PART TWO CHAPTER FIVE
THE PHARMACOLOGICAL CONSIDERATIONS AND ASSOCIATED CLINICAL REVELATIONS OF INTRAPULMONARY PERCUSSIVE VENTILATION (IPV®)

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DEDICATION

The contents of this text are directed toward answering questions posed by Clinicians, Researchers and Pharmaceutical Investigators, relative to the concepts employed in the sequential maturation of Intrapulmonary Percussive Ventilation (IPV). Because of the pharmacological interest, in the need for an ethically stable combined alpha/beta agent for topical aerosolized endobronchial delivery, the nature and action of Racemic Epinephrine has been expanded upon.

It is realized that most Physicians are not familiar with Racemic Epinephrine as a topical Alpha and Beta acting aerosol, with the many patent Beta Agents currently employed as topical bronchodilators. Because all patients with endobronchial infections have a component of mucosal and sub mucosal edema, the use of a topical Alpha vasoconstrictor can play a major role in maintaining airway patency. The major reason Racemic Epinephrine is presented, is because there is no other topical Apha Agent with minimal rebound available for endobronchial delivery, in an aerosolized solution. Neosynephrin is an excellent agent, however; it is noted for its major rebound effect. Therefore, until the pharmaceutical industry presents us with a more effective combined Alpha Beta solution for endobronchial aerosolization than Racemic Epinephrine, there is no other rational choice if we are to treat a patient with a pulmonary infection, to control mucosal and sub mucosal edema as well as terminal bronchiolar spasm. Compounding the lack of overall understanding, sources of Racemic Epinephine are limited to children's hospitals where it is employed as an aerosol for the treatment of "croup".

The following text employs Classical textbook discussions, directed toward a better understand of the role of Intrapulmonary Percussive Ventilation (IPV®) as well as the use of Racemic Epinephrine, as a possible alternative topical combination Alpha and Beta agent for aerosolization, during the administration of IPV. Additionally, academic comparisons to high frequency ventilatory devices has been advanced.

WHAT IS 2.25% AQUEOUS RACEMIC EPINEPHRINE?

Racemic epinephrine hydrochloride is produced by a series of chemical reactions from catechol, a white crystalline distillation product of coal. The process normally requires about four weeks to add a side chain of several carbon atoms to the original benzine ring of the catechol, an amine group to this side chain, and finally a hydrogen molecule.

The product of each reaction is purified through treatment with activated carbon, filtration, re-crystallization, and precipitation. The final product requires extreme purity in order to remain stable since epinephrine is catalytically oxidized by minute traces of impurities. This synthesization process also precludes the presence of nor epinephrine which may exist in products prepared by extraction from natural sources.

HOW DOES RACEMIC EPINEPHRINE DIFFER FROM EPINEPHRINE USP?

The term racemic epinephrine refers to a mixture of the dextro-rotatory and levo-rotatory isomers in equal parts. The l-isomer is present in the adrenal glands of animals and humans and is produced commercially by extraction from animal glands or by separation of the d- and l-isomers in the synthetic preparation. It is the epinephrine listed in the US Pharmacopoeia. The important difference in these isomers, however, is in their physiological properties. The d-isomer has about one fifteenth the pressor effect of the l-isomer (18), but has a more sustained action (45). Together the two isomers give a somewhat more prolonged result than the l-form--epinephrine USP--alone (23). The racemic form has also been shown to be more stable under varying conditions of storage (41). Studies have further demonstrated the racemic form gives better protection as an antihistaminic (13). More complete comparisons will be made below.

WHEN WAS RACEMIC EPINEPHRINE SYNTHESIZED?

Late in the nineteenth century Oliver and Schafer (42) noted a strong pressor effect of extracts of the adrenal medulla. Abel (2) separated the benzoyl derivative of the hormonal base from the medullary portion of the suprarenal gland in 1887. Aldrich (5), Takamine (50), and von Furth (43) isolated the pure base about 1901, giving it the names suprarenin or adrenaline. But Abel's original label of epinephrine was accepted as the official name.

