External Scintigraphy in Evaluating Delivery Techniques of Sodium Cromolyn–[^{99m}Tc] Diethylenetriaminepentacetic Acid Aerosol in the Lungs of the Horse

Keyphrases □ Scintigraphy—noninvasive method of study, aerosol dispersion, horse respiratory tract □ Nebulization—^{99m}Tc-labeled sodium cromolyn, device comparison □ Sodium cromolyn—technectium-99m labeling, nebulization, scintigraphy in the horse

To the Editor:

Aerosol delivery of drugs has been used in the prophylaxis and therapy of acute and chronic conditions of the lower respiratory tract. The aerosol methods for drug delivery allow targeting of the drug in the lungs, thereby eliminating the need for systemic administration. This in turn may reduce the level and frequency of dosing as well as the incidence and severity of adverse drug effects, thereby improving the therapeutic effect–toxicity ratio (1, 2). Administration of the same dose of nebulized drug using different nebulization devices and modes may conceivably give rise to the same blood levels if the drug is systemically absorbed; however, this does not imply uniform distribution of the drug throughout the lung mass.

External scintigraphy may provide a good opportunity for noninvasive study of the distribution of aerosols labeled with gamma ray-emitting nuclides in the lungs. In this investigation, external scintigraphy was used to explore two different modes of administering nebulized sodium cromolyn to the horse. Four male and two female horses ranging in age from 2 to 6 years and in weight from 338 to 540 kg were used in this study. These animals were free from clinical signs of respiratory disease.

Two different devices were used to nebulize a solution of sodium cromolyn[1] (7 ml, 2% w/v) in separate nebulizer studies on the same six animals. The first device was an air compressor assembly[2], connected to a nebulizer chamber[3]. A corrugated delivery tube (105-cm length, 3.2-cm diameter) was connected to the outlet of the nebulizer and to the face mask[4] which completely covered the nostrils and muzzle of the horse. The diameter of 63.1% of the droplets produced from this nebulizer was <6.5 μm[5]. The second device consisted of a noncollapsible nylon tube (100-cm length, 0.5-cm diameter) which bore a sintered glass disk at one end and was connected with a hand-operated nebulizer at the other end. The tube was inserted through the nostril and placed in the pharynx of the horse. The diameter of 99.6% of the droplets produced by this nebulizer was >8.5 μm[5].

The sodium cromolyn solution (7 ml) was mixed with 1 ml of [^{99m}Tc] diethylenetriaminepentacetic acid (I[6], 40 mCi/ml) in the nebulizer to form a homogeneous solution. In both techniques, the delivery of the nebulized sodium cromolyn–[^{99m}Tc]I solution to the lung required multiple inhalations by the animal. Blood samples (5 ml) taken immediately after the aerosol administration was completed showed that the radioactivity levels were <2000 dpm/ml, implying that only a small amount of [^{99m}Tc]I had diffused into the circulation at that point.

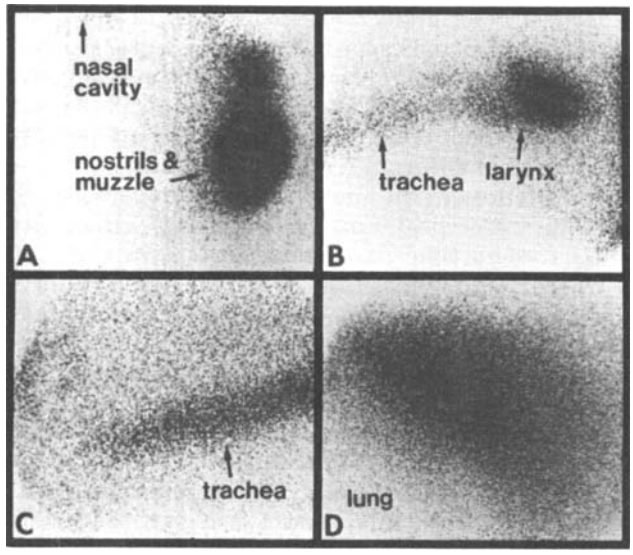

Figure 1—*Scintigraphic images of the distribution of sodium cromolyn–[^{99m}Tc]I aerosol in the respiratory tract of a horse administered through an air compressor–nebulizer–face mask. Radioactivity in the (A) nostrils and muzzle, (B) larynx, and (C) trachea; and (D) homogeneous spread of activity in the lung.*

