effect of dipyridamole and its monoglucononide derivative on adenosine uptake by human platelets and ADP-induced platelet aggregation. Biochem. Pharmacol 26, 906-907, 1977.

30. EMMONS, P.R., HARRISON, M.J.G., HONOUR, A.J., and MITCHELL, J.R.A. Effect of dipyridamole on human platelet behavior. Lancet 2, 603-606, 1965.

31. CUCUIANU, M.P., NISHIZAWA, E., and MUSTARD, J.F. Effect of pyrimido-pyrimidine compounds on platelet function. J. Lab. Clin. Med. 77, 958-974, 1971.

32. BUCHANAN, M.R., and HIRSH, J. A comparison of the effects of aspirin and dipyridamole on platelet aggregation in vivo and ex vivo. Thromb. Res. 13, 517-529, 1978.

33. BEST, L.C., MCGUIRE, M.B., JONES, P.B.B., HOLLAND, T.K., MARTIN, T.J., PRESTON, F.E., SEGAL, D.S., and RUSSELL, R.G.G. Mode of action of dipyridamole on human platelets. Thromb. Res. 16, 367-379, 1979.

34. FUKAWA, K., SAITOH, K., IRINO, O., OHKUBO, K., and HASHIMOTO, S. Inhibitory mechanism of dipyridamole on platelet aggregation ex vivo. Thromb. Res. 27, 33-340, 1982.

35. MILLS, D.C.B., and SMITH, J.B. The influence on platelet aggregation of drugs that affect the accumulation of adenosine 3':5'-cyclic monophosphate in platelets. Biochem. J. 121, 185-196, 1971.

36. VIGDAHL, R.L., MONGIN, J., and MARQUIS, N.R. Platelet aggregation. IV. Platelet phosphodiesterase and its inhibition by vasodilators. Biochem. Biophys. Res. Comm. 42, 1088-1094, 1971.

37. MONCADA, S., and KORBUT, R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacycline. Lancet 1, 1286-1289, 1978.

38. WIDSTROM, O., BUSCH, C., TORNLING, G., NILSSON, B.S., and UNGE, G. Dipyridamole suppresses uptake of thymidine in human and bovine cells in vitro. Agents and Actions 11, 287-289, 1981.

39. KRZYSZTOF, J.P., and KOPEC, K.M. Effects of dipyridamole on human blood lymphocytes. Biochem. Pharmacol. 29, 2515-2517, 1980.

40. PLAGEMAN, P.G.W., and RICHEY, D.P. Transport of nucleosides, nucleic acid bases, choline and glucose by animal cells in culture. Biochim. Biophys. Acta 344, 263-305, 1974.

41. ROGLER-BROWN, T., and PARKS, R.E. Tight binding inhibitors. VIII. Studies of 2'-deoxycoformycin and transport inhibitors with the erythrocytic nucleoside transport system. Biochem. Pharmacol. 29, 2491-2497, 1980.

42. SUMMERS, A., SUBBARAO, K., RUCINSKI, B., and NIEWIAROWSKI, S. The effect of dipyridamole on adenosine uptake by platelets ex vivo. Thromb. Res. 11, 611-618, 1977.

43. CRUTCHLEY, D.J., RYAN, U.S., and RYAN, J.W. Effects of aspirin and dipyridamole on the degradation of adenosine diphosphate by cultured cells derived from bovine pulmonary artery. J. Clin. Invest. 66, 29-35, 1980.

44. MENTZ, Von P., PONICKE, K., BLOCK, H.-U., GIESSLER, Ch., BLASS, K.-E., BAYER, B.-L., and FORSTER, W. Stimulierung der Prostazyklin-Biosynthese

als moglicher Wirkungsmechanismus von Dipyridamol. Arzneimittelforsch. 31, 2075-2082, 1981.

45. NERI SERNERI, G.G., MASOTTI, G., POGGESI, L., GALANTI, G., and MORETTINI, A. Enhanced prostacyclin production by dipyridamole in man. Eur. J. Clin. Pharmacol. 21, 9-15, 1981.

46. VIINIKKE, L., and YLIKORKALA, O. Effect of various doses of acetylsalicyclic acid in combination with dipyridamole on the balance between prostacyclin and thromboxane in human serum. Br. J. Pharmacol 72, 299-303, 1981.

47. SANO, T., MOTOMIYA, T., and YAMAZAKI, H. Platelet release reaction in vivo in patients wit ischaemic heart disease after isometric exercise and its prevention with dipyridamole. Thrombos. Haemostas. 42, 1589-1597, 1979.

## SYMPOSIUM DISCUSSION

Dr. Reilly - I'm probably stirring a few things up here directing questions to both Dr. Bjornsson and Dr. Brickl. Is terminal half-life of dipyridamole important? If it is Dr. Bjornsson, you seem to be proposing a b.i.d. dosage regimen and I'm not sure what Dr. Brickl's data indicated...is there a critical concentration below which the drug may be significantly more often that after b.i.d. dosing and t.i.d. dosing? If that is so, then your model doesn't fit Dr. Bjornsson's data.

Dr. Bjornsson - There are two parts to the question and both are very valid points. To start with, "What is the contribution of a terminal phase to pharmacological response during chronic dosing?", we know of several examples of drugs where pharmacological effect or toxicity is determined by the longer final elimination phase, for example, gentamicin with a final half-life of one to several days compared with the preceding T1/2 of 1-8 hours. That half-life determines in part the toxicity represented by uptake into the kidneys. "How does this information relate to the design of dosage regimens for dipyridamole?". For the design of optimal dosage regimens, one would like to know the relationship between the time courses of drug concentrations and effects over a dosing interval, and, what are the minimal effective concentrations. Neither is known for dipyridamole, but since patient compliance is likely to be better when drugs are presented twice rather than three times a day, this new information warranted further study. As it turned out, when we compared dosage regimens in patients through blood levels, they were not significantly lower when giving dipyridamole b.i.d. compared with t.i.d.

Dr. Brickl - I'm in complete agreement with the last part but I think the basic difference between our data and Dr. Bjornsson's is that we showed accumulation in hospitalized patients who are sick and bedridden and this may have some influence. I think b.i.d. dosage regimen is better than q.i.d. or t.i.d. because you reach higher peak levels more rapidly.

Dr. Keirns - Dr. Bjornsson brought up the analogy that gentamicin accumulation in the tissue was responsible for the slow release and hence for the terminal half-life. But, in the case of dipyridamole, it is mainly cleared by the biliary system. The compartment may be the GI tract rather than tissue and consequently the interpretation and relevance of the terminal half-life may be quite different.