Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1968, 39, 775-779

Toxicity of Pyrazinamide, Administered Once Weekly in High Dosage, in Tuberculous Patients*

C. V. RAMAKRISHNAN, B. JANARDHANAM, D. V. KRISHNAMURTHY,[1] H. STOTT,[2] S. SUBBAMMAL & S. P. TRIPATHY

The success of a twice-weekly regimen of streptomycin plus isoniazid, reported earlier from the Tuberculosis Chemotherapy Centre, Madras, prompted an investigation at the Centre of various once-weekly regimens of chemotherapy. In this context, a pilot study was undertaken in 19 patients to assess the toxicity of high-dosage pyrazinamide (70 mg/kg of body-weight), when administered once weekly, together with isoniazid (14 mg/kg of body-weight) and streptomycin (1 g), for at least 6 months. Serial estimations of SGOT and SGPT activity, urine tests for urobilin and bilirubin and haematological investigations were undertaken at frequent intervals. None of the patients showed any clinical evidence of hepatotoxicity; however, there was a slight and transient elevation in aminotransferase activity, probably of a non-specific nature, at 2 weeks. These findings are encouraging for the use of high-dosage pyrazinamide in once-weekly regimens of chemotherapy.

INTRODUCTION

Intermittent chemotherapy with 1 g of streptomycin plus isoniazid in high dosage (approximately 14 mg/kg of body-weight), both drugs being given together twice weekly, has been found to be highly effective in the treatment of pulmonary tuberculosis at this Centre (Tuberculosis Chemotherapy Centre, Madras, 1964; Nazareth et al., 1966). Since a regimen with a longer interval between the doses would offer further practical advantages, a study was planned to investigate the principle of once-weekly chemotherapy. One of the regimens in this study was streptomycin plus isoniazid plus pyrazinamide, all three drugs given together once a week. It was proposed to administer the pyrazinamide also in a high dosage, but since the drug is hepatotoxic in conventional daily dosages (McDermott et al., 1954; Morrissey & Rubin, 1959; United States Public Health Service, 1959), a pilot study was undertaken to assess its toxicity when administered once weekly in a dosage of approximately 70 mg/kg of body-weight, together with 1 g of streptomycin and 14 mg of isoniazid per kg of body-weight.

This paper reports the findings in 19 patients with bacteriologically confirmed pulmonary tuberculosis, none of whom had received pyrazinamide previously. Of these, 14 were males; 13 were aged 35 years or more. On admission, 3 patients weighed less than 70 lb (31.75 kg), 7 weighed 70 lb–89 lb (31.75 kg–40.4 kg) and 9 weighed 90 lb (40.8 kg) or more.

Treatment regimen

Once a week, all patients received 1 g of streptomycin (irrespective of body-weight), 14 mg of isoniazid per kg of body-weight and pyrazinamide (as in the schedule below):

Body-weight (lb)	[*Approx. kg equivalent*]	*Pyrazinamide dosage (g)*
<70	[<32]	2.0
70–89	[32–40]	2.5
≥90	[≥40]	3.0

The mean initial dosage of pyrazinamide was 68 mg/kg, the range being 55 mg/kg to 78 mg/kg. If, at a monthly examination, a patient was found to have gained weight since the previous monthly examination and moved into a higher weight

* From the Tuberculosis Chemotherapy Centre, Madras-31, India. The Centre is under the joint auspices of the Indian Council of Medical Research, the Madras State Government, and the World Health Organization in collaboration with the Medical Research Council of Great Britain.

[1] Present address: Syntex Research Centre, Palo Alto, Calif., USA.

[2] Present address: Tuberculosis and Chest Diseases Research Unit (Medical Research Council), London, England.

category, the dosage of pyrazinamide was increased; however, the dosage was not decreased for loss in weight.

Duration of treatment

The regimen was prescribed for 6 months in the first instance. Subsequently, it was continued up to 12 months unless the clinical, radiographic or bacteriological findings warranted a change of chemotherapy. In the event, 4 patients had their treatment changed at 6 months, 1 at 7 months and 3 at 11 months; thus, only 11 patients completed the year of treatment.

