A Short Early History (and Mesa-Analysis) of Pyrazinamide Toxicity

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Solman T. Postgrad Med 1953; 13: A-34.

“The administration of potent drugs involves a calculated risk where **the presumptive benefit** is balanced against **the possibility of toxic effects and idiosyncrasies…”**

We need to know **“…as accurately as possible, what the risk may be in kind , degree and frequency…”**

Only then can we plan on a secure foundation.

A Mesa-analysis?

META

about/above/beyond content

MESA

into/inside/within content

Introduction

Saukkonen JJ, Cohn DL, Jasmer RM, et al. An Official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-952.

Definitions of antituberculosis drug-induced hepatotoxicity.

- Several definitions of ADIH and approaches to possible ADIH appear in different texts. That recommended by the ATS and Centers for Disease Control (CDC) is most frequently used:

If the alanine aminotransferase (ALT) is **≥ X3** the upper limit of normal for the laboratory in question and there are **symptoms of ADIH** reported the hepatotoxic drugs should be stopped.

Saukkonen JJ, Cohn DL, Jasmer RM, et al. An Official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-952.

Definitions of antituberculosis drug-induced hepatotoxicity.

The hepatotoxic drugs should also be stopped if the **ALT rises to at least X5** the upper limit of normal, even in the absence of symptoms.

Saukkonen JJ, Cohn DL, Jasmer RM, et al. An Official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-952.

- ADIH may result from the agent itself or a metabolite and be ***predictable*** and dosage-related; alternatively the toxic response may be immunologically mediated and ***unpredictable*** and not dosage-related.
- The commonest form of hepatotoxicity in response to our three "essential" antituberculosis agents INH, RMP and PZA **tends to be dosage-related** and is *probably* caused by the drugs or their metabolites

LFT performed **before** the start of TB therapy or chemoprophylaxis may be abnormal in a significant proportion of adult and paediatric patients. This particularly likely in those with more severe forms of disease.

Dieckhoff von J. Funktionelle Untersuchengen zur frage einer Leberschädigung durch Isonikotinsäuerehydrazid (INH) im Kindesalter. Munchen Med Wchskr 1957; 99: 1408-1411.

Morrisey JF, Rubin R. The detection of pyrazinamide-induced liver damage by serum enzyme determinations. Am Rev Respir Dis 1959; 80: 855-865.

Brown M, Beuchner HA. Clinical experience with the routine use of serum glutamic-oxalacetic transaminase in all tuberculosis patients under chemotherapy. Transactions of the 26th VA-Armed Forces pulmonary disease research conference. 1967:1-2.

Pickroth G. Leberschadigungen bei Tuberkulose. Z Tuberkulose 1968; 128: 265-270.

Simon K. Rifampicin behandlung der Tuberkulose im Kindesalter. Med Klin 1975; 70: 1095-1097.

Dickinson DS, Bailey WC, Hirschowitz BI, Soong S-J, Eidus L, Hodgkin MM. Risk factors for isoniazid (INH)-induced liver dysfunction J Clin Gastroenterol 1981; 3: 271-279.

- **Liver biopsy studies** and **autopsies** reveal that a significant proportion of adults and children, both before, and after, the commencement of treatment, have abnormalities of liver tissue including tuberculous granulomata, histiocytic nodules and non-specific reactive hepatitis.

- Galen RS, Weiner D, Hartman SA. Functional hepatic impairment in pulmonary tuberculosis. Dis Chest 1950; 17: 524-531.
- Sarin LR, Samuel KC, Bhargava RK. Hepatic derangement in pulmonary tuberculosis. Am Rev uberc 1957; 76: 410-425.
- Korn RJ, Kellow WF, Heller P, Chomet B, Zimmerman HJ. Hepatic involvement in extrapulmonary tuberculosis. Am J Med 1959; 27: 60-71.
- Choremis C, Vlachos J, Anastassea-Vlachou C, Matsaniotis N. Needle biopsy of the liver in various forms of childhood tuberculosis.J Pediatr 1963; 62: 203-207.
- Pickroth G. Leberschadigungen bei Tuberkulose. Z Tuberkulose 1968; 128: 265-270.
- Praharaj KC, Praharaj SC, Nanda BK, Rao PG. Hepatic involvement in childhood tuberculosis. Indian Pediatr 1979; 16: 497-502.

Saukkonen JJ, Cohn DL, Jasmer RM, et al. An Official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-952.

- The ATS also pointed out that, in any individual, transaminase values may vary by as much as **45%** during a single day or **10-30%** on successive days.

Uncertain role of infectious hepatitis

Kumar A, Misra PK, Mehotra R, Govil YC, Rana GS. Hepatotoxicity of rifampin and isoniazid. Is it all drug-induced. Am Rev Respir Dis 1991; 143: 1350-1352.

Hoffmann CJ, Charalambous SA, Thio CL, et al. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. AIDS 2007; 21: 1301-1308.

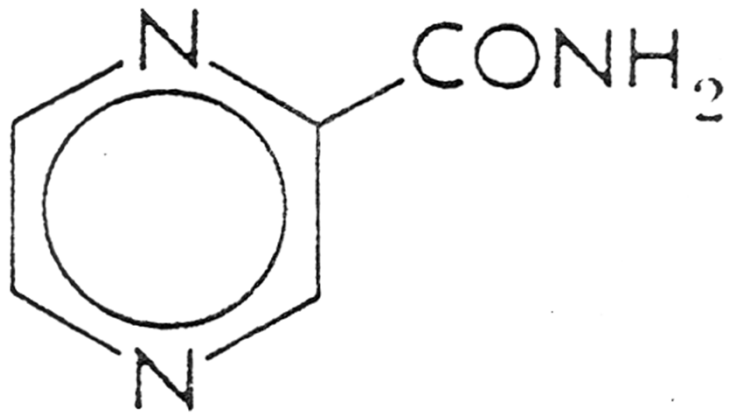
Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and human immunodeficiency virus. Am J Respir Crit Care 1998; 157: 1871-1876.

Reviews of PZA Hepatotoxicity

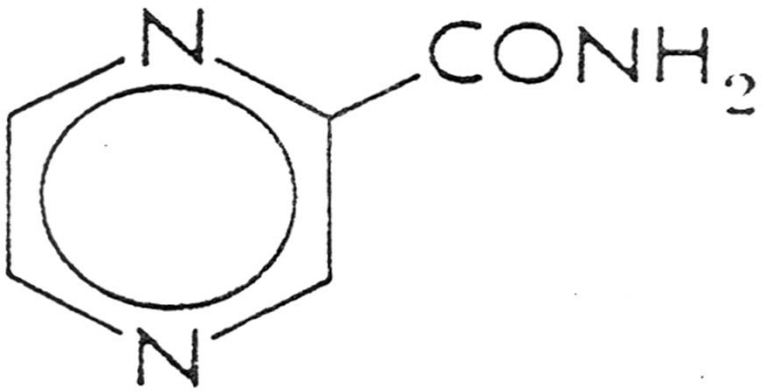
- Hong Kong Tuberculosis Treatment Services/ British Medical Research Council. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. Tubercle 1976; 57: 81-95.
- Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1978; 13-32.
- Zierski M. Pharmakologie, toxikologie unf klinische Anwendung von pyrazinamid. Prax Pneumol 1981; 35: 1075-1105.
- Tostman A, Boeree MJ, Aarnoutse RB, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 2008; 23: 192-202.
- Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. Antimicrob Agents Chemother 2010; 54: 2847-2854.

The early literature(1950-1969) related to the efficacy and toxicity of pyrazinamide

Dalmer O, Walter E. Verfahren zur Herstellung von Derivaten der Pyrazinmonocarbonsaure. DRP 1936; 623: 257.



