Overview of Artemisinin Neurotoxity

Research and Development Findings to Policy Impacts

Presentation to National Academy of Sciences, Engineering, Medicine

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Qinhaosu (QHS)—Artemisinin (ART) Discovery and Development

- Chinese discovery ‘Program 526’ - 1967
- US Army Walter Reed Army Institute of Research (WRAIR) 1975-8
- WHO - CHEMAL
- Hong Kong, Wellcome Trust Unit & Armed Forces Research Medical Institute (AFRIMS) Bangkok

Qinhaosu (QHS)-Artemisinin (ART) A New Molecular Class

- Chinese project 526 reports:
  - 'Fast acting'; reverses malaria coma
  - Thought to be active against resistant parasites
  - Suggested activity against gametocytes
  - 'No toxicity concerns' No formal toxicology
- Unique structure - sesquiterpene endoperoxide lactone -confirmed
- Analogs of QHS-Artemisinin dihydro with methyl & ethyl ether and succinate salt
- Oral, IM derivatives and, ultimately, IV AS available

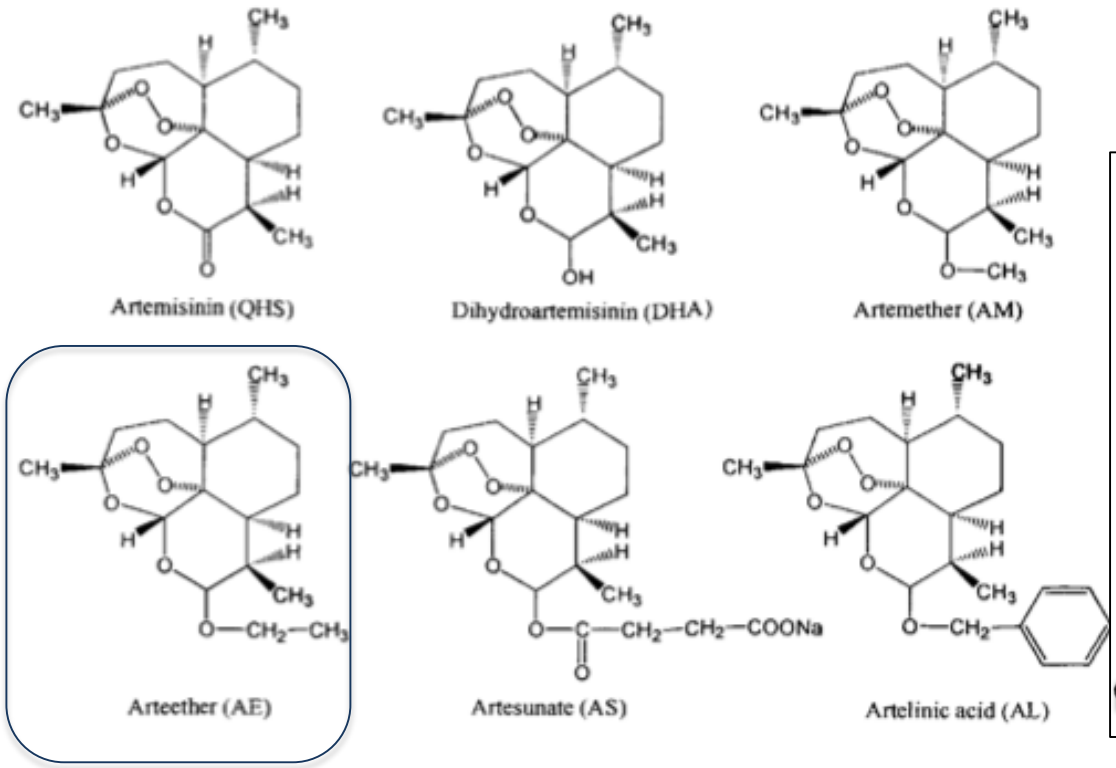
QHS-ART Development
US Army (WRAIR)-WHO,
Other Partners

- Arteether (AE) analog in sesame oil formulation selected for development (WHO-Army 'TPP')
- No quantitative method for biologic fluids
- No metabolism, ADME
- No PK, PD
- No formal toxicology – reported 'no toxicity'
- Basic treatment regimens had been worked out by Chinese scientists with empirical studies

