EXPERIMENTAL CHEMOTHERAPY AND RESISTANCE

EMANUEL GRUNBERG, PH.D.

The discovery of streptomycin has shown the way by which therapeutic activity against the causative agent of tuberculosis can be found and evaluated in the laboratory prior to its administration in patients. A great number of substances synthesized by the chemist in his laboratory or isolated from natural sources have been found to exert activity against the bacillus of tuberculosis. Many of these show this effect only in the test tube and prove without effectiveness if studied in experimental animals infected with tuberculosis.

The new antituberculous agent, isonicotinic acid hydrazide (rimifon®), is a rather simple synthetic compound which was found to be superior to known antituberculous drugs during early stages of the laboratory investigation. Rimifon® possesses not only a remarkably high growth inhibiting effect against the tubercle bacillus in the test tube but also unusual features if studied in infected animals. Most of the fundamental work which has been confirmed in laboratories all over the world was done in mice which were infected with high and fatal doses of human tubercle bacilli. In this infection rimifon® showed 4 characteristic properties which had not been observed with any of the known drugs: (1) the drug protected heavily infected mice after administration of very small doses, (2) the drug successfully prevented the multiplication of the tubercle bacilli in the infected tissues of the animal and therefore (3) produced a lasting protection after discontinuance of therapy, and (4) if given therapeutically in animals in which the disease had already produced its characteristic lesions the drug tended to stop further development of the disease and to prepare the ground for the final cure.

In sharp contrast to the broad spectrum antibiotics acting on a multitude of pathogenic bacteria and even viruses, rimifon® is a specific drug in the strict sense of Ehrlich’s concept of chemotherapy in that it exerts its activity only against the group of mycobacteria of which the most important representatives are the tubercle bacillus and bacillus of Hansen’s disease (bacillus leprae).

Like all drugs of high potency rimifon® also produces drug-resistant strains. This phenomenon can be demonstrated in the test tube but has so far not been observed in infected animals although it has been seen in about 5 to 10% of the cases of human tuberculosis treated with this agent. It is well known that also the administration of our leading drug against tuberculosis, streptomycin, quite frequently leads to highly resistant strains of tubercle bacilli. One has learned that combination therapy overcomes this unfavorable feature of streptomycin to a certain extent and studies are presently under way to determine whether drug resistance to rimifon® can be delayed or overcome by combination of it with other antituberculous substances.

THE PHARMACOLOGY OF ISONIAZID

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Isoniazid has been shown to be an effective antituberculous agent both in experimental and human tuberculosis. The purpose of this paper is to describe some of the pharmacologic properties of this class of drugs.

Absorption, Distribution and Elimination: Isoniazid is readily absorbed from the gastrointestinal tract. Peak blood levels are usually achieved within ½ to 2 hours in the dog or man, and is closely predictable from the dose. It is distributed in most tissues and its concentration in these tissues follows the plasma concentration quite closely.

The rate of disappearance of the drug from the plasma is about 19% per hour in the dog and

about 17% per hour in man. Approximately 25 to 50% of the isoniazid administered to dogs is eliminated in the urine apparently unchanged. Another 30 to 50% is converted to isonicotinic acid before elimination. This situation is closely paralleled in man.

Toxicity: The acute lethal dosage of isoniazid in most species tested is very similar for either parenteral or oral administration. Death occurs after convulsions, generally in $\frac{1}{2}$ to 2 hours after dosage. The lethal plasma concentration of isoniazid in mice is at least 87 µg/cc., while the acute lethal intravenous dose in the dog is about 50 mg./kg. body weight.

Degree and severity of chronic toxic signs in dogs with isoniazid were proportional to dosage and survival time inversely proportional to dosage. Slight or transient anemia appeared with not more than 10 to 15% reduction in hemoglobin and RBC. Severe toxicity has been found only at more than 3.5 times current clinical dosage and was characterized by progressive occurrence of anorexia, central nervous stimulation, and fatty degeneration of the liver which may be accompanied by jaundice. Occasionally some pathology of the kidneys has been observed.

Pharmacodynamic Action: At the equivalent of current clinical dosage or plasma concentrations isoniazid apparently manifests no acute pharmacodynamic action on respiration, basal metabolism, ECG, heart rate, systemic blood pressure and peripheral resistance, neuromuscular transmission or urine output in experimental animals. Postural hypotension has not been observed. Little or no effect has been noted on autonomic ganglia, specifically cervical sympathetic, adrenomedullary or vagal. Neither has the compound shown antipyretic nor analgetic effects in animals. There has been no evidence of antihistaminic or epinephrine-like action on bronchial or intestinal smooth muscle.

No atropine-like effect has been observed on the pupil, on salivary secretions, nor on the heart, intestine or bladder, although one report of antagonism to cholinergic bronchospasm in the guinea pig has appeared.

In summary it may be pointed out that isoniazid is pharmacologically well suited for chronic chemotherapy. The drug may be used orally, it is both well absorbed and distributed in the body including the spinal fluid. Localization or cumulation does not appear to occur. High kidney concentrations are apparently related to the mode of excretion. Drug toxicity in man has appeared to be negligible or minor in nature. Toxicologic characteristics of isoniazid, however, indicate the continuing need for cautious dosage in hepatic or renal insufficiency, and appropriate sedation in patients with known or suspected convulsive tendencies.

CLINICAL EXPERIENCE WITH ISONIAZID IN CHILDHOOD TUBERCULOUS MENINGITIS*

BRET RATNER, M.D.