Pyrazinamide



Pyrazinamide

MÉDECINE EXPÉRIMENTALE. — *Action de l'amide nicotinique sur les bacilles du genre* Mycobacterium. Note (¹) de M. VITAL CHORINE, présentée par M. Émile Roubaud.

En poursuivant l'étude de l'influence des diverses vitamines sur l'évolution de la lèpre murine, nous avons été surpris de constater que les Rats lépreux, traités avec des doses élevées de vitamine antipellagreuse, ne présentaient apparemment aucune lésion de la maladie.

Voici l'une de nos expériences, commencée le 21 juillet 1944. 10 Rats sont inoculés sous la peau de l'aine droite avec un broyat de lépreme prélevé chez un animal infecté 65 jours auparavant. Cinq de ces animaux servent de témoins, cinq autres reçoivent 4 ou 5 fois par semaine, soit par voie sous-cutanée, soit par voie buccale, de l'amide nicotinique, d'abord à la dose de $0^g,30$ et ensuite de $0^g,50$ par kilogramme. Les Rats traités n'ont jamais présenté aucune lésion apparente de lèpre. Les trois premiers Rats sont morts respectivement après 86 jours, 103 jours et 110 jours du traitement. Ils ont reçu respectivement les doses totales de médicament de $2^g,01$, $2^g,56$ et $2^g,71$. Le 4e et le 5e Rat traités sont sacrifiés les 7 et 28 décembre 1944, le dernier donc plus de 5 mois après l'inoculation; ils ont reçu respectivement $3^g,76$ et $4^g,61$ de vitamine PP. Les résultats de l'autopsie de tous les animaux traités sont sensiblement identiques : on ne trouve chez eux aucune lésion de lèpre. Les bacilles acido-résistants ont été rencontrés seulement au point d'inoculation, mais ils sont petits et souvent réduits à quelques granules. Les Rats témoins ont présenté l'évolution habituelle de la maladie, avec une formation de lépromes au point d'inoculation, au 3e mois d'infection, et une généralisation de la maladie. Chez les deux derniers animaux, sacrifiés

(¹) Séance du 15 janvier 1945.

Yeager RL, Munroe WGC, Dessau FI. Pyrazinamide (Aldinamide) in the treatment of pulmonary tuberculosis. Am Rev Tuberc **1952**; 65: 523-534.

- Monotherapy - **43** PTB patients, Sept 1949
- Far advanced tuberculosis
- Not responding to then available therapies
- Very high dosages initially; highest dose is recorded as 200 mg/kg body weight per day
- The final schedule: 350 mg four times daily for the first day, **700 mg four times daily** thereafter usually for 42 days, but longer in some cases.

Yeager RL, Munroe WGC, Dessau FI. Pyrazinamide (Aldinamide) in the treatment of pulmonary tuberculosis. Am Rev Tuberc 1952; 65: 523-534.

The authors concluded that PZA appeared to have "**a moderate degree of antituberculous activity**", but that this appeared to be limited by the **rapid appearance of drug-resistance**, accompanied by failure to maintain symptomatic response.

Appreciable degree of PZA resistance developed in the 12 patients with bacilli tested before and after treatment.

Yeager RL, Munroe WGC, Dessau FI. Pyrazinamide (Aldinamide) in the treatment of pulmonary tuberculosis. Am Rev Tuberc **1952**; 65: 523-534.

- **Two patients (4.7%) became jaundiced,**
- One after 142 g of PZA during 42 days
- The second after 159 g of PZA during 87 days.
- Both patients recovered after termination of treatment without further hepatic problems.
- 33 patients (77%) were “discharging tubercle bacilli in the sputum” when PZA treatment commenced.
- In 15 (45%) there was no change.
- Bacillary content was reduced in 18 (55%).
- In 10 of the 18, bacilli no longer present on smear.

Cordice JWV, Hill LM, Wright LT. Use of pyrazinamide (Aldinamide) in the treatment of tuberculous lymphadenopathy and draining sinuses. J Nat Med Assoc 1953; 45: 87-98

- **19** cases of lymphadenopathy.
- Treatment from 11-90 days.
- **1 g thrice daily (3 g)** for all patients except the smaller children and the elderly.
- One possible “side reaction”.
- Increasingly frequent bouts of dizziness, GI upsets with abdominal cramps, pain, nausea and diarhoea.

Campagna M, Calix AA, Hauser G. Observations on the combined use of pyrazinamide (Aldinamide) and isoniazid in the treatment of pulmonary tuberculosis. Am Rev Tuberc 1954; 69: 334-350.

- **21** patients **far advanced PTB** previously **treated unsuccessfully** with SM and PAS, but failed therapy.
- INH 4 mg/kg and **PZA 1 g thrice daily (3 g)** for 18 months.
- All positive sputum microscopy positive for acid-fast bacilli and culture of *M tuberculosis.*

Campagna M, Calix AA, Hauser G. Observations on the combined use of pyrazinamide (Aldinamide) and isoniazid in the treatment of pulmonary tuberculosis. Am Rev Tuberc 1954; 69: 334-350.

- In **12 (57%)**cases the sputum became culture negative after two months of treatment.
- In a further **2 (9%)** in the third month and in **5 (24%)** patients during the fourth month of the study. (Overall **90%**)
- These patients all remained culture negative for the entire 18 month period of the study.
- Mild **jaundice** lasting a week appeared in **3 (14%)** patients, but without any other abnormalities in liver function tests being noted; the jaundice regressed **without any alteration in medication.**

Campagna M, Hauser G, Greenberg HB. The readication of mycobacterium tuberculosis form the sputum of patients treated with pyrazinamide and isoniazid. Am Rev Tuberc 1962; 86: 636-639.

Patients followed up 10 years later.

- One patient had sputum cultures for *M tuberculosis* positive until death 9 years later.
- Three patients died as result of myocardial disease.
- One patient lost to follow up.
- **16 patients had no evidence of disease; all sputum cultures remained negative.**

Phillips S, Larkin JC, Litzenberger WL, Horton GE, Haimsohn JS. Observations on pyrazinamide (Aldinamide) in pulmonary tuberculosis. Am Rev Tuberc Pulmon Dis 1954; 69: 443-450.

Heterogenous group of 29 PTB patients

- **11** PZA monotherapy.700 mg X4 daily for 6-weeks. **18**: 10 PZA&SM, 4 PZA&INH

3PZA, SM&PAS, 1 PZA&PAS.

- One patient **(3,4%)** "chronic" PTB became **jaundiced**; Probably"toxic", but indications of infectious hepatitis. 5 **(29%)** others **"mild hepatic dysfunction**".
- Frequent clinical improvement but no patient's sputum became culture negative

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

- Non-randomized evaluation of PZA in PTB tuberculosis patients, mostly **previously unsuccessfully treated** with PAS/SM.

1. **19** patients **PZA alone** in a daily dosage of **2.8 g**. Most cases only 42 days.
2. **28** patients **SM 1 g** and **PZA 3 g** daily for 4-12 months.
3. **53** patients **PZA 3 g** daily & **PAS 12 g** daily for 4-12 months.
4. **102** patients received **INH 300 mg** and **PZA 3 g** daily for 4-16 months.

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

Evaluation of hepatic function.

- **All patients** included in toxicity evaluation
- Blood urea nitrogen
- Bromsulphalein excretion
- Cephalin floculation
- Icteric index

All done before treatment and weekly thereafter.

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

PZA monotherapy:

- All **19** patients experienced a “marked improvement in feeling of well-being”.
- This was soon reversed.
- ”Pyrazinamide lost its effectiveness in most cases after **one** or **two months** of therapy”.

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

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SM 1g/PZA 3g

- **16** patients were placed on this regimen. This regimen also proved unsatisfactory. Only **3 patients had not previously received SM**, but by the 4th month all three were discharging SM-resistant bacilli.

