Cyanacethydrazide Therapy in Pulmonary Tuberculosis

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The efficacy of isoniazid in the treatment of pulmonary tuberculosis stimulated the search for related drugs that might increase the effectiveness of antituberculosis therapy especially in those chronically ill patients in whom INH does not produce the desired effect or who are unable to tolerate it. Such a compound is cyanacethydrazide** which as its formula indicates is structurally related to INH.

\[
\text{INH} \quad \text{CAH} \\
\begin{array}{c}
\text{O} = \text{C} - \text{NH} - \text{NH}_2 \\
\text{N}
\end{array} \\
\begin{array}{c}
\text{O} = \text{C} - \text{NH} - \text{NH}_2 \\
\text{CH}_2 \\
\text{C} \\
\text{N}
\end{array}
\]

The introduction of this drug was based on the reasoning\(^1\) that the specific arrangement of the nitrogen atoms in the pyridine nucleus and the side chain, and not the pyridine nucleus as such were responsible for the action of INH and therefore the substitution of an aliphatic chain for the pyridine nucleus would allow for less toxicity while retaining its chemotherapeutic effectiveness. It was also felt by these investigators that this substitution would be less likely to produce bacillary resistance. CAH like INH had been synthesized about a half century earlier without attempt having been made to find therapeutic application for it.

Promising results with this drug were reported by European investigators\(^2-5\) in limited studies. CAH has been studied at Eagleville for the past two years. The object of the study was to determine:

1. The toxicity of the drug and its acceptability by patients.
2. The presence of cross resistance to INH.
3. The clinical effectiveness of the drug.

The study comprised 150 patients who were treated with CAH for varying periods. Our clinical results are based on an analysis of 75 who used the drug from four months to one year or longer. The other 75 left the sanatorium or discontinued treatment before they had used the drug

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*Medical Director, Eagleville Sanatorium
Presented at Annual Meeting American College of Chest Physicians, Chicago, Ill., June 9, 1956

**Kindly supplied for this study by Lakeside Laboratories, Inc., Milwaukee, Wisconsin
four months. These patients are included in our observations on toxicity and bacillary resistance.

CAH was used primarily on those with far advanced pulmonary tuberculosis who were still sputum positive on smear and culture in spite of long term antimicrobial (INH) therapy. Thirteen whose organisms were INH resistant were given the drug. There were three who were unable to tolerate INH. Twenty new admissions with active disease who had had no previous INH therapy were included in the study. The ages of the patients ranged from 20 to 70 years. The study comprised all types of pulmonary tuberculosis except miliary disease.

The dose of the drug varied from 5 to 15 milligrams per kilogram of body weight. It was given in 50 mg. tablets. The average dose ranged from 450-600 mg./day in three divided doses. Since the drug was studied as a substitute for INH, it was used like INH in combination with streptomycin and/or para-aminosalicylic acid. Pneumoperitoneum and surgery were not withheld when indicated.

Results

A—Toxicity:

The drug was well tolerated even in the large doses used. There was
no toxic effect evident clinically or by laboratory studies. The patients followed the normal sanatorium regimen and were closely observed clinically by the resident physicians, nurses, and attending physicians. There was no instance of drug fever, tachycardia, arrhythmia or changes in blood pressure. There were no noticeable or ascertainable effects on bowel or urinary bladder function. Vertigo occurred after a few doses in a 66 year old white man with chronic auricular fibrillation and was severe enough for him to discontinue the use of the drug. He was able to tolerate INH without difficulty. Numbness and tingling of the hands and feet occurred in one but was mild and with B6 the patient continued the drug. The commonest complaint was headache, which although not severe occurred in approximately 10 per cent of the patients. This was usually related to large doses of the drug, 500-600 mg./day. The headache would
disappear if the dose was reduced slightly, or if the drug was begun in low dosage and gradually increased. In those who persisted with the drug without reducing the dose, the headache gradually subsided. There was no instance of jaundice or hematopoietic change. The laboratory studies included complete blood count, urinalysis, fasting blood sugar and urea nitrogen. Liver function studies included blood proteins with A/G ratio, cephalin cholesterol and thymol turbidity. These studies were repeated routinely during the drug investigation. A noticeable effect and one which was frequently commented on, especially by the younger women, was the infrequency of acne as compared to INH.

B—Resistance and Cross Resistance Studies:

All admissions to the sanatorium have routine sputum studies both by
smear and culture. The organisms are tested for susceptibility to streptomycin, and isoniazid according to the technique outlined in the 1955 revision of Tuberculosis Laboratory Methods. The same technique was followed with CAH, and organisms were routinely tested with 50 micrograms of CAH inoculated into the culture medium. 400 patients form the basis of this study. Sputum studies were done routinely as is the custom at Eagleville. Susceptibility studies were repeated usually at three or at the most, six month intervals.

