synthetic congeners.[5,7,9] Vitamin K has not generally been found to be of value in the treatment of hemorrhagic diseases accompanied by normal prothrombin levels in the blood. These include the various purpuras, hemophilia, menorrhagia, etc. Hykinone is not recommended for the treatment of these disorders.

## PACKAGES

**Hykinone, 4.8 mg., 1-cc. ampoules (List No. 3242), Hykinone, 2.4 mg., ½-cc. ampoules (List No. 3243) and Hykinone, 10 mg., 1-cc. ampoules (List No. 3383) are supplied in boxes of 6, 25, and in bulk packages of 100. Hykinone, 72 mg., 10-cc. ampoules (List No. 3331) are supplied in boxes of 3.**

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# HYKINONE

REG. U. S. PAT. OFF.

**(Abbott's Menadione Sodium Bisulfite Injection, U.S.P.)**

**A Synthetic Substance Having Vitamin K Action in an Aqueous, Isotonic, Injectable Solution**

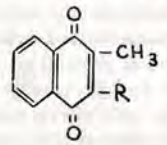
U. S. PATENT NO. 2,367,302

Abbott

HYKINONE is the Abbott trade mark for a water-soluble injectable substance having vitamin K action, to be used in cases requiring vitamin K therapy where the usual oral method of administration is difficult or impossible. The material may be injected intravenously, intramuscularly or subcutaneously.

## RELATION TO VITAMIN K

Studies have elucidated the chemical structure of vitamin $K_1$ isolated from alfalfa and have shown that a series of naphthoquinones having the general formula




possess to a greater or lesser extent the activity of natural vitamin K. One of these, 2-methyl-1,4-naphthoquinone, has been found especially active and a number of reports on its clinical use have already appeared. 2-methyl-1,4-naphthoquinone itself is practically insoluble in water and has usually been given orally in combination with bile salts. This procedure may

prove difficult or impossible in patients with obstructive jaundice who are nauseated and vomiting and, therefore, an injectable preparation has a definite value.

By combining 2-methyl-1,4-naphthoquinone with sodium bisulfite, the water-soluble Hykinone is obtained.

## PHARMACOLOGY

Pharmacologic studies on Hykinone carried out at the Abbott Laboratories indicate that its toxicity is relatively low. In dogs, intravenous injection causes no appreciable change in respiration or blood pressure. Richards and Shapiro[22] found the approximate lethal dose 50 of Hykinone in rabbits to be 120 mg. per kilogram (144 mg. Menadione Bisulfite, U.S.P.); in mice, 250 mg. per kilogram (300 mg. Menadione Bisulfite, U.S.P.). Acute toxic effects of Hykinone in experimental animals were found not to be related to its action on the prothrombin level. Sublethal doses produced transitory methemoglobinemia, and repeated administrations led to reversible depression of red blood cells and hemoglobin in dogs. In man, however, doses approximately ten times as great as those generally recommended for therapeutic use, given daily for a period of one week, induced no significant changes in the blood.

## CLINICAL TRIALS

Butt, Snell, Osterberg and Bollman[1] reported eight cases of obstructive jaundice, one case of acute hepatitis and one case of cirrhosis treated with Hykinone. All except the case of cirrhosis showed an increase in blood prothrombin, which had previously been at a level lower than normal. No toxic effects were noted from the material. Thorough clinical trials have demonstrated that Hykinone may be used safely and successfully wherever vitamin K therapy is indicated.[5-8,10-16,24] These include cases of obstructive jaundice, biliary fistula, hemorrhagic disease of the newborn due to low prothrombin levels, and other hemorrhagic diatheses associated with hypoprothrombinemia. No toxic effects due to the administration of Hykinone have been noted.

