COMPOSITIONS WITH REDUCED HEPATOTOXICITY

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ABSTRACT

Pharmaceutical compositions of hepatotoxic compounds are provided in which the hepatotoxicity of the compounds is mitigated by including quantities of nicotinamide and methionine in the composition. Folic acid also can be included to further mitigate the hepatotoxic effects. The hepatotoxic compounds can include acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid.
COMPOSITIONS WITH REDUCED HEPATOTOXICITY

BACKGROUND OF THE INVENTION

[0001] This invention relates to compositions of pharmaceutical compounds having hepatotoxicity, in which compositions the hepatotoxicity is mitigated. More particularly, this invention relates to compositions of hepatotoxic compounds such as acetaminophen, methotrexate, statin drugs, niacin, divalproex sodium, valproic acid or fluconazole, each of which is known to have hepatotoxic properties, in which compositions the hepatotoxicity of the compound is mitigated.

[0002] Acetaminophen is the active metabolite of phenacetin, a drug whose use extends back to the 1880’s. Although acetaminophen was first used as an analgesic and antipyretic in 1893, it did not achieve widespread use until after 1949. For many years, acetaminophen was used as a second-line choice to aspirin as an analgesic/antipyretic, but the elucidation of the relationship between aspirin use and Reye’s Syndrome and the recognition of aspirin’s propensity to produce gastrointestinal bleeding allowed acetaminophen into its current day position as the analgesic/antipyretic of first choice in both children and adults. While acetaminophen is usually well tolerated, its use can be accompanied by a very serious adverse effect—potentially fatal hepatic necrosis. Hepatic necrosis with acetaminophen is largely confined to two groups of patients: 1. Patients who ingest acute overdoses or who chronically utilize high dosage regimens of acetaminophen, 2. Ingestion of acetaminophen by alcoholics or in combination with alcohol ingestion. It has been reported that more than 26,000 patients per year are hospitalized in the U.S. for acetaminophen induced hepatic necroses, and of these, more than 400 die each year. Many of these overdoses are the result of suicide attempts, but reports indicate that more than 2,000 hospitalizations and 100 deaths a year were attributable to non-intentional acetaminophen overdoses. In fact, an Advisory Panel of the U.S. Food and Drug Administration has recommended that new warning language be added to the label of acetaminophen containing products concerning the danger of hepatic necroses.

[0003] Methotrexate, an inhibitor of cell metabolism, has been utilized for several decades as a therapeutic agent widely used in several different diseases including rheumatoid arthritis and psoriasis. While methotrexate administration is associated with various other side effects, severe and sometimes fatal liver toxicity is a significant limiting factor in its therapeutic usefulness. Atorvastatin, simvastatin and other cholesterol lowering agents of the “statin” family are the most widely used pharmaceuticals in the world. In spite of their widespread use, liver toxicity is a significant problem, and patients with a history of old or active hepatitis must avoid these drugs even if they could benefit from their cholesterol lowering actions. Niacin (also known as nicotinic acid or vitamin B3), another agent frequently employed as a cholesterol lowering agent, is also associated with a high incidence of liver toxicity. Fluconazole, a potent antifungal agent, and divalproex sodium and valproic acid, widely used antiepileptics are three other agents whose clinical use is limited by their hepatotoxicity.

[0004] The concerns about the hepatic toxicity of acetaminophen, methotrexate, the “statin” cholesterol lowering agents, niacin, fluconazole, divalproex sodium and valproic acid, prompted me to search for a substitute or a mixture of substances that in combination with any of these drugs would substantially reduce the risk of hepatic toxicity without adversely affecting the therapeutic benefits conferred by these drugs. In reviewing the scientific literature, I learned that nicotinamide (also known as niacinamide), which is the amide of vitamin B3 (niacin), and methionine, an essential amino acid which is a DL racemic mixture of D & L methionine, have been used in very high dosages to prevent liver damage from acetaminophen or methotrexate. These drugs have been administered as single large doses or multiple large doses over a short (usually 24 hr) period. Published dosages of methionine for such usage range from about 2.5 gm to over 21 gm administered as a single dose for over 24 hours. Wright, B., Crowe, M., British Medical Journal (England), vol. 317, Dec. 12, 1998, p. 1656; Vale, J. A., Proudfoot, A. T., The Lancet, 1995, vol. 346, pp. 547-52. Similarly, doses of nicotinamide utilized for a similar purpose have ranged from about 2 gm to 7 gm per 24 hours. Kroger, H., et al., General Pharmacology 33 (1999) 203-206.