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

PZA 3 g/PAS12 g

- **35** patients received this regimen. 23 completed 2 months and 21, 4 months, but only 4 completed 6 months treatment.
- **All but I patient had received PAS previously.**
- 16 known to be PAS susceptible, but **4 (25%)** developed PAS resistance. Remainder became culture negative.
- Concluded that PZA/PAS an unsatisfactory regimen.

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

INH/PZA

- **30** patients on this regimen; the results were "excellent".
- After **4 months** bacilli could be cultured from the sputum of only **5 (17%)** of 29 patients.
- Of these 5, 2 (7%) were INH-resistant.

Schwartz WS, Moyer RE. The chemotherapy of pulmonary tuberculosis with pyrazinamide used alone and in combination with streptomycin, para-aminosalicylic acid, or isoniazid. Am Rev Tuberc 1954; 70: 413-422.

Toxicity

- In $2^{1/2}$ years **181** patients treated with PZA alone or in combination with PAS, SM or INH
- The regimens interrupted in **2 (1.1%)** cases in patients receiving 42.4 mg/kg and 44.8 mg/kg because of **mild jaundice**, that appeared after **72** and **149** days of PZA therapy; in a **3rd** patient treatment stopped after an abnormal cephalin flocculation test.

McDermott W, Ormond L, Muschenheim C, Deuschle K, McCune R, Tompsett R. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 69: 319-333.
Muschenheim C, McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1954; 70: 743-747.

- **61** PTB patients received PZA for **at least 3-months**. *M tuberculosis* was cultured from all but **8** patients before study.
- PTB: “far advanced or moderately advanced”
- Only 3 had received previous therapy.
- PZA dosage of **50 mg/kg**, INH 5 mg/kg, both drugs **twice daily.** Given initially for 6-months (16 patients); then 90 days.
- **LFT** assessed by serum bilirubin, bromsulphalein excretion, thymol turbidity.

McDermott W, Ormond L, Muschenheim C, Deuschle K, McCune R, Tompsett R. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 69: 319-333. Muschenheim C, McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1954; 70: 743-747.

- **53** patients: **3** month and **6** month bacteriological results were available. **Four (8%)** of these had positive cultures for *M tuberculosis* at **3 months** and these same 4 patients remained culture-positive at 6 months.
- Sustained **"reversal of infectiousness"** was thus associated with the use of INH and PZA in the remainder of these patients (93%). At nine months only 2 of 31 patients available for evaluation remained sputum culture-positive.

McDermott W, Ormond L, Muschenheim C, Deuschle K, McCune R, Tompsett R. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 69: 319-333.
Muschenheim C, McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1954; 70: 743-747.

However:

- **Hepatic dysfunction in 6 (10%) patients**.
- **4** became **jaundiced**; one died of **fulminant hepatitis.**
- The first four cases of hepatitis occurred during the **fifth** month of treatment; the first in an **alcoholic patient** with suspected **liver cirrhosis**.
- PZA treatment duration shortened to **90 days**, but the fatal case of hepatitis then occurred after **55 days** treatment
- PZA use stopped altogether.

McDermott W, Ormond L, Muschenheim C, Deuschle K, McCune R, Tompsett R. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 69: 319-333.
Muschenheim C, McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1954; 70: 743-747.

The fatal case occurred in a 45-year old alcoholic woman with suspected liver cirrhosis.

McDermott W, Ormond L, Muschenheim C, Deuschle K, McCune R, Tompsett R. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 69: 319-333.
Muschenheim C, McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1954; 70: 743-747.

- *"An obviously alluring possibility is that the high degree of antituberculous effectiveness of pyrazinamide-isoniazid observed with the present dosage would also be exerted with a lower dosage which at the same time would be reasonably non-toxic*".

Muschenheim C. McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 70: 743-747.

- Further report of the study 1-year later. Results the same as at 6-months.
- Literature review: **355** patients have received PZA either alone or with other drugs. **Overall hepatitis incidence 3.4%.**

Muschenheim C. McDermott W, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc 1954; 70: 743-747.

- Pyrazinamide-isoniazid therapy cannot attain widespread usefulness unless it is possible to avoid or minimize the the incidence of the toxic reaction of hepatitis.
- **Only one of the 12 reported cases of icteric hepatitis received a PZA dose of < 40 mg/kg**
- "Satisfactory" results for patients who received 10-13 weeks of INH-PZA

Muschenheim C, Organick A, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1955; 72: 851-855.

PZA at a lower dosage.

- A series of **61 patients** treated at New York Hospital and the Navajo Medical Center Services.
- **56 (92%)** no previous treatment, but **advanced disease** with a poor prognosis.
- Total daily **PZA dose 20-30 mg/kg**, INH 5 mg/kg for **12-13 weeks** and INH alone thereafter.
- **52** completed at least **3 months** treatment

Muschenheim C, Organick A, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1955; 72: 851-855.

- 12 patients removed from the study
- 2 self-discharge
- 3 transfer to other hospitals
- 2 surgery
- 1 given another experimental drug
- 4 toxicity; **3 (5.8%) liver involvement**

Muschenheim C, Organick A, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1955; 72: 851-855.

- In **2 cases** hepatitis occurred, both receiving **PZA 30 mg/kg**; both **"moderately heavy alcohol drinkers".**
- **77 days** treatment, jaundice "moderately severe hepatitis."
- **60 days**. Bromsulphalien retention increased, palpable, tender liver and splenomegaly, but no jaundice.
- **11 days**. Fever, urticaria and liver tenderness, but LFT normal. Not looked upon as hepatitis.

Muschenheim C, Organick A, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1955; 72: 851-855.

The authors comment **"therapeutic inferiority was particularly evident at the lowest dosage level of 20 mg/kg."**

PZA Dosage	Month 3	Month 6
50 mg/kg	49/53 (92%)	48/53 (91%)
20-30 mg/kg	37/52 (71%)	28/42 (66%)

Muschenheim C, Organick A, McCune R, et al. Pyrazinamide-isoniazid in tuberculosis. Am Rev Tuberc Pulmon 1955; 72: 851-855.

"In view of these findings it is believed that further clinical investigations of pyrazinamide in tuberculosis might be more advantageously directed to the search for **simple methods for the detection of hepatic toxicity** than toward manipulation of dosage."

Potter BP, Chang SF. Experience with pyrazinamide. Dis Chest 1955; 27: 44-50.

- 1952-1953. **60 previously treated patients** who had responded unfavourably.
- **3 g PZA** daily in four doses for a mean 4-6 months.
- **27 PZA alone**; remainder with **SM 1 g (27)** or **PAS 8-12 g (6)**.
- Patients evaluated clinically and radiologically.
- Great scepticism expressed as to the value of sputum bacteriology! Chest radiography response used to assess PZA efficacy.
- **LFT:** cephalin flocculation twice monthly.

Potter BP, Chang SF. Experience with pyrazinamide. Dis Chest 1955; 27: 44-50.

- Only **13 (22%)** favourable radiological response. **11 (18.3%) sputum conversion**.
- **8 (13%)** developed **jaundice 1-6 months** after treatment start; **1 death.**
- In **11 cases PZA** resistance was documented and emerged early; mean 7.3 weeks.

Allison ST. Pyrazinamide-isoniazid in low dosage in the treatment of pulmonary tuberculosis. Am Rev Tuberc Pulmon Dis 1956; 74: 400-405.

- Low **INH** dosage (**50 mg thrice daily**) and **PZA** (**0.5 g also thrice daily**)
- **69** PTB patients all "discharging tubercle bacilli in the sputum".
- **None previously treated**; Patients with abnormal LFT or alcohol problems excluded. LFT fortnightly.
- **LFT:** Serum bilirubin, thymol turbidity, cephalin flocculation, repeated fortnightly.

