

The Use of Quinacrine (Atabrine) in Rheumatic Diseases: A Reexamination

By Daniel J. Wallace

INDEX WORDS: Quinacrine; Atabrine; rheumatic diseases.

UPON BECOMING Edmund Dubois' associate in 1979, I was startled to learn that 200 of the 600 lupus patients he was following were taking quinacrine (Atabrine). In attempting to learn more about a drug that I knew next to nothing about, I became fascinated by the agent's remarkable variety of actions, as well as its apparent efficacy in mild to moderate lupus. The following review of this underused and underappreciated drug is dedicated to Dr Dubois' memory.

HISTORY

Atabrine (quinacrine, mepacrine, atebtrin, chinacrin, erion, acriquine, acrichine, palacrin, me-toquin, halchin) was developed by IG Farbenindustrie in Germany during the 1920s and first introduced as an antimalarial therapy in 1930.¹⁻³ The cutoff of quinine supplies by the Japanese invasion of the Southwest Pacific at the start of World War II prompted the manufacture of an "American Atabrine" that was chemically and pharmacologically identical to the German variety. When the office of the Surgeon General declared Atabrine the official drug for the treatment of malaria in 1943,⁴ production increased from the prewar levels of 1,200 pounds per year to one ton each day. Millions of American servicemen took 100 mg daily for prophylaxis. Impressive follow-up studies by US armed forces physicians provided health professionals with information ranking it among the best studied drugs ever introduced—3 million soldiers took the drug in a "controlled" setting for up to 4

years. By the conclusion of hostilities, the superiority of chloroquine over Atabrine for malaria became apparent and its use declined markedly.⁵

Atabrine was first used in discoid lupus by Prokoptochouk in 1939⁶ and Sorinson in 1941.⁷ The first English-language report of its use in lupus by Page, in a 1951⁸ issue of the *Lancet*, generated much interest and prompted a series of large-scale studies in the 1950s. During this period, Atabrine was found to have many other uses. Although Atabrine is a trade name, the term has become "generic" because the millions of soldiers who took it daily knew it by no other description. Many articles use the term Atabrine rather than quinacrine; most British publications call the drug mepacrine. Hence, these appellations are used interchangeably throughout the text.

CHEMISTRY AND PHARMACOKINETICS

Atabrine is 6-chloro-9-(1-methyl-4-diethylamino)butylamino-2-methoxyacridine (Fig 1). It is available as the dihydrochloride (quinacrine hydrochloride, USP) in 100-mg tablets as a bright yellow, odorless, bitter crystalline powder that is water soluble (1:35) and 80% quinacrine base. Inactive ingredients include pharmaceutical glaze, starch, talc, and stearic acid.⁹ It differs from chloroquine only in having an acridine nucleus (an extra benzene ring) instead of a quinolone.

The usual route of administration is by mouth with a full glass of water after a meal. The drug is rapidly absorbed, even in the presence of severe diarrhea. Plasma levels increase in two to four hours, reaching a peak in eight to 12 hours.¹⁰ Plasma concentration increases rapidly during the first week, and 94% equilibrium is attained by the fourth week. Although plasma levels of Atabrine are usually low, tissue concentrations are quite high.¹¹ Widely distributed in tissue but slowly liberated, the highest concentrations are found in the liver, spleen, lungs, and adrenal glands, and the lowest are found in the brain, heart, and skeletal muscle. Concentrations in the liver may be 20,000 times the plasma level, in leukocytes 200 times, and in erythrocytes twice.

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0049-0172/89/1804-0008\$5.00/0

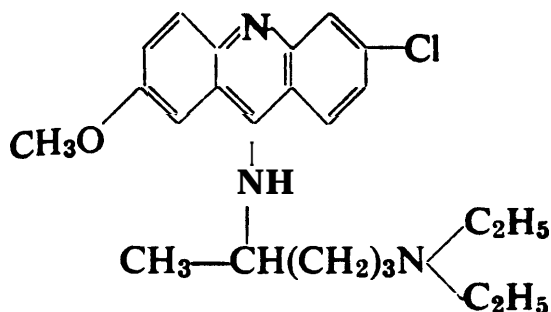


Fig 1. Structural formula of Atabrine.

