Indian Journal of Experimental Biology
Vol. 42, March 2004, pp. 323-325

Disposition of uric acid upon administration of ofloxacin alone and in combination with other anti-tuberculosis drugs

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Received 18 July 2003; revised 20 November 2003

Disposition of uric acid upon administration of ofloxacin (O) alone and in combination with other anti-tuberculosis drugs, rifampicin (R), isoniazid (H) and pyrazinamide (Z) was studied. Twelve male healthy volunteers were investigated on four different occasions with the four drugs alone or in combinations. A partially balanced incomplete block design was adopted and the subjects were randomly allocated to each group. Uric acid concentration in urine samples excreted over 0-8 hr, were determined after coding the samples. There was significant decrease in the group receiving Z when compared to other groups. Though there was a decrease in uric acid excretion in the group receiving O, it was not statistically significant. Rifampicin and H seem to increase the uric acid excretion. The incidence of arthralgia was mainly due to Z and not due to either O or other drugs in the treatment of pulmonary tuberculosis.

Keywords: Anti-tuberculosis drugs, Ofloxacin, Uric acid disposition

It is well known that uric acid is derived from purines which are primarily formed from the normal breakdown of body tissue and secondarily from dietary sources. In the human, approximately 2/3 of the total uric acid production is excreted via kidney. It is clearly established that uric acid is freely filterable by the glomerulus, re-absorbed almost completely by the proximal tubules and secreted by the tubules. A blockage of tubular secretion results in uricosuria. Urate excretion is a complex process and a familiarity with the complexities of uric acid excretion is essential, since drugs can alter these processes.

Administration of pyrazinamide (Z) in the chemotherapy of tuberculosis (TB) results in arthralgia[1]. Pyrazinamide suppresses the urinary excretion of uric acid by inhibiting tubular secretion, thereby retaining uric acid. The retained uric acid as sodium urate is probably deposited in the joints, leading to arthralgia.

There are several reports that uric acid excretion is suppressed in TB patients receiving Z containing regimen[2]. This results in arthralgia which is probably due to hyperuricaemia caused by pyrazinoic acid, the primary metabolite of Z. When rifampicin (R) is administered together with Z, the incidence of arthralgia is reduced[3].

Ofloxacin (O), a synthetic carboxy fluoroquinolone, is a valuable addition to the existing chemotherapy of pulmonary tuberculosis. In vitro studies demonstrate the bactericidal activity of O which suggests that it is the most useful drug in the early stages of treatment and prevents the emergence of resistance to other drugs[4]. Anti-tuberculosis (TB) regimens of 4 or 5 months duration that contain O and other anti-TB drugs achieve more than 95% efficacy with no increased incidence of adverse reactions and minimal relapses, permitting shortening of duration[5].

Very little information is available on the disposition of uric acid upon administration of O together with other anti-TB drugs. Therefore, it was aimed to study the clinical implications of uric acid disposition when O was administered alone and in combination with other anti-TB drugs.

Treatment and sample collection — Twelve male healthy volunteers with the mean age of 23 years (19-27 years) and the mean body weight of 56 kg (45-69 kg) are included in this study and all the volunteers gave written informed consent prior to participation in the study. The volunteers are healthy as determined by comprehensive medical history, physical examinations and laboratory profiles. None of the subjects was taking medications within one week or during the study and also are non-alcoholics. None of the subjects had a history or current evidence of significant renal, hepatic or haematological disease. The Institutional Ethic Committee clearance was obtained prior to start of the study.

Each volunteer was investigated on four different occasions with the four drugs, viz., O (Dee Pharma Ltd.), R (Asojsof Caps. Pvt. Ltd.), Z (Lupin Laboratories) and H (Pfizer), either alone or in combinations, viz., O, R, H, Z, OR, OH, OZ and ORHZ with an interval of atleast one week between occasions. A partially balanced incomplete block design was adopted where the drugs were administered to the volunteers at random.

The dosages of the drugs administered were approximately 10 mg/kg body weight for R, 35 mg/kg for Z and 15 mg/kg body weight for O and H.

The drugs were administered on an empty stomach and urine sample excreted over the period of 0-8 hr

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were collected. The volume of the urine excreted was measured and the aliquots stored at –20°Cuntil assay was performed.

Uric acid concentration in urine were determined by the phosphotungstate reduction method[6] after coding the samples. Uric acid in urine reduces an alkaline phosphotungstase solution to a tungsten blue. The intensity of the colour is proportional to the concentration of uric acid present in the urine and is measured photometrically against the standard. Creatinine estimation was also carried out by Jaffe's method[7] to ascertain the completeness of urine collection.

Urinary excretion of uric acid when O was given alone and in combination was estimated in the samples collected over the periods 0-8 hr. The mean urinary excretion of uric acid following administration of O, R, H, Z alone and in combinations have been presented in Fig. 1. The uric acid excretion was significantly decreased in OZ group (65.4 mg/dl), compared to O alone (196.5 mg/dl). When OZ group was compared with Z alone (53.7 mg/dl), there was a decrease in the urinary excretion of uric acid and it was not statistically significant.

