CONTROLLED HYPOTENSION

II. A PRELIMINARY REPORT ON "ARFONAD"® (RO 2-2222)*

MAX S. SADOVE, M.D., GORDON M. WYANT, M.D., GWEN GLEAVE, M.D.,
AND PAUL C. BUCY, M.D.

Departments of Surgery (Anesthesiology), Neurology and Neurological Surgery, University
of Illinois College of Medicine, the Veterans Administration Hospital, Hines,
Illinois, and the Chicago Memorial Hospital, Chicago, Illinois

(Received for publication July 31, 1958)

In a previous communication we discussed the subject of induced hypotension for surgical operations, and in particular as it affects the field of neurosurgery. We placed special emphasis on the methonium compounds which then represented the latest means of obtaining a lowered blood pressure during surgical operations. We pointed out in our paper the advantages of this method over previous attempts at controlled hypotension, but we also mentioned the definite limitations and disadvantages of the methonium compounds. Among these are the large individual variations in response to the drug and in the amount of the drug that is required, the uncertainty of obtaining adequate hypotension with the agent, and the occasional occurrence of marked diminution of response to subsequent doses. Also, hypotension tends to be fixed at a certain level rather than be flexible in response to variations in the dose. In essence then, the limitations of the methonium drugs consist in a certain unpredictability of action. In addition, once adequate hypotension is obtained, it can be reversed only either by elimination or destruction of the drug, or the hypotension may be counteracted by a vasopressor. Further hypotension then becomes practically impossible until the effect of the vasopressor has been dissipated. The elimination or destruction of the drug requires time, and even if the blood pressure returns to normal levels, patients remain vasolabile for a period of hours up to two days. Nevertheless the methonium drugs have their uses, although they are not the perfect solution to the problem of controlled hypotension for surgical procedures. Any agent that is capable of altering blood pressure gradually to any desired level and that would permit this level to be altered both in an upward and downward direction on a minute-to-minute basis would represent a decided advantage over the methonium compounds. Such an agent seems to be available in "Arfonad" (RO 2-2222). It has been used by us in 62 cases with satisfactory results in most instances.

* Supplies of Arfonad (RO 2-2222) have been generously donated by Hoffmann-LaRoche, Inc. through the courtesy of E. L. Sevringhaus, M.D. and M. J. Schiffin, Ph.D.

Published with approval of the Chief Medical Director, Veterans Administration. Statements and conclusions published by the authors are the result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.
Pharmacology

Arfonad is a thiophanium derivative with the formula: 
\[ \text{--d-3,4(1',3'-dibenzyl-2'-keto-imidazolido)-1,2-trimethylene thiophanium d-camphor sulphonate.} \]
The structural formula is:

\[
\begin{align*}
\text{O} & \quad \text{C} & \quad \text{N} & \quad \text{N--CH}_2 \\
\text{CH}_2 & \quad \text{--CH} & \quad \text{CH}_2 \\
\text{S} & \quad \text{CH}_2 & \quad \text{CH}_3 & \quad \text{SO}_3 & \quad \text{CH}_2 & \quad \text{C--C--CH} \\
\text{CH}_2 & \quad \text{CH}_3 & \quad \text{CH}_2 & \quad \text{CO--CH}_2
\end{align*}
\]

It is capable of reducing arterial blood pressure in anesthetized animals and in man. The hypotension is in part produced by sympathetic ganglionic blockade which causes metarteriolar dilatation. The part played by reduced cardiac output and possibly by other mechanisms is as yet undetermined. Vasodilatation is responsible for pooling of blood in the periphery of the body, and this in turn causes reduction of venous return to the heart and consequently decrease of cardiac output. The vasodilatation also causes marked diminution of peripheral resistance, and this decreased resistance far outweighs the reduction in cardiac output; in consequence the over-all workload of the heart is reduced. This fact first led to the use of Arfonad in the treatment of pulmonary edema of cardiac origin by Sarnoff and Goodale, who also reported on its use for hypotension in four neurosurgical procedures.\(^5\)

According to Randall, Peterson and Lehmann\(^2\) the acute toxicity of Arfonad varies greatly with the route of administration and the species of animals employed. Ephedrine, epinephrine, and similar vasopressors will abolish the vasodepressor effects of Arfonad; Arfonad is ineffective on arterial pressure during the pressor response to these drugs. In dogs, but not in man, histamine release has been demonstrated after the administration of Arfonad.\(^1\)

There is suggestive evidence that sympathetic ganglionic blockade is only one of the factors involved in the production of hypotension with Arfonad. Although no histamine release has as yet been demonstrated in man, it is conceivable that this may be one of the other mechanisms. From work carried out on ourselves and on volunteers\(^4\) we have been able to draw the following conclusions: After administration of the drug to conscious,