A Preliminary Report on the Safety and Therapeutic Activity of a Salizid INH Derivative

W. E. ROYE, M.D., F.C.C.P. and G. E. EWART, M.D.
Richmond, Virginia

Although the development of INH greatly advanced the chemotherapy of pulmonary tuberculosis, there are many cases that still cannot be controlled adequately. As a consequence there is a continued search for agents which might provide greater inhibition of the tubercle bacillus with even less toxicity for man. Among the newer of the hydrazine derivatives is salicylidene hydrazine (Salizid® Nepera). This report covers our preliminary investigation of the toxicity, and the therapeutic activity of this compound.

Salizid is obtained from the interaction of the isonicotinic acid hydrazide and salicylaldehyde. It is sparingly soluble in the ordinary solvents and does not lose its inhibitory activity against mycobacterium upon autoclaving for two hours at 20 pounds pressure. The difference in chemical structure between INH and Salazid is shown in Figure 1.

![Chemical Structure](attachment:chemical_structure.png)

Hart et al first reported that Salizid was strongly inhibitory against H₃R. in vitro. Resistant H₃R cultures were found to die out in a few passages and organisms resistant to several other antituberculosis compounds were found, in vitro, to be sensitive to this compound. Steenkens et al, however, found that Salizid retained only a slight degree of inhibitory activity against the resistant H₃R strain. This in vitro finding was substantiated by animal studies as only a few of the guinea pigs inoculated with INH resistant strain responded better to Salizid than to INH and other INH derivatives. Both of these authors suggested that Salizid merited thorough clinical study, particularly in INH sensitive disease.

In early clinical trials, McCormick et al reported that Salizid was well tolerated in large doses and that a majority of the patients who develop peripheral neuritis as a result of INH therapy may be treated safely with this agent. The response in 50 original treatment patients was prompt and excellent in 41, delayed, but good in four, symptomatic improvement

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From the Medical Service, Veterans Administration Hospital.

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N—Normal
M. A.—Mildly and moderately abnormal

"mgm" refers to mgm. of Salizid per day at the time of the E.E.G.
with only slight roentgenographic improvement in two, and three deaths. Ewart and Wingo also reported that this compound was safe in doses of at least 1200 mgm. per day. These investigators found that INH resistant cases at 300 mgm. per day were not benefited by larger doses of Salizid. Recently, Nagley reported that Salizid was an excellent and safe agent for the treatment of pulmonary tuberculosis and that in human beings, resistance was not built up as quickly to Salizid as to INH.

In our preliminary investigations, in 18 tuberculous men we attempted to determine the toxicity of this compound and its therapeautic value in:

a) cases of peripheral neuritis, b) SM-PAS failures, c) seriously ill cases of pulmonary tuberculosis, d) INH resistant cases.

1) Toxicity Evaluation.—This part of our evaluation was carried out in seven colored men 25 to 65 years of age. All of these had a history of multiple admissions for chronic, far advanced active pulmonary tuberculosis. All had failed to respond to SM-PAS therapy, and had shown all clinical and laboratory evidence of being resistant to INH. Salizid was given for a minimal period of eight months and a maximum of 22 months.

The average dosage received by this group is summarized as follows:

- 4 months on 400 mgms. a day
- 5 months on 800 mgms. a day
- 6 months on 1200 mgms. a day

and in addition two other patients received 1600 mgm. daily for 10 months.

All were studied for possible neurotoxicity and hepatotoxicity:

a) Neurotoxicity—there was no objective evidence of neurotoxicity. There was no euphoria or nervousness. In all, 23 electroencephalograms were carried out on six patients, and no abnormality was initiated or aggravated in any. The data for an 11 month period during the study is shown in Table I. Serial study gave the impression that there was a serial slowing of the pattern. This slowing was greater than one could expect from six unselected patients; but nevertheless was not enough of a slowing to be considered abnormal in any one of the cases studied.

b) Liver toxicity—no case was discontinued and no dosage reduced because of toxicity. A battery of liver function tests were performed at two week intervals during the first two months. After the second month, the tests were reduced to monthly determinations of serum bilirubin, thymol turbidity, cephalin flocculation and B.S.P. retention. Thymol turbidity, cephalin flocculation, cholesterol, prothrombin time, alkaline phosphatase and cholesterol esters, produced a number of minor variations similar to previous values on these and similar patients on INH therapy. Direct, indirect and total serum bilirubin demonstrated no abnormality on approximately 200 determinations.