Quinacrine is deposited in the skin, especially in the fingernails and in brunette hair. Atabrine crosses the placenta and easily reaches the fetus. Spinal fluid concentrations are 1% to 5% of plasma levels. Eighty percent to 90% of the drug is bound to plasma proteins in therapeutic doses. It is slowly eliminated from the body. Negligible amounts are excreted in sweat, breast milk, saliva, and bile. Less than 11% is eliminated in the urine daily.^{5,10} This can be enhanced by acidification (up to 14% daily excretion) and retarded by alkalinization of the urine (as little as 0.2%).

Atabrine was successfully administered intraleitionally for discoid lupus in the 1950s.^{12,13} If severe nausea and vomiting are present, 0.2 g atabrine powder dissolved in 7 mL sterile distilled water can be administered intramuscularly. Intravenous infusion can be used when 0.1 g is dissolved in 10 mL sterile distilled water. Atabrine can also be administered rectally in aqueous acacia solution,⁷ transcervically in a suspension of 2% xylocaine,¹⁴ or as a uterine pellet.⁸ For malignant pleural effusions,¹⁶ 100 to 200 mg Atabrine is dissolved in 30 mL sterile saline and delivered via a chest tube.

MECHANISM OF ACTION

The activities of Atabrine (Table 1) are multifaceted and will be considered by categories.

Antiprostaglandin Actions

One of the least appreciated but best studied actions of Atabrine concerns its role as a potent inhibitor of phospholipase A2. First described in 1977, this action occurs directly on membrane phospholipids, especially phosphatidyl ethanolamine.^{17,18} This results in the drug's antiplatelet activity and its inhibition of leukotrienes and

Table 1. Mechanisms of Action

Antiprostaglandin actions
Platelet aggregation inhibition
DNA, RNA polymerase inhibition
Blocking of LE cell factor
Antioxidant effects
Antihemolysin activity
Neutrophil and lysosome stabilization
Na-Ca exchange impedance
Hormonal interactions: antagonism of prolactin and insulin
Bradykinin and histamine antagonization
Antiproliferative and radiation potentiation effects
Antimutagenic effects
Photochemical blockade
Anticholinesterase and sympatholytic actions
Depression of immune responsiveness
Quinidine-like cardiac actions and reduction of infarct size
Antimicrobial activities
Sclerosing actions

cyclooxygenase.^{17,19-27} In platelets, the conversion of 14-C arachidonic acid to 14-C thromboxane B2 and thromboxane A2 is suppressed. The latter substance is a major factor in blocking the release of arachidonic acid from cellular phospholipases and its conversion to proaggregatory products. Atabrine is a nonselective antilipolytic agent that decreases prostaglandin E₂ (PGE₂) production in a dose-dependent fashion, thus blocking cyclooxygenase. This might contribute to its Na, K-adenosine triphosphatase (ATPase)-inhibitory effects, thus stabilizing cell membranes. Such interference reduces the basal rates of phospholipase methylation in mononuclear cells.²⁰

Platelet Aggregation Inhibition

Atabrine inhibits fibrinogen-binding, thrombin-induced platelet responses and adenosine diphosphate (ADP)-induced platelet aggregation.²⁸⁻³⁰ This probably results from its antiphospholipase actions or its interaction with cyclic GMP.^{29,31} The author has recently reviewed the clinical implications of hydroxychloroquine's antiplatelet actions and its use for thromboprophylaxis.³²

DNA and RNA Polymerase Inhibition/Suppression of Lupus Erythematosus Cell Factor

Atabrine binds to DNA by intercalation between adjacent base pairs. This bond stabilizes DNA, inhibiting its heat denaturation, enzymatic depolymerization, and both transcription and translation to RNA.³³⁻³⁵ Atabrine can stimulate hydrolysis of transfer RNA by pancreatic

ribonuclease A. Its high affinity for nuclear and chromosomal DNA via intercalation can be impeded by denaturation or **depurination**.^{36,37} Quinacrine mustard fluorescent staining has been a mainstay procedure in genetics laboratories for 20 years. Its affinity for the Y chromosome has proved to be very **useful**.^{38,39} Work from Dubois' and Kunkel's laboratories documented that the binding of Atabrine to nucleoproteins can block the lupus erythematosus (LE) cell factor.⁴⁰⁻⁴²

Antioxidant

Superoxide anion generation is antagonized by **Atabrine**.^{20,43} The inhibition of reactive oxygen species probably is a consequence of its effects on membrane phospholipid generation.⁴⁴

Antihemolysin

Both halothane and phospholipase A2-induced hemolysis can be prevented by Atabrine and **danazol**.⁴⁵ The former agent protects vitamin E-deficient rat erythrocytes from peroxidative hemolysis induced by **dialuric acid** or reduced **glutathione**.⁴⁶