1. Resistance to INH:

Twenty-one patients were found resistant to INH. These all had chronic disease and long term INH therapy. There was no patient naturally resistant to INH (without previous INH therapy).

Thirteen were INH resistant prior to treatment with CAH.

Eight showed resistance after treatment with CAH for periods of three months to one year.

Six of them had had long term treatment with INH prior to use of CAH.

Two who became resistant had used INH only for a few weeks prior to CAH therapy. These were the only definite instances of cross resistance. In both cultures six months later revealed organisms susceptible to both drugs.

Three who developed INH resistance remained susceptible to CAH and could continue with the drug.

2. Resistance to CAH:

Resistance to CAH was encountered in 34 patients.

Seven were found to be naturally resistant. They were new admissions who had had no previous antimicrobial drugs. The initial sputum culture showed organisms resistant to CAH. This is difficult to explain but is too large a group to ascribe to technical error.

Twenty-seven were found to harbor resistant organisms after treatment with CAH. The time interval varied from three months to over a year.

Three developed resistance rapidly, after days to a few weeks. They had had long term treatment with INH previously.

3. Streptomycin Resistance:

Twenty-nine were found resistant to streptomycin. They had chronic disease and long term antimicrobial drug treatment. There was no instance of natural resistance to streptomycin. There was no evidence of definite relationship between streptomycin resistance and CAH resistance as there appeared to be between INH and CAH resistance. Those with advanced chronic cavitory disease who developed resistance to streptomycin/INH usually showed resistance to CAH at some time during the course of the study.

4. Changing Susceptibility Patterns:

Five who exhibited streptomycin resistance later showed susceptibility.
Seven who were both INH and CAH resistant showed susceptibility to both drugs in later cultures.

These changing resistance patterns apparently reflect the mixed bacterial population that chronically ill persons harbor. One, a 40 year old man, with bilateral upper lobe disease with a cavity in the left upper lobe showed CAH resistant organisms on culture. Following resection of the left lobe, sputum cultures revealed organisms susceptible to CAH.

New admissions who had had no previous antimicrobial drug treatment, and who did not show sputum conversion after six to nine months of CAH were routinely changed to INH. As indicated above there were only two instances of apparent cross resistance to INH and these patients showed susceptible organisms on later cultures.

These resistance studies appear to bear out the in vitro investigations of Barclay who found that organisms resistant to CAH remained susceptible to INH and that INH resistant organisms were partially sensitive to CAH in large doses.

C—Clinical Effectiveness:

The therapeutic effect of CAH is of the order of INH although much less so. It must be remembered that the great majority of the patients had chronic disease with prolonged INH administration previously. In general, the effect on fever, toxicity, cough and sputum was similar to INH, although certainly less dramatic. As with INH, appetite was stimulated and weight gain was common. The patients were given CAH as a routine therapeutic measure without preliminary discussion in order to minimize psychological bias.

One hundred and fifty were treated with CAH.

Seventy-five for four months or longer and form the basis for our clinical results.

Twenty-eight converted to negative sputum smear and culture and were discharged.

Two relapsed and were readmitted for surgery.

Four who converted had surgery.

Eleven were new admissions, in general, with new disease and had had no previous drug treatment. Their improvement was noted by x-ray films clearing as well.

Seventeen had had drugs previously over long terms. They responded more slowly but converted and remained negative. The x-ray film changes were not too marked although cavity closure and clearing was seen.

There was no patient INH resistant who turned negative with CAH, although seven who showed favorable clinical response left the sanatorium before they had taken the drug more than three months.

X-ray film changes were not significant except in those with acute or subacute (exudative) disease. The drug appeared more effective in larger dosage. Attempts to correlate blood levels of the drug with clinical effectiveness were unsuccessful. It was our feeling that the laboratory method was unreliable and the figures were, therefore, not included in this study.
CASE REPORTS

Case No. 7965, M. B. (Figure 1A, 1B): This white 60 year old diabetic housewife was admitted July 10, 1954 with chronic fibroid tuberculosis and essential hypertension. She had been followed by x-ray film inspections for many years and was always sputum negative. No treatment had been administered. On admission she had positive sputum, fever with bilateral cavitory apical disease. Diabetes was controlled by diet and 15 units of NPH insulin. CAH 600 mg. daily and streptomycin one gram twice weekly were administered. Her sputum was negative on September 23, 1954. She was discharged November 2, 1954 with negative sputum both by smear and culture and has remained so. No great change occurred in x-ray film appearance. She gained 23 pounds.

Case No. 7914, E. H. (Figure 1A, 2B): This white 48 year old waitress was admitted April 28, 1954 following discovery of a left upper lobe exudative lesion in routine annual food handler survey. Her sputum was positive. Drug treatment consisted of streptomycin one gram twice weekly. CAH was started 200 mg./day and gradually increased to 600 mg./day. Her sputum converted in September 1954 and she was discharged October 30, 1954 and has remained negative with satisfactory x-ray film clearing. Her weight gain was 13 pounds.

