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Adjusting the Polymerization Time of Isobutyl-2 Cyanoacrylate

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Isobutyl-2 cyanoacrylate (IBCA) polymerizes by an anionic mechanism. The initiation of polymerization depends on an alkaline medium and can be inhibited with the addition of small amounts of acid. Using small amounts of glacial acetic acid (3.7%–7.1% by volume), the polymerization time was prolonged from 2.3 sec to 7.8 sec. In vivo experiments in dogs demonstrated no additional inflammatory reactions to the mixture of IBCA, iophendylate, and tantalum powder when acetic acid was added. Glacial acetic acid offers a safe and effective way, without increase in viscosity, to manipulate the polymerization time of IBCA.

One of the most widely used liquid embolic agents is isobutyl-2 cyanoacrylate (IBCA). The commonly used mixture of IBCA, iophendylate, and tantalum powder was described by Cromwell and Kerber [1] in 1979. As used in embolization therapy, this mixture has a practical maximum polymerization time of about 3 sec. Although longer polymerization times were demonstrated with in vitro testing, the increase in viscosity renders the injection of any mixture containing more than 50% iophendylate impractical. This short polymerization time has led to a few problems, such as incomplete embolization and gluing the catheter to the vessel wall. Therefore, we undertook this investigation to find a safe agent that would prolong the polymerization time of IBCA in a controlled fashion, without increasing the viscosity of the IBCA, iophendylate, and tantalum powder mixture.

Materials and Methods

Glacial acetic acid was tested on the advice of one of the authors (J. M. G.). The mixture to be tested contained IBCA (0.5 ml), iophendylate (0.15 ml), and various amounts of acetic acid (0–50 μL).

In Vitro Experiments

The experimental model chosen was very similar to that published by Debrun et al. [2]. It consists of a plastic, transparent connecting tube connected to a Cook sidearm. The sidearm is connected to a pressure infusion of plasma that simulates blood and is chosen for its property of inducing polymerization of IBCA. The distal end of the connecting tube is connected to tubing that empties into an infusion bag. Teflon catheters were used to introduce the various mixtures into the flowing plasma. The catheter was filled with the mixture to be tested, introduced into the straight arm, and pushed until the catheter extended about 1.0 cm into the transparent connecting tube. Small amounts (0.15 ml) of the various mixtures were then injected into the flowing plasma. The time between the start of injection and the first change in appearance of a mixture in the plasma was measured by a second observer. At least five measurements were made for each of the mixtures.

Animal Experiments

Four dogs were used in the experiments. A 7 French catheter was introduced into the

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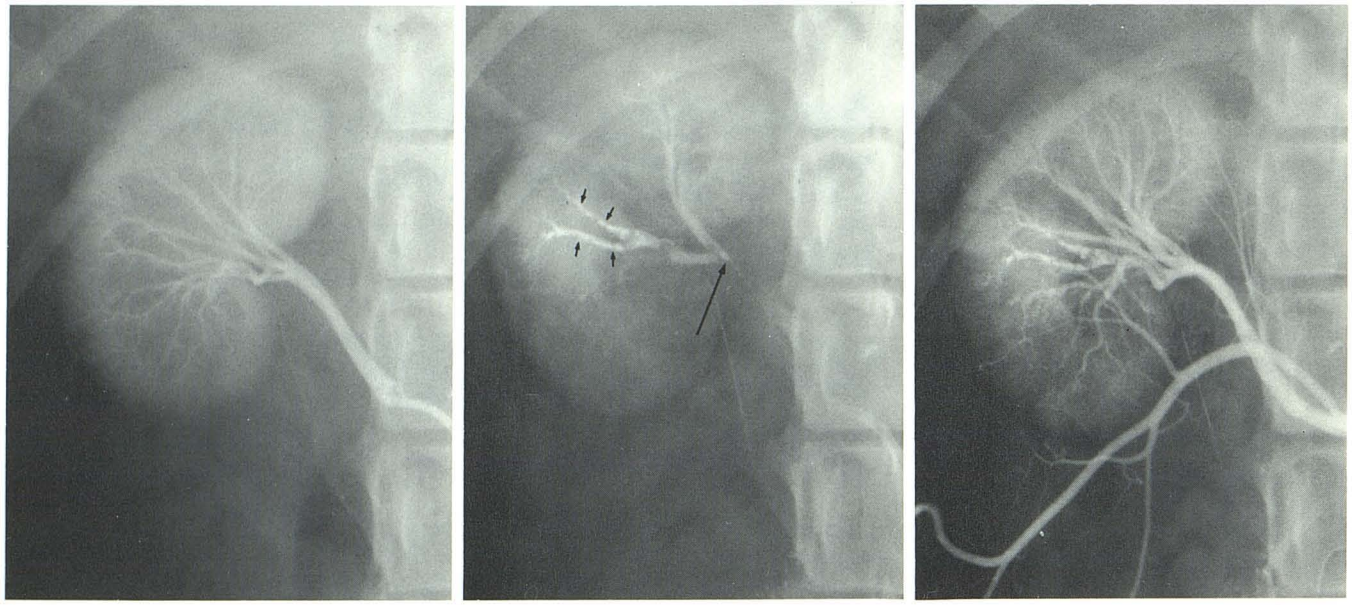