The bromsulfalein excretion tests were more difficult to interpret. The three most severely ill patients had a scattering of B. S. P. retention values ranging from 10 to 25 per cent. They demonstrated no consistent pattern. There was no liver damage demonstrated when they were examined at post-mortem and the mode of death did not suggest liver toxicity.

The individual cases are summarized in Table II. Only one case (A. S.)
### TABLE II

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<th>Patients Name</th>
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<th>Function Findings</th>
<th>E. E. C.</th>
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| Change | Not evaluated because of edema | Normal | No change, on serial study | Liver normal | Not done too weak | Liver normal | Liver normal | Liver normal |

**March, 1958**
showed any abnormal change in liver function (B. S. P.) during the entire study which might have indicated possible liver damage. On post-mortem examination the liver showed no evidence of toxic changes.

**Effect in Cases with Peripheral Neuritis**

Salizid was administered to a total of seven tuberculous patients, whom we desired to treat with INH, but who had various neurological disorders. The dosage of Salizid for these cases was 300 mgm. a day, a dosage equivalent to the routine dose of INH. The neurologic conditions were a result of either alcoholism, post-gastrectomy syndrome, nutritional deficiency, or diabetes.

Four of these cases were in on their first admission for treatment of tuberculosis. Clinically, they all did well in regard to both the pulmonary tuberculosis as well as the neurologic symptoms. All were dismissed from the hospital, after six months or more of therapy, three being classified as having inactive tuberculosis and the fourth was discharged with apparently negative sputum but an open healing cavity.

One hospitalized chronic patient receiving INH developed peripheral neuritis which cleared when placed on Salizid therapy. This case was complicated by a nutritional deficiency, so that we could not be entirely certain that the neuritis was completely a result of INH. However, whatever the cause, it cleared during treatment. The sixth case had neurologic symptoms due to a spinal cord compression. The severity of symptoms was reduced during Salizid administration, however, the chronic, minimal tuberculous focus in this patient has been unchanged.

The last case in this group presented a diagnostic chest problem. In addition he had a chronic, progressive neurologic disease, which made INH therapy precarious. However, following one year of Salizid, he was released from the hospital with a negative sputum and no aggravation of the neurologic condition either during or following the period of Salizid therapy.

**SM-PAS Failure**

A man with a persistent open cavity, positive sputum and laboratory studies indicative of resistance to both streptomycin and PAS was on his initial treatment with INH. Salizid 100 mgm. t.i.d. was added to his SM-PAS therapy. Eleven months later, he was discharged with a diagnosis of inactive tuberculosis.

**Seriously Ill Admissions**

One of the cases in this group, a first admission, required, because of severity of lesions, what can be considered as heroic treatment. Salizid 800 mgm. a day with pyrazinamide 3 gm. a day was selected. The hospital course thereafter was uneventful. Examination of the lobe resected 11 months later revealed only a 1 cm. epitheloid cavity and no soft caseous nodule. The PZA was stopped after 14 months. He remains on Salizid 800 mgm. a day with no evidence of adverse effects.

One of the cases listed under peripheral neuritis can be included also in this group of desperately ill patients. In addition to having far advanced pulmonary tuberculosis and severe nutritional deficiency, he pre-
sented tuberculous peritonitis and a history of alcoholism and chronic liver disease. There was evidence of abnormal liver function. Running a stormy, febrile course with alternating brief remissions and exacerbations, he received in a three month period, varying combinations of streptomycin, INH, PZA, tetracycline and oxytetracycline; and death seemed imminent. Following these various therapies, and as a last resort, he was placed on Salizid 300 mgm. a day and streptomycin 1 gm. twice a week. The clinical course was uneventful. It is difficult in retrospect to separate the findings of severe disease from those of drug reactions during the first three months, however, the clinical improvement upon shifting to the SM-Salizid in this case was definite.