Case No. 7927, D. A. (Figure 3A, 3B): This white 23 year old housewife was admitted September 29, 1954 with history of tuberculosis dating to 1946. She had previously been institutionalized and received streptomycin, PAS and bilateral pneumothorax from 1946 to 1952. Following discharge she remained well and was followed in chest clinic. After the birth of baby in June 1954 she developed toxic symptoms and x-ray film showed evidence of progression. Her sputum was positive. She was treated with streptomycin one gram twice weekly, PAS 12 grams daily, CAH 450 mg./day and artificial pneumoperitoneum. She responded well and has had negative sputum since November 30, 1954. She was discharged on February 23, 1955 and has remained well.

Case No. 7766, J. K. (Figure 1A, 4B): This white obese printer 50 years of age was admitted on March 4, 1953. He had extensive disease and positive sputum. He received streptomycin, PAS and INH. Drugs were continued at Eagleville and pneumoperitoneum induced October 28, 1953. He remained positive and on April 21, 1954 PAS and INH were discontinued. He was then given CAH and PAS. He received CAH daily and converted on October 14, 1954. There was satisfactory clearing of lung fields on x-ray film and sputum has remained negative.

Case No. 8095, J. McC. (Figure 5A, 5B): This white 41 year old truck driver was admitted February 19, 1955 with history of acute onset. He was markedly underweight, toxic, had far advanced bilateral exudative disease and positive sputum. Streptomycin one gram twice weekly, PAS 12 grams daily and CAH 600 mg./day were administered. He showed excellent clinical response and his sputum converted on August 25, 1955. He was discharged at his request December 10, 1955 with a weight gain of 34 pounds.

Case No. 7954, A. W. (Figure 6A, 6B): This male Negro of 32 years was admitted July 7, 1954 with positive sputum. Streptomycin one gram twice weekly, PAS 12 grams daily and CAH 450 mg./day were prescribed. His sputum converted by May 24, 1955 and remained so. He was discharged on September 16, 1955 with a total gain of 32 pounds.

Discussion

CAH has had extensive clinical trial at Eagleville Sanatorium. Clinical improvement and weight gain were common findings, but may be discounted because of use of other drugs and excellent sanatorium care. However, because of absence of toxicity and frequency of sputum conversion (35 per cent) it is evident that the drug has merit.

It has produced results in chronic retreatment cases as well as in new ones without evidence of toxicity. The problem of cross resistance must be considered since two patients who had had only a few weeks of INH were found to be INH resistant after CAH therapy, and six long term INH patients who were INH susceptible showed INH resistance after receiving CAH.

SUMMARY

1. Cyanacethydrazone appears to be an effective antituberculosis agent although less so than isoniazid.
2. It is non-toxic and is well tolerated in large doses.
3. Resistance studies indicate that it may possibly impair the usefulness of isoniazid.
4. It appears to be of limited value in isoniazid resistant patients.
5. It is a valuable drug for those who cannot tolerate INH.

The writer wishes to acknowledge his indebtedness to Miss Betty Kane, bacteriologist, and to the Staff of Eagleville Sanatorium for their assistance in this study.

RESUMEN
1. La Hidracida cianacética parece ser un medicamento antituberculoso efectivo aunque menos que la isoniacida.
2. No es tóxico y es tolerado en grandes dosis.
3. Los estudios sobre resistencia indican que quizá puede ser desfavorable para la utilización de la isoniacida.
4. Parece que es de poca utilidad en los enfermos con isoniacida resistencia.
5. Es una droga valiosa para los que no toleran la isoniacida.

RESUME
1. L’hydrazide cyanacétique semble être une médication antituberculeuse efficace, bien qu’à un degré moindre que l’isoniazide.
2. Il n’est pas toxique et est bien toléré à hautes doses.
3. Des études sur la résistance montrent qu’il est peut-être possible que ce produit gêne l’utilisation de l’isoniazide.
4. Son action semble limitée chez les malades résistants à l’isoniazide.
5. C’est une médication valable pour ceux qui ne supportent pas l’isoniazide.

ZUSAMMENFASSUNG
1. Cyanacethydrasit scheint ein wirksamer antituberkulöser Stoff zu sein, wenngleich in geringerem Grade als INH.
2. Er ist nicht toxisch und wird in hohen Dosen gut vertragen.
3. Resistenzbestimmungen ergeben, dass er möglicherweise die Brauchbarkeit von INH beeinträchtigen kann.
4. Er scheint von begrenztem Wert bei gegen INH resistenten Patienten.
5. Er ist ein wertvollen Medikament für solche Fälle, die INH nicht vertragen können.

REFERENCES