Randomization to:

- **INH/PZA (69 patients)**
- **SM 1 g** twice weekly and **PAS 12 g** daily (54 patients).
- Treatment duration not >8 months

Allison ST. Pyrazinamide-isoniazid in low dosage in the treatment of pulmonary tuberculosis.Am Rev Tuberc Pulmon Dis 1956; 74: 400-405.

Findings after 8 months of chemotherapy

Feature	PZA/INH (n=38)	SM/PAS (n-28)
Reversal of infectiousness	63%	54%
Substantial CR improvement	74%	54%
Drug resistance amongst positive cultures	50%	30%
Died	3%	7%

Allison ST. Pyrazinamide-isoniazid in low dosage in the treatment of pulmonary tuberculosis. Am Rev Tuberc Pulmon Dis 1956; 74: 400-405.

- In the INH/PZA group **5 (13%) patients developed LFT abnormalities; one became "very slightly" jaundiced (18 weeks). Of the remaining 4, 3 discontinued PZA after 2-5 months treatment.**

  In selecting patients for treatment with PZA those with a history of alcoholism, previous jaundice or liver disease should be excluded.

Phillips S, Horton GE. Pyrazinamide-isoniazid. Am Rev Tuberc 1956; 73: 704-714.

- **93 PTB** patients not previously treated with INH or PZA. Prior PAS accepted if not resistant.
- **LFT** before enrolment (bromsulphalien excretion).
- **38 INH&PZA** (retreatment 53%).
- **55 INH&PAS** (retreatment 47%).
- **PZA 3 g** daily in four 750 mg doses.

Phillips S, Horton GE. Pyrazinamide-isoniazid. Am Rev Tuberc 1956; 73: 704-714.

No emergence of INH resistance in the INH&PZA group.

1 case of INH resistance in INH&PAS, but culture negative later.

Regimen	Culture negative	
	4 months	8 months
INH&PZA	82%	91%
INH&PAS	67%	87%

Phillips S, Horton GE. Pyrazinamide-isoniazid. Am Rev Tuberc 1956; 73: 704-714.

- **Hepatotoxicity** in **5 (13.2%)** patients receiving PZA; **2** (5.1%) became **jaundiced**, in 3 increasing bromsulphalien retention.
  The occurrence of jaundice was preceded by increased bromsulphalein retention.
- None of the INH&PAS group developed any “serious toxicity”. 4 did have gastro-intestinal symptoms, but these resolved in 3 patients when PAS was temporarily stopped.

Phillips S, Horton GE. Pyrazinamide-isoniazid. Am Rev Tuberc 1956; 73: 704-714.

"…pyrazinamide-isoniazid is a very effective combination of drugs in the treatment of active pulmonary tuberculosis, but …**the combination offers little more than can be obtained…with a safer regimen such as isoniazid-PAS.**"

Phillips S, Horton GE. Pyrazinamide-isoniazid: Its apparent influence on the reactivation rate in pulmonary tuberculosis. Am Rev Respir Dis 1967; 95: 503-505.

However!

- **INH-PAS,** cumulative 10 year relapse rate **15%**

- **INH-PZA, 3%** and some doubt about this single case.

Morrisey JF, Rubin R. The detection of pyrazinamide-induced liver damage by serum enzyme determinations. Am Rev Respir Dis 1959; 80: 855-865.

- 86 patients far advanced PTB, 9 moderately advanced, received PZA 3 g daily in divided doses with INH.
- Therapy given in association with the Veterans Administration-Armed Forces studies.
- Bromsulphalein retention, cephalin flocculation and **SGOT** determined before therapy and regularly thereafter.

Morrisey JF, Rubin R. The detection of pyrazinamide-induced liver damage by serum enzyme determinations. Am Rev Respir Dis 1959; 80: 855-865.

- Significant enzyme elevations suggesting liver injury appeared in **19 (18.6%)**of the 102 courses of pyrazinamide administered to 95 patients.
- The frequency of elevated values before treatment was very similar to the frequency after start of treatment (approximately 15% elevated).

Morrisey JF, Rubin R. The detection of pyrazinamide-induced liver damage by serum enzyme determinations. Am Rev Respir Dis 1959; 80: 855-865.

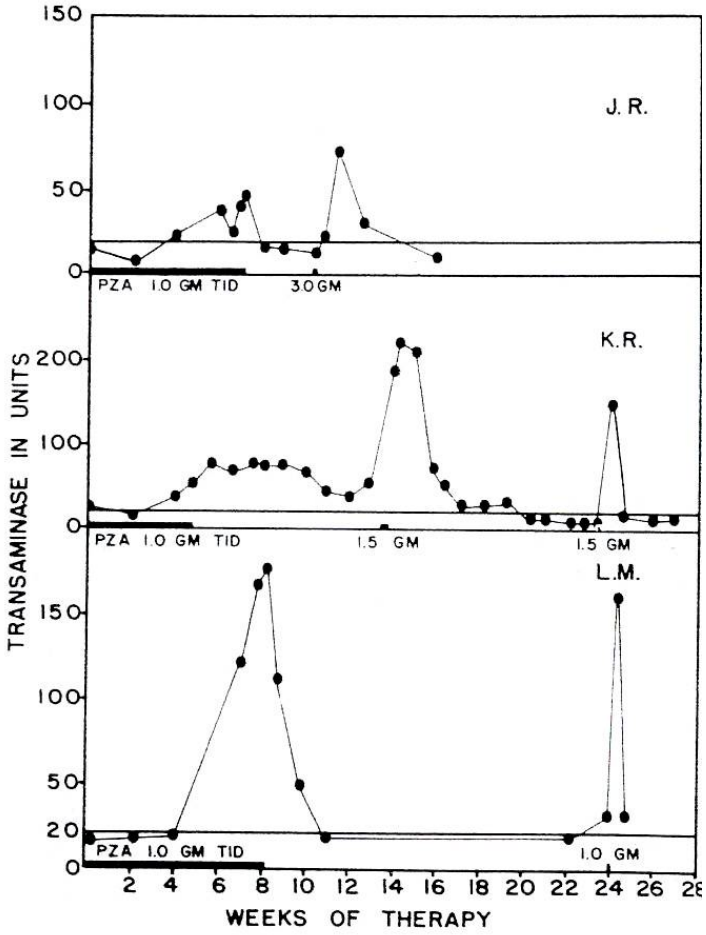

FIG. 1. Serum enzyme changes following test doses of pyrazinamide in 3 patients who developed hypersensitivity to the drug.

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387.

- This study attempted to resolve the dilemma of very positive reports of efficacy of the INH/PZA combination and the occurrence of significant hepatotoxicity.
- **Twenty** Public Health Service Tuberculosis Hospitals participated in the study and **780** patients were centrally **randomly** allocated to **five regimens**.
- Bacteriologically confirmed PTB
- No evidence of recognized liver disease.
- **(85%) of patients had previously failed treatment and more than 90% had far advanced cavitary PTB.**

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387.

- **Five** regimens evaluated
- The occurrence of hepatotoxicity assessed in the **645** patients.
- **LFT done**: Total serum bilirubin and cephalin cholesterol flocculation tests weekly and bromsulphalein retention evaluated at the beginning and end of the study period.

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387.

Each drug given daily in 2 or 3 doses

Regimen	Drugs	Duration (weeks)	n
1	INH&PZA (25 mg/kg)	24	160
2	INH&PAS	24	123
3	INH&PZA (25 mg/kg)	12	101
	Followed by INH&PAS	12	
4	INH&PZA (40 mg/kg)	24	167
5	INH&PZA (40 mg/kg)	12	91
	Followed byINH&PAS	12	

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387

Regimen	Drugs	Duration (weeks)	n	Hepatotoxicity (%)
1	INH & PZA. (25 mg/kg)	24	160	4 (2.5)
2	INH & PAS	24	123	1 (0.8)
3	INH & PZA.(25 mg/kg)	12	101	3 (3.0)
	Followed by INH & PAS	12		
4	INH & PZA.(40 mg/kg)	24	167	11 (6.6)
5	INH & PZA.(40 mg/kg)	12	91	2 (2.1)
	Followed by INH & PAS	12		

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387

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	Followed by INH & PAS	12		

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387.

