Liver metabolized drugs

Pyrimethamine + sulfadoxine
Both pyrimethamine and sulfonamides are liver enzyme inhibitors, and can cause interactions with drugs that are normally metabolized in the liver.

References

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Pyritinol

General Information

Pyritinol is a sulfhydryl-containing compound, a dimer of 5-thiopyridoxine. It was used from 1961 onwards as a psychostimulant of doubtful efficacy, but apparently without adverse effects, and then largely abandoned. When it was re-introduced in some countries for rheumatoid arthritis, adverse effects were registered in 25% of patients.

Cross-allergy with D-penicillamine has been hypothesized to explain the apparently higher frequency of adverse effects of pyritinol in patients with rheumatoid arthritis (1).

In usual doses, 600–800 mg/day, pyritinol has a profile of adverse reactions reminiscent of that of penicillamine (2,3). Some 40% of users have adverse reactions, leading to withdrawal in about 23% of the total. The most common are non-specific rashes and stomatitis; in addition, pemphigus, lichen planus, and photosensitivity have occurred. Gastrointestinal symptoms (diarrhea, gastralgia, nausea, loss of taste) can occur, but are less frequent than with penicillamine. Thrombocytopenia, reversible extramembranous glomerulonephritis with nephrotic syndrome (4), a myasthenia-like picture, and acute polymyositis with positive rechallenge have also been described (5).

In a collaborative study of the French Pharmacovigilance Centers there were 23 reports of suspected reactions to pyritinol, including four cases of pemphigus, three of agranulocytosis (but other drugs taken were oxyphenbutazone or clomipramine), two of nephrosis, and two of a lupus-like syndrome (6).

Comparative studies

In a multicenter, double-blind study, patients with rheumatoid arthritis took pyritinol 600 mg/day or auranofin 6 mg/day for 1 year (7). Of 139 patients randomized to pyritinol, 61 (44%) dropped out because of adverse events or response failure compared with 44 (31%) of the 142 patients randomized to auranofin. Among the rest, adverse events occurred in 64% of patients taking pyritinol and in 58% of patients taking auranofin: the main events were mucocutaneous symptoms (pyritinol 36%, auranofin 23%) and gastrointestinal complaints (pyritinol 30%, auranofin 37%). There were single cases of proteinuria, hepatic abnormalities, and hematological abnormalities in both groups.

Organs and Systems

Metabolism

Autoimmune hypoglycemia with detectable anti-insulin antibodies, probably caused by pyritinol, has been described in one patient (8). This syndrome has previously been reported in connection with other thiol compounds, (penicillamine, methimazole, and tiopronin).

Liver

Pyritinol-induced acute hepatitis has been described (9).

Pancreas

Pancreatitis has been attributed to pyritinol.

- A 23-year-old student had three episodes of acute pancreatitis after the occasional ingestion of pyritinol for better performance in examinations. Immunological investigations pointed to a probable T cell-mediated hypersensitivity reaction (10).

Immunologic

A high titer of antinuclear antibodies and anti-double-stranded native DNA antibodies occurred during treatment with pyritinol 400 mg/day in a woman with rheumatoid arthritis (11). A clear temporal relation and a reduction in antinuclear antibody titers and disappearance of anti-DNA antibodies after drug withdrawal strongly suggested a causal relation.

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Pyrrolizidine alkaloids

General Information

Pyrrolizidine alkaloids occur in a large number of plants, notably the genera *Crotalaria* (Fabaceae), *Cynoglossum* (Boraginaceae), *Eupatorium* (Asteraceae), *Heliotropium* (Boraginaceae), *Petasites* (Asteraceae), *Senecio* (Asteraceae), and *Symphytum* (Boraginaceae) (Table 1). Certain representatives of this class and the plants in which they occur are hepatotoxic as well as mutagenic and hepatocarcinogenic. They can produce veno-occlusive disease of the liver with clinical features like abdominal pain with ascites, hepatomegaly and splenomegaly, anorexia with nausea, vomiting, and diarrhea. Sometimes there is also damage to the pulmonary region.

The German Federal Health Office has restricted the availability of botanical medicines containing unsaturated pyrrolizidine alkaloids (1,2). Herbal medicines that provide over 1 mg/day internally or over 100 mg/day externally are not permitted; herbal medicines that provide 0.1–1 mg/day internally or 10–100 mg/day externally may be applied for only a maximum of 6 weeks per year, and they should not be used during pregnancy or lactation.