

Cyclosporine monitoring: consensus recommendations and guidelines

Randall W. Yatscoff, PhD, FCACB

Cyclosporine has been used for a number of years to prevent organ rejection in allogeneic transplantation and graft-v.-host disease in bone marrow transplantation and to treat autoimmune disease.¹ Clinical experience has shown that the therapeutic index for cyclosporine is low. Therefore, monitoring of the blood concentrations of the drug and other elements is now regarded as an essential aid in adjusting the dosage for optimal efficacy and minimal toxicity.¹

There are many issues and controversies involved in the monitoring of cyclosporine, including the use of different nonspecific and specific methods of measurement, the role of the drug's metabolites in immunosuppression and toxicity, the use of different sample matrices by which to measure the drug and the varied criteria used for defining nephrotoxicity and rejection. The Bureau of Drug Research, Health Protection Branch (HPB), Department of National Health and Welfare (DNHW), Ottawa, asked the Canadian Society of Clinical Chemists and the Canadian Transplant Society to develop a consensus on the monitoring of cyclosporine. In response the two societies sponsored the Canadian Consensus Meeting on Cyclosporine Monitoring, held May 11 to 13, 1990, at Minaki Lodge, Minaki, Ont.

Twenty-one clinicians and scientists presented the latest research data on the clinical, methodologic and pharmacologic aspects of cyclosporine. These presentations have been published elsewhere.² The consensus panel comprised myself and Dr. Leslie M. Shaw, University of Pennsylvania, Philadelphia, as co-chairmen and Drs. Larry D. Bowers, University of Minnesota, Minneapolis; David J. Freeman, University of Western Ontario, London; John R. Jeffery, Health Sciences Centre, University of Manitoba, Winnipeg; Paul A. Keown, University of British Columbia, Vancouver; Ian McGilveray, Bureau of Drug Research, HPB, DNHW; Thomas Rosano, Albany Medical College, Albany, NY; and Piu-Yuen Wong, University of Toronto. The panel used the information presented to formulate recommendations and guidelines for cyclosporine monitoring, as follows.

- The recommended interval between the last

dose of cyclosporine and the collection of a sample in which the drug level will be measured is 11 to 12 hours for patients receiving the drug twice a day and 23 to 24 hours for those receiving it once a day.

- The time of food intake in relation to cyclosporine administration should be consistent, since the effect of food on cyclosporine absorption can be considerable.

- Information on the amount and timing of the last cyclosporine dose should be submitted to the laboratory along with the request for determination of the drug level.

- In most clinical situations the recommended maximum frequency of monitoring immediately after transplantation is once every 24 hours.

- Until one matrix is shown to be clinically superior to another, analytic reasons — including the pressing need for consistency among centres — are the basis for the selection of a sample matrix. Whole blood has been chosen as the recommended sample. Ethylenediamine tetra-acetate is the recommended anticoagulant. It is important to ensure artefact-free collection of the blood specimen; therefore, for patients receiving the drug intravenously venipuncture of the other arm is required.

- Cyclosporine is stable over a wide range of temperatures. If required, samples can be shipped at ambient temperatures.

- A validated, specific method for measuring the level of the parent drug is recommended.

- Performance characteristics of measuring the cyclosporine level should meet the criteria for acceptable laboratory practice.

- The current data do not support the need to monitor cyclosporine metabolites to guide dosage adjustment in transplant recipients. If one or more metabolites is shown to be clinically important its concentration should be measured with the use of a specific method.

- Target or therapeutic doses have been empirically derived and are subject to all the difficulties resulting from multiple confounding factors, including the method used for measuring the cyclosporine level and the criteria used for defining rejection and nephrotoxicity.

Reprint requests to: Dr. Randall W. Yatscoff, Department of Clinical Chemistry, Health Sciences Centre, 820 Sherbrook St., Winnipeg, MB R3A 1R9

• Laboratories should provide results on the same day (before the next dose) for recent transplant recipients.

• To maintain the quality of the method for measuring the cyclosporine concentration, participation in an external quality assurance program and an effective internal quality control program is essential. A pure, well-characterized preparation should be developed so that standardization of the method can be effectively assessed.

These recommendations and guidelines have recently been published in detail elsewhere.³ They will also be distributed to all transplant centres in

Canada. We hope that they will lead to improvements in the monitoring of transplant recipients and ultimately to improved patient care.