Hepatic toxicity in 21 patients

- 20 received INH & PZA
- 5 completed therapy
- Only significant difference was INH&PAS vs INH&PZA 40 mg/kg for 24 weeks ($P<0.05$)

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis **1959**; 80: 371-387.

- Detailed account is given of each case of hepatotoxicity The majority occurred relatively late in therapy
- But **4 cases** did occur in the **first two months** therapy.
- "…24 weeks' administration of the 40 mg per kg dose resulted in a distinctly higher rate, (of hepatotoxicity), 6.6%."
- Although it was considered unlikely that the occurrence of hepatotoxicity was random, no precipitating factors could be identified in this patient population.

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387.

<u>6 patients developed jaundice.</u>

- 2/261 (0.77%) on PZA 25 mg/kg in 7^{th} and 12^{th} weeks;
- 4/258 (1.60%) on PZA 40 mg/kg in 19^{th},22^{nd}, 23^{rd} and 23^{rd} weeks

United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 1959; 80: 371-387

- "Reversal of infectiousness occurred too rarely to make comparisons of regimens useful"
- Hepatic toxicity was "highly selective".

Conclusion

"Therefore the participants in the United States Public Health Service Tuberculosis Therapy Trials have undertaken a controlled investigation of pyrazinamide's therapeutic effectiveness in combination with various antimicrobial agents as one segment of long-term chemotherapy."

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

- Studies of different PZA regimens showed an early, prompt and steady response to treatment

But

- Virtually no further change after 24 weeks
- A previous trial evaluated “swopping regimens”.
- No apparent effect when SM substituted for INH, but there was an effect when INH was substituted for SM

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

The relative infrequency of hepatitis early in therapy encouraged the evaluation of PZA in a similar switching investigation.

Regimen	First course (1-16 weeks)	Second Course (17-32 weeks)
1	INH-PAS	INH-PAS
2	INH-PAS	SM (biweekly)-**PZA**
3	INH-**PZA**	SM (biweekly)-PAS
4	SM (bi-weekly)-**PZA**	INH-PAS
5	SM (daily)-**PZA**	INH-PAS

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

- PZA dosage: **35-45 mg/kg**.
- PTB patients "**bacteriological proof"** with **no more than 2-weeks previous therapy.**
- INH 4-6 mg/kg
- SM 1g
- PAS 10-12 g
- Although routine LFT were not required, as the primary purpose was not an assessment of hepatotoxicity, they were usually performed regularly.

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

- Minimal disease 10%
- Failure to grow Mtb 17%
- **No previous TB chemotherapy 95%**
- 1882 entered the course; **toxicity assessed 1654**
- 1492 entered the 2nd course; **toxicity assessed in 1229**

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

- **1236** patients received **PZA**&SM or **PZA**&INH
- **58 (4.7%)** were intolerant.
- **48 (3.9%)** developed hepatitis; **2 deaths**
- "…severity of the hepatic episode was directly related to the duration of treatment"
- **14** of **29** instances of severe hepatitis detected between the **12^{th}-16^{th}** treatment weeks.

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

Length of treatment before hepatitis in PZA recipients.

	Severity of reaction			
	Marked	Moderate	Mild	Very mild
N	19	10	11	8
Mean weeks	12.4	10.3	9.5	7.2

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

Regimen 5 (SM&PZA) produced the most rapid reversal of culture positivity

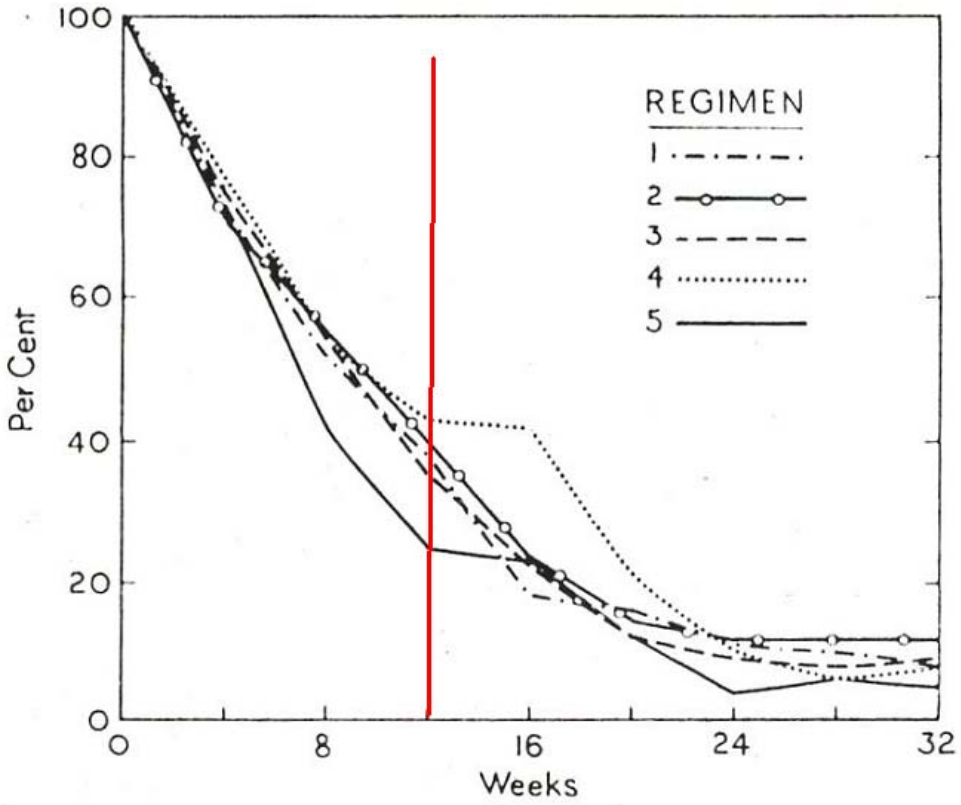


FIG. 7. Percentage of cultures positive for tubercle bacilli among patients treated on 5 regimens.