[0005] I have discovered, surprisingly, that nicotinamide and methionine can be administered in combination with hepatotoxic pharmaceutical compounds such as acetaminophen, methotrexate, a “statin” cholesterol lowering agent, fluconazole, divalproex sodium or valproic acid, in substantially lower doses than disclosed in the prior art, and when administered as such, can provide a substantive protective effect against the hepatotoxicity of these agents without negatively affecting their beneficial therapeutic activity. I have furthermore discovered that by adding a modest amount of folic acid to the nicotinamide and methionine mixture, in combination with hepatotoxic pharmaceutical compounds such as acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, valproic acid, and related drugs, I can achieve a therapeutic product which provides the therapeutic benefits of each of these agents with almost no potential for liver toxicity.

[0006] It is thus the object of the invention to provide pharmaceutically acceptable compositions of hepatotoxic therapeutic drugs such as acetaminophen, methotrexate, the “statins,” niacin, fluconazole, divalproex sodium, valproic acid, and related drugs, which compositions provide the therapeutic benefits of the active drug with markedly reduced potential for serious hepatotoxicity.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0007] In accordance with the invention, compounds having known hepatotoxic properties are formulated into compositions in which the hepatotoxic properties are mitigated. The compositions can include a standard dose of the hepatotoxic compound, together with relatively low dosages of nicotinamide and methionine. Low dosages of folic acid also can be added to the compositions to further mitigate the hepatotoxic properties.

[0008] Specific embodiments of the invention can be in the form of formulations of acetaminophen together with mixtures of low dosages of nicotinamide and methionine, or together with low dosages of nicotinamide, methionine and folic acid; or formulations of methotrexate together with mixtures of low dosages of nicotinamide and methionine, or...
together with low dosages of nicotinamide, methionine and folic acid. These formulations are incorporated into pharmaceutically acceptable vehicles for use in humans and animals. Similarly, formulations of atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium or valproic acid each can be formulated into pharmaceutically acceptable vehicles for use in humans and animals together with mixtures of low dosages of nicotinamide and methionine, or together with low dosages of nicotinamide, methionine and folic acid. Such formulations include those suitable for oral administration such as capsules, tablets, caplets, or liquid solutions or suspensions, as well as sterile solutions or suspensions suitable for intradermal, subcutaneous, intramuscular, intravenous or intrathecal injection.

[0009] In each of the foregoing formulations, whether for oral ingestion or for injection, when combined with standard dosages of either acetaminophen (80 mg - 1000 mg per single dose form, e.g. single capsule, single tablet, etc.), methotrexate (2.5 mg - 250 mg per single dose form), atorvastatin or simvastatin (5 mg - 100 mg per single dose form), niacin (250 mg - 1000 mg per single dose form), fluconazole (10 mg - 250 mg per single dose form), divalproex sodium (100 mg - 750 mg per single dose form), and valproic acid (25 mg - 500 mg per single dose form), methionine may be present in the amount of about 5 mg to about 500 mg per single dose form, and preferably about 10 mg to 100 mg per single dose form, and nicotinamide may be present in the amount of about 10 mg to 500 mg per single dose form, and preferably about 25 mg to about 200 mg per single dose form. When folic acid is included in the standard dose formulation, folic acid may be present in the amount of about 50 mcg to about 5 mg, and preferably about 500 mcg to 1 mg per single dose form.

[0010] Suitable pharmaceutical vehicles for the combinations of hepatotoxic compounds such as acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium or valproic acid, with hepatotoxicity mitigators methionine, nicotinamide and folic acid, and methods of preparing such formulations as are within the scope of the invention, will be readily apparent to and understood by those skilled in the art.