Each horse was lightly sedated with 100 mg iv of xylazine[7], before administration of the nebulized sodium cromolyn solution. Each horse was then placed parallel to the front of the detector of a gamma camera[8] fitted with a high-resolution parallel-hole collimator. Scintigraphic images in the right lateral plane were obtained of the head, neck, and thorax. A maximum of 100,000 counts were collected for each image. Areas of high activity, such as the nostrils and thorax, required 2–3 min to yield 100,000 counts, while areas of low activity, such as the trachea, yielded only 20,000–60,000 counts in the same period.

Similar distribution patterns were present in all six animals that were administered the nebulized sodium cromolyn solution using the nebulizer connected to the air compressor. A large amount of radioactivity was evident around the nostrils and muzzle, but there was relatively little in the nasal cavity (Fig. 1A). A distinct localized area of radioactivity was detected in the larynx (Fig. 1B). There was very little radioactivity in the trachea, but a homogeneous spread of radioactivity was evident in the lung (Fig. 1C and D).

The distribution pattern of sodium cromolyn solution was different when the hand-operated nebulizer was used. A large amount of radioactivity was present in the posterior pharynx, corresponding to the position of the fritted glass disk (Fig. 2A). Radioactivity extended down the trachea, reaching a peak at the thoracic inlet, suggesting that pooling may have occurred at this level (Fig. 2B). The ^{99m}Tc-labeled sodium cromolyn solution was very poorly

[1] Cromovet, Fisons Animal Health, Fisons Limited, Pharmaceutical Division, Leicestershire, England.
[2] De Vilbiss Pulmo-Aide series 561 Portable Compressor.
[3] Cromovet Nebuliser, Fisons Animal Health, Fisons Limited, Pharmaceutical Division, Leicestershire, England.
[4] Cromovet Face Mask Kit, Fisons Animal Health, Fisons Limited, Pharmaceutical Division, Leicestershire, England.
[5] Droplet size estimates were provided by Fison Limited, Pharmaceutical Division.
[6] Mallinckrodt Diagnostics, Mallinckrodt, St. Louis, Mo.
[7] Rompun (xylazine), Bagvet, Division of Cutter Laboratories, Shawnee, Kans.
[8] Siemens Gammasonics, Pho/Gamma HP (formerly Searle Diagnostics), Des Plaines, Ill.

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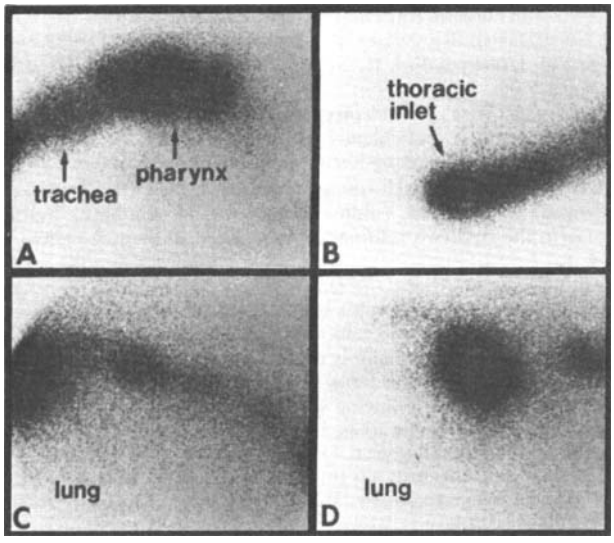

Figure 2—*Scintigraphic images of the distribution of sodium cromolyn-[^{99m}Tc]I aerosol in the respiratory tract of a horse administered through a hand-operated nebulizer. Radioactivity in the (A) posterior pharynx and trachea, (B) thoracic inlet, and (C) and (D) caudodorsal region of the lung.*

distributed in the lungs using this method of administration, detectable radioactivity being largely confined to the caudodorsal region (Fig. 2C and D).