The racemic form was first synthesized by Stolz (48) in 1904. Cushny (18) investigated the relative strengths of the dextro- and levo-rotatory isomers and reported the l-isomers to have a pressor potency approximately fifteen times that of the d-isomer, Richaud (45) demonstrated that the racemic solution had about one-half the pressor potency of an equal volume of the l-form alone, but had a somewhat more prolonged effect.

A method for breaking dl-epinephrine down into its optically active components was developed by Flacher (24), who noted many of the chemically identifiable features of each. Review of these early findings by Cushny, Flacher, Richaud, Abderhalden and Muller (1) was made by Fromherz (25) in 1923. This early definitive research of dl- and l-epinephrine provided for a greater understanding of Epinephrine Compounds.

WHEN DID RACEMIC EPINEPHRINE COME INTO COMMON USE?

The levo-rotatory form of epinephrine as a drug was accepted as official because it most closely approximated the naturally occurring form in humans, in what became the standard solution strength of 1:1000.

1:1000 Epinrphrine concentrations were used in parenteral injection where a mimicking of the actions of the sympathetic division of the nervous system was desirable. The racemic form of Epinephrine was utilized by several companies in the US and overseas in OTC products- mainly preparations for the relief of bronchospasm in asthma. Since the same standards, regarding claims of effectiveness, did not apply to both the epinephrine USP and dl-epinephrine products, some manufacturers of the latter overstated their claims and were not as ethical in labeling practices as they might have been. This incautiousness led the Council on Pharmacy and Chemistry of the American Medical Association to condemn OTC sale of dl-epinephrine products in 1942 (6). This labeling condemnation carried over to all dl-epinephrine compounds by implication and caused many pulmonary physicians to dismiss any such product, without checking the actual effectiveness and appropriateness of the preparation.

When Graeser and Rowe (30) suggested in 1935 the inhalation rather than the injection of epinephrine for relief of bronchospasm, most physicians made use of l-epinephrine rather than the racemic form.

Inhalation was first suggested by Ephraim in 1910 (22), but his method was not regarded as a major advance until re-exploration in 1935. Although cardiopulmonary oriented physicians, and particularly medical researchers, utilized dl-epinephrine (3, 7,12, 13, 23, 27, 28, 31, 32, 35, 40, 44, 49, 53), most continued the use of the levo-rotatory form and left the former to the OTC pharmacists.

This dichotomy has continued, with alteration, to the present. During the past twenty five years, there has been a noticeable change in certain professional attitude toward dl-epinephrine which is reflected in the literature, particularly that dealing with racemic epinephrine (for example, see 3, 35, 53). Current FDA control over all pharmaceuticals determine pharmacological purity

HOW DOES EPINEPHRINE WORK?

Early in this century Langley (37) and Dale (19) introduced the concept of a receptive mechanism and developed the association with the sympathetic nervous system, including the effect of epinephrine upon it.

Canon and Rosenblueth (16) introduced the idea in 1937 that two mediator substances (sympathin E and sympathin l) caused different reactions to either excite or inhibit action, but their theory was challenged by Ahlquist (4).

In 1948 he presented his concept of two receptor-type adrenergic nerve endings. He found that Epinephrine had all of the chemical, physical, and physiological properties necessary to be an adrenergic mediator. It is the most active substance on the alpha receptors and almost the most active on the beta receptors. It is, therefore, the one amine which is both the best excitatory agent and the best inhibitory agent on the effector cells thus far evaluated.

Stimulation of the Alpha receptors produce various effects, among them bronchial vasoconstriction,while stimulation of the Beta receptors produces inhibition of the terminal bronchiolar musculature, among other effects. This is thought to occur because either alpha or beta receptors predominate in those respective areas of the body.

In general, dl-epinephrine is used in inhalation therapy. In this mode of treatment, a smoke-like epinephrine vapor, propelled by various gases, is introduced into the lungs. Authors through the years have proposed numerous vehicles for, or modes of deposition of this vapor in the bonchioles and alveoli (see 3, 7, 8, 9, 15, 23, 27, 28, 29, 30, 44, 46, 51, 53). The inhalation of an aerosol has been found to be a method superior to parenteral injection because of the reduced appearance of side-effects (10) and the increased safety with regard to toxic dosage (39). Thus, formulated epinephrine works as a bonchodilator to provide relief of bronchiolar spasm and as a vasoconstrictor to reduce mucosal and submucosal edema, thereby creating a more patent airway.