## INDICATIONS

Hykinone is indicated in cases of hypoprothrombinemia due to vitamin K deficiency, in which the oral administration of natural vitamin K or its synthetic congeners is impracticable or proves ineffective owing to poor absorption. Cases in which vitamin K is of benefit include most prominently those in which bile is excluded from the intestinal tract or enters the intestine in insufficient amount or concentration. Obstruction of the bile passages by stones, strictures or neoplasms, diversion of bile through fistulas and failure of the hepatic parenchyma to supply bile of proper quality, are all capable of producing a deficiency of prothrombin in the circulating blood. This condition, when sufficiently advanced, may give rise to severe hemorrhage. Many studies of the prothrombin content of the blood of newborn infants indicate that prothrombin deficiency may exist in a fairly large number of cases and attempts have been made to correlate this condition with certain types of "hemorrhagic disease" of the newborn. It has been shown that oral administration of vitamin K concentrates to the newborn infant or to the mother shortly before parturition is able to raise the prothrombin level in the infant. Hykinone is likewise able to produce this effect when administered to the mother and may be used for this purpose. Where newborn infants are known to be suffering from hypoprothrombinemia and where, for some reason, vitamin K cannot be administered orally, Hykinone may be injected either subcutaneously or intramuscularly.[6]

Some investigators, notably Potter,[23] have reported that they found no reduction in infant mortality rate from hemorrhagic disease after the administration of vitamin K to mothers prior to delivery or to the infant after birth. Prolongation of prothrombin time as a direct cause of infantile hemorrhage is questioned.

Patients being treated with Dicumarol occasionally show an excessive reaction, with a dangerous fall in the prothrombin level of the blood. The prothrombin activity in these cases may go below 15 percent of normal. Cromer and Barker[25] found that large doses of water-soluble vitamin K tended to correct this condition, and Hykinone may be used for this purpose. The usual adult dose in such cases is 72 mg. intravenously. If the prothrombin level fails to rise within 18 to 24 hours following one such dose, a second dose of the same size should be given, accompanied by a transfusion of fresh citrated blood.

Various methods are in use for the determination of prothrombin levels in the blood. The two-stage titration method of Warner, Brinkhous and Smith[2] is suitable for research work in well-equipped laboratories. The method of Quick[3] is less complicated, as is the "bedside" method of Smith, *et al.*,[4] and Warner.[20] One of these tests is almost essential for the intelligent use of Hykinone, for it will give information not only as to those cases for which the medication is indicated but will also keep the clinician informed as to the progress of the treatment and the need for further medication.

## DOSAGE

In obstructive jaundice of moderate severity with only moderate reduction of prothrombin, the initial dose is 2.4 to 4.8 mg. and is injected intravenously, intramuscularly or subcutaneously. If the prothrombin level shows no improvement within twelve hours after the initial dose, an additional dose of the same size or up to 10 mg. may be given and repeated at twelve-hour intervals depending upon the gravity of the case. In severe cases 4.8 to 10 mg. may be given daily as needed.

The dose for newborn infants with hypoprothrombinemia is 2.4 to 4.8 mg. Hykinone daily for the first three days of life.

If a hemorrhagic diathesis is associated with severe hepatic damage, as in cases of cirrhosis or acute yellow atrophy, the effectiveness of vitamin K therapy or Hykinone may be limited by the ability of the liver to produce prothrombin. Recent observations seem to indicate that if parenchymatous disease of this organ has progressed far enough, little beneficial effect on the prothrombin level can be produced by vitamin K and this would logically seem to apply as well to its

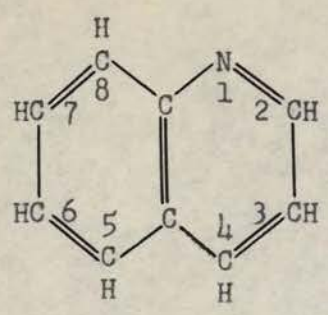
THREE MAJOR TYPES OF TOXIC REACTIONS FOLLOWING ADMINISTRATION OF

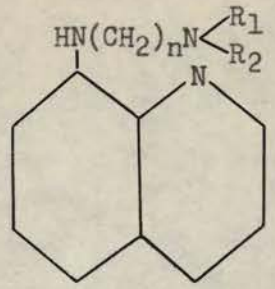
8-AMINOQUINOLINES TO RHESUS MONKEYS

1. Effects on CNS.

2. Effects on heart and circulation.

3. Effects on formed elements of peripheral blood and bone marrow.





Where $R_1 + R_2 = H_2$, compound acts primarily on formed elements of peripheral blood and marrow.