**INH Resistant Cases**

Included in this group of INH resistant cases receiving Salizid are the seven cases from the toxicity study, one of the neurologic cases, and an additional case resistant to INH. Large doses up to 1600 mgm. were given. In some instances the clinical impression was that the advance of the tuberculous lesion was slower than it would have been had the patient gone untreated. However, the effect of Salizid in these INH resistant cases was not impressive enough to encourage us to continue Salizid therapy indefinitely. In another instance we employed Salizid, 800 mg., in a patient whose tuberculosis was rapidly increasing in severity. These lesions appeared to be arrested, but we could not attribute the therapeutic benefit obtained entirely to the Salizid, as other chemotherapeutic agents had been administered concomitantly. However, in spite of clinical improvement the cavity has not closed after five months of therapy.

**SUMMARY**

Salizid, the salicylaldehyde salt of INH, was tried in a series of 18 cases. In a toxicity evaluation doses up to 1600 mg. daily were employed for as long as 10 months. No evidence of neurotoxicity or hepatic damage was obtained from EEG tracings, liver functions tests, or post-mortem examinations. In addition, it is well tolerated in doses of 300 mgm. daily by patients having neurologic disease even with peripheral neuritis resulting from INH. Cases resistant to INH do not respond to larger doses of Salizid. When given in combination with other chemotherapeutic agents, in advanced pulmonary tuberculosis it may be of some benefit. Salizid is an excellent drug and merits further usage in pulmonary tuberculosis because of its safety and chemotherapeutic action in cases of INH sensitive tubercle bacilli.

**RESUMEN**

El Salizid, que es el salicilaldehído de INH, se ensayó en un grupo de 18 casos. Al valorar su toxicidad se usaron dosis hasta de 1.600 mgr. diarios hasta por diez meses. No se encontró evidencia de neurotoxicidad o de daño hepático según los ECG, las pruebas de función hepática o los exámenes postmortem. Además, se bien tolerado a la dosis de 300 mgr. diarios por enfermos con afecciones neurológicas y aún con neuritis periférica consecutiva a la INH.

Los casos resistentes a la INH no responden a dosis más grandes de
Salizid. Cuando se da combinado con otros agentes quimioterápicos en tuberculosis pulmonar avanzada, puede ser de alguna utilidad.

El Salizid es una droga excelente y merece que se le use más en tuberculosis pulmonar por su seguridad y su acción quimioterápica en casos de bacilo tuberculoso sensible a la INH.

RESUME

Le "salizide," sel salicylaldehyde de l'isoniazide, a été essayé sur un groupe de 18 malades. Pour évaluer la toxicité de ce produit, des doses allant jusqu'à 1600 mmgr. par jour furent utilisées pendant une durée atteignant dix mois. On n'obtint aucune preuve de neurotoxicité ou d'atteinte hépatique d'après les tracés encéphalographiques, les tests de la fonction hépatique, et les examens post-mortem. De plus, il fut bien toléré aux doses de 300 mmgr. par jour chez des malades ayant des affections neurologiques, avec atteinte périphérique résultant de l'isoniazide. Les cas résistants à l'isoniazide ne sont pas influencés par des doses plus importantes de "salizide." Lorsque ce produit est donné en association avec d'autres agents chimiothérapeutiques, dans les cas de tuberculose grave, il peut avoir quelque action favorable. Le salizide est une excellente médication et mérite un emploi plus étendu en tuberculose pulmonaire, à cause de son innocuité et de son action chimiothérapeutique dans les cas de bacilles tuberculeux sensibles à l'isoniazide.

ZUSAMMENFASSUNG


REFERENCES


