

## Isoniazid liver injury during chemoprophylaxis in children

P. SPYRIDIS, C. SINANIOTIS, I. PAPADEA, L. OREOPOULOS, S. HADJIYIANNIS,  
AND C. PAPADATOS

Athens University School of Medicine, Greece

**SUMMARY** The incidence of INH-associated liver injury was evaluated in 239 children aged between 9 and 14 years, who were receiving 300 mg INH/day for tuberculosis prophylaxis. Serum SGOT and SGPT levels were determined before INH administration and at 4-weekly intervals thereafter. Levels of both enzymes were raised during the first 3 months of treatment in 18 (7.5%) children, while in 23 (9.6%) children either SGOT or SGPT exceeded normal levels (SGOT >40 units, SGPT >30 units). Only 2 (0.8%) children showed SGOT and SGPT values above 100 units and in them treatment with INH had to be discontinued. In all other children transaminases returned to normal during uninterrupted INH administration. It was noted also that transaminase values in children who did not exhibit a rise above normal, still had significantly higher levels during treatment compared with before. The findings of this study suggest that liver injury in children receiving INH for prophylaxis occurs more often than it had hitherto been believed but that it is usually mild and transient.

Isoniazid (INH) has been recognised as a cause of liver injury in patients receiving it. Several studies have shown there is an asymptomatic rise in the level of SGOT in 10-20% of adults given INH (Scharer and Smith, 1969; Bailey *et al.*, 1973; Mitchell *et al.*, 1975), although clinically overt hepatitis appears to be rare in such patients (Martin and Arthaud, 1970; Garibaldi *et al.*, 1972; Moss *et al.*, 1972; Black *et al.*, 1975; Mitchell *et al.*, 1976).

Most studies on the incidence of INH-associated liver dysfunction have been on adults. However Beaudry *et al.* (1974) estimated serum SGOT levels in children aged between 1 and 18 years and found that 6.8% of children receiving INH had higher levels of SGOT 2 months after the start of treatment. As treatment with INH is still used extensively in children, and because there is a lack of information on the incidence and clinical significance of liver injury during INH administration, this study was undertaken.

### Materials and methods

The study group comprised 239 schoolchildren (128 boys and 111 girls) 9-14 years old (mean age 11.2). These children had been found to have a positive result to a tuberculin test during routine tests at elementary schools in Athens between November 1976 and March 1977, and they were therefore taking INH.

None of the children had active tuberculosis as shown in chest x-rays and by a normal ESR. Each child was given a month's supply of INH, to be taken as a single daily dose of 300 mg, and instructed to return to the clinic each month. Baseline determinations of SGOT and SGPT were obtained immediately before taking the INH and at monthly intervals thereafter.

Serum transaminase levels were determined using a modification of the Reitman and Frankel (1957) colorimetric method (kits from Dade Diagnostic, Inc.). Normal values for this method are 5-40 units for SGOT and 5-30 units for SGPT.

All children were examined for HB<sub>s</sub>Ag before INH administration. Any patient who subsequently showed an increase in the level of SGOT or SGPT in his or her blood sample was examined for HB<sub>s</sub>Ag by counterimmunoelectrophoresis and for infectious mononucleosis by the Monosticon test (Organon Technika).

---

The Second Department of Paediatrics, Athens University School of Medicine, Greece

P. SPYRIDIS, research associate

C. SINANIOTIS, associate professor of paediatrics

I. PAPADEA, research fellow

L. OREOPOULOS, consultant physician

S. HADJIYIANNIS, consultant physician

C. PAPADATOS, professor of paediatrics

---

## Results

None of the 239 children had abnormal transaminase concentrations before taking INH.

In 41 (17.1%) of them a rise of at least one transaminase above the normal level was observed during the 12-week period after starting treatment. Two children who showed an increase in SGOT and SGPT but were found to have a positive result in the test for infectious mononucleosis, and 2 others who became HB<sub>e</sub>Ag positive at the time that transaminase values increased were excluded from the analysis of the data. The increase in enzyme levels that took place during treatment with INH followed three different patterns (Table 1): 18 (7.5%) children showed an increase in both SGOT and SGPT levels. In another 18 children (Table 2) only SGOT increased above 40 units, and in 5 (2.1%) SGPT exceeded 30 units. A rise in the level of SGOT was noted in 36 (15%) children and in 23 (9.6%) children there was an increase in the SGPT level (Table 2).