A simple visual comparison of images showed that satisfactory pulmonary distribution of sodium cromolyn aerosol in normal horses occurred following administration by the combination air compressor–nebulizer–face mask. Preliminary analysis of the distribution data of the radioactivity in the respiratory tract indicated that 7.5% of the initial dose remained in the nebulizer, while 30–40% remained in the tubing and face mask. It is estimated that 40–50% of the radioactivity was confined to the nostrils and muzzle, while 10–15% of the radioactivity was distributed in the lungs.

In conclusion, external scintigraphy may provide a convenient noninvasive method for evaluating the different techniques and modes of aerosol administration and visualizing their distribution in the lungs of the horse. Further research is in progress to assess the effect of the droplet size on the resolution of the technique and the distribution of the aerosol in the lungs. In addition, an effort is being made to develop a model in which the count rates taken from the lung area are weighted for tissue attenuation and variable geometry so that more accurate estimates can be obtained.

(1) A. Pines, H. Raafat, G. M. Siddiqui, and J. S. B. Greenfield, *Br. Med. J.*, 1, 663 (1970).

(2) R. E. Wood, J. D. Klinger, M. J. Thomassen, and H. A. Cash, in "Proceedings of the 8th International Cystic Fibrosis Congress," J. Sturgess, Ed., Canadian Cystic Fibrosis Foundation, Toronto, Canada, 1980, p. 365.

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BOOKS

REVIEWS

Recent Advances in the Biology of Alcoholism. Edited by C. S. LIEBER and B. STIMMEL. (Advances in Alcoholism and Substance Abuse, Vol. 1 No. 2). The Haworth Press, 28 East 22nd Street, New York, N.Y. 10010. 1982. Hardcover.

This book contains several authoritative and timely review articles about the effects of ethanol on the liver and the endocrine system. The coverage is much narrower than indicated by the title: effects of the drug on the brain are not included. The chapters are papers delivered in a 1980 symposium at the Alcohol Research and Treatment Center at the Bronx VA Hospital; several of the papers are by Dr. Lieber and his group at the Center. The authors are recognized experts in their fields, which vary from pure biochemistry to clinical gastroenterology.

J.-P. Von Wartburg provides a lucid review of alcohol metabolism by alcohol and aldehyde dehydrogenases, including recent genetic information about racial differences in responses to alcohol. S. Orrenius writes a concise description of metabolic drug interactions from a biochemist's point of view, and Lieber and Pirola follow with a detailed clinically oriented review of the same topic, with many specific examples. Both reviews of drug interaction emphasize and explain the role of MEOS, the hepatic microsomal ethanol-oxidizing system. Lieber also contributes a general chapter on the effects of ethanol on the liver, largely from his own extensive work. The final chapter by T. J. Cicero covers recent important advances in our understanding of effects of ethanol on the endocrine system, with emphasis on the factors that affect testosterone levels. This is a logical and sensible essay which minimizes controversy and brings scattered data together into a reasonably coherent picture.

Technical details such as typographical errors, poor quality paper, and inadequate reproduction of some figures detract slightly from the otherwise admirable text. More important is the lack of an index, which will greatly reduce the usefulness of this book.

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Handbook of Dissolution Testing. By WILLIAM A. HANSON. Pharmaceutical Technology Book Division, 320 N. A St., P.O. Box 50, Springfield, OR 97477. 1982. 163 pp. 13 × 22 cm. Price $26.50.

This book describes in detail the two official USP-NF dissolution test methods and the nonofficial flow-through method. The author views dissolution testing solely as a quality control test whether or not the test