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TPMT in the treatment of inflammatory bowel disease with azathioprine

We read with interest the recent article by Leonard on the role of thiopurine methyltransferase (TPMT) enzyme in predicting azathioprine related toxicity in patients with inflammatory bowel disease (IBD) (*Gut* 2002;51:145-51). He concludes that measurements of TPMT activity has no specific role in identifying the risk of significant bone marrow toxicity in long term users of azathioprine. This conclusion is in agreement with other published work and emphasises the importance of ongoing haematological monitoring in IBD patients receiving this drug. The importance of haematological monitoring in the early detection and prevention of azathioprine related toxicity is well recognised. However, the duration of early monitoring is a matter of controversy. The current British National Formulary guidelines recommend that patients undergo blood tests on at least a weekly basis for the initial four weeks of therapy. The drug's manufacturer's recommend a more stringent monitoring policy and in their view, initial monitoring should continue for the first eight weeks of

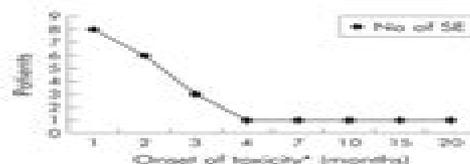


Figure 1 Time of occurrence of various toxicities during azathioprine therapy. *Onset of toxicity relates to time (in months) from the start of azathioprine treatment to the appearance/detection of toxicity. SE, side effects.

treatment. The American College of Gastroenterology guidelines recommend a slightly different approach, with fortnightly blood counts for the initial three months of therapy. The key issue in determining the value of these different approaches is monitoring in the time of onset of potentially life threatening bone marrow suppression following initiation of azathioprine treatment. These data are not available for patients with IBD.

In a retrospective study, we analysed the time of onset of all drug related toxicity in IBD patients post initiation of azathioprine therapy. A total of 110 consecutive IBD patients with a history of azathioprine use were identified (table 1). Patients were identified from the Hospital Inpatient enquiry system, IBD clinic, and pharmacy records. Mean azathioprine dose was 2 mg/kg/day (range 1-3). Mean age of the patients on azathioprine was 38.11 years (18-76). Seventeen of 110 patients (17%) suffered from azathioprine related early toxicity (table 1). Mean azathioprine dose in those showing drug toxicity was 100 mg/day (30-150). Most (77%) drug related toxic events manifested within the first 12 weeks of therapy (fig 1). However, the mean time of onset of drug related toxicity depended on the side effect observed. For example, most drug related marrow was observed within two weeks of commencing treatment while all cases of damaged liver function tests were detected within eight weeks of treatment onset. Significantly, this

was not true for bone marrow suppression. The mean duration of treatment in the two patients who experienced this side effect was 11 weeks (range 10-12). Both cases occurred outside the "stringent" eight week monitoring period recommended by the drug's manufacturer. Hence identification of bone marrow suppression would have been delayed using the current British and manufacturer's guidelines. Three further episodes of neutropenia were identified during long term (>3 months) treatment in these patients who continued on maintenance azathioprine (mean duration 100 weeks/patient, range 2 weeks to 5 years). In our practice, we feel that significant toxicity during the early (<3 months) period of therapy could have been missed by strictly following existing guidelines.

Early detection of abnormalities in asymptomatic patients helped in dose adjustment with resolution of side effects. In addition, early detection of azathioprine related bone marrow suppression is likely to save lives. We recommend that gastroenterologists employ an extended (three months) period of intensive haematological monitoring after initiation of azathioprine therapy in IBD. Although neutropenia is occasionally observed beyond this point, intensive monitoring for the duration of treatment, which may continue for years, is clearly not practical from a patient or service perspective. However, this serves to emphasise the importance of continuous patient education concerning "alarm symptoms" throughout the duration of azathioprine therapy.

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Author's reply

Measurements of thiopurine methyltransferase (TPMT) status, prior to the start of azathioprine therapy, has a role in identifying the TPMT deficient patient at risk of severe myelosuppression and TPMT heterozygous individuals who are prone to early myelosuppression.¹⁻³ The risk of azathioprine toxicity is well recognised but, as the authors state, the duration of early monitoring is a matter of controversy. The matter for debate is the time of onset of potentially life threatening myelosuppression.