In children in whom levels of SGOT and SGPT remained normal, an upward trend of the values during the first weeks of treatment was observed (Tables 3, 4). Although the difference between the mean values during each period of observation was small, the statistical analysis (paired *t* test) showed that it was highly significant ( $P < 0.001$ ).

The rise in the levels of enzymes took place during the first 2 months of treatment in most children (Table 4), but generally it was mild and transient. Only 2 (0.8%) children were found to have SGOT and SGPT values above 100 units and INH had to be discontinued. In the remaining 39 cases treatment was continued, but with close supervision and

Table 1 *Children receiving INH who had SGOT values >40 units and SGPT values >30 units*

	No. of children	% of total
SGOT+SGPT	18	7.5
SGOT	18	7.5
SGPT	5	2.1
Total	41	17.1

Table 2 *Mean SGOT values in 203 children with SGOT levels <40 units during treatment with INH*

	Before treatment	Weeks on INH		
		4	8	12
Mean	20.7	23.8	24.3	23.0
SD	7.0	7.8	7.8	6.4
S E M	0.49	0.54	0.54	0.45

1, 2  $t=4.1$   $P<0.001$  1, 3  $t=4.8$   $P<0.001$   
1, 4  $t=3.3$   $P<0.001$

Table 3 *Mean SGPT values in 216 children with levels <30 units during treatment with INH*

	Before treatment	Weeks on INH		
		4	8	12
Mean	9.3	11.7	11.6	11.8
SD	4.0	5.2	5.2	4.9
S E M	0.27	0.35	0.35	0.33

1, 2  $t=5.5$   $P<0.001$  1, 3  $t=5.1$   $P<0.001$   
1, 4  $t=5.9$   $P<0.001$

Table 4 *Children showing raised transaminase values in relationship to duration of INH administration*

	No. of children	Weeks on treatment					
		4		8		12	
		No.	(%)	No.	(%)	No.	(%)
SGOT	36	19	(53)	11	(30)	6	(17)
SGPT	23	13	(57)	8	(35)	2	(8)

frequent monitoring. In these children the transaminases returned to normal levels within 4–8 weeks.

## Discussion

These data confirm earlier observations—made mainly in adults—that some patients receiving INH may develop high levels of serum transaminase without overt signs of liver disease (Scharer and Smith, 1969; Bailey *et al.*, 1973; Mitchell *et al.*, 1975).

In most previous studies patients were monitored for liver injury by determination of one transaminase. The incidence of abnormal SGOT values in these studies ranged from 10 to 20% of the patients taking the drug (Byrd *et al.*, 1972; Bailey *et al.*, 1973; Mitchell *et al.*, 1976).

In a similar study in 178 adolescents SGPT values became abnormally high in 10% of patients within 10 weeks of taking INH (Litt *et al.*, 1976).

Until recently no data of hepatic function had been reported in children receiving INH for prophylaxis and the *ad hoc* Committee on Isoniazid and Liver Disease in Atlanta, Georgia, USA, stated in a report issued in 1971 that 'isoniazid-associated liver disease does not appear to occur in children.' Since then reports have suggested that severe hepatic injury (Rudoy *et al.*, 1973) or even death (Vanderhoof and Ament, 1976) might occur in children taking INH. Beaudry *et al.* (1974) who studied SGOT levels in 369 children on INH prophylaxis reported increased levels of SGOT in 6.8% of them.

In the present study in which both SGOT and SGPT concentrations were monitored, a rise above normal values for both enzymes was detected in 18 (7.5%) out of the 239 children. In addition 23 (9.6%) more children showed an increase either in SGOT or SGPT, during the period of observation (Table 1). The incidence of 17.1% for children with raised transaminase values is significantly higher than the 6.8% incidence reported by Beaudry *et al.* (1974). The reason for this difference is not clear and it could be due to differences in the techniques used to determine enzyme levels. It is evident that it is difficult to compare data from different studies. More studies using strict criteria are needed.

Another interesting finding in the present study was that higher values of SGOT and SGPT were noted in most patients compared with levels before treatment (Tables 2, 3). Although this difference was small, the statistical analysis (paired *t* test) showed that it was highly significant ( $P < 0.001$ ). This finding, not reported by others, suggests that liver injury is more common than is shown by an increase in the level of enzymes. It has been suggested that the degree of liver injury may be greater if INH is given at the same time as enzyme-inducing drugs such as rifampicin (Pessayre *et al.*, 1977).