Where $R_1$ = alkyl and $R_2$ = either H or alkyl, n determines type of toxic reaction as follows:

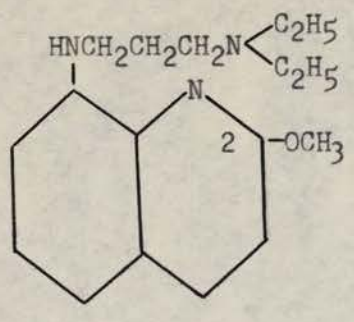
a. Where n = 2 or 3 (straight or branched), compound acts primarily on CNS, irrespective of nuclear substituent (6 exceptions).

b. Where n = 4 or 5 (straight), compound acts primarily on heart and circulation, irrespective of nuclear substituent.

c. Where n = 4 or 5 (branched), or 6 or greater (straight), compound acts primarily on formed elements of peripheral blood and bone marrow, again irrespective of nuclear substituent.

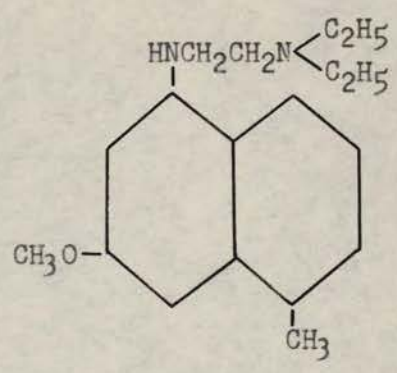
## EXCEPTIONS TO a.

SN 13,058 (Isoplasmocid)