Neutrophil and Lysosome Stabilization

Strongly concentrated by leukocytes and in lysosomes, Atabrine has a stabilizing, almost **corticosteroidlike** effect.²² In addition to phagocytosis, **polymorph locomotion**, RNA synthesis, and hexose monophosphate shunt burst activity are inhibited by the drug.^{43,47-50} These actions may result from its dissociation of neutrophil membrane depolarization. The salvage of pulmonary function in models of adult respiratory distress syndrome (ARDS) has been reported.⁵¹⁻⁵⁵

Blockage of Na-Ca Exchange

The inhibition of Na-Ca exchange by **Atabrine** may stabilize **membranes**.²¹ It involves a local electrostatic effect of the bound cations in accelerating a rate-limiting step in cardiac **sarcolemmal vessels**⁵⁶ and **synaptosomes**^{57,58} and as an antagonist of the calmodulin-dependent stimulation of erythrocyte Ca⁺⁺ -ATPase.⁵⁹

Hormonal Interactions

Atabrine accumulates in **peptide hormone-producing cells**^{60,61} and can specifically block the actions of prolactin in **casein**, RNA, and lipid biosynthesis via its antiphospholipase actions.^{62,63}

Islet cell insulin release is also **suppressed**.⁶⁴ Atabrine may increase urinary 17-ketosteroids,⁶⁵ but this claim has been **challenged**.⁶⁶

Bradykinin and Histamine Antagonization

As an inhibitor of phospholipase A2, Atabrine can block the actions of bradykinin in synovial fibroblasts and suppress its **algescic effects**.⁶⁷⁻⁶⁹ **Atabrine** impedes the induction of **cAMP** release in synovial fibroblasts by bradykinin, which would otherwise result in arachidonic acid and PGE release.⁶⁸ Inhibition of phospholipase A2 decreases histamine release from human basophils and **anti-IgE**.^{65,70,71}

Antiproliferative/Antimutagenic Effects

Atabrine can block radiation-induced DNA strand breaks and potentiates the **antiproliferative effects of radiation**.^{33,72,73-76} It reduces the incidence of cancer in rats given **nitrosourea**,⁷⁷ decreases the number of somatic mutations induced in murine leukemia **cells**,^{73,78} and reverses resistance to **vincristine**.⁷⁹ Radioprotective actions might be due to the scavenging of water radicals that has been observed when Atabrine is bound to DNA.⁸⁰

Photochemical Blockade

One of the major aggravating factors of systemic lupus is ultraviolet light exposure. Like other antimalarials, Atabrine can block **photodynamic actions**, inhibit laser-induced **photosensitization**,^{81,82} and increase ultraviolet light tolerance.*

Anticholinesterase and Sympatholytic Actions

Atabrine is a strong inhibitor of **cholinesterase**.^{25,67,83} These actions could result from blocking acetylcholine (ACh) release and calcium influx by its inhibition of cyclic **GMP**.⁸⁴ Both release and synthesis of ACh are affected, and both muscarinic and nicotinic receptor sites are **involved**,^{38,85-87} probably a consequence of a slow voltage-dependent blockage of open-end plate channels.**

Atabrine prevents the release of **norepinephrine** via an intraneural **mechanism**.^{25,84,89} This may be secondary to its antiphospholipase effects. The drug inhibits beta agonists at the receptor complex of cell membranes and prevents the desensitization of beta **receptors**.^{90,91} It also

has a-adrenergic blocking actions²⁵ and may be antiasthmatic.^{92,93}

Effects on Immunologic Responsiveness

Atabrine inhibits natural killer-cell cytotoxicity and enhances the killing response of cells by x-rays.^{50,94} It blocks the primary but not the secondary proliferative response of human cytotoxic T cells to allogeneic non-T cell antigen and impedes Tac antigen (interleukin-2 receptor) expression due to its phospholipase A2-blocking actions. Atabrine does not interfere with the recognition of antigens by cytotoxic T cells but suppresses the mitogenic response of T cells to allogeneic antigen.⁹⁵ It can impede the uptake and incorporation of leucine, thymidine, and uridine in acid-insoluble material in human lymphocytes stimulated by phytohemagglutinin (PHA).⁹⁶