Urinary excretion of uric acid was compared between the groups O alone and ORHZ (189.6 mg/dl) where the difference was not statistically significant. On the other hand, when Z alone group was compared with ORHZ, there was significant increase in uric acid excretion.

OR group (275.1 mg/dl) when compared with R alone (279.6 mg/dl), the urinary excretion of uric acid remained the same. Similarly, OH group (372.8 mg/dl) was compared with H alone (275.2 mg/dl), and observed no significant difference in the uric acid value.

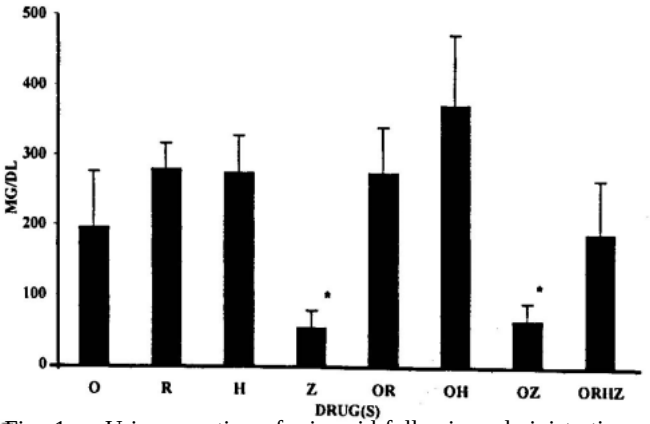

Fig. 1 — Urinary excretion of uric acid following administration of O, R, H and Z alone and in combinations. The vertical bars denote standard deviation. [*Significant at P<0.05 when compared to O alone]

It was evident from the findings that the suppression of urinary excretion of uric acid was mainly due to Z. There was significant decrease in the mean rate of urinary excretion of uric acid when OZ was compared with O group. Pyrazinamide is metabolized to pyrazinoic acid (PZC) by hepatic microsomal pyrazinamide deamida[8,9] and the latter suppresses urinary excretion of uric acid by inhibiting its tubular secretion[2,10,16]. Urinary excretion of uric acid in Z and OZ group remained unchanged and it was not statistically significant proving that O does not decrease the uric acid excretion, when combined with Z. Therefore, Z played a major role in the urinary excretion of uric acid which was evident from uric acid retention.

Studies conducted by Sarma *et al.*[2] have shown that Z caused a significant decrease in the renal excretion of uric acid. Rifampicin enhanced the renal excretion of uric acid both in the presence and absence of Z. This effect could lead to a decrease in the deposition of uric acid in joints and consequently to a lower incidence of arthralgia.

Present results showed that O alone when compared with ORHZ group, there was no significant difference in the urinary excretion of uric acid whereas when Z alone was compared with ORHZ group, the uric acid excretion was significantly elevated. Rifampicin and H seemed to increase the uric acid excretion. In pulmonary TB patients, treated with all the four drugs (O, R, H and Z), the incidence of arthralgia was mainly due to Z and not due to O or other drugs.

A controlled clinical trial of 3, 4 and 5 months regimens containing O for the treatment of patients with sputum positive pulmonary TB in South India, was conducted at the centre, with an objective of shortening the duration of treatment[5]. The results have shown that 4 and 5 months regimens using O as one of the drugs in the initial-intensive phase, can be as effective as the currently widely recommended regimens in patients with drug sensitive bacilli and have great promise for application in TB control in the future. In these patients, the serum uric acid values were monitored during the course of treatment. It was found that the serum uric acid levels were elevated only during the first phase of treatment which contained all the four drugs (O, H, R and Z) and it returned to normal during the second phase of treatment which contained only R and H (unpublished data). Therefore, the elevation of serum uric acid must be due to Z or O. Studies have shown that the incidence of arthralgia is due to Z[1]. Since O is also

administered in the multiple regimen therapy, the question arises whether O also plays a role in the suppression of uric acid excretion.

Toxicologic evaluation of O has shown that it is well tolerated within reasonable multiples of the intended clinical dose[17]. Safety profiles of O are evaluated on the basis of adverse reactions[18]. Adverse reactions are not serious and usually rapidly reversible. Present results clearly demonstrated that the administration of O did not play a role in the suppression of urinary excretion of uric acid. The data presented provides a clear evidence that urinary excretion of uric acid was significantly decreased upon administration with Z, thereby leading to arthralgia. Therefore, O could be a valuable therapeutic agent in the treatment of pulmonary TB besides a variety of indications. The shorter duration of treatment with O containing regimens would hopefully improve patient adherence.

The authors wish to thank the volunteers for their willingness to participate in this study and Mr B Doraiswamy for secretarial assistance.

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