Fig. 1.—Right renal angiogram in a dog. **A**, Preembolization. **B**, Mixture of IBCA, iophendylate, tantalum, and acetic acid (0.05 ml of acetic acid) had, at same setting, been previously injected into mid renal artery (*short arrows*). Upper pole artery was then selectively catheterized with balloon catheter (*long arrow*) before injection of dilute solution of acetic acid (0.05 ml in 1.6 ml saline). **C**, Right renal angiogram after embolization of mid renal branch with bucrylate mixture and injection of dilute solution of acetic acid into upper pole branch. No angiographic abnormality of upper pole branches.

femoral artery and positioned in the main renal artery. Angiography was performed to identify the different branches of the renal artery. A calibrated-leak balloon was positioned at various sites within the main renal arteries and its branches. Embolization with a mixture of IBCA (1.0 ml), iophendylate (0.3 ml), tantalum powder (1.0 g of 1 μm particles), and glacial acetic acid (0.05 ml) was carried out, involving the main renal arteries and/or their branches in five kidneys. Pure acetic acid (0.05 ml) was injected into one main renal artery. One upper pole branch was injected with undiluted acetic acid (0.05 ml), and there was injection of acetic acid (0.05 ml) diluted with saline (1.6 ml) into another upper pole branch. One dog was sacrificed 1 week after embolization; the other dogs were sacrificed immediately after embolization. After embolization, another angiogram was obtained to demonstrate the results (fig. 1). The kidneys were submitted to a pathologist for assessment of any inflammatory reactions.

TABLE 1: **Effect of Acetic Acid on the Polymerization of IBCA**

% Mixture Glacial Acetic Acid	Average Polymerization Time (sec)
0.0	2.3 ± 0.3
3.7	3.0 ± 0.1
4.1	3.7 ± 0.1
4.4	5.2 ± 0.4
5.1	5.8 ± 0.3
5.8	6.4 ± 0.3
7.1	7.8 ± 0.1

Note.—The mixture tested contained isobutyl-2 cyanoacrylate (IBCA) (0.5 ml) and iophendylate (0.15 ml). Polymerization end point was arbitrarily chosen as earliest appearance of opacity in bucrylate mixture in flowing plasma. Average of at least five observations is given.

Results

In Vitro Experiments

In vitro, the mixture of IBCA (0.5 ml) and iophendylate (0.15 ml) polymerized at 2.3 ± 0.3 sec (table 1). This particular mixture was tested several times at many different sessions and was consistently within this time frame. Tantalum powder was not used in these experiments, as it interfered with the end point, which was the first change in appearance of the IBCA mixture. Tantalum powder does not react with the other constituents of the mixture and its absence decreases the viscosity of the mixture and renders it less radiopaque. With the addition of acetic acid (25 μl–50 μl), polymerization times of 3.1 ± 0.1 sec to 7.8 ± 0.1 sec were obtained (fig. 2). As the mixture of IBCA, iophendylate, and acetic acid forms an emulsion rather than a true solution, it was technically impossible to measure the pH. The mixture of IBCA and iophendylate without acetic acid behaves differently from the mixture with acetic acid in the connecting tubes. The former tends to polymerize in small clumps. The mixture with acetic acid tends to polymerize in one long solid strand (fig. 3). No difference in viscosity between the mixture without acetic acid and that with acetic acid was noticed by the observers.

Animal Experiments

The IBCA mixture with acetic acid, because of its longer polymerization time, reached more distally, angiographically, than did the mixture without acetic acid. On pathologic study, the mixture of IBCA, iophendylate, and tantalum powder injected into the main renal artery, reached to the level of the

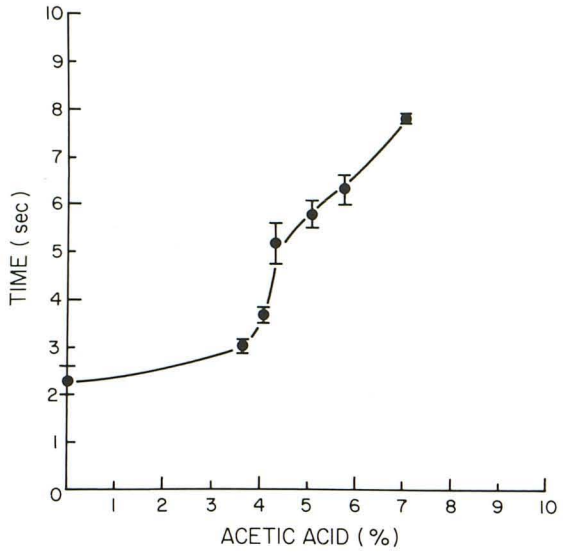

Fig. 2.—Polymerization concentrations times plotted against various concentrations of acetic acid.