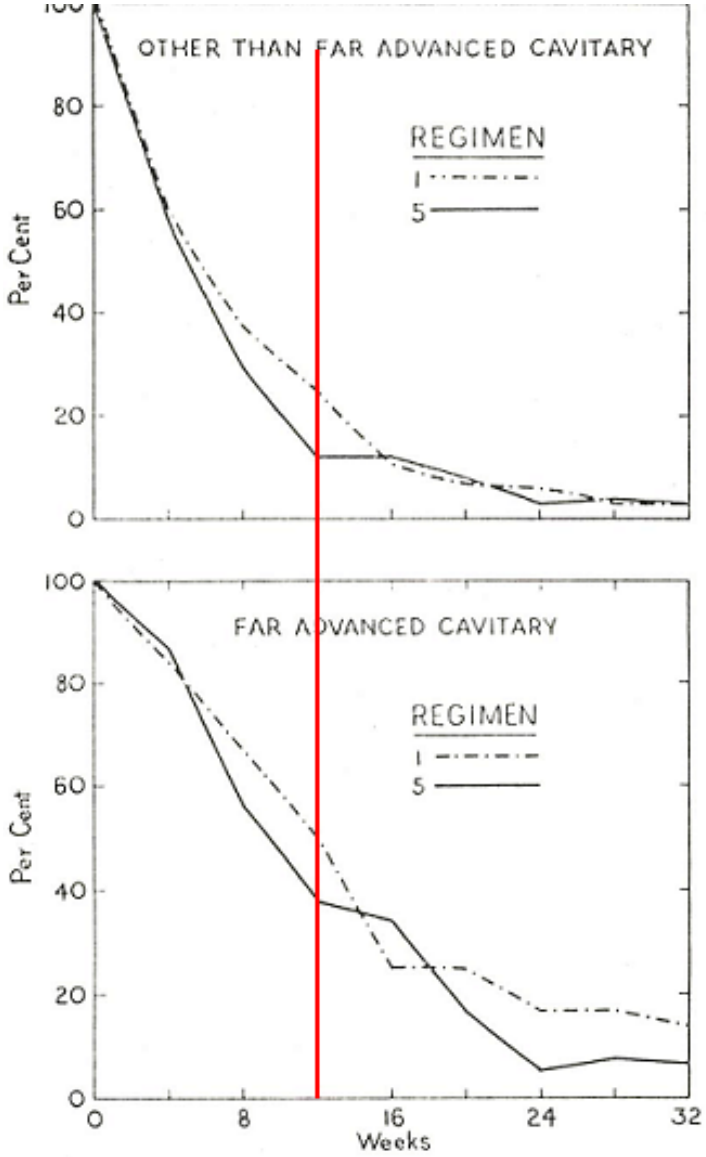


FIG. 11. Percentage of cultures positive for tubercle bacilli during thirty-two weeks of treatment with isoniazid—PAS and with daily streptomycin—pyrazinamide followed by isoniazid—PAS, among patients divided by type of disease on admission.

United States Public Health Service. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid and pyrazinamide. Am Rev Respir Dis 1959; 80: 627-640.

Appearance of resistance to INH

INH&PAS: weeks 0-16. 2.0%

INH&PZA: " . 10.8%

Appearance of resistance to SM

SM twice weekly &PZA. 9.6%

SM daily & PZA. 10.5%

Macleod HM, Hay D, Stewart SM. The use of pyrazinamide plus isoniazid in the treatment of pulmonary tuberculosis. Tubercle 1959; 40: 14-20.

- 11 PTB patients, 5 in “poor condition”, with extensive bilateral disease received **PZA 40 mg/kg** two divided doses for 2-24 months. 5 with INH resistant isolates.
- INH 100 mg twice daily.
- **Hepatitis** in **2 (18.2%)** cases after **2 months** and **8 months** treatment.
- **Serum bilirubin rose** but neither patient was clinically jaundiced. Treatment stopped in one patient. In the other patient the only abnormality was a rise in bilirubin; treatment continued without further incident and the bilirubin returned to normal.
- 2 (INH susceptible) converted permanently.

Matthews JH. Pyrazinamide and isoniazid used in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1960; 81: 348-351.

- Active PTB producing *M tuberculosis* "as demonstrated by sputum or gastric cultures"
- Random allocation to receive:
- INH 300 mg & PAS 12 g daily (**237** patients)
- INH 300 mg & **PZA 3 g daily** (**219** patients)

- Results presented for the first **4 months.**
- No significant differences between the groups in their treatment response.

Matthews JH. Pyrazinamide and isoniazid used in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1960; 81: 348-351.

% Culture conversion			
Regimen	2-4 months	5-8 months	9-12 months
INH&PAS	45	73	93
INH&PZA	41	78	96

Matthews JH. Pyrazinamide and isoniazid used in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1960; 81: 348-351.

Emergence of resistance

- Months 0-4: INH&PAS 1%; INH&PZA 4%
- Months 5-8: INH&PAS 3%; INH&PZA 4%

Toxicity

INH&PAS: 19 (7%) mainly GI intolerance

INH&**PZA**: PZA discontinued in 35 (13%);

- **21 (8%) hepatocellular damage** - abnormal LFT, but LFT not identified.
- An additional **6 (2.7%)** jaundiced.

Matthews JH. Pyrazinamide and isoniazid used in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1960; 81: 348-351.

"…while pyrazinamide-isoniazid is an effective drug combination , it does not result in sufficient superiority to justify its routine use in the treatment of pulmonary tuberculosis in view of the established hepatotoxicity of pyrazinamide."

Velu S, Andrews RH, Devadatta S, Fox W, Ramakrishnan CV, SubbaiahTV. The results of treatment with streptomycin plus pyrazinamide in patients with active pulmonary tuberculosis despite prolonged treatment with isoniazid plus PAS. Ind J Tuberc 1960; 7: 85-94.

- **SM 1 g daily /PZA 30-40 mg/kg in a single dose 6 days weekly**
- **20 PTB** patients with advanced disease, sputum culture-positive for *M tuberculosis* in Madras (Chennai) India.
- All previously failed the combination of INH/PAS.
- Drugs given under clinic supervision, with a single dose being given to the patient to take at home. Four patients spent part of the treatment period in a sanatorium, but the majority received their treatment in the community.

Velu S, Andrews RH, Devadatta S, Fox W, Ramakrishnan CV, SubbaiahTV. The results of treatment with streptomycin plus pyrazinamide in patients with active pulmonary tuberculosis despite prolonged treatment with isoniazid plus PAS. Ind J Tuberc **1960**; 7: 85-94.

- **6 patients** had their treatment changed due to failure to respond bacteriologically and one other patient because of radiological deterioration.
- Sputum cultures were done on an average of 2.7 per month and there was an immediate fall in the bacterial content of the sputum.
- At **2 months** only **1 (5%)**of the **20** patients produced sputum positive on culture.
- However at **3** and at **6 months 7 (35%)**patients had positive sputum cultures.
- At one year **10 (50%)** of **20** patients had sputum positive on culture and all positive cultures were SM resistant.
- **No patients developed signs or symptoms of hepatotoxicity.**

Velu S, Andrews RH, Angel JH, et al. Streptomycin plus pyrazinamide in the treatment of patients excreting isoniazid-resistant tubercle bacilli, following previous chemotherapy. Tubercle 1961; 42: 136-147.

57 "chronic PTB" patients, all previously treated with INH&PAS or INH monotherapy. (20 derived from the Previous paper)

Daily SM & PZA **1.0-1.5 g daily** (range13-39 mg/kg) minimum of 1 year and maximum 2 years.

At 1 month **42%** culture negative

2 months **75%** "

3 months **60%** "

12 months **58%** "

No benefit in 20 patients; treatment stopped

Velu S, Andrews RH, Angel JH, et al. Streptomycin plus pyrazinamide in the treatment of patients excreting isoniazid-resistant tubercle bacilli, following previous chemotherapy. Tubercle 1961; 42: 136-147.

- Urine examined for bilirubin twice weekly.
- If positive spectroscopic test for bilirubin was done
- No symptoms or signs of hepatotoxicity were detected.
- Weakly positive urine test for bilirubin in 7 (12%) patients during first 3 months of treatment, but spectroscopy for urobilin negative

Velu S, Andrews RH, Angel JH, et al. Streptomycin plus pyrazinamide in the treatment of patients excreting isoniazid-resistant tubercle bacilli, following previous chemotherapy. Tubercle 1961; 42: 136-147.

- By the end of 1 month **6** of **27** strains were SM resistant
- At 2 and 6 months **12 of 14** strains tested were SM resistant.

British Tuberculosis Association. An investigation of the value of ethionamide with pyrazinamide or cycloserine in the treatment of chronic pulmonary tuberculosis. Tubercle 1961; 42: 269-286.