Arteether (AE) Development Activities

- Primary synthesis of ART and ^{14}C primary/metabolite;
- Assay development for sensitive (ng/mL), specific HPLC with reductive electrochemical detection and HPLC-MS.
  [Melendez V, Peggins JO, Brewer TG, Theoharides AD.
  J Pharm Sci. 1991. 80(2):132-8]
- Additional use of LC-MS metabolism [Theoharides AD, Melendez V, Teja-Isavadharm P]
- Further pre-clinical research for parasitologic evaluation, metabolism, development of bioassay and PK studies [Kyle D, Teja-Isavarh P, Peggins J, Li Q]

Arteether (AE) Development Activities con't



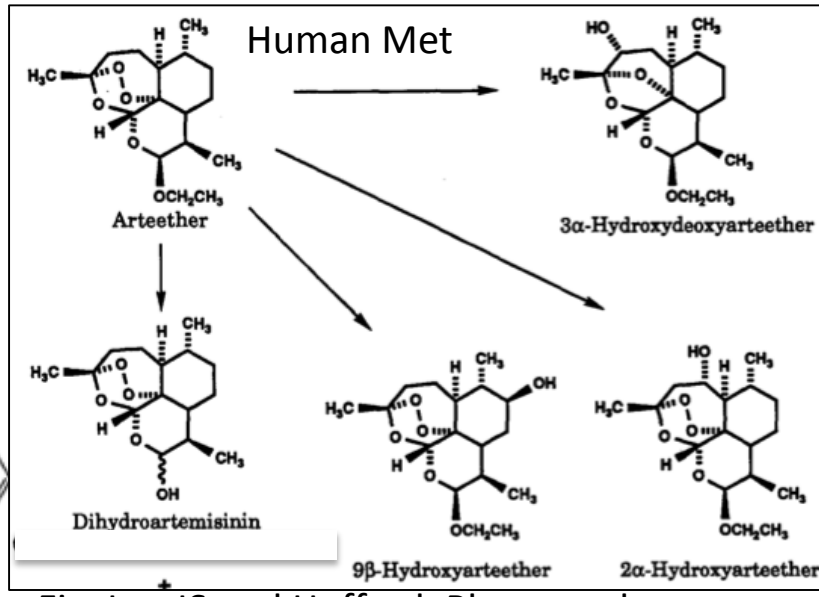


Fig. Lee IS and Hufford. Pharmacol & Ther 1990,48,345

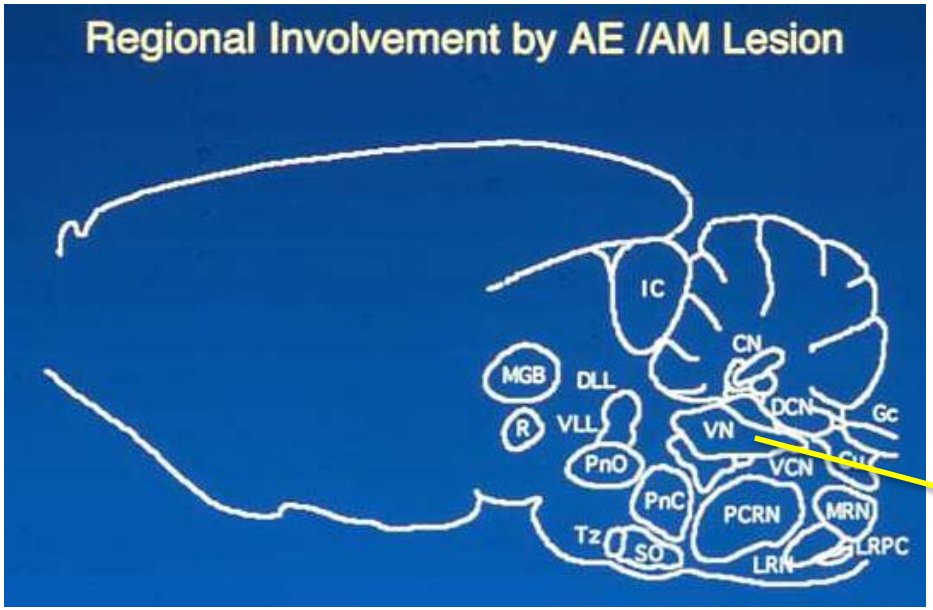
- Contract Toxicology Sponsored by WHO (14 and 28 d studies two species) all initially reported negative. Small number of unexplained deaths
- During multiple dose dog PK study at WRAIR, sudden death syndrome noted in high dose animals