Management

The patients were managed on an ambulatory basis and attended the clinic once a week, at which time they swallowed a dose of isoniazid and of pyrazinamide under the supervision of a clinic nurse; they then received an injection of streptomycin. Patients were not interrogated to elicit symptoms of side-effects from the drugs but all spontaneous complaints were recorded.

Investigations

Routine clinical, radiographic and bacteriological examinations were undertaken at monthly intervals during the year. In addition, the following investigations were undertaken to assess toxicity:

(1) Serum L-aspartate : 2-oxoglutarate aminotransferase [1] (serum glutamic-oxaloacetic transaminase; SGOT) activity and serum L-alanine : 2-oxoglutarate aminotransferase [1] (serum glutamic-pyruvic transaminase; SGPT) activity, were determined on specimens of blood collected (*a*) before the start of chemotherapy, (*b*) on days 1 and 8 (i.e., about 24 hours *after* the first and second doses, respectively) and (*c*) at 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 weeks after the start of treatment and at intervals of 4 weeks thereafter (immediately *before* the administration of the dose of pyrazinamide on that day).

The SGOT and SGPT activities were determined by employing the procedures described by the Sigma Chemical Company (1961), and were expressed in Karmen units. Since normal values of SGOT and SGPT activity are defined as 8–40 units and 5–35 units, respectively, and values of 40–50 and 35–45 units, respectively, are regarded as border-line (see Sigma Chemical Company, 1961), SGOT values of over 50 units and SGPT values of over 45 units have been regarded as abnormal in the present study.

(2) A test for the presence of bilirubin (Sobotka et al., 1953) and a spectroscopic examination for urobilin (Harrison, 1957) were undertaken in urine specimens collected at weekly intervals.

(3) Estimations of the haemoglobin and packed cell volume (PCV) were undertaken before the start of chemotherapy, at 1, 2, 3, 4, 6, 8, 10 and 12 weeks, and at intervals of 4 weeks thereafter.

RESULTS

Clinical toxicity

There was no clinical evidence of liver toxicity in any of the 19 patients. Vomiting, following the administration of the drugs, was the only complaint recorded, and occurred once in 1 patient and 3 times in 2 others.

Serum aminotransferase activity in the first 6 months

SGOT. The mean SGOT activity on admission was 27 units, the range being 14–54 units (see accompanying table). With the commencement of treat-