Quinidine-like Effects and Cardiac Hemodynamics

The quinidine-like effects of quinacrine were appreciated in the 1940s. Reviews of studies reported in 1954 and 1972 document the agent's ability to restore normal sinus rhythm to dogs with experimental atrial fibrillation and prevent ventricular fibrillation induced by epinephrine in dogs under chloroform anesthesia.^{5,97} The drug also has a mild negative inotropic effect. Recently, the drug's blockage of phospholipase A2 activation (which induces irreversible myocardial injury during ischemia) has been shown to reduce infarct size in rats.⁹⁸ In an insitu pig's heart, Atabrine improved oxygen consumption, coronary blood flow, and cardiac compliance.⁹⁹ It inhibits reactive hyperemia in dogs and reduces their infarct size,^{100,101} although these contentions have been challenged.¹⁰²

Other Muscle and Nerve Actions

In animal models, Atabrine can dilate the cecum and proximal colon and induce crypt hyperplasia.^{103,104} It accumulates in noncholinergic and nonadrenergic myenteric plexus ganglionic cells in large amounts,^{103,105,106} impeding gastric emptying.^{107,108} Atabrine does not cause CNS lipidosis due to the blood brain barrier but can reduce glutathione in brain membrane fractions.^{109,110} However, its brain uptake is significant, as observed by fluorescence of cerebellar

Purkinje cells, cortexpyramidal cells, and the hippocampus. Its greatest concentration in a guinea pig brain was in the basal ganglia, where high levels of ATP were found as part of a dense Atabrine staining positive nerve plexus.¹¹¹

Antimicrobial Properties

Antiparasitic, antiprotozoan, antibacterial, antiviral, and antifungal actions have been described. Atabrine's antimalarial properties are based on its dose-related inhibition of adenosine into host cells of parasitized blood as well as the RNA and DNA of the plasmodium.¹² Antiprotozoan actions are attributable to its inhibition of succinate oxidation and interference with electron transport.¹³ Quinacrine can prevent bacterial resistance to various antibiotics,^{74,119-126} and demonstrates bacteriostatic activities.¹²⁷⁻¹²⁹ Interferon production is increased by Atabrine, and intralesional administration can treat warts.¹³⁰⁻¹³² In vitro antifungal properties have been noted.^{133,134}

Sclerosing Actions

Atabrine is a locally effective sclerosing agent and its intracavitary administration is capable of preventing recurrent pleural and pericardial effusions as well as pneumothorax.^{16,135-144} Quinacrine pellet instillation into the uterus results in nonsurgical sterilization as clots of granulomatous tissue are formed by quinacrine-epithelial DNA complexes.^{15,145-150}

Miscellaneous Biochemical Interactions

Like chloroquine, Atabrine can inhibit the incorporation of ³⁵S into cartilage polysaccharide sulfates in rats.¹⁵¹ Quinacrine suppresses the expression of endotoxin-induced tissue factor,¹⁵² competitively interferes with dehydrogenases and kinases,¹⁵³ and may block F1-ATpase,¹⁵⁴⁻¹⁵⁶ although this has been disputed.¹⁵⁵⁻¹⁵⁷ It has antipyrogenic activity in rabbits.¹⁵⁸⁻¹⁵⁹

THERAPEUTIC USES

The therapeutic uses of Atabrine are presented in Table 2.

Lupus Erythematosus

Antimalarials have been used to treat lupus since 1894, when Payne used quinine.¹⁶⁰ In November 1939, Professor Prokoptchouk of

Table 2. Therapeutic Uses of **Atabrine**

FDA-approved
Malaria
Giardia
Beef tapeworm (<i>Taenia saginata</i>)
Pork tapeworm (<i>Taenia solium</i>)
Dwarf tapeworm (<i>Hymenolepis nana</i>)
Fish tapeworm (<i>Diphyllobothrium latum</i>)
Therapeutic effectiveness demonstrated in controlled studies
Lupus erythematosus
Malignant pleural and pericardial effusions
Nonsurgical female sterilization
Prevention of recurrent pneumothorax
Prevention of antibiotic resistance
Probable therapeutic actions
Rheumatoid arthritis
<i>Tetrahymena pyriformis</i>
Vitiligo
Possible therapeutic actions
Amebiasis
Leprosy
Viral
Fungal
Adult respiratory distress syndrome
Asthma
Pemphigus
Pinworm
<i>Railletina sirira ji</i>

Minsk reported to a Soviet academy on his experiments with Atabrine in 35 lupus patients.⁶ However, it was not until 1951, when Page independently reported similar findings,* that serious interest was aroused. From 1939 to 1961, 20 clinical trials on the use of Atabrine in LE were published.^{6-8,161-177} As noted in Table 3, an overall 73% response rate was found (range, 53% to 92%) among the 771 patients who were studied. The introduction of hydroxychloroquine (Plaquenil; Winthrop-Breon, New York) as an alternative antimalarial in 1955 was largely responsible for the dramatic decrease in interest by the late 1950s. The following paragraphs summarize the principal insights derived from the studies in Table 3. Most of these were provided by Edmund Dubois and the Mayo Clinic, two centers where Atabrine use persisted long after it was neither a fad nor in fashion.