The new isoniazid group of drugs has aroused considerable interest and hope for the eventual conquest of tuberculosis. The results first achieved by Robitzek, Selikoff and Ornstein have been substantiated by others.

The isoniazid derivatives, like other chemotherapeutic agents, should be used as adjuncts to well tried measures such as surgical procedures, collapse therapy and bed rest.

In certain situations streptomycin and para-aminosalicylic acid should be employed in conjunction with these newer drugs. Drug resistance may be reduced or prevented when they are administered conjointly.

The isoniazids are signal ly free of toxicity and oral administration makes them invaluable, particularly for sections of the world where injectant materials would be difficult to use.

On the Pediatric Service of Sea View Hospital and New York Medical College an evaluation is being made of their effectiveness in tuberculous meningitis, primary and cavitary pulmonary tuberculosis. Isonicotinic acid hydrazide (rimifon®) and to a lesser extent the isopropyl derivative of isoniazid (marsilid®) are the drugs used.

We have for evaluation 8 cases of tuberculous meningitis treated with streptomycin and/or isoniazid.

In the first case (RW) a child with miliary tuberculosis treated with streptomycin, P.A.S. and promizole was cured of pulmonary tuberculosis but developed, while on this therapy, meningitis that

* This study was done in the Pediatric Division of Sea View Hospital and New York Medical College, in collaboration with Drs. George Romuald Klimkiewicz, Joseph Dolgin, H. John Malone, Mary Retina and Eduardo Margado.
deteriorated progressively. At this time when the glucose was 17 mg./100 cc. and the cell count 173 he was put on rimifon® alone and made an uneventful recovery. Within 3 months he became a healthy child. Five months of further treatment showed no exacerbation and finally, in the last 4 months, with no treatment, he has remained well mentally and physically, with normal spinal fluid components.

The second case (DC) was a child who apparently recovered from meningitis with streptomycin and P.A.S. therapy of 2 months’ duration. This child was then placed on rimifon® alone and has had no exacerbation of her meningitis for a period of 5 months. Her spinal fluid findings have been normal for the past 5 months.

The third case (LF), one of miliary tuberculosis treated with streptomycin and P.A.S., cleared of pulmonary tuberculosis but developed meningitis. Rimifon® was then given alone. After 35 days her spinal fluid still contained M. tuberculosis but after 51 days more became sterile. Despite the fact that her spinal fluid became sterile, with normal values of the various components, she died from hydrocephalus 6½ months after rimifon® was started. One is tempted to assume that though she showed a residual tuberculous involvement of her leptomeninges at necropsy, her tuberculous process was on the road to recovery for the brain, lungs and all other organs were free of tuberculous pathology.

The fourth case (BR) was an infant with primary tuberculosis, treated at the inception of her meningitis with rimifon® alone, and made a complete recovery in 2 months. She was observed for 5 more months and remained clinically free of meningitis with spinal fluid normal in every respect.

The fifth child (NP) with miliary tuberculosis, meningitis and cerebral localization was treated with streptomycin, then received rimifon® alone. She died of meningitis 4½ months later.

The sixth case (GH), treated with streptomycin and P.A.S., developed decerebrate rigidity. The child was a mental vegetable. After about 6 months of this therapy, rimifon® was started. He still remains a decerebrate individual after 9 months of isoniazid therapy but his spinal fluid components are normal.

The seventh case (WF) was a child treated with rimifon® alone for one month. Because of slow improvement he has been on rimifon® with streptomycin and P.A.S. for the past 3 months. The spinal fluid components have been normal for the 3 months but the child still has spastic and cerebral involvement. Further observations are in progress.

The eighth case (DW) after 2 months of rimifon® and a combination of streptomycin, P.A.S. and marsilid® still shows abnormal spinal fluid findings. Further observations are in progress.

Rimifon levels were determined in the blood plasma and spinal fluid in a number of cases. There is evidence that this antituberculosis drug does penetrate into the cerebrospinal fluid.

This group of drugs augurs the possibility of being ancillary to streptomycin when streptomycin has failed to achieve its result. Second, it may be very valuable in cases which appear to be arrested tuberculosis treated with streptomycin, but in which instances exacerbations have been known to occur. The use of isoniazid may prevent such exacerbations. Lastly it may become a drug of great value in the prevention of tuberculous meningitis when given during the course of cavitary, progressive primary or miliary tuberculosis.

One cannot deny that streptomycin has earned an important and enviable place in the therapy of tuberculosis. However, its toxic effects, particularly that of deafness which may become permanent, the necessity for giving this drug intramuscularly and intrathecally and the tendency for M. tuberculosis to become resistant to it, prohibit its widespread use throughout the world.

It would be foolhardy at this time for us to state that exacerbations will not occur in our cases detailed above and a much larger period of observation will have to be made before such a hopeful conjecture can be substantiated.

The essential thing for us to do is to attempt a wide investigation of this drug to prove whether certain strains of M. tuberculosis will become resistant to it and to determine whether the giving of streptomycin combined with isoniazid may actually hinder the progress of sterilization of the spinal fluid.

We feel that there is enough evidence to justify the use of isoniazid alone in the treatment of tuberculous meningitis. If this fails, then streptomycin and P.A.S. may be used as a corollary to the present method of using streptomycin and P.A.S. first, then isoniazid.

The signal absence of toxicity of the isoniazid drugs, their undoubted antituberculosis action and the ease with which they are administered orally makes one sanguine enough to hope that these drugs may prove to be a real advance in the chemotherapy of tuberculosis.
Symposium: HYDRAZINE DERIVATIVES OF ISONICOTINIC ACID
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