HOW DOES RACEMIC EPINEPHRINE COMPARE WITH OTHER SYMPATHOMIMETIC AMINES?

The group of basic compounds called sympathomimetic amines include those two occurring naturally -- epinephrine and nor epinephrine --which are types of alkylamines. Also included are the cycloalkylamines, the alkyl amines, and the imidazolines. However, as a practical matter, only three substances will be compared here --dl-epinephrine, l-epinephrine, and iso-proterenol.

In the early years of inhalation therapy epinephrine USP was considered the amine of choice. Graeser and Rowe, as well as Richards, Barach, and Cromwell (44), for example, routinely used this solution and made it the standard, until other researchers brought to light factors that caused a shift toward the racemic form of epinephrine. In 1939 Galgiani (26) drew the conclusion from his experiments that inhalation of l-epinephrine in the standard dose could cause damage to the mucous membranes of the trachea and bronchi.

This put l-epinephrine under a cloud that had already begun to form due to emphasis on certain side-effects (see Cori and Welch (17) in particular).

Although later literature (21, 33, 51) tended to refute Galgiani's findings, researchers began to investigate dl-epinephrine as a more satisfactory amine.

They found it to be a more stable solution in storage (41), to have a greater immediate and more prolonged effect (23), to have greater antihistaminic protecting ability (13), and found toxicity levels in inhalation to be virtually nonexistent (10, 39).

In the forties a product called Aleudrin was developed in Europe (20, 36) and its sister compound, Isuprel, in the US (47). Isoproterenol was hailed as having superior bonchodilator effects as well as bronchospasmolytic properties (46, 33). However, recent literature is quite specific in pointing out drawbacks inherent in the use of isoproterenol for endobronchial inhalation.

Tysinger (53) noted, that since the body detoxifies isoproterenol more slowly, higher and more toxic levels could develop with the administration of doses comparable to those of dl-epinephrine. This presented a real dilemma, since many clinicians believed both solutions to be the same - treating their prescriptions as true equals. He also pointed out -- which was strongly supported by Jordan et al (35) -- that isoproterenol is a vasodilator as well as a bonchodilator and does not relieve mucosal edema, but may even cause such a condition to exacerbate. Other comparisons are made in the articles cited, but the conclusion they lead to is, that dl-epinephrine is the available sympathomimetic amine of choice for inhalation therapy.

WHERE IS THE USE OF RACEMIC EPINEPHINE INDICATED?

The major discussions of dl-epinephrine have centered around the treatment of the symptoms of bronchial asthma. Considerable literature refers to this therapeutic approach in a rather complimentary fashion (3, 12, 21, 23, 31, 35, 39, 43, 44, 53) while still other state its effectiveness and safety (7, 8, 9, 13, 14, 29, 32, 46, 49 59, 60).

The Digilio article (21) is of particular interest, since his tests of effectiveness and safety were on patients having the usual contraindications of hypertension, rheumatic disease, thyrotoxicosis, or diabetes. Other indications include emphysema (7, 8, 11, 23, 27, 34, 44), tuberculosis (28), extreme allergic reactions (15), laryngo-tracheobronchitis (3), and tracheitis (35). Beside covering those entities already mentioned, other conditions are additionally discussed with regard to dl-epinephrine, for example: Cystic fibrosis, distressed breathing syndrome in the neonate, epiglottitis in infants and small children, acute bronchitis and bronchiolitis in pediatrics, fibrotic pulmonary disease, and the management of acute and chronic left heart failure.

It can be realized that, while much of the literature deals only with treatment in cases of bronchial asthma and emphysema, dl-epinephrine --racemic epinephrine specifically -- plays an important role in the treatment programs developed to deal with many other diseases. Racemic epinephrine has a long history of clinical application, however; has been ignored by certain segments of the medical profession. Yet it has proven it-self to be an effective agent, deserving due consideration as a combination alpha/beta for use as an aerosol for endobronchial delivery.

