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PARENTERAL SOLUTION OF ANTI-HEMORRHAGIC COMPOUNDS

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7 Claims. (Cl. 167—81)

This invention relates to anti-hemorrhagic compositions and more particularly relates to parenteral solutions of anti-hemorrhagic compounds in organic esters.

A number of anti-hemorrhagic compounds of the vitamin K type have been found to be useful in the prevention and treatment of hypoprothrombinemia and the hemorrhagic diathesis of the newly born and in the treatment of post-operative bleeding in jaundice or persons having prothrombin deficiencies.

In the past these substances have been administered orally or parenterally in solutions of fixed oils such as olive oil; or in some instances, water soluble salts of the compounds have been used for parenteral injection. The parenteral solutions available heretofore have not been entirely satisfactory. The oil solutions are not entirely stable to light, the rate of absorption is retarded somewhat, and frequently anatomical changes occur at the site of injection. The aqueous parenteral solutions of the salts are somewhat more desirable than the oil solutions but have the disadvantages that the salts are not always equivalent in activity to that of the parent substance and some of the anti-hemorrhagic compounds do not form water soluble salts which are suitable for parenteral injection.

In accordance with the present invention it has been found that certain organic esters may be used as solvents for anti-hemorrhagic compounds and that the solutions are suitable for parenteral use.

Suitable esters for preparing the solutions of the present invention include the ethyl and butyl esters of certain dicarboxylic acids; namely, succinic and pimelic. These esters have been found to be satisfactory solvents for producing parenteral solutions of any of the water insoluble substances possessing vitamin K activity. These anti-hemorrhagic compounds include those such as: 2-methyl-3-phytyl-1,4-naphthoquinone, 2-methyl-3-hydroxy-1,4-naphthoquinone, 2-methyl-1,4-naphthoquinone, 2-methyl-1,4-naphthohydroquinone, dimethoxynaphthalene, 2,3-dimethyl-1,4-naphthoquinone, 4-amino-2-methyl-1-naphthol, 2-methyl-1-naphthol, and 2-methyl-1-naphthylamine. The first-mentioned compound above is the natural vitamin K and the remainder of the compounds for the most part are vitamin K analogs. One of the simplest members of this series of anti-hemorrhagic substances is 2-methyl-1,4-naphthoquinone, and it is the preferred substance for preparing the parenteral solution of the present invention because of its outstanding anti-hemorrhagic action.

A number of tests have been carried out using solutions of this anti-hemorrhagic substance in ethyl succinate, n-butyl succinate, ethyl pimelate, and n-butyl pimelate, and the solutions were found to be suitable for parenteral administration. The solutions showed no toxic effects and produced no anatomical changes at the site of injection. Absorption of the quinone from the esters was rapid and the anti-hemorrhagic effect was at least equivalent to that of the quinone when used by other methods.

In carrying out the present invention it has been found that the esters of aliphatic alcohols having an even number of carbon atoms and the dicarboxylic acids, succinic and pimelic, produce satisfactory parenteral solutions, whereas the alcohols having an uneven number of carbon atoms such as methyl and propyl do not form esters which are suitable for parenteral administration even with succinic and pimelic acid. This would appear to indicate that certain esters produce unforeseen toxicities and that even chemically closely related esters behave differently. Toxicity tests, however, on ethyl succinate, n-butyl succinate, ethyl pimelate, and n-butyl pimelate show the specificity of these applicable esters. These esters may likewise be used for preparing parenteral solutions of water insoluble therapeutic compounds other than those specifically claimed in this invention.

In general, the parenteral solutions of this invention are prepared by dissolving, for example, 2-methyl-1,4-naphthoquinone in one of the esters mentioned above in such a proportion that 0.5 cc. of solution will contain about 2 mg. of the quinone. These proportions, of course, may be varied to suit the individual case and solutions may contain from 0.6 to 4 mg. per each 0.5 cc. of solution or the same quantity may be con-

tained in 1 cc. of the solution. In practice it has been found that 0.5 to 2 cc. of the solution may be safely injected parenterally and the amount of anti-hemorrhagic substance may be increased or decreased depending upon the dosage desired. The invention is not restricted to the proportions set forth herein.

The invention will be further illustrated in conjunction with the following specific tests. It is to be understood, however, that the tests are for the purpose of illustration only and the invention is not to be limited to the details set forth therein.

The procedure used in the vitamin K tests was as follows: Day-old chicks were placed on a vitamin K-free diet of the following composition: fish meal, 17.5%; yeast, 7.5% (both the fish meal and the yeast were ether extracted); ground polished rice, 74%; NaCl (plus "traces" of Cu and Fe), 1%; A and D concentrate, 3 drops per week. Usually after seven days on this diet, the blood clotting time of the chicks exceeded 30 minutes and the chicks were then used for the test. In the positive control groups each chick received 0.1 cc. of a solution of 10 micrograms of the naphthoquinone in 1 cc. of cottonseed oil, introduced into the crop by means of a pipette. Injections (0.1 cc. of test solution) were made into the muscle of the leg and, in all except the early test, an eighteen-hour period elapsed between administration of the supplement and clotting time determinations.

