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# THERAPEUTIC COMPOSITIONS CONTAINING 1-HEXYL 3,7-DIMETHYLXANTHINE AND NICOTINATES

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This invention relates to novel therapeutic compositions. More particularly, it relates to a composition comprising 1-hexyl 3,7-dimethylxanthine and nicotinic acid or its salts having particular value in the treatment of the symptoms of cerebral sclerosis.

There are known therapeutic utilities for derivatives of xanthine, such as theophylline, theobromine and caffeine, in their therapeutic pure form, and in the form of their salts or double salts (for instance, caffeine citrate, theophylline sodium salicylate). Their therapeutic indications are maintainly attributable to their dilating effect on peripheral blood vessels and their diuretic properties. In the case of caffeine, there is a certain observable, analeptic effect. Derivatives of these same substances have also been suggested for the same use due to their superior water solubility. Such derivatives include compounds such as dihydroxypropyltheophylline, oxyethyl-theophylline, and like compounds.

The compounds mentioned in the foregoing paragraph have been suggested for use in the treatment of cerebral sclerosis. However, it is generally recognized and experience proves that they do not have any direct effect on functional failures or dysfunctioning associated with the illness. At most, these known xanthine derivatives have an indirect effect in that they mitigate hypertonia, which accompanies cerebral sclerosis, to a moderate extent.

Also, β-pyridine carbonic acid (nicotinic acid), is known to have a blood vessel dilating effect. Yet, it is known that this dilating effect is only temporary or transitory. For instance, scientific publications indicate that the effect extends over a few minutes only. Nevertheless, it has been suggested that nicotinic acid be applied therapeutically for the treatment of cerebral sclerosis. Likewise, clinical experience has taught that nicotinic acid has a very mild, or no effect, in the treatment of cerebral sclerosis. According to Drill (Pharmacology in Medicine, 1954, p. 61/9) has no therapeutic effect whatsoever in the treatment of cerebral sclerosis.

Recently a xanthine derivative, akin to those mentioned above, has become available. This product, 1-hexyl 3,7-dimethylxanthine, is disclosed in German Patent No. 860,217. This new product, sometimes referred to herein as 1-hexyl compound, has very pronounced peripheral blood vessel dilating effects which is many times that of the known xanthine derivatives, discussed above, such as theophylline, and the like. Even though the 1-hexyl compound has striking vasodilating effects, it has not proven satisfactory as a medicament for obtaining a remission of cerebral sclerosis.

Now it has been found that the combination of 1-hexyl-3,7-dimethylxanthine and nicotinic acid (or sodium nicotinate) has a stronger peripheral dilating effect than either of the two substances alone. This can be proven by administering a combination, and the two substances separately, to healthy pesrons and measuring the skin temperature. Actually the skin temperature rises more strongly with the peroral intake of both components than with the intake of the individual components. As is known, the rise in temperature of the skin is an indication, or measure, of the dilation of the skin vessels. Also, the synergistic effect of the combination of the substances can be proven on the coronary vessels of a cat. The coronary spasm produced experimentally by the injection of hormones derived from the posterior lobe of the pituitary gland (method according to Antopol and Roessler) can indeed be prevented, or, in some cases weakened by the prophylactic administration of the 1-hexyl compound and sodium nicotinate. (For reasons of pH control the sodium salt of nicotinic acid rather than nicotinic acid is used in this test.) Yet, the same effect cannot be produced by using one of the two components alone even by using greater doses.



Even more strikingly, however, the combination of 1-hexyl 3,7-dimethylxanthine and sodium nicotinate can be used in therapeutically effective doses to obtain remission of the symptoms of cerebral sclerosis without having any deleterious side effects.

In accordance with a practical application of the invention, 1-hexyl 3,7-dimethylxanthine and sodium nicotinate are tableted in a ratio, by weight, of about 4:1. A typical tablet contains 50 mgs. of sodium nicotinate and 200 mgs. of 1-hexyl 3,7-dimethylxanthine. In the treatment of cerebral sclerosis, the normal dose is one tablet at a time. Generally speaking, in initiating the treatment, one tablet is taken 3 or 4 times daily. After about two weeks, one tablet is taken twice daily. Eventually one tablet may be taken daily for maintenance purposes, and where remission of the symptoms of cerebral sclerosis is apparently complete, the medication may be discontinued.

It will be seen from the foregoing that an effective dose of the compositions hereof is well within the dose recommended for known xanthine derivatives of the type mentioned above for their field of therapeutic use. Yet, the compositions of this invention may be used with great flexibility of doses without having a toxic effect. This absence of deleterious side effects in effective doses may be attributable to the very low toxic effect of the 1-hexyl compound. For example, theophyllene is 2.5 times as toxic as the 1-hexyl 3,7-dimethylxanthine.

It will be understood that it is not necessary to use the 1-hexyl 3,7-dimethylxanthine and the sodium nicotinate in the ratio of 4:1. Experience indicates that the 1-hexyl 3,7-dimethylxanthine should be used in a dose of the order of 200 mgs. The sodium nicotinate is usually used in a lesser quantity than the 1-hexyl compound but may be used satisfactorily in any quantity between the ratio of 1:10 and 1:1. Thus, in practical embodiments of the invention, the therapeutic compositions of this invention are prepared in tablets containing 200 mgs. of the 1-hexyl compound and between 20 and 200 mgs. of sodium nicotinate.

In the practical embodiments of this invention sodium nicotinate has been used. It is generally understood, however, that nicotinic acid and therapeutic inorganic salts of nicotinic acid are therapeutically substantially equivalent, although the sodium nicotinate is usually preferred. For example, the inorganic salts of nicotinic acid usually provide a more favorable pH than nicotinic acid per se. Yet, nicotinic acid can be substituted, somewhat less advantageously, for the sodium nicotinate and like therapeutic inorganic salts of nicotinic acid.

Parts are expressed herein as parts by weight.

The foregoing description constitutes illustrative embodiments of the invention but clearly they are not a limitation thereupon. The invention contemplates various adaptations, alterations and modifications which will

occur to those skilled in the art and which are within the scope and spirit of the invention defined by the appended claims.

We claim:

1. A therapeutic composition comprising 1-hexyl 3,7-dimethylxanthine and a nicotinic acid compound selected from the group consisting of nicotinic acid and its inorganic salts.

2. A composition effective in the remission of cerebral sclerosis comprising nicotinic acid and at least an equal quantity of 1-hexyl 3,7-dimethylxanthine.

3. A therapeutical composition consisting essentially of 1-hexyl 3,7-dimethylxanthine and 10–100% as much by weight of an inorganic salt of nicotinic acid.



4. A therapeutical composition comprising 1-hexyl 3,7-dimethylxanthine and sodium nicotinate in a ratio of about 4:1.

**References Cited** in the file of this patent

Chemische Chem. Abst., vol. 47, 1953, p. 11238C.

U.S. Dispensatory, 25th ed., 1955, Lippincott Co., Phila., pp. 893–896, 1407, 1408.