The extended use of Racemic Epinephrine as an aerosol, has been enhanced by the innovation of Intrapulmonary Percussive Ventilation by Bird (IPV®) (54) which offers superior dispersal of the aerosol throughout the periperal pulmonary airways. Topical delivery secondary to a superior peripheral endobronchial distribution allows a more dilute solution to be employed. In IPV® the recommended solution is .5 cc of an aqueous 2.25% Racemic Epinephrine diluted with 20 cc of water. While this dosage may seem to border a "homeopathic" concentration it has now proven to be topically effective for over eighteen years in all patient populations.

The basic Principles of Aerosol Therapy have been addressed by Abramson as well as others (55, 57, 58). In their texts they have discussed the rational for the particulate size of the therapeutic aerosol spectrum.
Additionally, the importance of the fractionating devices (nebulizers) as well as the propelling vehicle into the pulmonary structures. Equally important is the salinity, as well as the cohesive properties of the diluent, in terms of traversal time across the endobronchial membranes.

The Percussional Sub Tidal Ebb and Flow of Aerosol within the tracheobronchial tree as the Functional Residual Capacities are shifted both physiologically and mechanically, play a major role in the endobronchial deposition of aerosol during IPV. DeVries (56) demonstrated the rapid peripheral deposition of a radioactively tagged aerosol during IPV®.

The salinity of the diluent employed with Racemic Epinephrine will in part, determine the rapidity of transport across the endobronchial mucosa.

When IPV, is employed as a diffuse intrapulmonary aerosol delivery system (with a unique particulate spectrum), the major applicable variable factors controlling absorption, become the salinity and/or cohesive forces of the solution within the Nebulizer. Water provides for the most rapid transport of deposited aerosol born particle into the endobronchial mucosa, secondary to the .85% salinity of the anatomical structures.

As the solution becomes increasingly hypertonic the absorption time is increased accordingly. When glycerol type agents are employed in therapeutic solutions, their cohesive forces are increased with retardation of molecular dispersal and uptake.

Many patients within all age groups with chronic or acute obstructive pulmonary airways, display a major component of mucosal and sub mucosal edema secondary to endobronchial inflammation. The alpha (vasoconstrictor) component of racemic epinephrine, when employed as an endobronchial aerosol, can serve to reduce mucosal and sub mucosal edema, as well as provide for a beta action on the smooth bronchiolar musculature. It follows, that with an effective diffuse endobronchial distribution of an airborne aerosol, the concentration and the rate of uptake of the active alpha and beta agents, will determine the rapidity and effectivity of vasoconstriction and bronchiolar relaxation.

Therefore, there are two controllable variables, they are: the concentration of the Racemic Epinephrine and the tissue solubility of the solution. In the case of racemic epinephrine, if the uptake of the agent is enhanced, the concentration of the active components can be reduced. Thus, when water is employed in lieu of normal saline, as a diluent for the Racemic Epinephrine, the transport rate of the alpha component into the edemateous endobronchial membranes is facilitated, allowing for a decrease in the concentration of the Racemic Epinephrine.

Time has revealed that under ideal conditions the stock R. E. solution for IPPB, administered with a volume oriented Bird® Mark 7A Respirator required a solution of .5 cc of Racemic Epinephrine diluted with 10 cc of water as opposed to the more effective delivery of endobronchial aerosol with IPV® now demonstrating an optimal solution of .5 cc of a 2.25% aqueous Racemic Epinephrine diluted with 20 cc of water.

The use of Neosynephrin is well documented from 1935 onward when employed as a topical endobronchial vasoconstrictor, in combination with a host of pharmaceuticals delivered endobronchially as airborne aerosols. The noted rebound effect of Neosynephrin may be one reason why the current literature does not reveal a combination study with the many Beta agents now available for aerosolization.

All too often, a patient with obstructive airway disease with an acute pulmonary inflammation, is treated with a Beta aerosol (as if bronchospastic disease was the only cause of airway obstruction), negating any direct Alpha action in reducing the associated bronchiolar mucosal and sub mucosal edema.

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