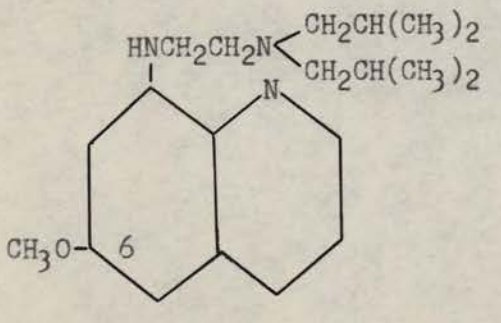

Effects on blood

NC 49



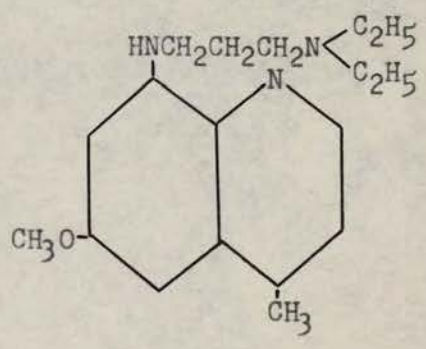

Mixed effects

SN 2842



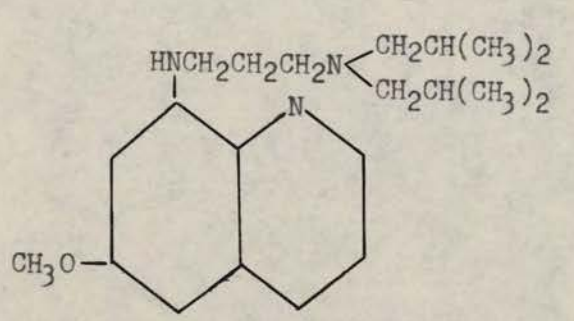

Effects on heart

NC 41

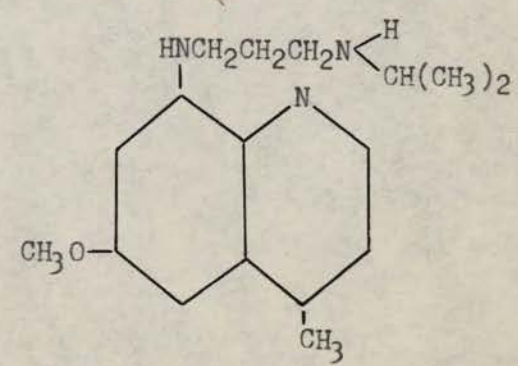



Mixed effects

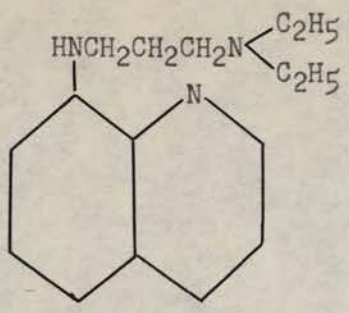
SN 3499




NC 48




Mixed effects

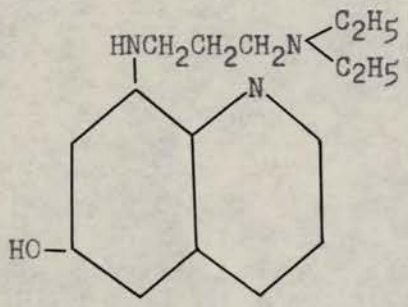



SN 13,457

3 mg/kg - symptoms

6 mg/kg - fatal, 12 days

CNS effects

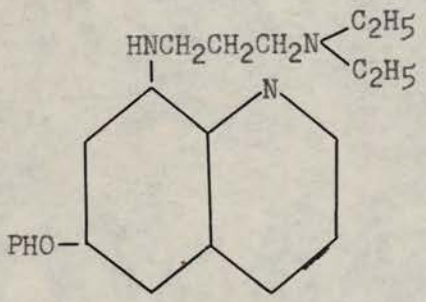



SN 13,125

24 mg/kg - symptoms

48 mg/kg - fatal, 12 days

CNS effects

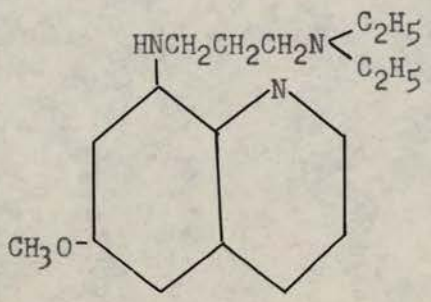



SN 12,465

3 mg/kg (or less) - symptoms

12 mg/kg - fatal, 9 days

CNS effects

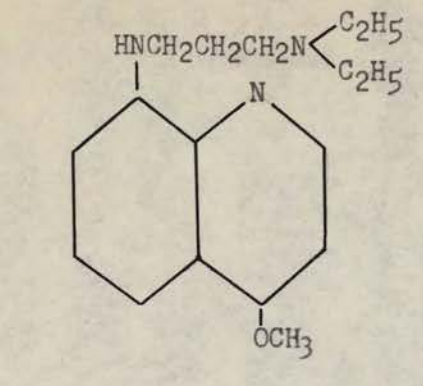



SN 3115 (Plasmocid)

1.5 mg/kg - symptoms

4.5 mg/kg - fatal, 2 - 3 days

CNS effects

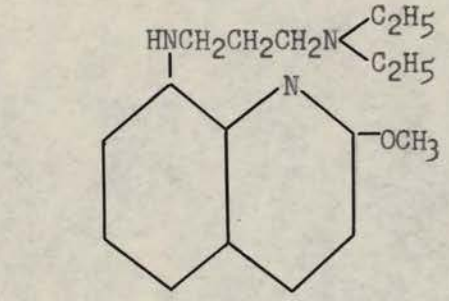


SN 12,009

6 mg/kg - symptoms

12 mg/kg - fatal, 9 days

CNS effects

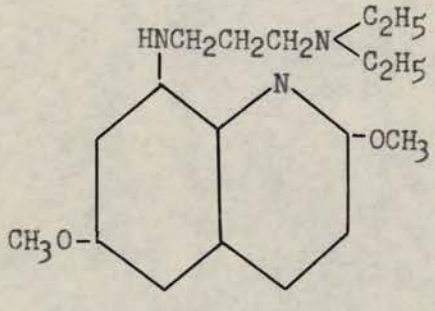


SN 13,058 (Isoplasmocid)

6 mg/kg - symptoms

24 mg/kg - fatal, 5 - 14 days

Effects on blood, etc.

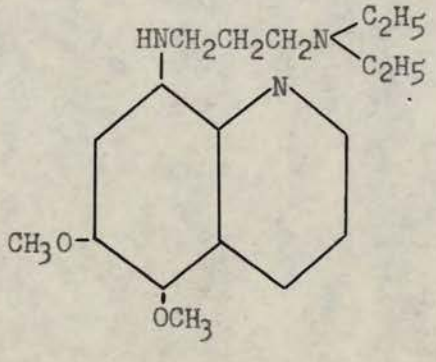


SN 12,251

12 mg/kg - symptoms

24 mg/kg - fatal, 11 days

CNS effects ??



SN 11,889

15 mg/kg - symptoms

30 mg/kg - fatal, 13 days