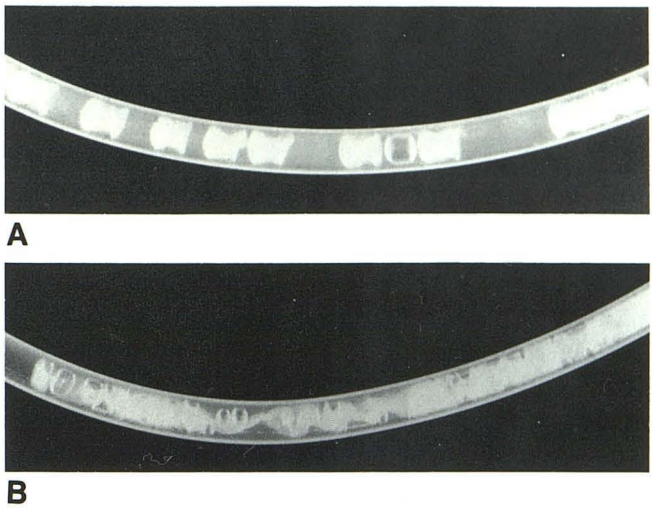

Fig. 3.—Appearance of bucrylate mixture after polymerization. **A**, Bucrylate mixture without acetic acid. After polymerization, it formed separate solid particles. **B**, Bucrylate mixture with acetic acid. After polymerization, it formed one long strand. Air bubbles result from delay between experimental work and photography.

arcuate arteries in the one kidney so injected. The IBCA mixture with acetic acid, injected into the main renal artery, reached vessels well into the cortex in the two kidneys so injected. In the four kidneys harvested the same day as the embolization, there was no perivasculitis or infarction of the kidney parenchyma. In the main renal artery near the site of injection, about half of the circumference demonstrated edema of the superficial half of the media and adjacent intima with a distinct paleness of the nuclei of the medial muscle cells. In the one kidney harvested 1 week after embolization, there was marked vasculitis with a surrounding mononuclear/fibroblastic proliferative response. The inflammatory reaction produced was quite similar to that produced by the bucrylate mixture without acetic acid [3, 4]. An injection of acetic acid (50 μl) mixed with saline (1.6 ml) produced no inflammatory response.

Discussion

IBCA polymerizes by an anionic mechanism [5]. The substituents on C-2, cyano and ester carbonyl, are both electron withdrawing (fig. 4A). This enables C-2 to stabilize a negative charge extremely well, and consequently, makes IBCA susceptible to anionic polymerization, even under very mildly basic conditions.

In the bloodstream, which is mildly basic, the anion (negative ion) initiates polymerization (fig. 4B). Propagation of the growing polymer chain proceeds via the reaction with an addition of more monomer units (figs. 4B and 4C). Chain termination takes place when the propagating polymer chain comes into contact with an electrophilic species (fig. 4D).

The introduction of acetic acid into the reaction mixture inhibits polymerization by interfering with this process until it is consumed. This may occur in two ways. The first way is by binding to the basic species in the local environment, so that no initiators are present until the acetic acid is consumed and the alkaline environment restored. The other way is by terminating any propagating chain that may have been initiated before chain growth can occur, again until the acetic acid is consumed. The first mechanism is much more likely to occur and should predominate, since the acetic acid should be more reactive toward the basic species than the monomer. This is despite the much greater monomer concentration than acetic acid concentration.

Since the article by Cromwell and Kerber [1], most radiologists have tended to assume that the polymerization of IBCA depended on the presence of ions. In fact, a Med-line search of the literature dealing with IBCA disclosed only two reports [6, 7] attributing the polymerization to the presence of weak bases. The one review article by Pevsner et al. [6] discusses many possible agents for polymerization control without detailing the authors' own experience with these agents, nor is any study quoted that demonstrates that these have any biologic effect.