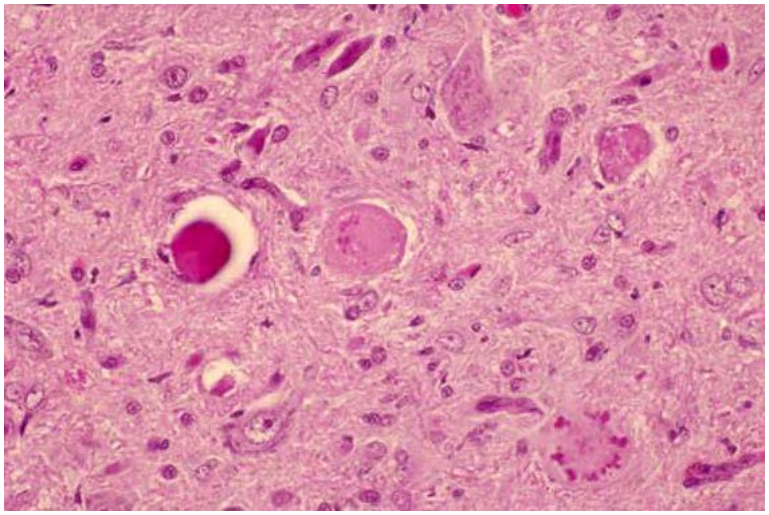
Theoharides, Melendez, Lin, Peggins

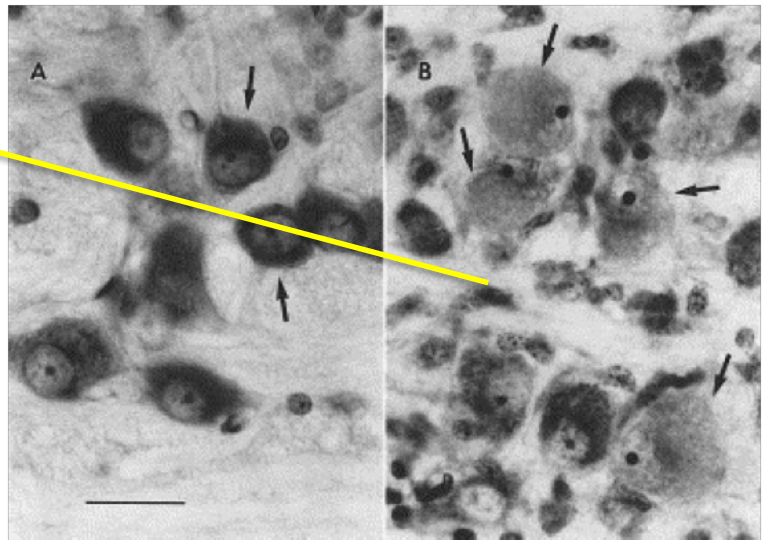
Neurotoxicity Studies and Findings

- R/O all other causes of death
- CNS lesion only recognized with detailed search
- Anatomically highly constrained neuronal injury/death in auditory vestibular nuclei, reticular, and visceral autonomic brainstem nuclei (AE & AM); *not* congruent with other known/reported lesions
- Further studies:
  - Neuro-anatomic /neuropathology evaluations w blinded scoring
  - *In vivo*: rat, (mouse), dog, monkey; toxico-kinetic studies dose, duration and route of exposure
  - *In vitro* neuronal cells: analog structure and formulation, time-concentration exposure, and other antimalarials
  - Behavioral neurotoxicity based on 'systems neurology' approach: general behavior, auditory detection/discrimination, brainstem auditory evoked response BAERS /ABRs(monkeys).