In reviewing these papers, the term *lupus erythematosus* (LE) is used advisedly. No criteria existed to define the disease in the 1950s and antinuclear antibodies were not yet available. Most of the patients given Atabrine had biopsy-documented discoid lesions (with or without systemic manifestations) and positive LE cell

preps. Atabrine was not generally administered to critically ill patients. Nevertheless, the 20 studies performed on three continents listed in Table 3 revealed strikingly similar results.

The original doses of Atabrine used in LE were 200 to 300 mg daily. At this dosage, favorable skin responses can be seen as early as 1 to 2 weeks. Most of the early studies then tapered the patients down to 100 mg daily maintenance. It was eventually agreed that a 100 mg daily initial dose was much less toxic and delayed response by only a week or two. Atabrine has an onset of action of 3 to 4 weeks, although its maximal benefits do not occur until 6 to 8 weeks after initiation. Lack of responsiveness after an 8-week trial should be considered a good reason to discontinue the agent. After 3 to 6 months, the dose of Atabrine can be reduced. Dubois tapered his patients by eliminating administration on a given day of the week. Over a 2-year period, he would gradually decrease the medication to one or two dosages each week. Early reports were rife with case presentations of patients who relapsed within 2 to 3 months of discontinuation of the drug. Dubois found that if he could maintain his patients on one to two Atabrine tablets each week, rebound flares could be avoided. He would discontinue administration of the drug after about 3 to 5 years or if the patient became pregnant. If the patient experienced diarrhea or any other adverse reactions, a 25- to 50-mg daily dose would be used. In these cases, it would sometimes take 2 to 3 months before Atabrine's beneficial effects would be clinically apparent.

The cutaneous manifestations of LE are particularly responsive to Atabrine. Impressive healing of discoid lesions and mouth ulcerations are observed in 2 to 3 weeks. After several weeks, hair loss stops and hair growth begins. Because Atabrine is a CNS stimulant, it is the most effective non-steroid-containing drug in managing the fatigue of lupus.¹⁷⁸ It has been half-jokingly conjectured that the drug won the Pacific theater of World War II for the Allies. A fascinating recent study suggested that tetrahydroaminoacridine, a chemical closely related to Atabrine, might be effective in treating the senile dementia of Alzheimer's disease.¹⁷⁹ Although ineffective in CNS lupus, Atabrine can alleviate the headache and fatigue often associated with the disease. Many of the studies listed in Table 3

Table 3. Twenty Clinical Trials of Atabrine in **Lupus**

Investigator	Year	No. of Patients	Response (%)		
			Excellent*	Improved+	None or Doubtful
Prokoptchouk ⁶	1940	(35)	?	?	?
Sorinson ⁷	1941	51	23	33	43
Page ⁸	1951	18	50	33	17
Somerville et al ¹⁶¹	1952	23	17	66	17
Cramer and Lewis ¹⁶²	1952	6	83	0	17
Wells ¹⁶³	1952	12	25	50	25
Sawicky et al ¹⁶⁴	1952	30	20	50	30
Black ¹⁶⁵	1953	60	17	38	45
O'Leary et al ¹⁶⁶	1953	40	40	36	25
Courville and Perry ¹⁶⁷	1953	13	38	54	8
Kaminsky and Knallinsky ¹⁶⁸	1953	61	16	62	21
Harvey and Cochrane ¹⁶⁹	1953	62	37	23	40
Kierland et al ¹⁷⁰	1953	52	33	46	21
Rogers and Finn ¹⁷¹	1954	45	47	38	15
Helanen ¹⁷²	1954	36	28	58	14
Christiansen and Nielson ¹⁷³	1956	97	32	40	28
Dubois ^{174, 174a}	1956	61	25	56	20
Nielsen ¹⁷⁵	1956	12	17	75	8
Buchanan ¹⁷⁶	1959	25	28	52	20
Winklemann et al ¹⁷⁷	1961	67	10	75	15
Totals (N)		771	209	352	210
Totals (%)		100	27	46	27

