Isoniazid and Food Interactions: —Fish, Cheese, and Wine

Key words: INH, histamine, tyramine, monoamine oxidase (MAO), diamine oxidase (DAO), scombroid poisoning

Isoniazid (INH) is one of the most effective anti-tuberculous agents and has been listed as the first-line agent for the treatment of tuberculosis in *Statements of ATS*, *CDC*, *and IDSA on Treatment of Tuberculosis* (1). As adverse effects of INH, hepatotoxic and neurotoxic effects are well known, the potential for frightening and dangerous interactions between INH and certain foods is presently little known. INH may interact with fish, cheeses or wine with high histamine and/or tyramine contents, because INH can indirectly inhibit the metabolism of ingested histamine and tyramine from food.

Histamine is a biogenic monoamine and thus present in animal foods and in some vegetables. Histamine causes vasodilation and an increase in permeability of blood vessel walls. Subsequently, vasodilation results in lowered peripheral vessel resistance and blood pressure. It also causes contraction of smooth muscle and regulates gastric acid production. Histamine is mainly metabolized by monoamine oxidase (MAO) and, to a lesser extent, by diamine oxidase (DAO) (2). On the other hand, tyramine is an indirect sympathomimetic amino acid which is found in various foods and can cause a hypertensive reaction. Tyramine is known to be metabolized by MAO (3), which is distributed in the gastrointestinal tract and liver. If the activity of MAO is inhibited, tyramine is not metabolized and readily reaches the systemic circulation after absorption in the intestines. Tyramine then induces the release of norepinephrine from sympathetic nerve endings and epinephrine from the adrenal glands (4). Intoxication by histamine and tyramine is likely to occur in patients receiving INH, due to the ability of INH to inhibit both MAO and DAO (5). The manifestations of histamine poisoning include headache, palpitations, sweating, flushing, diarrhea, itching, and hypotension (6, 7). Those of tyramine intoxication are very similar and are not easily distinguishable. The major difference may be the tendency of histamine to decrease and of tyramine to increase blood pressure.

Cheeses may contain both histamine and tyramine causing intoxication in patients receiving INH (7–9), but the levels vary widely in different types. Red wine also contains tyramine and has been reported to cause the same intoxication (7). The tyramine content of food increases if they are aged, fermented or left to spoil. Certain fish are known to contain high levels of histamine. Scombroid fish, including skipjack and tuna, are particularly rich in histidine and have been reported to cause histamine poisoning in patients receiving INH (7). Histamine fish poisoning is thus called "scombroid fish poisoning", although other fish species, including mahi-mahi, bluefish, sardines, marlin and Australian salmon, are associated with the poisoning (10–12). Histamine in fish is primarily produced by bacterial conversion of the amino acid, histidine. During spoilage of fish, bacteria within the fish multiply and the conversion of histidine into histamine also increases.

In this issue of this journal, there is a very interesting and informative report of an outbreak of histamine poisoning after ingestion of ground saury paste in the tuberculous ward (13). Of all the patients who ate ground saury paste, only those under treatment with INH experienced histamine poisoning. Those patients receiving INH who did not eat the paste were unaffected. Moreover, all patients who experienced histamine poisoning were confirmed to have reduced levels of serum MAO. Analysis of the paste revealed that histamine content was very high but below the hazardous threshold. It was clearly diagnosed as histamine poisoning from ground saury paste due to the inhibition of MAO activity by INH. This outbreak occurred even though the fish was cooked. Although the bacteria die during the cooking process, histamine contained in the fish is heat resistant. We should therefore know that cooking fish will not reduce the risk of histamine poisoning.

See also p 1133.

In conclusion, we should be aware of the possible adverse effects, not only of INH itself, but of the interactions between INH and certain foods. It is prudent to advise patients under treatment with INH to be cautious with certain foods, such as scombroid fish, cheeses and red wine.

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