Graphically, the polymerization time, expressed as a function of percentage of acetic acid added, follows an S-shaped curve (fig. 2). We believe that this reflects the various physical and chemical processes involved. With the addition of less than 3.7% acetic acid by volume, the base in the immediate vicinity of the bucrylate mixture is sufficient to consume the acetic acid and cause polymerization. Thus, there is little difference in the polymerization time with the addition of very small amounts of acid. With the addition of 3.7%–4.4% by volume of acetic acid, there is a relative balance between the amount of acid and base in the immediate vicinity of the isobutyl-2 cyanoacrylate. The physical processes of convection and diffusion in the flowing plasma or blood will both dilute the acetic acid and make more base available for consumption of the acetic acid. Because of the approximate

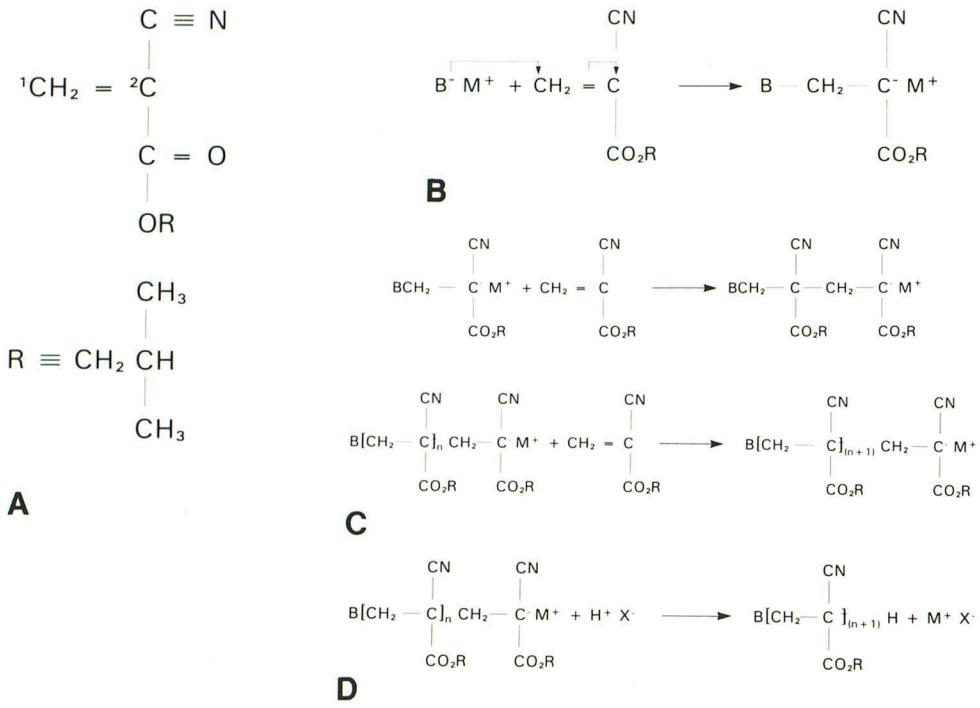

Fig. 4.—Chemistry of IBCA. **A**, Structure of IBCA. C-2 atom (^2C), with its substituents, cyano group (C–N) and the ester carbonyl group O = C. Alkyl group

in this compound (R) is isobutane. **B**, Polymerization of IBCA. Negative ion (B^-) initiates polymerization by attacking C-1 atom, which transfers electron to C-2 atom. B^- and M^+ represent dissassociated ions in local environment of IBCA. **C**, Propagation of IBCA polymerization. Bucrylate monomer with its free electron reacts with another bucrylate monomer and transfers free electron to its C-2 atom (*top row*). Bucrylate polymer, with its free electron at C-2 atom, can then react with other bucrylate monomers and transfer electron to then free C-2 atom (*bottom row*). **D**, Termination of IBCA polymerization. Propagating polymer chain comes into contact with electrophilic species (H^+), which binds to negative ion and terminates propagation of polymer.

balance in the immediate vicinity of the IBCA, small additions of acetic acid will have larger effects on the polymerization time. With the addition of more than about 4.5% by volume of acetic acid, there is sufficient acid in the immediate vicinity of the bucrylate to inhibit polymerization. Thus, polymerization cannot occur until the acetic acid is sufficiently dispersed and there is sufficient base to consume the acetic acid. This will occur by the processes of diffusion and convection, which are not as rapid as the consumption of the acetic acid by the basic elements in the blood in the immediate vicinity of the IBCA. The curve of acetic acid versus time as produced by our results reflects this interplay between the chemical and physical factors discussed above.

In the article by Cromwell and Kerber [1], the graph of their results of percentage concentration iophendylate plotted against time in seconds is about exponential. Because they conducted their in vitro experiments in static, citrated human blood, there is no convection present to disperse the iophendylate and expose the IBCA to base. Therefore, their results reflect only the processes of diffusion and consumption of iophendylate by the anions. Since in our experimental model, convection plays a large role, as it does in human beings and animals, the difference in the results between the two reports is not surprising.

In our study, we have shown that acetic acid offers a way to control the polymerization time of IBCA, over a practical range of times, without increasing the viscosity of the bucrylate mixture. The inflammatory reaction produced by the bucrylate mixture with acetic acid was not different from that without acetic acid. Thus, we have shown that glacial acetic acid is a safe and effective way to manipulate the polymerization time of IBCA.

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