Clinical Versus Experimental Use of Isobutyl-2-Cyanoacrylate

To THE EDITOR: We read with interest the letter to the editor from Drs. Samson and Marshall regarding the possibility that isobutyl-2-cyanoacrylate (IBCA) is carcinogenic (Samson D, Marshall D: Carcinogenic potential of isobutyl-2-cyanoacrylate. J Neurosurg 65:571–572, October, 1986, Letter). We would like to point out that their findings are based on preliminary data from a single unpublished study that is unavailable, even upon request.

This tissue adhesive has been used for more than a decade as an embolic liquid agent for the management of arteriovenous malformations, some arteriovenous fistulas, tumors, and vessel lacerations. Ethicon, the manufacturer, has provided the material free of charge to those clinical investigators in the United States who have submitted a protocol and obtained an Investigational Drug and Device Exemption (IDE) from the Food and Drug Administration (FDA), and who have obtained the approval of their institutional review board. The use of IBCA for embolic occlusion is still considered experimental and is reserved for those cases in which the indication for treatment outweighs receiving no treatment, in which other forms of treatment are not available, or in which the risk of other measures is such that an experimental procedure is the sole or best alternative as a life-saving or function-preserving measure.

The preliminary data sent by Ethicon, Inc., to investigators working under an IDE and to the FDA in a December, 1985, letter describe the use of intraperitoneal IBCA in rats at doses 100 times higher than those used in humans. In embolotherapy the material is not used in the peritoneum, but it is used endovascularly as an embolic agent. The study results are preliminary and have been interpreted by Ethicon to mean that the “data strongly suggest a dose-related carcinogenic potential for isobutyl-2-cyanoacrylate in this specific animal model.” The likelihood of these data representing a Oppenheimer effect is high (that is, a dose-related effect not specific for the substance investigated): a strong probability that is ignored in the letter by Samson and Marshall.

We would like to assume that the Joint Commission on Drugs and Devices of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), for which Dr. Samson writes, has reviewed and evaluated the mentioned study, as well as the extensive literature available on the histotoxicity of the alkyl-2-cyanoacrylate, prior to issuing their strong letter in the Journal. However, no references are cited. The numerous published toxicity studies performed in various animal species, the examination of pathological specimens in humans, and studies on various acrylic polymers in experimental and human applications all point to a purely foreign-body giant-cell inflammatory reaction rather than to a neoplastic tissue response. Tissue reaction is not unique to IBCA and has been described by some investigators as similar in degree and kind to that seen with nonabsorbable silk suture. Furthermore, not one case of toxic, neoplastic, or allergic reaction to IBCA has been reported. The complications produced by this embolic agent have all been due to mechanical factors common to all liquid embolic agents.

The alkyl-cyanoacrylates have been used intraperitoneally in humans for over 19 years by Matsumoto, et al., and others and for emergency hemostasis by Heisterkamp, et al. In over 2000 patients we have treated with intravascular IBCA in the last 10 years and reported to the FDA and Ethicon, Inc., no single report of associated or concomitant neoplasm exists. This is also true in more than 15,000 patients treated in France as well as in large numbers of other patients treated in the United States, Japan, and various countries in Europe. Some of these latter studies are known to Ethicon, Inc.

An absolute statement denying a carcinogenic potential in man cannot be made, however. In 1982, Mark, et al., reported on the mutagenicity of n-butyl and isobutyl monomers using the Ames test in bacteria, in which a positive result can imply that the product under study may be mutagenic in man. They reported a “weak” mutagenicity of the isobutyl monomer. Although extrapolation of this study to the development of human neoplasm is not conclusive, especially with the doses used in embolotherapy, precautions and considerations as to potential carcinogenesis have led users to employ these materials with caution, care, and discrimination.

Based on the body of information available, the proper way to address the question of benefit versus long-term potential risk would be to restrict the use of the material to investigators working under an IDE who would use IBCA experimentally under proper clinical circumstances, with yearly reports, long-term registry of results, and follow-up evaluations. It is not proper to withdraw a most useful therapeutic agent, for which there is at times no alternative, without a scientifically valid intravascular experimental study that would mitigate against its use.
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For a responsible organization like the Joint Commission on Drugs and Devices of the AANS and CNS and a company such as Ethicon to make such strong recommendations to responsible physicians prior to releasing the results of a single study in which the scientific procedures and conclusions may be controversial, and in which the purported conclusions are contrary to a large body of literature, may not only be premature but may be irresponsible, and could jeopardize those patients who may benefit from this treatment. Such actions may also lead to deterioration of an already precarious medicolegal atmosphere.

Those investigators using IBCA or those patients in need of IBCA should urge Ethicon to continue providing this embolic agent on a per-case basis, under proper circumstances, to qualified investigators as a humanitarian gesture. We also urge the Joint Commission of the AANS and CNS to work with us at the American Society of Neuroradiology and to assist Ethicon, Inc., in obtaining FDA approval for IBCA as an orphan drug until a suitable alternative can be found or until the long-term effects of endovascular IBCA in humans are established.

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References


RESPONSE: The letter from Drs. Berenstein and Hieshima voices the understandable concern of interventional radiologists that our prior remarks regarding the possibility of a dose-related carcinogenic potential of isobutyl-2-cyanoacrylate will negatively affect its admittedly “still experimental” use for embolic occlusion. Despite their several objections, the preliminary reports of this study on the agent’s carcinogenic potential (supplied to Dr. Berenstein by Ethicon at his request) are sufficiently clear both to Ethicon and to the Joint Committee so as to warrant our advisory letter to the neurosurgical community. That the results are as yet incomplete and represent the first experimental study to suggest this carcinogenic effect does not negate their