References

1. Kahan BD: Cyclosporine. *N Engl J Med* 1989; 321: 1725-1738
2. Yatscoff RW (ed): Selected papers from the Canadian Consensus Meeting on Cyclosporine Monitoring. *Clin Biochem* 1991; 24 (1): 1-105
3. Shaw LM, Yatscoff RW, Bowers LD et al: Canadian consensus meeting on cyclosporine monitoring: report of the consensus panel. *Clin Chem* 1990; 36: 1841-1846

Conferences

continued from page 1115

Sept. 22-25, 1991: International Conference on Alzheimer's Disease
Amsterdam
Alzheimer Society, Seadwei 8, 9261 XM, Oostermeer, the Netherlands

Sept. 23, 1991: Precongress courses on Cytogenetics, Molecular Genetics and Endoscopy (in conjunction with the 5th International Symposium on Colorectal Cancer)
Turin, Italy
Organizing Secretariat, Francorosso Health Congress, 26 Corso Vittorio Emanuele, 20122 Milano, Italy; telephone 011-39-2-76008561, fax 011-39-2-784967

Sept. 24-26, 1991: 5th International Symposium on Colorectal Cancer — Biology and Management of High Risk Groups
Turin, Italy
Abstract deadline is May 15, 1991.
Organizing Secretariat, Francorosso Health Congress, 26 Corso Vittorio Emanuele, 20122 Milano, Italy; telephone 011-39-2-76008561, fax 011-39-2-784967

Oct. 5-12, 1991: 16th Annual International Body Imaging Congress
Grand Hyatt Wailea, Maui, Hawaii
Dr. Ronald J. Friedman, c/o Medical Seminars International, Inc., 303-18981 Ventura Blvd., Tarzana, CA 91356; (818) 774-9077, fax (818) 774-0244

Nov. 8-15, 1991: 6th World Conference on Lung Cancer
Melbourne, Australia
Dr. Heine H. Hanson, secretary general, International Association for the Study of Lung Cancer, Finseninstitutet Radiumstationnen, Strand Culevarden 49, 2100 Copenhagen, Denmark

Nov. 14-17, 1991: Québec Association of Urologists
16th Annual Meeting
Hilton Hotel, Quebec
Jacqueline Deschênes, Québec Association of Urologists, 2 Complexe Desjardins, East Tower, Rm. 3000, Montreal, PQ H5B 1G8; (514) 844-9523

Dec. 8-11, 1991: International Conference on the Care of the Elderly
Hong Kong
International and Regional Affairs Department, Hong Kong Council of Social Service, 11/F, Duke of Windsor Social Service Building, 15 Hennessy Rd., Wanchai, Hong Kong; (852) 864-2992, fax (852) 865-4916

Feb. 11-14, 1992: 2nd International Conference on Recent Advances in Crisis Intervention and Community Mental Health (organized by the International Institute of Crisis Intervention and Community Psychiatry in association with International Crisis Therapists)
Krishna Oberoi Hotel, Hyderabad, India
International Conference Secretariat, 63 Nabcroft Lane, Crosland Moor, Huddersfield HD4 5DU, England; telephone 011-44-0484-658054, fax 011-44-0484-654777

May 25-29, 1992: 12th International Congress of Hospital Engineering (in concurrence with the Hospital-Health Care International Exhibition)
Congress Hall, Bologna, Italy
Organizing Secretariat, SENAF, Via Michelino 69, 40127 Bologna, Italy; telephone 011-39-51-503318, fax 011-39-51-505282

July 21-25, 1992: 6th International Conference on Human-Animal Interactions (hosted by the Human-Animal Bond Association of Canada)
Palais des Congrès, Montreal
Taylor and Associates, 676 Shefford Ct., Gloucester, ON K1J 6X3; (613) 747-0262

Sept. 6-10, 1992: Medinfo '92 — 7th World Congress on Medical Informatics
Palexpo Congress Center, Geneva
Abstract deadline is Nov. 15, 1991.
Official language: English
Medinfo '92, Administrative Office, Symporg SA, 108, route de Frontenex, CH-1208 Geneva, Switzerland; telephone 011-41-22-786-37-44, fax 011-41-22-786-40-80