*Excellent or improved response, 73%.

comment on its ability to ameliorate synovitis. The drug has also been evaluated in rheumatoid arthritis (see next paragraph). My impression is that Atabrine is more powerful than a **nonsteroidal** agent but less effective than Plaquenil in managing inflammatory arthritis. Atabrine appears to have a beneficial effect on the constitutional symptoms of lupus: fever, aching, and fatigue. If internal organ involvement is present (eg, heart, lung, kidney, liver), Atabrine has no place in the management of lupus. In other words, Atabrine is indicated for mild to moderate lupus with skin or joint involvement and constitutional symptoms. It can also act as a **sunblock** (Table 4).

Synergism with hydroxychloroquine and chloroquine. Dubois was impressed with the synergy between Atabrine and chloroquine or hydroxychloroquine, and his papers **document case** histories of patients with partial responses to a single antimalarial who had spectacular effects from combination therapy. His efforts prompted Winthrop Laboratories to develop a product originally known as **APA**. Containing 65 mg of aralen (chloroquine), 50 mg of Plaquenil, and 25 mg of Atabrine, this mixture of antimalarials proved to be a potent combination. After demon-

strating synergy in rats,¹⁸⁰ subsequent clinical investigations documented the considerable efficacy of this combination product.¹⁸¹ This culminated in a study published in an issue of the **New England Journal of Medicine** in 1959. A phenomenal 44 of 45 patients with lupus at the Boston City Hospital given the drug, many of whom had failed single-agent antimalarial therapy, **demon-**

Table 4. Atabrine v Plaquenil in Lupus: A Comparison

Advantages of Atabrine
No retinal toxicity
Initial dose: one tablet/day
Onset of action in 2 to 4 weeks
Promotes energy; decreases fatigue
Disadvantages of Atabrine
Greater skin toxicity
Greater gastrointestinal symptoms
1/50,000 chance of aplastic anemia
Advantages of Plaquenil
FDA-approved for lupus
Greater activity against synovitis
Little skin or gastrointestinal toxicity
Disadvantages of Plaquenil
2- to 4-month onset of action
Retinal toxicity
Not as powerful in vitro as Atabrine
Advantages of both
Documented synergy when administered together

In response to
innumerable requests
from dermatologists

Winthrop Laboratories
now makes available

TRIQUIN®

FOR LUPUS ERYTHEMATOSUS AND
LIGHT-SENSITIVITY ERUPTIONS

WHAT IT IS:

A combination of Atabrine® hydrochloride
25 mg., Aralen® phosphate 65 mg. and
Plaquenil® sulfate 50 mg.

WHAT IT'S FOR:

Treatment of lupus erythematosus (chronic
discoid type) and polymorphic light eruptions
(light-sensitivity eruptions, solar urticaria
or dermatitis).

HOW IT ACTS:

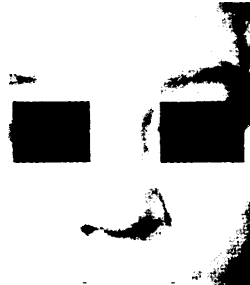
Each of the three components produces
beneficial response in lupus erythematosus
and light-sensitivity eruptions. Since the **dose**
of each of the **Triquin components is very**
low, overall toxicity is **reduced** and clinical
tolerance improved. Furthermore, the
three components **appear to act**
synergistically.

HOW SUPPLIED:

Triquin tablets in bottles of 100, sold on
prescription only.

Write for TRIQUIN booklet.

Triquin, Atabrine (brand of quinacrine), Aralen (brand of chloro-
quine), and Plaquenil (brand of hydroxychloroquine), trademarks
reg. U. S. Pat. Off.



DOSAGE:
lupus. Average initial adult dose, 1 or 2
tablets after meals and at bedtime. Dosage
should be reduced gradually at two week
interval, to 1 or 2 daily.

Light-Sensitivity Eruptions. Average initial
adult dose, 1 tablet after breakfast and
lunch. May be reduced after several weeks to
maintenance dosage of 1 tablet daily.

Winthrop LABORATORIES New York 18, N. Y.