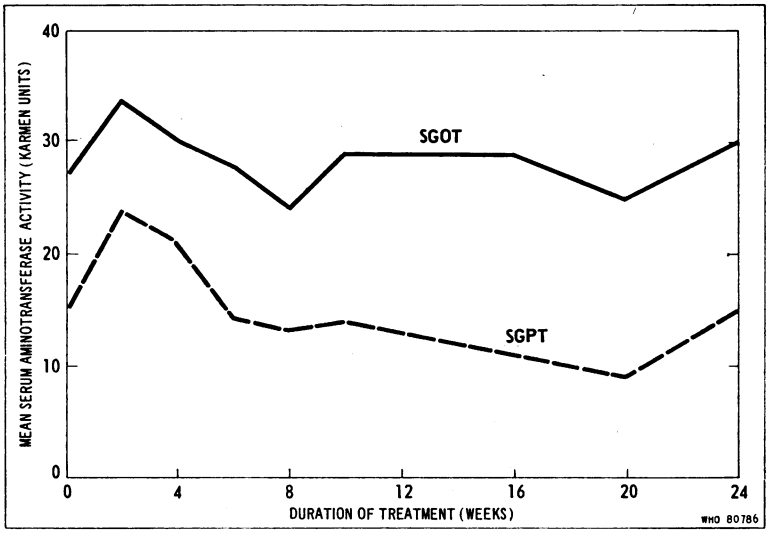
SGOT AND SGPT VALUES ON ADMISSION AND DURING TREATMENT

Time of blood collection	No. of patients examined[a]	SGOT activity (Karmen units)		SGPT activity (Karmen units)	
		Mean	Range	Mean	Range
On admission	19	27	14–54	15	6–31
1 day	17	28	15–52	15	6–37
8 days	19	31	17–74	18	2–58
2 weeks	17	34	17–52	24	4–43
3 weeks	19	28	13–48	19	5–42
4 weeks	18	30	13–84	21	8–63
6 weeks	18	28	11–71	14	2–56
8 weeks	18	24	16–36	13	0–24
10 weeks	19	29	18–69	14	0–54
12 weeks	18	29	15–60	13	0–34
16 weeks	18	29	13–56	11	0–26
20 weeks	19	25	10–49	9	0–31
24 weeks	19	30	19–58	15	4–42
28 weeks	14	28	16–52	14	0–43
32 weeks	13	33	20–56	16	7–31
36 weeks	9	38	31–48	20	9–31
40 weeks	12	31	18–46	15	4–37
44 weeks	14	29	16–49	15	0–30
48 weeks	14	32	22–49	17	4–38
52 weeks	11	34	22–72	18	4–38

[a] Patients who had a change of chemotherapy on account of clinical or radiographic deterioration or the bacteriological results have been included up to the time of change.

[1] Terminology recommended by the Commission on Enzymes of the International Union of Biochemistry (Florkin & Stotz, 1965).

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



ment, the mean SGOT activity showed a significant increase to 34 units at 2 weeks ($P = 0.02$), followed immediately by a decrease to almost the value on admission (see accompanying figure).

Considering the findings in individual patients (not tabulated here), an SGOT value of higher than 50 units was repeatedly obtained during treatment (namely, on 8 of 12 occasions) in only 1 patient; however, this patient had an SGOT value of 54 units on admission. Only 4 others had a value higher than 50 units during treatment, all on 1 occasion only—1 at 8 days, 2 at 2 weeks and 1 at 4 weeks. Finally, in none of the patients did the treatment mean (that is, the mean of all values during treatment) exceed the value on admission by 10 units or more.

SGPT. The mean SGPT activity was 15 units on admission, the range being 6–31 units (see accompanying table). It increased significantly ($P < 0.01$) to 24 units at 2 weeks, was still high at 4 weeks (21 units) but decreased subsequently to the mean value at the time of admission.

The patient with an SGOT of higher than 50 units on admission had an SGPT of 31 units at this time, and an SGPT of higher than 45 units in 3 of 12 specimens collected during treatment. Only 2 other patients had an SGPT of higher than 45 units during treatment, both on 1 occasion only (at 8 days and 4 weeks) and both associated with an SGOT activity of more than 50 units. Finally, in none of the patients did the treatment mean exceed the value on admission by 10 units or more.

Serum aminotransferase activity in patients who continued to receive the prescribed regimen up to 12 months

Of the 11 patients who received the prescribed regimen for 12 months, none had clinical evidence of liver damage. The mean SGOT activities in these patients were 32, 34, 33 and 34 units at 0, 12, 24 and 52 weeks, respectively; the corresponding mean SGPT values were 17, 15, 18 and 18, respectively.

Between 24 and 52 weeks, the SGOT value was higher than 50 units in only 2 patients, one at 28 and 32 weeks, and the other (who had a value of 54 units on admission) at 32 weeks; the SGPT value was higher than 45 units in none.

Bilirubin and urobilin in urine

Only 2 urine specimens were positive for bilirubin. Both were obtained in the first month and from the same patient. Positive results for urobilin were obtained from 2 others, both in the third month. All the 3 patients had SGOT values of 50 units or less at the time; they continued to receive the regimen for 52 weeks and had no evidence of toxicity.

Haematological examinations

The mean haemoglobin value was 12.0 g per 100 ml on admission, and steadily increased to 13.0 g at

12 weeks, 13.8 g at 24 weeks and 14.3 g at 52 weeks. The corresponding PCV values were 39%, 39%, 42% and 41%, respectively.