ART Selective Brainstem Damage

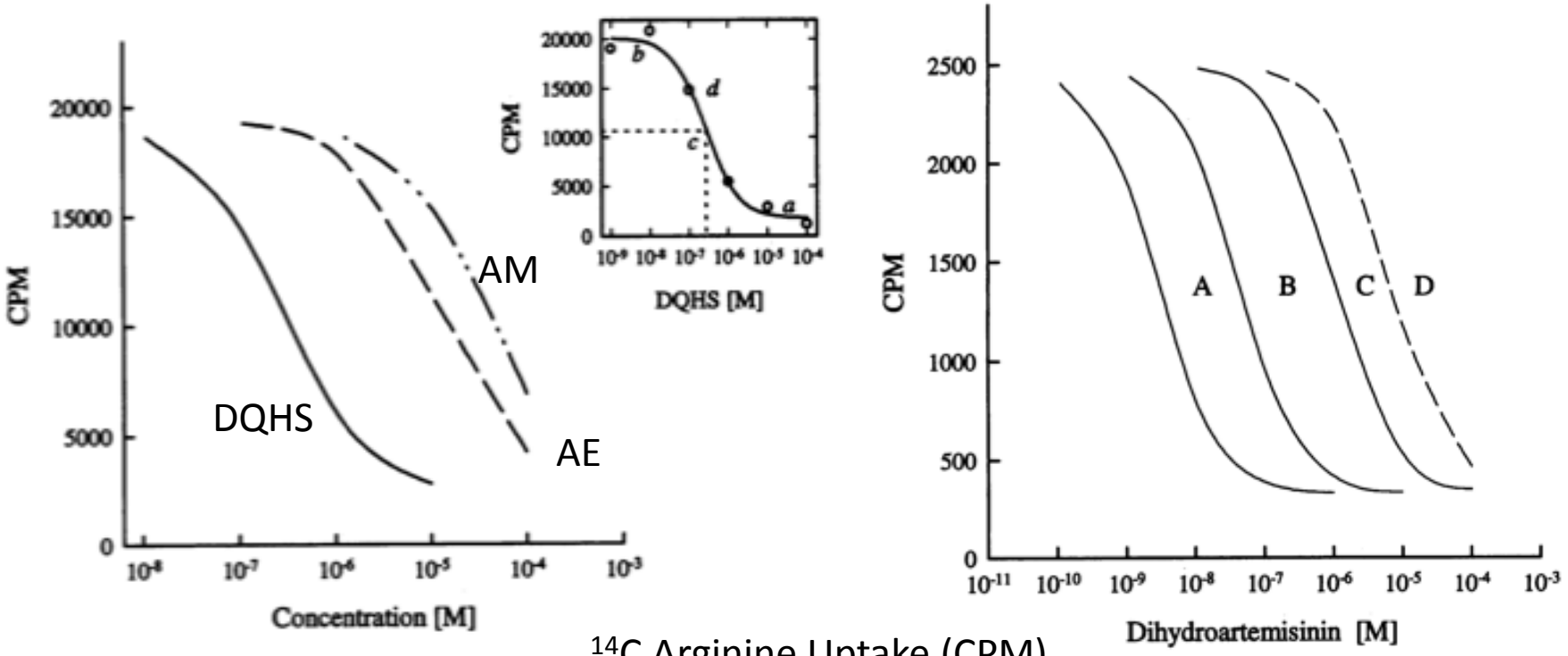






Petras, Grate, Newman, Mog

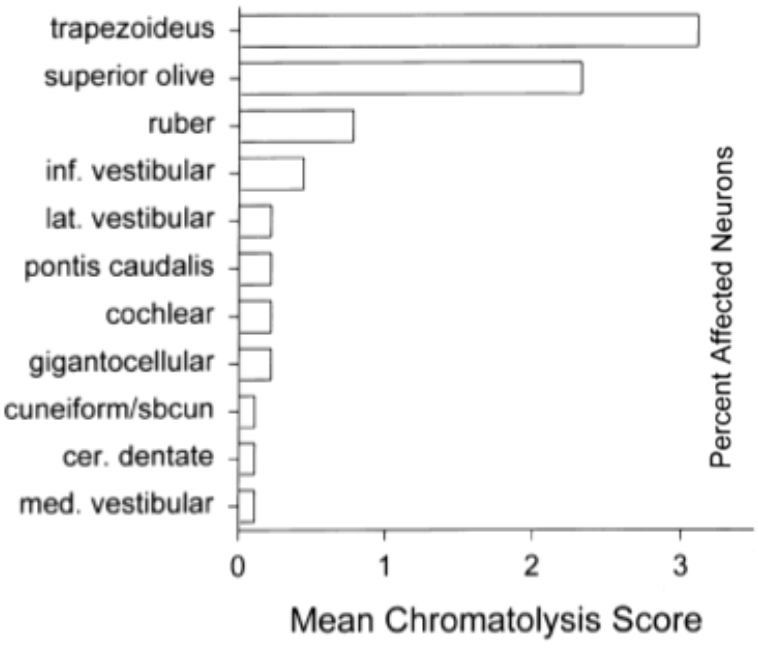
ART Analog, Concentration, Brain Cell-type, and Exposure Time Activity,