Fig 2. Advertisement for Triquin, 1959.

strated improvement.¹⁸² Released as Triquin by Winthrop, the drug sold well until it was discontinued in the early 1970s (Fig 2). The reason for its withdrawal was that if an adverse reaction occurred, the culpable component could not be discovered easily. This left Atabrine with the rather awkward status of being approved by the Food and Drug Administration (FDA) for lupus only if given in combination with chloroquine and hydroxychloroquine!

Rheumatoid Arthritis

Three small-scale studies in the early 1950s suggested that Atabrine had powerful antirheumatic properties.¹⁸³⁻¹⁸⁵ Since that time, the drug has occasionally been used, usually in refractory cases.¹⁸⁶⁻¹⁸⁹ Despite the lack of negative rheumatoid arthritis studies, no real Atabrine-rheumatoid arthritis trial protocol has ever been performed.

Miscellaneous Autoimmune Diseases

A controlled trial failed to show Atabrine's effectiveness in chronic active hepatitis.¹⁹⁰ Quinacrine has been used to treat various forms of autoimmune dermatitis. For example, it has been used successfully for vitiligo^{191,192} and as part of a combination therapy for pemphigus.^{193,194} A single paper reported its use in collagenous colitis.¹⁹⁵

ADVERSE REACTIONS

General

About half of the patients who are initially prescribed 100 mg of Atabrine daily experience adverse reactions, most of which are minor or reversible. One third may complain of mild or transient headache, dizziness, or gastrointestinal symptoms (diarrhea, anorexia, nausea, abdominal cramps). These reactions either are short-lived or disappear with a decrease in dosage. Approximately 20% of those receiving Atabrine find the side effects disagreeable enough to discontinue the drug. Patients treated for giardiasis or parasitic infestations require loading doses of 300 to 1,000 mg each day during the first week of therapy and nearly all experience the above reactions. Some infrequent serious side effects of Atabrine have been reported.

Gastrointestinal and liver effects. A small group of lupus patients have extremely favorable results from the drug but are plagued by persistent abdominal cramping or diarrhea. For these individuals, bismuth-containing suspensions or antispasmodic agents are administered concurrently. Because Atabrine is heavily concentrated in the liver, long-term high-dose malarial suppressive therapy was occasionally associated with reversible hepatitis. One case of transient lupus-associated Atabrine hepatitis and one case of peritonitis have been reported.^{196,197} Both patients are taking 300 mg daily (three times the current recommended dose).

Eyes. One of the major advantages of Atabrine over the chloroquines is its lack of retinal toxicity. In 1981, Zuelhke et al¹⁸⁹ published their experience from the University of Iowa, where 26 patients given Atabrine over a 30-year period were carefully followed. No retinopathy was found. The world's literature contains only one report of "Atabrine retinotoxicity."¹⁹⁸ In this

case, retinal pathology was found in 1963 in a lupus patient who had been receiving 100 mg daily for 12 years. The drug was not discontinued, and in 1967 her eye findings were unchanged. No information is provided about any other antimalarial therapy this patient might have received. High doses of Atabrine can rarely induce a hypersensitivity reaction resulting in a reversible corneal edema.^{199,200} One case has been reported in a lupus patient receiving 600 mg daily.

Central nervous system. Engel's classic study documented the cortical stimulatory effect of Atabrine on a group of healthy volunteers given 200 to 1,200 mg daily for ten days. EEGs consistently showed a shift to fast frequencies and pronounced psychic stimulation. In low doses, the drug alleviates fatigue and increases energy levels. As the dose is increased, restlessness, vertigo, insomnia, nightmares, hyperirritability, psychosis, and convulsions may be observed.^{199,200} Gaskill and Fitz-Hugh²⁰¹ reported a 0.4% incidence of toxic psychosis among 7,604 US soldiers given Atabrine (100 mg/d) in World War II, and 28 CNS-toxic cases were observed among 30,000 treated for malaria (0.1%).²⁰² These changes in mental status are quickly reversed with discontinuation of the drug and have only been reported twice in lupus.^{203,204} Dubois observed personality changes in two of his 61 patients.²⁰⁵

Hematologic changes. The most serious adverse reaction of Atabrine is aplastic anemia. The incidence of aplastic anemia among US soldiers in the South and Southwest Pacific during World War II increased from 0.66/100,000 before the drug's introduction to 2.84/100,000 in 1945.²⁰⁶ The represented 57 patients, 48 of whom received Atabrine. In 16 of the 48, Atabrine overdose could be documented, and two other soldiers took other marrow-suppressant drugs during this period. Twenty-five of the 48 cases were preceded by a lichen planus rash, but despite this the drug was not discontinued. It has since been learned that stopping Atabrine administration when a lichen planus rash appears can prevent subsequent bone marrow hypoplasia. The incidence of aplasia increases with drug dose and duration of therapy. Eleven cases have been reported in lupus and two in rheumatoid arthritis patients.^{205,207-211} All but one were receiving more

than 100 mg daily, and half had a premonitory lichen planus rash. Most of the patients had gone long periods without having their blood counts checked. Hypoplastic anemia²¹⁰ can be identified with frequent monitoring and is reversible. The mortality rate in these aplastic patients was about 50%.