DISCUSSION

Hepatotoxicity resulting from daily administration of pyrazinamide has been reported by earlier workers (McDermott et al., 1954; Morrissey & Rubin, 1959; Allison, 1959). The United States Public Health Service (1959) showed that the incidence of hepatotoxicity due to pyrazinamide was related to the daily dosage of the drug; thus, 4.8% of 167 patients who received 40 mg of pyrazinamide per kg of body-weight for 24 weeks developed clinical evidence of hepatic damage, as compared with only 1.2% of 160 patients who received 25 mg/kg of body-weight for the same duration. At this Centre, however, there was no clinical evidence of hepatotoxicity in a group of South Indian patients treated with a daily regimen of pyrazinamide ranging from 26 mg to 43 mg/kg of body-weight (average, 33.0 mg/kg) plus streptomycin for 1-2 years (Velu et al., 1961).

The present study was undertaken in 19 patients to determine the incidence of toxicity with once-weekly pyrazinamide in a dose of approximately 70 mg/kg of body-weight. Routine estimations of serum aminotransferase activity, reported to be of value in the early detection of hepatotoxicity due to pyrazinamide (Wingo et al., 1957), were undertaken for all patients at frequent intervals. There was a rise in the mean SGOT and SGPT values at 2 weeks followed by a fall to the values recorded on admission. It is possible that this rise in the aminotransferase activity at 2 weeks may be of a non-specific nature, similar to the transient rise in aminotransferase activity observed with drugs such as penicillin, viomycin and *p*-aminosalicylic acid (Morrissey & Rubin, 1959), and with oral contraceptives, certain hypotensive and vasodilator drugs, and carbenoxolone sodium (Sherlock, 1968). Excluding the patient who had a high SGOT value on admission, 4 patients showed a rise in SGOT activity to greater than 50 units during treatment, all on 1 occasion; the corresponding number showing a rise in SGPT activity to more than 45 units was 2, both showing it on 1 occasion only.

In conclusion, there was no clinical evidence of hepatotoxicity; however, there was a slight and transient elevation in aminotransferase activity at 2 weeks, which could have been of a non-specific nature. Haematological investigations showed no evidence of anaemia, nor did urine tests for bilirubin and urobilin show any evidence of toxicity.

ACKNOWLEDGEMENT

We are grateful to the medical and nursing staff who arranged for the collection of blood and urine specimens.

RÉSUMÉ

Des études menées au Centre de Chimiothérapie de la tuberculose de Madras, Inde, ont montré qu'administrée à raison de deux fois par semaine, la chimiothérapie intermittente au moyen d'une association de streptomycine et de hautes doses d'isoniazide (environ 14 mg par kg de poids corporel) donnait d'excellents résultats dans le traitement de la tuberculose pulmonaire. Etant donné qu'il y aurait de réels avantages à prolonger encore l'intervalle séparant les prises de médicament, il a été décidé d'étudier des thérapeutiques susceptibles d'être administrées une fois par semaine. L'un des traitements proposés comportait l'administration de pyrazinamide à hautes doses, mais ce médicament étant hépatotoxique aux doses quotidiennes usuelles, il était important d'évaluer sa toxicité lorsqu'il était administré une fois par semaine à raison d'environ 70 mg/kg en association avec la streptomycine et l'isoniazide.

On a constitué un groupe de 19 malades dont 13 âgés de 35 ans ou plus, comprenant 14 hommes, atteints de tuberculose pulmonaire confirmée par les examens bactériologiques et dont aucun n'avait encore été traité à la pyrazinamide. Les malades se présentaient une fois par semaine dans un dispensaire et recevaient, sous surveillance, de la streptomycine (1 g), de l'isoniazide (14 mg/kg) et de la pyrazinamide (dose initiale moyenne: 68 mg/kg, variation: 55 mg/kg à 78 mg/kg). Le traitement a tout d'abord duré six mois, mais ensuite on l'a continué pendant six mois encore chez 11 sujets.