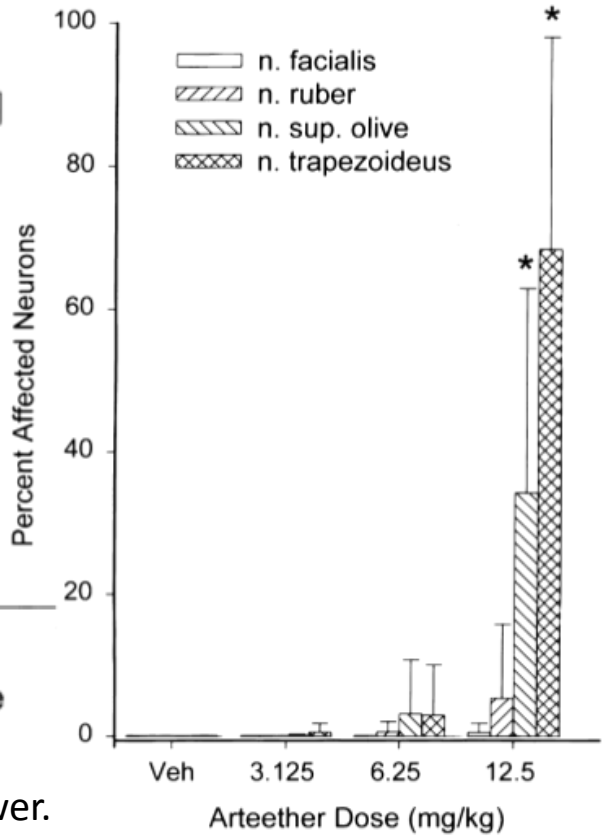


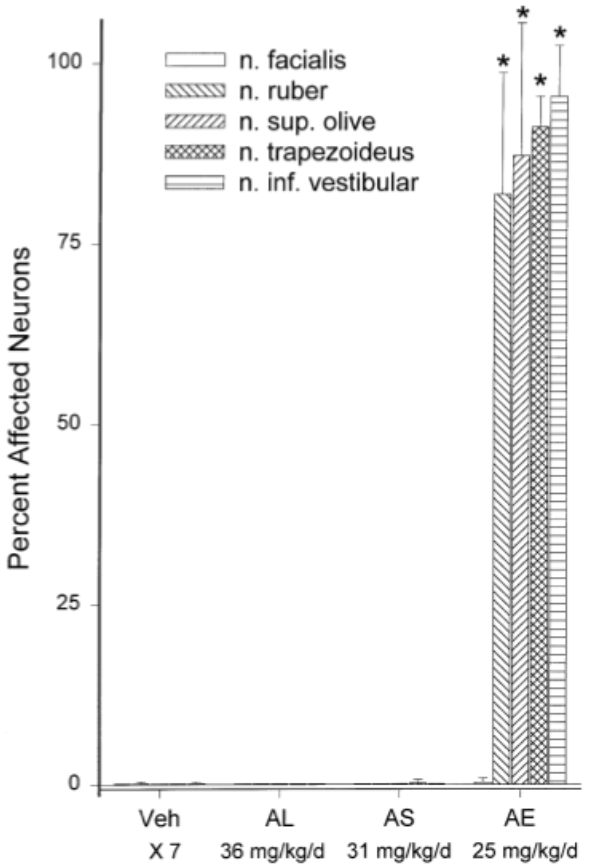
^{14}C Arginine Uptake (CPM)
LDH release not shown

Neurotoxicity of artemisinin analogs *in vitro*. Wesche DL1, DeCoster MA, Tortella FC, Brewer TG. Antimicrob Agents Chemother. 1994;38(8):1813

ART *In Vivo* Neurotoxicity– Anatomic Selectivity, Dose Response, and Analog Specificity



