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Irritability in Autistic Children Treated with Fenfluramine

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reported for Feldene exceed those reported to the System for benoxa-profen (Oralac), a structurally unrelated nonsteroidal antiinflammatory agent that has been withdrawn from the market. The original package insert for Feldene does not list photosensitivity as an adverse reaction associated with its use. Yet 29 of 36 reactions associated with this drug were clinically consistent with photosensitivity reactions, and 2 of the remaining 7 reports of reactions were highly suggestive of exacerbation by exposure to sunlight. The 29 patients who had photosensitive eruptions (16 men and 13 women) ranged in age from 20 to 74 years; one patient (a man) was black. In 19 of the 29 patients the eruption occurred within four days and after their first sun exposure after the initiation of Feldene therapy. A majority of the cases included vesicles or bullae in sun-exposed areas. Pruritus was frequently associated with the eruption.

The prompt onset of the eruption in relation to initial treatment and sun exposure suggests a photosensitivity rather than a photosensitization reaction. Three patients who had used thiazide diuretics for extended periods of time experienced photosensitivity reactions after Feldene was added to their therapeutic regimen, suggesting possible additive or synergistic phototoxic effects of Feldene and thiazides.

Boston, MA 02215

Robert S. Stern, M.D.
Beth Israel Hospital

The above letter was referred to Pfizer Laboratories, manufacturers of Feldene, who offer the following reply:

To the Editor: Although Dr. Stern correctly notes that the original Feldene (piroxicam) package insert did not list photosensitivity reactions, they were added in August 1982, three months before we received a communication from him. We made this change voluntarily, because we had received reports of such reactions (including cases from Dr. Stern) after Feldene was introduced, even though we had not received more than 1000 patients studied in our controlled clinical trials. We believe that our current labeling, which states that these reactions occur in fewer than 1 per cent of patients, is supported by this experience.

Some government agencies, such as the Committee on Safety of Medicines in the United Kingdom and the Swedish Regulatory Authority, routinely report information on adverse reactions. Data from these agencies suggest that the incidence of photosensitivity reactions with Feldene is probably on the same order of magnitude as the incidence with other marketed nonsteroidal antiinflammatory drugs, including ibuprofen, indomethacin, and naproxen.

Pfizer has recently reviewed side effects in over 70,000 patients around the world who were treated with Feldene, as well as in comparative studies with indomethacin and naproxen. Dermatologic reactions of any kind occurred in about 1 to 3 per cent of patients and had a similar incidence with each of the drugs.

Finally, it should be noted that benoxaprofen was withdrawn from the market because of hepatic and renal toxicity, not because of photosensitivity, as implied in Dr. Stern's letter.

New York, NY 10017

Roger Sacks, M.D.
Pfizer Laboratories

HERITABILITY IN AUTISTIC CHILDREN TREATED WITH FENFLURAMINE

To the Editor: A report by Geller et al. presented preliminary results suggesting the possible usefulness of fenfluramine (a substituted phenethylamine widely used as an appetite suppressant) in the treatment of autistic autism (July 15, 1982, issue). The rationale for the use of this agent rests on its ability to lower peripheral- and central-basin levels of serotonin and on the observation that a substantial minority of autistic children have decreased peripheral and central-basin serotonin levels. The report emphasized the preliminary nature of the results in a small sample of three young autistic boys with elevated serotonin levels. We have seen two cases in which autistic children were treated with this agent and appeared to have adverse reactions to it. In neither case was peripheral serotonin measured before treatment.

A seven-year-old boy had been diagnosed as autistic at the age of five. The child had a variety of the features typical of autistic children and was enrolled in a special-education program. His pediatrician had given him fenfluramine, 10 mg four times a day. During one month of treatment with this agent the child became progressively irritable and fearful. His activity level increased, and his appetite decreased. Sleep was also disrupted. He deteriorated behaviorally, and his family discontinued the medication. At our examination, performed two months after treatment had been stopped, his serotonin levels were not elevated (152 ng per milliliter).

An 11-year-old autistic boy had been started on fenfluramine (10 mg four times a day) by his father, who had read the preliminary report by Geller et al. Serotonin levels were not determined before treatment. Over several days of treatment the child became more irritable and agitated. Fenfluramine was discontinued. The boy's activity level was markedly increased during the time of treatment, and his father sought an examination. At our examination, one month after treatment had been discontinued, the child had a serotonin level of 212 ng per milliliter.

Adverse reactions to fenfluramine have been noted previously. In one double-blind investigation the efficacy of this agent as an appetite suppressant was evaluated; both patients and physicians were able to identify the active agent correctly in over 70 per cent of cases—largely on the basis of side effects.

There is no rationale for the use of fenfluramine in autistic children who do not have elevated levels of serotonin. Furthermore, its efficacy in this population remains to be clearly established. Physicians should be aware of possible adverse effects of this agent in autistic children and in its investigational nature.

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To the Editor: Watson et al. recently reported a case of polymyositis induced by cimetidine, a drug with a possible role as an immunomodulator (Jan. 20 issue). Since November 1982, we have had the opportunity to follow the patient described in their report and wish to provide follow-up data that argue against the role of cimetidine in inducing polymyositis in this patient.

Although cimetidine had been discontinued in January 1982, the patient had active myositis when first seen by us. In January 1983, while taking prednisone (50 mg per day) and mercaptopurine (50 mg three times a day), he had a severe exacerbation of myositis with profound weakness and elevation of creatine kinase to 289,000 UI per liter. He denied using cimetidine or alcohol. Since then his myositis has remained active despite treatment with high doses of prednisone and methotrexate.

It is apparent that 15 months after discontinuation of cimetidine, this patient continues to have progressive polymyositis. This contrasts sharply with previously reported cases of drug-induced polymyositis, in which remission of disease was observed soon after discontinuation of the drug. For example, in all previously reported cases of penicillamine-associated polymyositis, remission or marked improvement in both clinical and laboratory features of the disease occurred within six months of stopping therapy. In no case was