Regimen	n	>LFT	Jaundice
Eth/PZA	32	9	2
Eth/Cs	22	0	0

Petty TL, Mitchell RS. Successful treatment of advanced isoniazid- and streptomycin-resistant pulmonary tuberculosis with ethionamide, pyrazinamide , and isoniazid. Am Rev Respir Dis 1962; 86: 503-512

- **70 PTB** patients studied at 6 hospitals selected solely on basis of **SM** & **INH resistance**.
- PZA: **2.0 g** single dose (minority 1.5-3 g in divided doses). **ETH**: 0.5-1.0 g daily in single or divided doses. **INH** 16-20 mg/kg added in some cases.
- Patients enrolled for < 3 months excluded
- Treatment for **3-18** months, but patients observed to **27** months.
- "Transaminases, alkaline phosphatase and blood urea nitrogen" fortnightly.

Petty TL, Mitchell RS. Successful treatment of advanced isoniazid- and streptomycin-resistant pulmonary tuberculosis with ethionamide, pyrazinamide , and isoniazid. Am Rev Respir Dis 1962; 86: 503-512

- **27** patients excluded; variety of reasons.
- **23 (53.4%)** of **43** achieved sustained reversal of “infectioness”. 14 failures and 6 relapses.
- **Toxicity** assessed in all 70 patients. **12 (17%)** experienced transient LFT abnormalities “presumably related “to PZA. PZA resumed in 8 cases. **One patient developed jaundice and died**; had considerable problems with alcohol and non-compliance.

Petty TL, Mitchell RS. Successful treatment of advanced isoniazid- and streptomycin-resistant pulmonary tuberculosis with ethionamide, pyrazinamide , and isoniazid. Am Rev Respir Dis 1962; 86: 503-512

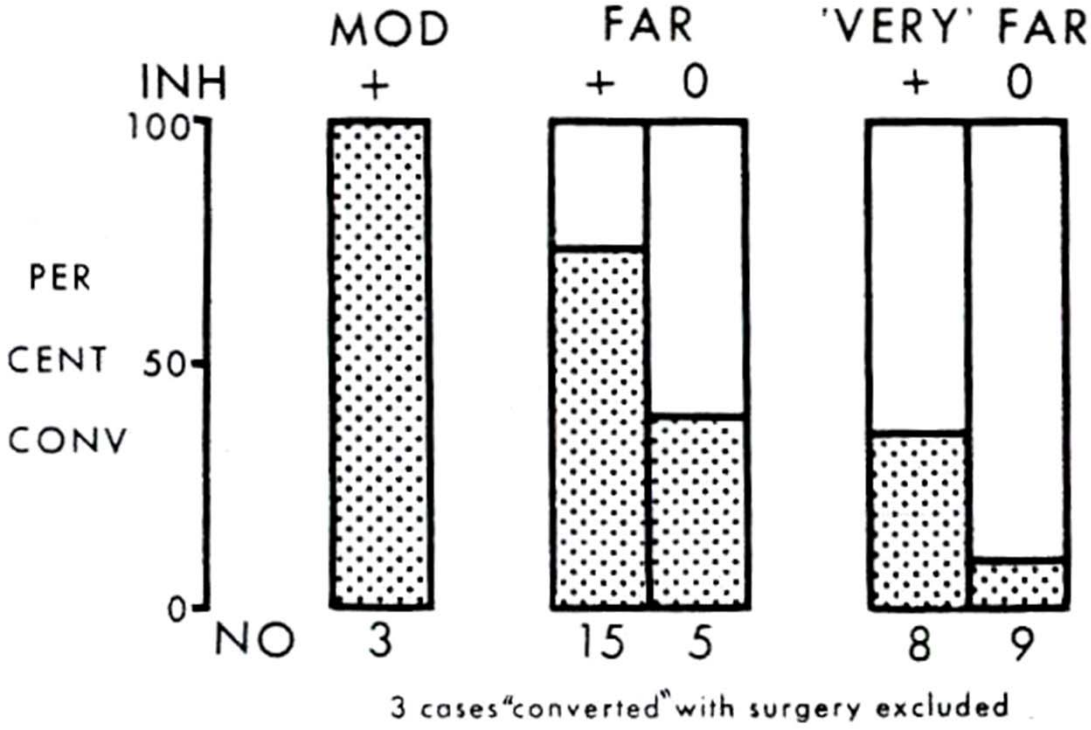


FIG. 1. Bacteriologic "conversion" with ethionamide-pyrazinamide by extent of disease and use of isoniazid (INH). MOD—moderately advanced; FAR—far advanced; 'VERY' FAR—very far advanced.

Brown M, Beuchner HA. Clinical experience with the routine use of serum glutamic-oxalacetic transaminase in all tuberculosis patients under chemotherapy. Transactions of the 26th VA-Armed Forces pulmonary disease research conference. 1967:1-2.

- Routine monitoring of liver function in 139 TB patients consecutively admitted.
- Pretreatment and monthly serum glutamic oxalacetic transaminase. (>40 units).

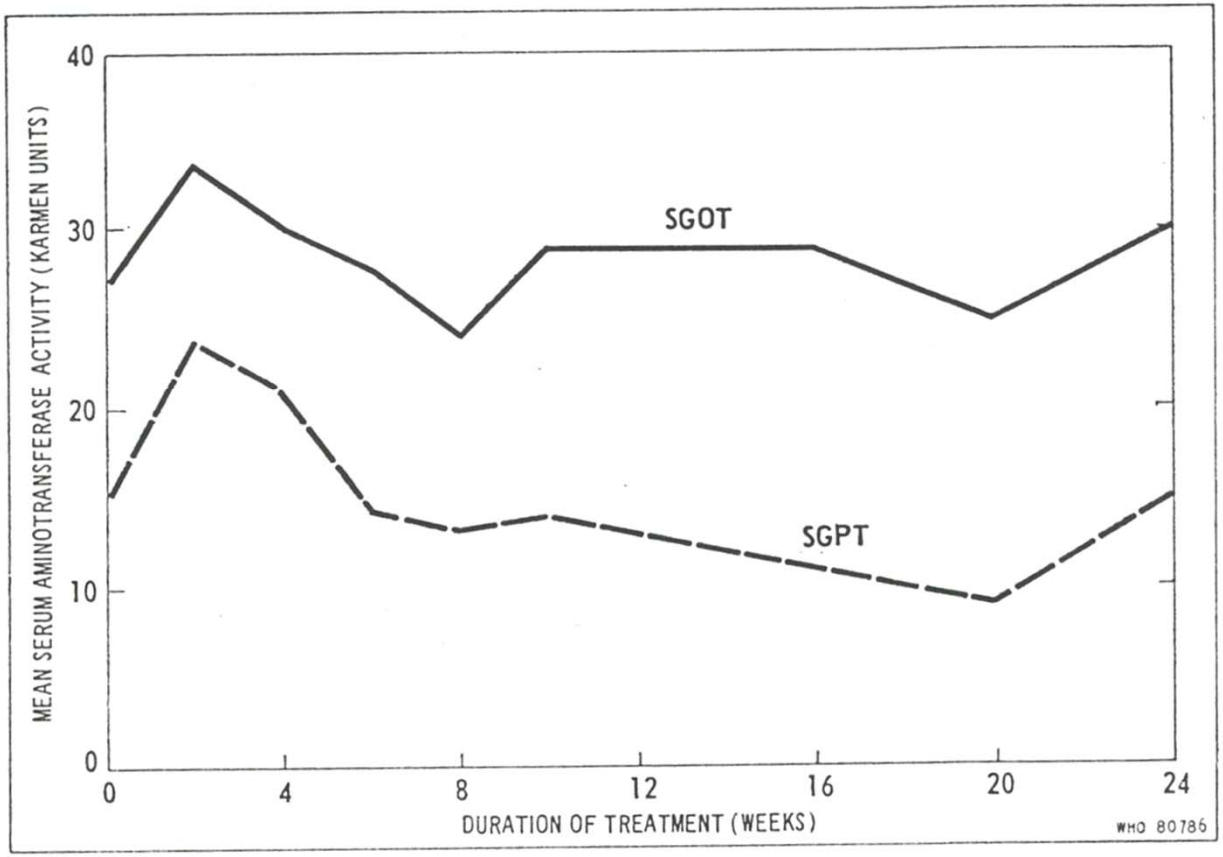
Brown M, Beuchner HA. Clinical experience with the routine use of serum glutamic-oxalacetic transaminase in all tuberculosis patients under chemotherapy. Transactions of the 26th VA-Armed Forces pulmonary disease research conference. 1967:1-2.