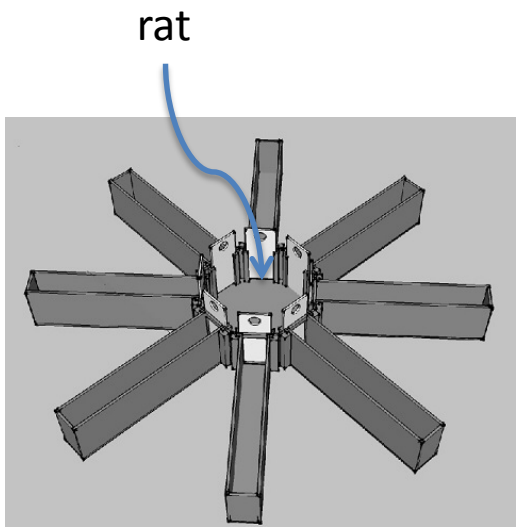


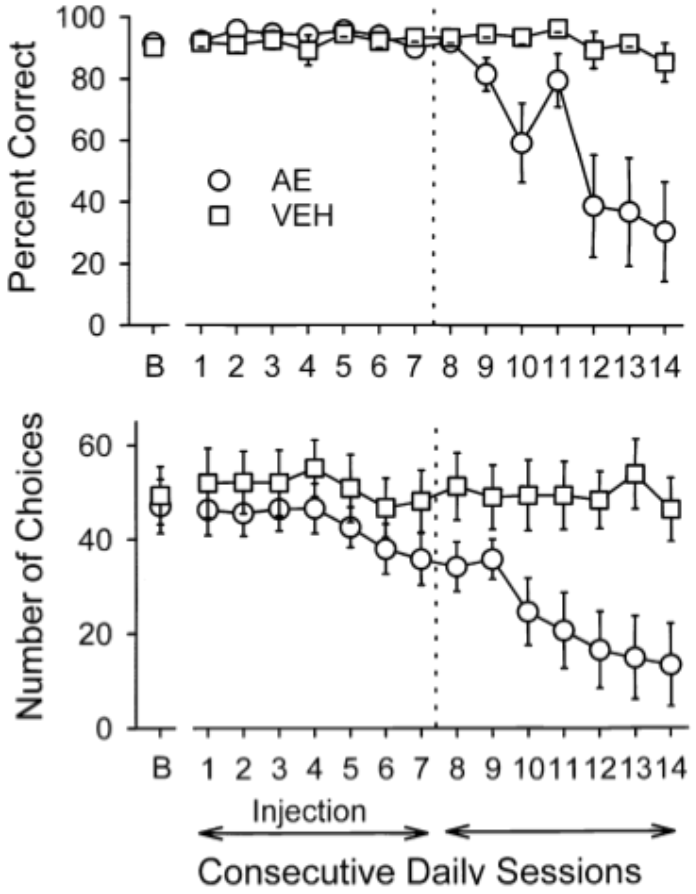


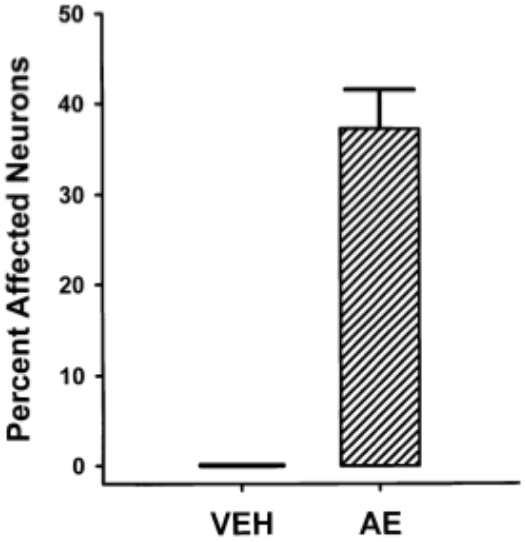
Genovese, Newman, Li, Peggins, Brewer. Dose-dependent brainstem neuropathology following repeated AE administration in rats. Brain Res Bull 1998, 45, 199

Genovese, Newman, Brewer. Behavioral and neural toxicity of the artemisinin AE but not AS and AL in rats. Pharm Biochem and Behavior 2000, 67, 37