Les malades ont été régulièrement soumis chaque mois à des examens bactériologiques, radiographiques et

cliniques et toutes les plaintes concernant des effets secondaires formulées spontanément ont été consignées. En outre, les examens suivants ont été effectués en vue d'évaluer l'hépatotoxicité de la médication: *a*) épreuves d'activité de la transaminase glutamique-oxalacétique (SGOT) et de la transaminase glutamique-pyruvique (SGPT); *b*) recherche de la bilirubine et de l'urobiline, et *c*) évaluation du taux d'hémoglobine et du volume globulaire à l'hématocrite.

Les épreuves n'ont révélé de manifestation clinique d'hépatotoxicité chez aucun des 19 malades; les médicaments n'ont pas eu d'autres effets secondaires que quelques vomissements: une fois chez un malade et trois fois chez deux autres. Les valeurs de la SGOT et de la SGPT ont augmenté de façon significative au cours des deux premières semaines du traitement, mais elles sont ensuite redescendues aux environs de la valeur moyenne enregistrée avant le début du traitement. Aucun des 11 malades dont le traitement a été poursuivi pendant 12 mois n'a présenté de signes cliniques de toxicité hépatique. On a trouvé deux échantillons d'urine contenant de la bilirubine pendant le premier mois de traitement chez un malade et la recherche de l'urobiline a été positive chez deux autres au cours du troisième mois, mais on a poursuivi leur traitement sans constater aucune manifestation d'hépatotoxicité. Le taux moyen d'hémoglobine dans le sang des malades était de 12 g/100 ml au moment de l'admission; il est monté à 13 g à la 12e semaine, 13,8 g à la 24e semaine et 14,3 g à la 52e semaine; les chiffres correspondants pour le volume globulaire étaient de 39%, 39%, 42% et 41%.

Il apparaît donc que si la pyrazinamide peut être hépatotoxique aux doses quotidiennes usuelles, les examens de laboratoire n'ont fourni que peu d'indications d'hépatotoxicité lorsque le médicament était administré à des doses hebdomadaires élevées (environ 70 mg/kg).

REFERENCES

Allison, S. T. (1959) *Amer. Rev. Tuberc.*, **79**, 102

Florkin, M. & Stotz, E. H., ed. (1965) *Comprehensive biochemistry, Vol. 13, Enzyme nomenclature*, 2nd ed., Amsterdam, Elsevier, p. 106

Harrison, G. A. (1957) *Chemical methods in clinical medicine*, 4th ed., London, Churchill, p. 78

McDermott, W., Ormond, L., Muschenheim, C., Deuschle, K., McCune, R. M., Jr & Tompsett, R. (1954) *Amer. Rev. Tuberc.*, **69**, 319

Morrissey, J. F. & Rubin, R. C. (1959) *Amer. Rev. resp. Dis.*, **80**, 855

Nazareth, O., Devadatta, S., Evans, C., Fox, W., Janardhanam, B., Menon, N. K., Radhakrishna, S., Ramakrishnan, C. V., Stott, H., Tripathy, S. P. & Velu, S. (1966) *Tubercle (Edinb.)*, **47**, 178

Sherlock, S. (1968) *Brit. med. J.*, **1**, 227

Sigma Chemical Company (1961) *Sigma techn. Bull.*, **505**

Sobotka, H., Luisada-Opper, A. V. & Reiner, M. (1953) *Amer. J. clin. Path.*, **23**, 607

Tuberculosis Chemotherapy Centre, Madras (1964) *Bull. Wld Hlth Org.*, **31**, 247

United States Public Health Service (1959) *Amer. Rev. resp. Dis.*, **80**, 371

Velu, S., Andrews, R. H., Angel, J. H., Devadatta, S., Fox, W., Jacob, P. G., Nair, C. N. & Ramakrishnan, C. V. (1961) *Tubercle (Edinb.)*, **42**, 136

Wingo, C. F., Fairly, J. L. & Roye, W. E. (1957) In: *Transactions of the 16th Conference on the Chemotherapy of Tuberculosis, (held from 11 to 14 February 1957, at St. Louis, Missouri)*, Washington, D.C., US Government Printing Office, p. 254