Skin changes. During World War II, 120,000 Australian troops received Atabrine and 2,000 developed rashes. Eighty percent were eczematous and 20% were lichenoid or exfoliative.²¹² Lichen planus was observed in one in 2,000 soldiers given 100 mg daily and in one in 500 given 200 mg daily. The dermatitis promptly resolved with discontinuation of the drug. Several cases of squamous-cell skin cancer were subsequently noted in areas of lichenoid lesions. A dermatitis developed in ten of 61 of Dubois' lupus patients,²⁰⁵ nearly all of whom were given 200 to 300 mg daily (two to three times current recommended doses). A review of the last 100 systemic lupus erythematosus patients seen by the author who had been given Atabrine (25 to 100 mg daily average dose) revealed a 5% incidence of mild, reversible dermatitis. Atabrine can produce a yellow stain in the skin and bind to melanin, which produces areas of discoloration appearing like "black and blue marks" or bruises.²¹³ These marks consist of membrane-bound intracellular granules of Atabrine that contain large amounts of iron and some sulphur.^{187,212-217} At currently used doses, about one half of the patients receiving the drug develop increased pigmentation; in half of these patients, a yellow stain is evident. It is asymptomatic, and the pigments resolve with drug withdrawal. Decreasing the average daily dose to ≤ 50 mg (maintenance levels) also results in disappearance of the stain or a great reduction in its intensity.

ATABRINE AND PREGNANCY

Atabrine freely crosses the placenta. Although it can cause fetal deaths in rats and was associated with a single case of possible renal agenesis and hydrocephalus, successful pregnancies have been reported with concurrent quinacrine administration.²¹⁸

Table 5. How to Use Atabrine and Maximize Its Effectiveness and Safety in Lupus

1. Never exceed doses of 100 mg daily.
2. If optimal effects achieved after 3 to 6 months, begin tapering drug by one day a week every 2 months. Maintain at 1 to 3 tablets a week for 3 to 5 years.
3. If optimal effects not achieved, add Plaquenil (or vice versa).
4. Discontinue if (a) no effect is seen after 8 weeks, (b) a lichen planus skin rash occurs, (c) significant drop in hemoglobin and reticulocyte counts are observed.
5. Adverse gastrointestinal or pigment reactions can be ameliorated by decreasing the dose to ≤ 50 mg daily. The drug takes longer to work under these circumstances.
6. If CBCs are obtained every 2 to 3 months and the above guidelines are followed, the incidence of aplastic anemia is 1/500,000.
7. Atabrine can improve symptoms and signs of fever, adenopathy, discoid lupus, sun sensitivity, mucous membrane lesions, alopecia, arthritis, headache, fatigue, and serositis.
8. Atabrine has no activity against nephritis, myocarditis, CNS, hematologic, hepatitis, or lung parenchymal involvement of lupus.

ATABRINE v CHLOROQUINE AND HYDROXYCHLOROQUINE

Seven studies have compared a variety of inflammatory and immunologic parameters of

both classes of antimalarials. These reports strongly suggest that Atabrine is a more powerful antiinflammatory agent than the chloroquine family.^{20,44,50,89,96,151,219}

SUMMARY

Atabrine has been available for nearly 60 years. It has a variety of actions and has been administered to millions of individuals. Its antirheumatic properties have been well documented but have not been exploited optimally for a variety of reasons. The drug is generally quite safe and could be used in low doses in lupus and rheumatoid arthritis patients as a steroid-sparing agent or synergistically with hydroxychloroquine. Its bothersome side effects should not deter the clinician from using it, because they are easy to deal with or prevent (Table 5). Future studies should attempt to better characterize the immunosuppressive actions of this powerful drug, particularly in the treatment of lupus erythematosus and rheumatoid arthritis. Studies of the role of combination or single-agent antimalarial therapy in combination with other "remittive" drugs could be of great potential benefit.

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