Sound Detection, Discrimination & Localization Studies in Rats



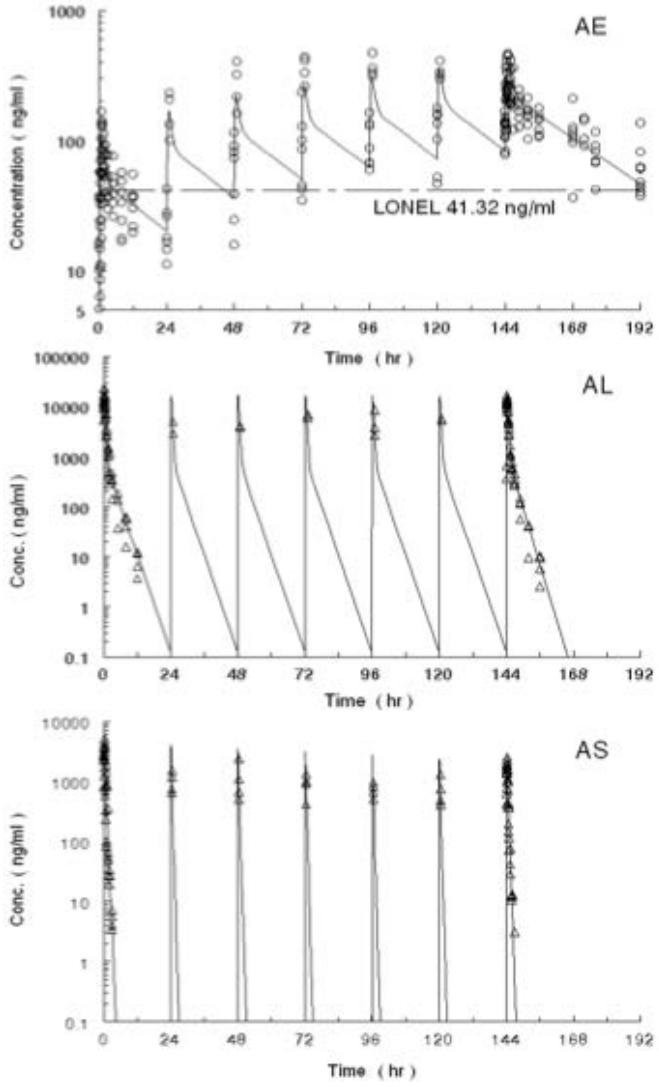




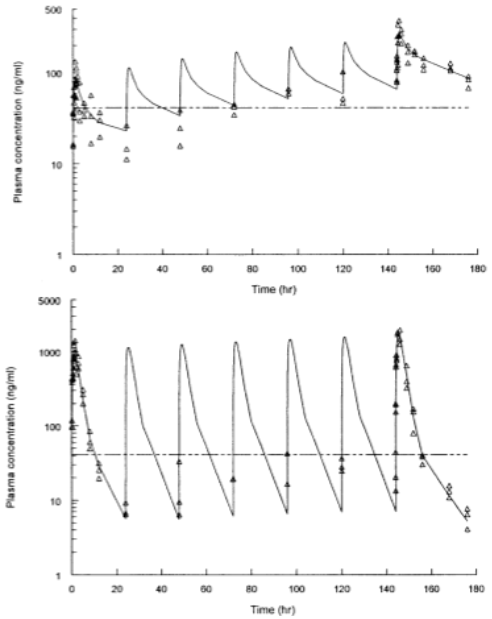
Genovese R, Nguyen H, Mog S. Effects of AE on auditory radial arm maze task in rats. Physiol & Behavior. 2001, 72, 87

Cumulative Dose Level with IM AE

AE Oil Compared to Water Soluble AS AL



AE Accumulation Affected by Formulation Seseame oil vs Cremophore



Li Q, Mog S, Kyle D, Gettamacamin M, Milhous. Neurotoxicity and Effacacy of Areether Related to its Exposure Times and Levels in Rodents. Am J Trop Med Hyg 2002, 66, 516

Li Q and Hickman M. Pharmacokinetic (PK) and Pharmacodynamic Profiles of Artemisinin Derivatives Influence Drug Neurotoxicity in Animals. *In*: Readings in Advanced Pharmacokinetics – Theory, Methods and Applications. www.intechopen.com

Use of Sensory Evoked Responses

Visual Evoked Response (VER)

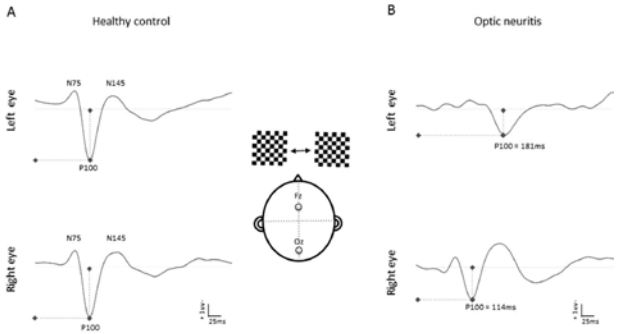


Fig: Lascano Clinical Evoked Potentials Rev JNeurol Neurosurg Psych 2017

Auditory Brainstem Evoked Response (ABR /BAERs)