The clotting times were determined as follows. The underside of the wing was trimmed clear of feathers with a scissors, extreme care being exercised to avoid abrasion of the skin. The large wing vein was then pricked with a hypodermic needle in such a way as to allow a large drop of blood to form rapidly. Three capillary tubes filled by suction were broken periodically until clotting was indicated by the "stringing" of the blood.

The response of the chicks in the assay group was compared with that given by the quinone and the results are expressed in terms of the percentage of chicks showing a given response. On the average, 1 microgram of 2-methyl-1,4-naphthoquinone is expected to bring 50% of the chicks to a clotting time of 10 minutes or less and the substance under test was fed at a level to give this response. Typical results of the eighteen-hour test conducted on different days are tabulated in Table 1.

In the three day test, three daily doses of 0.6 microgram of the quinone or 1.5 micrograms of vitamin K_1 were given and the blood clotting time determined on the fourth day in the usual way. Typical results for such a determination appear in Table 2.

Table 1—Eighteen hour test

A-GROUP OF TESTS

Control:								
Chick number	2352	2351	2349	2347	2353	2346		
Clotting time minutes	>30	>30	>30	>30	>30	>30		
1 γ quinone in oil:								
Chick number	2355	2356	2361	2357	2359	2360	2354	2358
Clotting time minutes	7	3	25	>30	6½	9	7	19
1 γ quinone in ethyl pimelate:								
Chick number	2364	2366	2365	2373	2368	2367	2362	2363
Clotting time minutes	17	9	10	14	7	3	4	9
1 γ quinone in butyl succinate:								
Chick number	2392	2391	2388	2385	2382	2387	2386	2384
Clotting time minutes	5	3	8	3	3	2	2	5

B-GROUP OF TESTS

Control:							
Chick number	3152	3169	3163	3153	3157		
Clotting time minutes	>30	>30	>30	>30	>30		
1 γ quinone in oil:							
Chick number	3119	3147	3126	3122			
Clotting time minutes	>30	14	22	23			
1 γ quinone in ethyl succinate:							
Chick number	3133	3131	3130	3132	3134	3129	
Clotting time minutes	2	2	3	9	6	4	

C-GROUP OF TESTS

Control:								
Chick number	4177	4169	4188	4187	4160	4144		
Clotting time minutes	>30	>30	>30	>30	>30	>30		
1 γ quinone in oil:								
Chick number	4165	4152	4168	4171	4142	4193	4179	4181
Clotting time minutes	>30	>30	15	29	29	10	5	4
1 γ quinone in ethyl succinate:								
Chick number	4147	4140	4139	4143	4145	4146	4141	
Clotting time minutes	7	4	3	8	27	13	24	
1 γ quinone in ethyl succinate:								
Chick number	4156	4153	4155	4151	4149	4148	4150	
Clotting time minutes	5	4	3	3	5	17	30	
1 γ quinone in ethyl succinate:								
Chick number	4163	4161	4162	4164	4157	4159		
Clotting time minutes	3	10	4	6	8	15		
1 γ quinone in ethyl succinate:								
Chick number	4167	4173	4175	4174	4166	4172	4170	
Clotting time minutes	5	4	4	4	16	21	18	
1 γ quinone in ethyl succinate:								
Chick number	4183	4185	4176	4178	4180	4182		
Clotting time minutes	14	19	3	3	8	14		
1 γ quinone in ethyl succinate:								
Chick number	4189	4190	4191	4192	4154	4194	4196	
Clotting time minutes	3	3	4	6	5	11	10	

D-GROUP OF TESTS

Control:										
Chick number	4536	4537	4538	4539	4540	4541	4542	4543	4544	4546
Clotting time minutes	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40
1 γ quinone in oil:										
Chick number	4556	4557	4558	4559	4560	4561	4562	4563		
Clotting time minutes	12	19	28	25	30	>40	10	40		
Chick number	4564	4565	4598	4600	4601	4603	4604			
Clotting time minutes	11	11	17	15	9	35	16			
1 γ quinone in butyl succinate:										
Chick number	4576	4577	4578	4579	4580	4581	4582	4583	4584	
Clotting time minutes	11	27	14	8	34	30	21	18	7	
Chick number	4606	4608	4609	4611	4614					
Clotting time minutes	9	14	17	13	15					

E-GROUP OF TESTS

Control:									
Chick number	4696	4698	4699	4700	4701	4702	4705	4706	4708
Clotting time minutes	>40	>40	>40	>40	>40	>40	>40	>40	31½
1γ quinone in oil:									
Chick number	4761	4762	4763	4764	4765	4766	4767	4768	4769
Clotting time minutes	4	9½	12	21	11½	8	13	8½	8
Chick number	4770	4771	4772	4773	4774				
Clotting time minutes	9½	10	6	9	16				
1γ quinone in n-butyl succinate:									
Chick number	4731	4732	4733	4734	4735	4736	4737	4738	4739
Clotting time minutes	14	16	12	13	17	12	26	12	7
Chick number	4740	4741	4742	4743	4744	4745			
Clotting time minutes	14	36	14	30	10	9			