[0011] The compositions of the instant invention will be more readily comprehended from the following examples:

**EXAMPLES**

**Example 1**

Two tablets, comprised of 500 mg acetaminophen, 50 mg methionine, and 25 mg nicotinamide, are administered four times daily for twelve (12) weeks to patients with osteoarthritis for relief of osteoarthritis pain without evidence of liver damage.

**Example 2**

Tablets prepared each containing 2.5 mg methotrexate, 100 mg methionine, 100 mg nicotinamide and 100 mcg folic acid. Two of such tablets are administered to patients with psoriasis of the skin twice daily for 6 months. Such patients demonstrate improvement in their psoriatic lesions without evidence of serious methotrexate-induced liver damage.

**Example 3**

Two caplets each containing 500 mg acetaminophen, 200 mg methionine, and 100 mg nicotinamide are administered four times daily for twelve (12) weeks to patients with osteoarthritis for relief of osteoarthritis pain without evidence of liver damage.
10. The composition of claim 7 wherein said composition is suitable for injection.

11. The composition of claim 10 wherein said composition is selected from the group consisting of sterile solutions or suspensions.

12. The composition of claim 11 wherein said composition is suitable for intradermal, subcutaneous, intramuscular, intravenous, or intrathecal injection.

13. The composition of claim 1 wherein said hepatotoxic compound is selected from the group consisting of acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid.

14. The composition of claim 13 wherein said hepatotoxic compound is acetaminophen.

15. The composition of claim 14 wherein said acetaminophen is present in the amount of about 80-1000 mg per standard dose.

16. The composition of claim 13 wherein said hepatotoxic compound is methotrexate.

17. The composition of claim 16 wherein said methotrexate is present in the amount of about 25-250 mg per standard dose.

18. The composition of claim 13 wherein said hepatotoxic compound is atorvastatin.

19. The composition of claim 18 wherein said atorvastatin is present in the amount of about 5-100 mg per standard dose per standard dose.

20. The composition of claim 13 wherein said hepatotoxic compound is simvastatin.

21. The composition of claim 20 wherein said simvastatin is present in the amount of about 5-100 mg per standard dose.

22. The composition of claim 13 wherein said hepatotoxic compound is niacin.

23. The composition of claim 22 wherein said niacin is present in the amount of about 250-1000 mg per standard dose.

24. The composition of claim 13 wherein said hepatotoxic compound is fluconazole.

25. The composition of claim 24 wherein said fluconazole is present in the amount of about 10-250 mg per standard dose.

26. The composition of claim 13 wherein said hepatotoxic compound is divalproex sodium.

27. The composition of claim 26 wherein said divalproex sodium is present in the amount of 100-750 mg per standard dose.

28. The composition of claim 13 wherein said hepatotoxic compound is valproic acid.

29. The composition of claim 28 wherein said valproic acid is present in the amount of 25-500 mg per standard dose.

30. A method of mitigating the hepatotoxicity of a hepatotoxic compound comprising formulating a composition comprising a quantity of the hepatotoxic compound, said composition comprising a quantity of nicotinamide, and a quantity of methionine.

31. The method of claim 30 wherein said composition is formulated such that for each standard dose of the hepatotoxic compound in the composition, the nicotinamide is present in the amount of about 5-500 mg, and the methionine is present in the amount of about 25-500 mg.

32. The method of claim 31 wherein said nicotinamide is present in the amount of about 25-200 mg per standard dose of the hepatotoxic compound.

33. The method of claim 31 wherein said methionine is present in the amount of about 10-100 mg per standard dose of the hepatotoxic compound.

34. The method of claim 30 wherein said composition further comprises a quantity of folic acid.

35. The method of claim 34 wherein said folic acid is present in the amount of about 50 mcg-5 mg per standard dose of the hepatotoxic compound.

36. The method of claim 35 wherein said folic acid is present in the amount of about 500 mg-1 mg per standard dose of the hepatotoxic compound.

37. The method of claim 30 wherein said hepatotoxic compound is selected from the group consisting of acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid.

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