Table 1 Patient characteristics and side effects encountered during the initial period of therapy (three months) with azathioprine in patients with inflammatory bowel disease

	Ulcerative colitis	Crohn's disease	Indeterminate	Total
Male	17	25	3	45
Female	15	48	2	65
Nonusers/smoking	1	5	0	6
Abnormal LFTs	3	1	0	4
Neutropenia	1	1	0	2
Thrombocytopenia	0	1	0	1
Infections	Herpes rash (1)	0	0	1
Pancernitis	0	1	0	1
Miscellaneous associated symptoms	Tiredness (1)	Headache (1), allergic skin rash (1)	0	3

LFT, Liver function test.

Therapeutic Roles Of Selective

M Lipman



Therapeutic Roles Of Selective:

Therapeutic Roles of Selective COX-2 Inhibitors John R. Vane, Regina M. Botting, 2001-01-01 This volume represents the comprehensive and definitive reference volume on cyclooxygenases 1 and 2 and their inhibitors The whole field is covered from the basic science all the way through to the clinic Several novel selective COX 2 inhibitors are now a liability and the publication coincides with an exciting stage in the development of therapeutic strategies using these drugs for the treatment of arthritis pain and inflammation and their potential value for treatment of various cancers Alzheimer's disease and premature labour Each chapter is written by an acknowledged expert in the field including the discoverers of COX 2 and the developers of the new drugs

COX-2 Inhibitors Michel Pairet, Joanne van Ryn, 2004-03-29 COX 2 inhibitors are important drugs with analgesic and anti-inflammatory effects The discovery of COX 2 the evolution of drug development in this field and the implications of these developments in patient therapy are topics of this volume This book presents both pre-clinical and clinical information and is important for clinicians interested in the latest information about this class of drugs for researchers and for students in the field

The Role of He P38/PLA2/Cox-2 Cascade and Microglia in Spinal Sensitization and Hyperalgesia Camilla Ingegerd Svensson, 2005

Pharmacology H. P. Rang, 2003 This highly acclaimed textbook is a worldwide bestseller recognized for its emphasis on the mechanisms by which drugs act at the cellular and molecular levels and how that relates to their overall pharmacological effects and clinical uses The 5th Edition includes four new chapters a reorganized and expanded section on treatments for infections and cancer and thorough updates throughout that explore new treatments and advances in molecular biology that may lead to future therapeutic options for cancer HIV infection osteoporosis neurodegenerative disorders erectile dysfunction obesity diabetes atherosclerosis cardiac failure and more User friendly features include new chapter overviews reviews of relevant physiology and biochemistry boxed key points and clinical uses references and reading lists a new full color art program and new small print sections that separate the more complex material from the main discussion thread in each chapter leaving the depth of coverage to the reader's discretion The smart way to study Elsevier titles with STUDENT CONSULT will help you master difficult concepts and study more efficiently in print and online Perform rapid searches Integrate bonus content from other disciplines Download text to your handheld device And a lot more Each STUDENT CONSULT title comes with full text online a unique image library case studies USMLE style questions and online note taking to enhance your learning experience Reviews relevant physiological and biochemical processes at the beginning of most chapters to provide a framework for discussing the mechanisms and actions of drugs that affect those processes Discusses not only what drugs do but also how they do it the mechanisms of action at the cellular and molecular levels Places boxed key points throughout the text offering readers at a glance access to essential knowledge Provides overviews of the therapeutic uses of different drug classes in clinical uses boxes throughout the text Offers brief coverage where appropriate of how certain pharmacological compounds

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Cardiomyocyte Microdomains: An Emerging Concept of Local Regulation and Remodeling Alexey V. Glukhov, Di Lang, Sarah Calaghan, Julia Gorelik, 2020-07-08 *Proceedings of the Australian Physiological and Pharmacological Society* Australian Physiological and Pharmacological Society, 1994