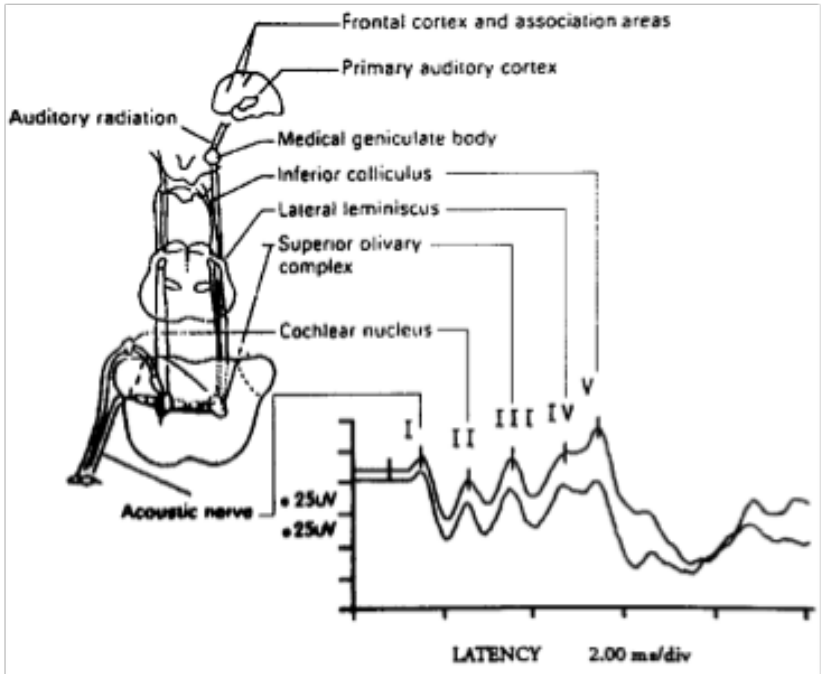
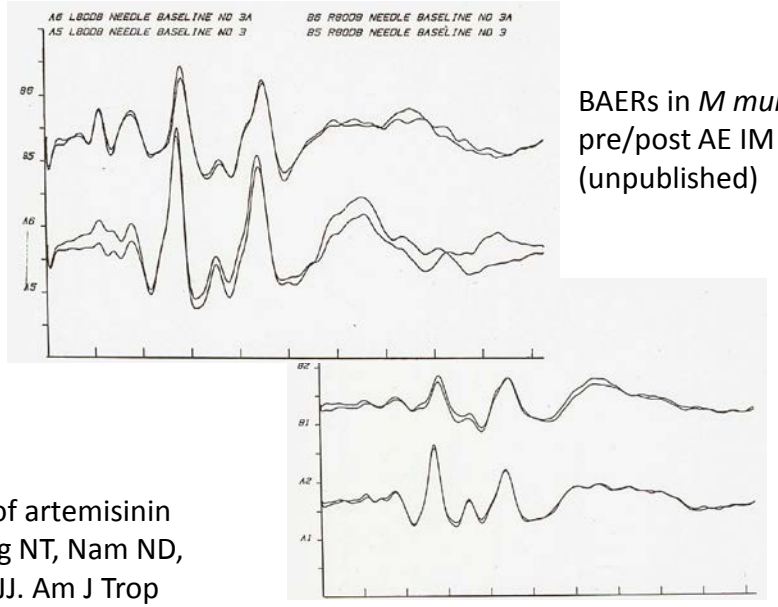


Fig. Clinical and neurophysiological study of the effects of multiple doses of artemisinin on brain-stem function in Vietnamese patients. Kissinger E1, Hien TT, Hung NT, Nam ND, Tuyen NL, Dinh BV, Mann C, Phu NH, Loc PP, Simpson JA, White NJ, Farrar JJ. Am J Trop Med Hyg. 2000;63(1-2):48-55



BAERs in *M mulatt*a pre/post AE IM 7d (unpublished)

Uhl, Newman, Li, Teja-Isvardharm

Experimental Data Informed Development and Use

- Metabolic product of all ART analogs, DHART, was a primary toxic species. Endoperoxide moiety necessary but not sufficient for toxicity
- Longer duration of exposure—related to oil solubility (AM & AE) and route of administration (IM) was *major* determinant of neurotoxicity
- AS (and AM & AE given PO) result in equivalent parasite clearance with short-term exposure and (no identified) neurotoxicity risk
- Policy-practice implications:
  1. * ART (ACTs) combination therapies
  2. Oral AM/AS or parenteral AS (AS Development completed under CRDA)
  3. Forward-looking strategy of systems neurology, non-invasive neurotoxicity evaluation with pre-clinical models and clinical brainstem evoked response potentials (auditory, or other tests)

Thank You – Questions?

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