- **15 (10.8%)** patients had an "objective clinical drug reaction"; **68%** of these had an associated unsuspected increase in SGOT.
- **11%** increased transaminase values without any clinical findings.
- Not one case of jaundice.
- **PZA (43%)** & ethionamide (20%) had the highest associated incidence of increased LFT values.

Ramakrishnan CV, et al. Toxicity of pyrazinamide administered once weekly in high dosage in tuberculous patients. Bull Wld Hlth Org 1968; 39: 775-779.

19 patients receiving PZA 70 mg/kg once weekly

MEAN SERUM AMINOTRANSFERASE ACTIVITY ON ADMISSION AND DURING 24 WEEKS OF TREATMENT



East African/British Medical Research Council. A controlled comparison of four regimens of streptomycin plus pyrazinamide in the retreatment of pulmonary tuberculosis. Tubercle 1969; 50: 81-115.

- 1. (SZ) SM 1.0 g daily/**PZA 1.5 g** given in **divided doses thrice daily** (**66** patients),
- 2. (SZ-1) SM 1.0 g daily/**PZA 1.5 g** given **once daily** (**72** patients),
- 3. (SZ3) SM 1.0 g daily/**PZA 3.0 g** given **once daily thrice weekly** (**73** patients)
- 4. (S3Z3) SM 1.0 g thrice weekly/**PZA 3.0 g** given **once daily thrice weekly** (**76** patients)
- Mean daily dosage approximately **31 mg/kg**

East African/British Medical Research Councils. A controlled comparison of four regimens of streptomycin plus pyrazinamide in the retreatment of pulmonary tuberculosis. Tubercle 1969; 50: 81-115.

While none of the regimens proved have satisfactory efficacy, PZA efficacy appeared to improve as the size of the PZA dosage increased

Feature at 6 months	SZ	SZ-1	SZ_3	P
Culture negative	42%	44%	58%	0.07
SM resistance	60%	55%	40%	0.02
PZA resistance	33%	31%	25%	
Unfavourable response[#]	59%	52%	48%	0.10

East African/British Medical Research Councils. A controlled comparison of four regimens of streptomycin plus pyrazinamide in the retreatment of pulmonary tuberculosis. Tubercle 1969; 50: 81-115.

Toxicity

Mean SGOT values (Karmen units) did not differ between groups. Treatment suspended in 3 patients with elevated SGOT, but recommenced without incident. **No jaundice was encountered**. Values of 50 units or more were found in 20% of patients before treatment was started

	Admission	3 months	6 months
SZ	33.8	37.5	40.1
SZ1	32.9	41.3	30.5
SZ3	32.3	35.6	25.8

Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. Antimicrob Agents Chemother 2010; 54: 2847-2854.

Extensive meta-analysis of the toxicity of PZA particularly in relation to PZA dosage.

- Persistence of concentration above some pharmacokinetic thresholds associated with overall adverse events (p=0.032), arthralgia (p=0.089) and elevated AST at 3 months (p=0.067)

Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. Antimicrob Agents Chemother 2010; 54: 2847-2854.

- The time concentration persisting above some thresholds was associated with overall adverse events such as arthralgia and an elevated AST level at 3 months.
- Arthralgia dose-dependent for once daily dosing, but less common with intermittent dosing.
- Higher dosages of pyrazinamide did not appear to significantly increase hepatotoxicity.

PZA dosage vs Hepatotoxicity

30 mg/kg 0.042 (CI 0.026-0.067)

40 mg/kg 0.055 (CI 0.031-0.094)

60 mg/kg 0.098 (CI 0.047-0.193)

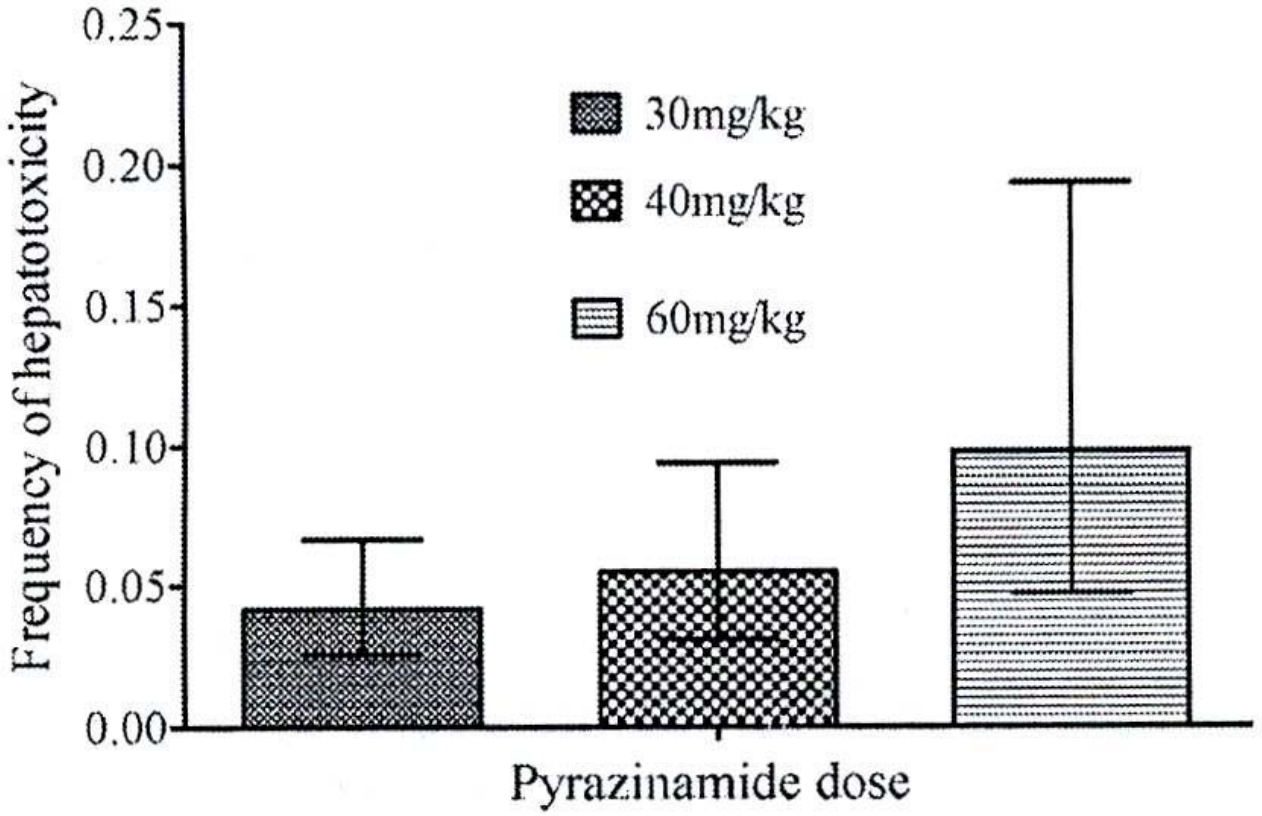


FIG. 5. Frequency of hepatotoxicity events with daily regimens of low (≥30 mg/kg), medium (40 mg/kg), and high (60 mg/kg) pyrazinamide doses.

Conclusion

- **PZA does cause hepatotoxicity.**
- **This appears to be more common when PZA is given together with INH or RMP.**
- **PZA toxicity is probably dosage related.**
- **Combination with antituberculosis agents in development?**


Thank You