Pharmacotherapy for Mood, Anxiety, and Cognitive Disorders Uriel Halbreich, S. A. Montgomery, 2000 This book takes a critical look at the medications available for treating mood anxiety and cognitive disorders their relevance to pathobiology and underlying mechanisms and their limitations The contributors provide background and rationale in understanding the underlying mechanisms of frontline treatments for these disorders *Current Medical Research and Opinion*, 2006

Encyclopedic Reference of Molecular Pharmacology Stefan Offermanns, Walter Rosenthal, 2004 Presents current information on the molecular mechanisms of drug action Provides 159 essays describing groups of drugs and drug targets Several essays deal with general principles of pharmacology such as drug tolerance drug addiction or drug metabolism *ACSM's Clinical Exercise Physiology* American College of Sports Medicine, 2019-02-01 ACSM's Clinical Exercise Physiology adapts and expands upon the disease related content from ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription 7th Edition to create a true classroom textbook This new resource offers research based coverage of more than 35 conditions commonly seen in practice from a host of cardiovascular disorders to immunological hematological disorders

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Clinical Rehabilitation Pavel Kolar et al., 2014-02-17 This is a comprehensive rehabilitation textbook emphasizing functional approach based on the aspects of the Prague School of Rehabilitation www.rehabps.com which was developed by Professors Vojta Janda Lewit and others The publication is divided into general and special sections The diagnostic section describes in detail clinical evaluation approaches for the musculoskeletal system testing and assessment of a motor and sensory involvement and limitations in the activities of daily living The text also includes psychological assessment in rehabilitation of painful conditions functional laboratory assessments and functional assessment using imaging methods In the general section of the therapeutic approaches the authors focus on treatment rehabilitation of the motor system and also focus on disorders of other organ systems The special section of the book includes rehabilitation of individual clinical specialties in which treatment rehabilitation plays an important part The individual chapters include rehabilitation in neurology orthopedics internal diseases gynecology oncology psychiatry pain and psychosomatic conditions This book is unique in its presentation of human development and the options for its implementation into diagnostic and therapeutic approaches of the movement system A chapter is also devoted to the original diagnostic therapeutic approach of Dynamic Neuromuscular Stabilization according to Professor Pavel Kolar the main editor of the book full color resource exceptional photographs of developmental sequences radiographic images diagrams and schematic drawings specific to the Prague School of Rehabilitation and Dynamic Neuromuscular Stabilization 800 text pages photographs of pediatric ontogenetic development

Serotonin, CNS Receptors, and Brain Function P. B.

Bradley,1992 This volume in the series Advances in the Biosciences consists of 25 chapters by many of the world s leading researchers in the fast growing field of central serotonin mechanisms and functions It provides an indispensable authoritative and up to date guide to major new scientific and clinical developments Molecular biology and serotonin receptor subtypes are covered in depth A great deal of the new pharmacology of these subtypes is reviewed and assessed by the innovating investigators Considerable coverage is given to the structure and functions of central serotonergic pathways and behavioural issues are strongly featured Clinicians will be particularly interested in the chapters devoted to anxiety depression obsessive compulsive disorder panic disorder and Tourette s syndrome The volume closes with an important section devoted to pain and cardiovascular function

Annual Reports in Medicinal Chemistry ,1994 Plant Molecules Antonio Tiezzi,Annalisa Santucci,2006 A Textbook of Radiological Diagnosis ,1988 *Pulmonary and Circulatory Abnormalities in Chronic Obstructive Airways Disease* Robert G. Richardson,1983 **Indian Journal of Experimental Biology** ,2005 *The Triptans* Patrick Humphrey,M. D. Ferrari,Jes Olesen,2001 A new era in the treatment of migraine headache arrived with development of a revolutionary class of drugs known as the triptans The book describes the development of this class of drugs starting with the discovery of sumatriptin covers the pharmacology and the mechanisms of action of the full range of triptans before comparing their clinical efficacy and tolerability Each drug is described by the company who produces it and then reviewed based on experimental and clinical evidence by independent scientists This comprehensive review will provide clinicians with guidance on which triptan to select for which patient The editors have gathered together the leading international experts to produce a book that will appeal to all neurologists and general physicians caring for headache patients as well as those with research interests in the field Mental Health in Virginia ,1967

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