Table 2—Three day test

F-GROUP OF TESTS

Control:							
Chick number	101	102	103	106	108	109	110
Clotting time	>30′	>30′	8′ 25″	>30′	>30′	28′ 25″	17′ 20″
1.5γ K_1 in ethyl succinate:							
Chick number	141	142	145	146	148	150	
Clotting time	30′	13′ 50″	20′	26′ 5″	8′ 10″	8′ 55″	

Table 3—Three day test

SUMMARY

Group test	Supplement	Level	Number chicks	Percent <10	Percent <15	Clotting time—minutes						
						0–5	6–10	11–15	16–20	21–25	26–30	>30
F	Control		7	14	14		1		1		1	4
	K_1 in ethyl succinate	1.5γ	6	30	67		3	1			2	

Table 4—Eighteen hour test summary

Group test	Supplement	Level	Number chicks	Percent <10	Percent <15	Clotting time—minutes						
						0–5	6–10	11–15	16–20	21–25	26–30	>30
A	Control		6	0	0							
A	Quinone in oil	1γ	8	63	63	1	4		1	1		6
A	Quinone in ethyl pimelate	1γ	8	75	88	2	4	1	1			1
A	Quinone in butyl succinate	1γ	8	100	100	7	1					
B	Control		5	0	0							
B	Quinone in oil	1γ	4	25	25		1		2			5
B	Quinone in ethyl succinate	1γ	6	100	100	4	2					1
C	Control		6	0								
C	Quinone in oil	1γ	8	25	50	2		2			2	6
C	Quinone in ethyl succinate	1γ	7	57	71	2	2	1		1	1	2
C	do	1γ	7	71	71	5			1			1
C	do	1γ	6	83	100	2	3	1				
C	do	1γ	7	57	57	4			2	1		
C	do	1γ	6	50	83	2	1	2	1			
C	do	1γ	7	86	100	4	2	1				
D	Control		10	0	0							
D	Quinone in oil	1γ	15	13	40		2	4	3	1	1	10
D	Quinone in butyl succinate	1γ	14	21	57		3	5	2	1	2	4
E	Control		9	0	0							1
E	Quinone in oil	1γ	14	60	80	1	8	3	1	1		9
E	Quinone in butyl succinate	1γ	15	20	67		3	7	2		2	1

γ=microgram (gamma).
<=less than.
>=more than.

An examination of the results in the above tables reveal that the activity of vitamin K_1 and 2-methyl-1,4-napthoquinone when administered in the organic esters of the present invention are in every instance at least the equivalent of similar quantities of vitamin K_1 or the quinone administered by the ordinary methods. Further, there were no toxic effects obtained by use of these parenteral solutions and there were no anatomical changes at the site of the injection.

It is an advantage of the present invention that the parenteral solutions are not photo-sensitive and the solutions of the quinone in the esters may be sterilized by heating without change. It is a further advantage that the parenteral solutions of this invention are rapidly absorbed and produce no anatomical change at the site of injection.

It has been known in the past that in some cases of prothrombin deficiency it is desirable to administer bile salts along with the antihemorrhagic substances and the present invention does not therefore preclude the use of bile salts and may be used in conjunction therewith. Similarly the use of surface active substances, such as di-octyl sodium sulfo-succinate is not precluded.

What we claim is:

1. A parenteral solution comprising a water insoluble anti-hemorrhagic substance and an ester included in the group consisting of ethyl succinate, n-butyl succinate, ethyl pimelate and n-butyl pimelate.

2. A parenteral solution comprising a water insoluble anti-hemorrhagic substance in ethyl succinate.

3. A parenteral solution comprising a water insoluble anti-hemorrhagic substance in n-butyl succinate.

4. A parenteral solution comprising a water insoluble anti-hemorrhagic substance in ethyl pimelate.

5. A composition suitable for parental administration comprising a solution of 2-methyl-1,4-naphthoquinone in ethyl succinate.

6. A composition suitable for parenteral administration comprising a solution of 2-methyl-1,4-naphthoquinone in n-butyl succinate.

7. A composition suitable for parenteral administration comprising a solution of 2-methyl-1,4-naphthoquinone in ethyl succinate.

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CERTIFICATE OF CORRECTION.

Patent No. 2,354,738. August 1, 1944.

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It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows: Page 1, first column, line 48, for "1-naphthlyamine" read --1-naphthylamine--; page 3, second column, line 56, claim 5, for "parental" read --parenteral--; line 64, claim 7, for "succinate" read --pimelate--; and that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 26th day of September, A. D. 1944.

Leslie Frazer

(Seal) Acting Commissioner of Patents.