It is apparent from previous studies, and confirmed by this one, that most patients with sub-clinical hepatic damage recover completely while continuing on INH, and do not progress to overt hepatitis. The fact that in the present study only 2 patients had a rise of SGOT and SGPT above 100 units and had to stop taking INH, while 39 children were able to continue to take it and their SGOT and SGPT levels returned to normal, shows that although INH prophylaxis is rarely associated with clinically significant liver injury, transaminase levels should be monitored in the first month of treatment to detect patients who might be susceptible to liver damage.

#### References

- ad hoc* Committee on Isoniazid and Liver Disease. (1971). Report. *American Review of Respiratory Diseases*, **104**, 454-459.
- Bailey, W. C., Taylor, S. T., Dascomb, H. E., Greenberg, H. G., and Ziskind, M. M. (1973). Disturbed hepatic function during isoniazid chemoprophylaxis. *American Review of Respiratory Diseases*, **107**, 523-529.

- Beaudry, P. H., Brickman, H. F., Wise, M. B., and MacDougall, D. (1974). Liver enzyme disturbances during isoniazid chemoprophylaxis in children. *American Review of Respiratory Diseases*, **110**, 581-584.
- Black, M., Mitchell, J. R., Zimmerman, H. J., Ishak, K., and Epler, G. R. (1975). Isoniazid-associated hepatitis in 114 patients. *Gastroenterology*, **69**, 289-301.
- Byrd, R. B., Nelson, R., and Elliott, R. C. (1972). Isoniazid toxicity. A prospective study in secondary chemoprophylaxis. *Journal of the American Medical Association*, **220**, 1471-1473.
- Garibaldi, R. A., Drusin, R. E., Ferebee, S. H., and Gregg, M. B. (1972). Isoniazid-associated hepatitis. Report of an outbreak. *American Review of Respiratory Diseases*, **106**, 357-365.
- Litt, I. F., Cohen, M. I., and McNamara, H. (1976). Isoniazid hepatitis in adolescents. *Journal of Pediatrics*, **89**, 133-135.
- Martin, C. E., and Arthaud, J. B. (1970). Hepatitis after isoniazid administration. *New England Journal of Medicine*, **282**, 433-434.
- Mitchell, J. R., Long, M. W., Thorgeirsson, U. P., and Jollow, D. J. (1975). Acetylation rates and monthly liver function tests during one year of isoniazid preventive therapy. *Chest*, **68**, 181-190.
- Mitchell, J. R., Zimmerman, H. J., Ishak, J. G., Thorgeirsson, U. P., Timbrell, J. A., Snodgrass, W. R., and Nelson, S. D. (1976). Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. *Annals of Internal Medicine*, **84**, 181-192.
- Moss, J. D., Lewis, J. E., and Knauer, C. M. (1972). Isoniazid-associated hepatitis. A study of five cases. *American Review of Respiratory Diseases*, **106**, 849-856.
- Pessayre, D., Bentata, M., Degott, C., Nouel, O., Miguet, J.-P., Rueff, B., and Benhamou, J.-P. (1977). Isoniazid-rifampin fulminant hepatitis. A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. *Gastroenterology*, **72**, 284-289.
- Reitman, S., and Frankel, S. (1957). A colorimetric method for the determination of serum glutamic oxaloacetic and glutamic pyruvic transaminases. *American Journal of Clinical Pathology*, **28**, 56-63.
- Rudoy, R., Stuemky, J., and Poley, J. R. (1973). Isoniazid administration and liver injury. *American Journal of Diseases of Children*, **125**, 733-736.
- Scharer, I., and Smith, J. P. (1969). Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. *Annals of Internal Medicine*, **71**, 1113-1120.
- Vanderhoof, J. A., and Ament, M. E. (1976). Fatal hepatic necrosis due to isoniazid chemoprophylaxis in a 15-year-old girl. *Journal of Pediatrics*, **88**, 867-868.

Correspondence to Dr C. Sinaniotis, Second Department of Paediatrics, Aglaia Kyriakoy Children's Hospital, Goudi, Athens, Greece.

Received 24 January 1978