LETTERS TO THE EDITOR

AZATHIOPRINE HYPERSENSITIVITY REACTIONS: CAUTION UPON RECHALLENGE

We read with interest and trepidation the letter to the editors entitled ''Fever as sole and delayed manifestation of azathioprine hypersensitivity.''[1] The authors report a patient who developed fever of unknown origin and elevated creatine kinase and erythrocyte sedimentation rate (ESR). He had been receiving azathioprine and prednisone therapy for 16 months. Workup for infectious causes was negative; after discontinuation of azathioprine, the fever resolved. The fever reappeared when azathioprine was reintroduced on two separate occasions.

Although the patient developed no serious consequences upon azathioprine rechallenge, there are over 30 cases in the literature describing severe reactions following rechallenge with azathioprine.[2,3] In these patients, a fever with or without gastrointestinal symptoms most commonly develops within hours or weeks after initiation of the azathioprine. Because the initial reaction is often misdiagnosed as an infection, a rechallenge is mistakenly carried out. Upon azathioprine rechallenge, the reaction is generally more severe and on many occasions life-threatening. As well, the ''rechallenge'' reaction usually manifests itself more rapidly than the initial episode. Hypotension or shock is reported in approximately one third of the cases. Dermatologic eruptions, hepatotoxicity, and nephritis have also been reported.

Because of the potential severity of the reaction upon rechallenge, we advise extreme caution in rechallenging any patient who experiences fever, hypotension, arthalgias, severe nausea, vomiting, and / or leukocytosis while on azathioprine.

Sandra Knowles, BScPhm
Neil H. Shear, MD, FRCPC
Sunnybrook Health Science Centre
Department of Clinical Pharmacology, E240
2075 Bayview Avenue
Toronto, Ontario
M4N 3M5, Canada

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AZATHIOPRINE HYPERSENSITIVITY REACTIONS: CAUTION UPON RECHALLENGE (A REPLY)

We appreciate the comments by S. Knowles and N.H. Shear that support our notion that azathioprine side reactions are sometimes difficult to recognize and in general might be underdiagnosed. However, the situation in our patient was different from the cases mentioned in their letter. In all previous reports hypersensitivity reactions to azathioprine occurred within days or weeks and besides fever were mostly accompanied by additional clinical signs. In our patient there was a delay of 16 months between the beginning of azathioprine treatment and the appearance of drug-induced fever. Therefore, and due to the lack of supportive evidence from the literature, azathioprine hypersensitivity was considered extremely unlikely. After the fever reappeared after the first reexposure, a different azathioprine preparation from another manufacturer was used to exclude sensitivity to constituents of the drug preparation. At present the patient still needs long-term immunosuppression because of reappearance of his interstitial lung disease and steadily increasing creatine kinase levels. He did not tolerate cyclophosphamide and in the meantime the maximal cumulative dose of methotrexate was reached, so that the drug was discontinued because of hepatic toxicity. Due to a small number of therapeutic options in the treatment of polymyositis,[1] the severe side effects of long-term steroid treatment, and the unusual late manifestation of the drug-induced fever, it was essential to prove that azathioprine was the offending drug and no longer a therapeutic option. Taken together, the comments by Knowles and Shear and our case focus attention on azathioprine hypersensitivity as a potentially harmful

cause of fever in patients under long-term immunosuppression independent of the time point of occurrence.

Hubertus Köller, MD
Guido Stoll, MD
Department of Neurology
Heinrich Heine University
P.O. Box 101007
D-4001 Düsseldorf, Germany

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NEUROSELECTIVE CURRENT PERCEPTION THRESHOLD QUANTITATIVE SENSORY TEST

The review article titled ''Quantitative Sensory Testing'' by David Yarnitsky, MD (*Muscle & Nerve* 1997;20:198–204),[13] inexplicably omitted the most widely used and documented computerized quantitative sensory test (QST) procedure. The modern current perception threshold (CPT) exam is an objective, neuroselective QST procedure which uses specifically formed and modulated electrical stimuli to determine the functional integrity of more than 90% of the sensory nerve fibers—including the large and small myelinated and unmyelinated fibers.[6] Dr. Yarnitsky did accurately report that the field of QSTs was started by the grandfathers of modern neurophysiology in the middle of the 19th century. What he failed to note, however, were the roles that these same men played in the development of electrical QSTs. Von Helmholtz (1851), Fleming (1892), Nernst (1908), Martin (1908), Lipique (1912), von Frey (1915), Adrian (1919), Bishop (1933), and of hundreds others conducted systematic studies of electrical QSTs which recognized that the frequency and other characteristics of the stimulus were critical parameters of electrical neuroexcitation.[5] A recent Internet search yielded over 300 peer-reviewed publications utilizing electrical stimuli for quantitative sensory testing—more articles than any other QST modality (e.g., vibratory or thermal) cited in the article.[5]

The modern CPT procedure utilizes constant current electrical stimuli, which are unencumbered by the physiological limitations imposed on vibratory and thermal QSTs by variations in skin thickness and elasticity.[12] The CPT procedure is also unaffected by the normal variations in skin temperatures which otherwise hamper the accuracy and reproducibility of vibratory, thermal, and sensory nerve conduction velocity examinations.[5] The modern CPT procedures use three neuroselective stimuli to assess the function of all major subpopulations of sensory fibers, overcoming yet another significant limitation cited by Dr. Yarnitsky in his review of QSTs.[2]

A unique feature of the CPT test is the ability to quantify hyperesthesia associated with inflammatory conditions such as neuritis or radiculitis.[1,7,10] The ability to detect the earliest, hyperesthetic stages of polyneuropathies, such as those that may result from diabetes or HIV, makes this test much more sensitive than those QSTs described by Dr. Yarnitsky, which are only able to demonstrate the more advanced hypoesthetic stages of nerve pathology.[5]

The modern CPT procedure is an objective standardized test which uses modifications of the method of limits, forced choice, and random staircase paradigms for automated double-blind threshold determinations. This procedure follows the widely accepted paradigms employed by standard auditory and vision tests. The newest application for the CPT technique involves the determination of neuroselective electrical pain perception thresholds which, in contrast to traditional methodologies of determination, are atraumatic to the sites being tested. Recent studies have successfully used these techniques to demonstrate the neuroselective effects of narcotics[8] and local analgesics[9] and to quantify conditions such as large and small fiber mediated allodynia.[4,10]

Over 4000 modern CPT devices are in clinical and research use worldwide and have generated more than 145 peer-reviewed publications attesting to their efficacy—including *Muscle & Nerve* in February, 1996.[3,5,11] I appreciate the Editors allowing this opportunity to fill in the unfortunate omissions in Dr. Yarnitsky's otherwise excellent and informative article.

Jefferson J. Katims, MD
Department of Physical Medicine and Rehabilitation
New York University, New York, NY 10016, USA
Neurotron, Inc.
Baltimore, MD 21209-3650, USA

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